BIOIVT

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GUIDE

Questions to Ask Your Human Biological Specimen Provider

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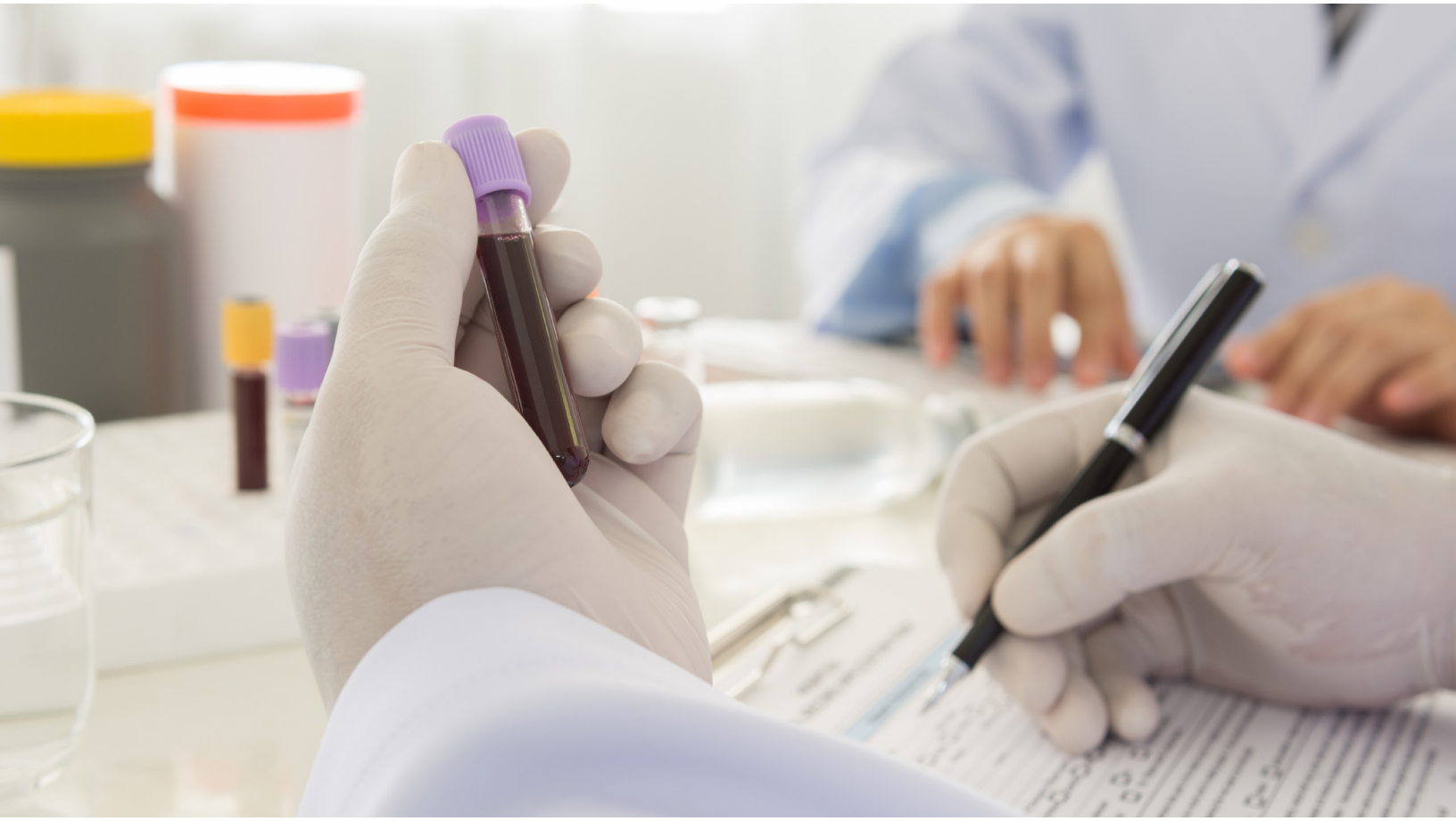


The foundations for protecting human research subjects come from the ethical principles surrounding the Belmont report : Respect for persons, beneficence, and justice. The use of human biospecimens in research supports these principles with legal and ethical regulations - the most important of which is permission.[1] As either a researcher or purchaser of Human Biological Specimens (HBS) for research, you need to ensure that your HBS provider operates within the limits of the regulatory oversite that is required for HBS procurement as well as in line with the best practices that have been developed over years by groups specializing in optimizing HBS procurement. Below are key questions that should be asked of every HBS provider.

1 Does the HBS provider have the expertise and resources required to meet all the necessary regulatory and quality requirements?

It is important that your HBS provider have an in-depth understanding of regulatory and industry requirements to support your ongoing research efforts. HBS sourcing, in most cases, is human subject research and requires the approval of an Institutional Review Board (IRB)/International Ethical Committee (IEC)/Research Ethics Committee (REC) or other similar ethical committee. For US based providers, the provider should be working with reputable IRBs registered with either the Office of Human Research Protection (OHRP) and/or accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP), as well as with the appropriate international research governing bodies in respective countries from where tissues are being procured. For providers based in non-US countries, the HBS provider should be working with reputable IECs/RECs as required by law. In addition, they should be registered with the appropriate governmental regulatory bodies, such as the Human Tissue Authority in the UK or Ministries of Health in many other countries. Your HBS provider should have the capacity to maintain regulatory and quality requirements. Importantly, they should also stay abreast of the ever-changing regulatory landscape, such as the implementation of GDPR and changes to the Common Rule, and translate these changes to relevant parties ahead of implementation.

BioIVT has a team of over 23 Regulatory and Quality personnel with **over 250 years** of combined experience. BioIVT works with local and centralized US-based IRBs, EU-based IECs, and Health Ministries in other countries as required and is in compliance with our UK HTA license for the storage, use and disposal of human biomaterials. Furthermore, our regulatory team stays abreast of current regulation changes and their impact through continuous education, such as attendance at seminars, webinars, white paper review, and on-going team meeting discussions, among other activities.

2 Does the HBS provider have a proven Strategic Partner Network (SPN) capable of servicing your HBS needs?

This question should be at the forefront when seeking a HBS provider. Having a proven and contracted SPN determines the efficiency and accuracy in fulfilling HBS criteria. SPN members should undergo a documented qualification program to ensure that specimens and associated clinical data are obtained in a manner that meets or exceeds quality standards. The HBS provider's SPN members should be experienced in conducting clinical research and trials. This experience allows the SPN members to understand the requirements in research terms and ensure Human Research Protection (HRP) and Good Clinical Practice (GCP) when sourcing HBS from donors. This experience also ensures that the SPN members themselves are aware and compliant with the laws and regulations applicable at their specific locations, with specific steps in place to comply with regulatory codes of practice. The HBS provider should be able to present data regarding types of available HBS, including various disease states represented, volumes and sizes able to be collected, and quantity of donors within their SPN as well as historical accrual rates. As the industry moves toward personalized medicine research applications, it is important that a HBS provider in conjunction with their SPN members has the ability to help design your study with varying inclusion and exclusion criteria as appropriate to the donor cohort required, so that the HBS provider may meet your experimental needs.

BioIVT has **over 200 IRB approved collection sites** located around the world, including US, EU, Asia, Africa and South America. Our sites span a range of clinical operations, from local doctor's offices to large health systems to donor centers. Our collaborative relationship with our SPN allow us to work closely to ensure that HBS are sourced with your specific experimental needs.

3 How is the HBS's SPN evaluated, contracted, and audited to ensure compliance with stated standards and objectives as defined above?

Not only is it important to have a proven SPN network, the HBS provider should also have contracts (research agreements), monitoring/audit, and training plans in place to ensure compliance with HRP, GCP and all other international, state and federal laws. Credentials of investigators and staff at each SPN site should be evaluated to determine years of research experience and regulatory compliance initially as well as periodically, ensuring that there are not lapses due to changes in personnel. The HBS provider should have an established bioethical

policy that ensures that the basic rights of human subjects are met, including 1) subject has received honest information about the research study/respect for person, 2) that the research is performed in the best interests of the subject/do no harm, 3) that the donation is freely given, without coercion or inducement, or authorized per local legal and ethical requirements/voluntary, and 4) specific to post-mortem collections, that next of kin are contacted to provide consent. The sites within the SPN should be assessed to determine capabilities to meet HBS provider and client's requirements including patient population, equipment, staff, staff training, and other resources.

BioIVT has a dedicated **Site Development Team** of trained professionals who understand what it takes to successfully incorporate a site into our SPN. Sites are rigorously vetted with assessments and evaluations prior to contracting. All our sites are under contract with defined compliance expectations and undergoing auditing on a yearly basis. Our team of project managers, trainers, and site monitors maintain a close relationship with each site, making sure that everyone is up to date on training, Standard Operating Procedures (SOPs) and other important project specific needs.

4 Does the HBS provider's SPN have the tools and ability to create dedicated donor recruitment processes and manage donors to meet the clients' needs?

The HBS provider's SPN must include the targeted donor cohort in line with your experimental needs. In addition, the HBS provider may allow SPN members to use advertising material to increase donor recruitment where necessary. Donor recruitment material must be reviewed by the IRB of record prior to use, in order to ensure coercion and undue influences are not a factor in a subject's voluntary participation in research. Each site within the SPN should have databases and other reliable methods to establish connections with potential donors as part of the research processes versus a clinical process.

BioIVT's industry-leading network of collection sites located around the world, have access to donor cohorts covering many different disease indications as well as normal cohorts. In addition, there are specific locations with large databases of potential subjects who can be called in to participate in a specific collection meeting their conditions. With our SPN covering a range of clinical operations, from local doctor's offices to large health systems to donor centers, we have access to the cohort your experimental design requires. Our Site Development Team will also identify, vet and contract with new collection sites for custom projects as well as continually expanding our ability to offer in-need cohorts, allowing BioIVT to offer prospective collections of unique and rare donor cohorts.

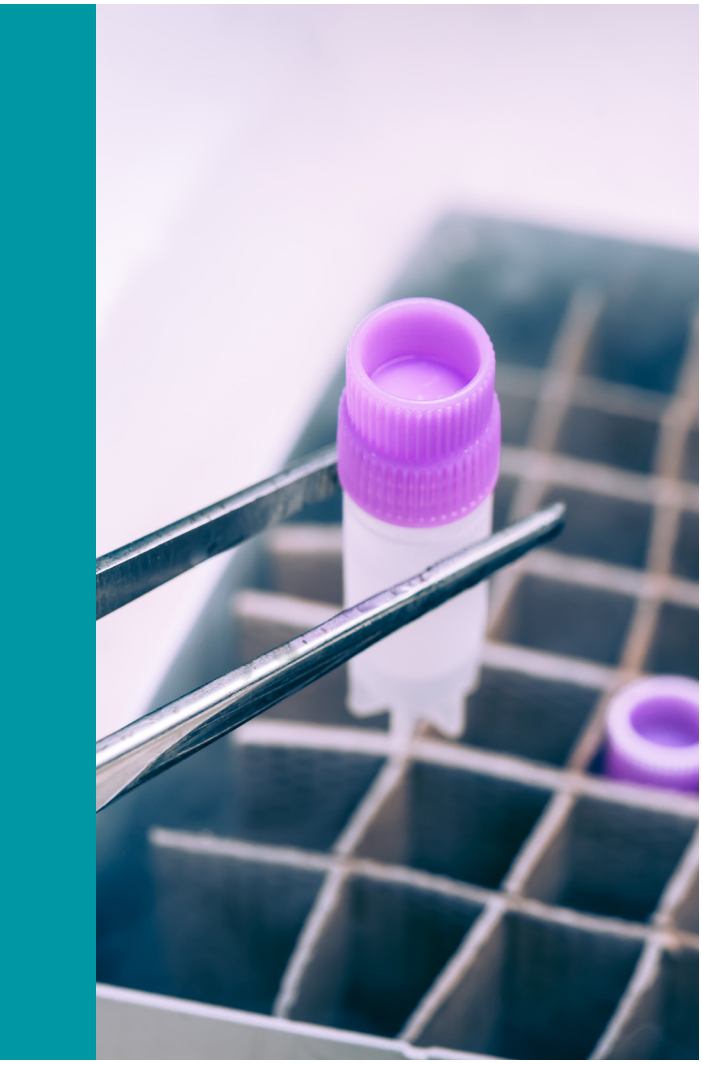
5 Is the HBS provider able to provide supporting regulatory documents such as blinded consents and IRB approvals?

Sample specific blinded/redacted consents and IRB approval letters must be available upon request. These documents serve as proof of compliance with laws and regulations governing human subject research. Consent forms and IRB approval letters are especially important in regulatory filings with the FDA, EMA, PMDA and other country specific regulatory organizations. If the supplier is unable to provide these documents, the reasons must be legitimate and supported by existing regulations.

In order to foster a more **transparent environment** regarding ethical HBS practices, BioIVT provides the appropriate blinded/redacted consents and IRB approval letters for HBS upon request. This allows clients to make informed decisions of which specimens are most appropriate and fitting for their research needs. For example, upon sample selection for ASTERAND™ Human Tissues, links to the appropriate regulatory documents are provided prior to sample selection. It should be noted that not all consents contain the appropriate wording for all research activities. At BioIVT, we review all regulatory documents via an expansive checklist review to ensure pertinent wording for research use.

6 Does the HBS Provider have procedures in place to deliver consistent, quality products?

Biospecimen quality and integrity is achieved through defined specimen retrieval and processing procedures. The provider must maintain documented SOPs including quality criteria for biospecimen and associated data, specimen retrieval and processing procedures, and a comprehensive training program for staff and all SPN member personnel. Defined proficiency standards ensure competent personnel are performing all biospecimen processing and evaluation. Biospecimen storage and processing temperature conditions are critical for maintaining specimen integrity from collection, storage, processing, and shipment; conditions should be specific for different specimen types. In addition, instruments and equipment should be properly operated, maintained, serviced and monitored. Laboratory procedures must be detailed and clinical research site management procedures must be in place.

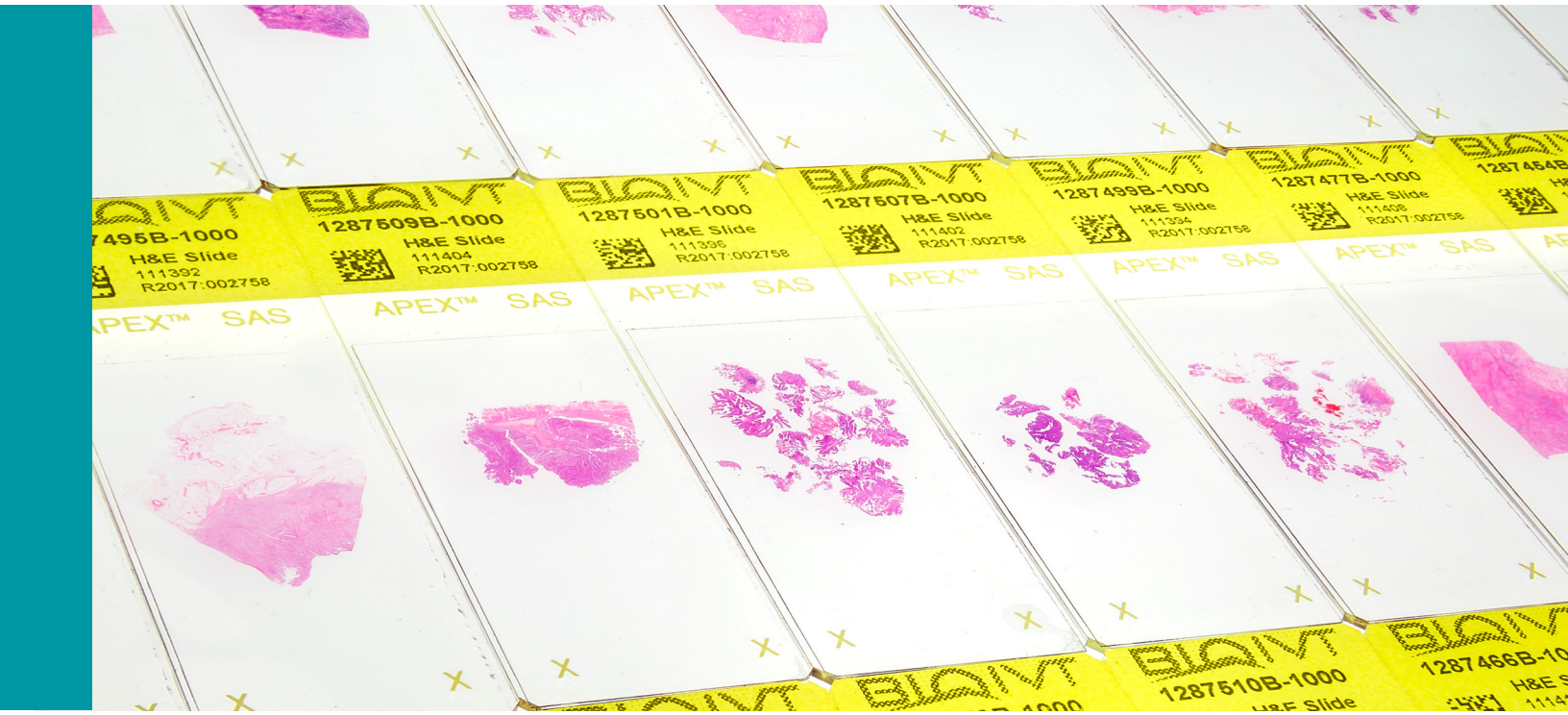


BioIVT has detailed biospecimen processing, storage, and transport procedures that are reviewed and updated regularly to ensure industry standards are employed. A training program is defined for employees and SPN personnel to establish minimum competency in regulatory compliance, subject/donor suitability, sample processing/handling, storage, shipping, and documentation requirements. Remote site monitoring and on-site audits are regularly performed to ensure all clinical supply sites supply suitable IRB-approved samples to BioIVT and are in compliance with company **SOPs** and written instructions. BioIVT operates, maintains, services and monitors instruments and equipment according to manufacturer recommendations and industry standards.

7 Does the HBS provider have a Quality Management (QM) program in place?

The Quality Management program helps coordinate and direct activities to meet both customer and regionally applicable regulatory requirements. An effective Quality Management system enhances customer satisfaction by identifying issues that affect the quality of products and services. The QM system should include methods to identify, investigate, and resolve any problems identified and mitigate recurrence. The HBS provider should also perform internal and supplier audits to verify compliance with standards and objectives. Systematically performing audits – and identifying corrective and preventative actions – ensures conformity to standards and identifies improvement opportunities.

The BioIVT Quality Management program is continually working to maintain QM systems and meet customer needs and expectations. The ASTERAND Human Tissue Biorepository is ISO9001:2015 certified for QM compliance and CAP certified for research biobanking best practices **compliance**. In addition, our UK-based PHASEZERO facility is GLP compliant underpinning our UK HTA license for sample storage in the UK. Thus, tissue processing required locally in the EU can be performed in our GLP/GCLP compliant laboratory.



8 Does the HBS provider have a Chain of Custody Policy in place to maintain specimen identity from initial collection through final disposition?

Ensuring the identity of the specimen is critical for associating the QC data, Informed Consent Form (ICF) (if relevant) and clinical data with the correct specimen and any derivatives of the specimen. The policy should include how specimen labeling and data are maintained from time of collection, through quality control processes, storage, shipping, and disposal. It is equally important to maintain a donor's anonymity, while providing researchers the ability to access clinical data to properly analyze results. An appropriate sample de-identification and delinking process must be in place that follows regulatory requirements, be they HIPAA or GDPR.

BioIVT provides a traceable specimen record for unbroken control over biospecimens and associated containers from initial collection to final storage and disposition. This is achieved with accurate and effective labeling, tracking, and reporting. In addition, BioIVT has in place a system of double de-identification, ensuring that donor anonymity is not compromised while providing researchers with the appropriate level of clinical associated data for research purposes.

9 Does the HBS provider certify specimen type and diagnosis with a Board Certified Pathologist (where applicable)?

The pathologist determines if the specimen meets product quality standards, confirms tissue origin and diagnosis, and verifies sample data quality and integrity. The provider should verify that the specimen and associated data (provided by the supplier) is consistent with the tissue pathology. A Board Certified Pathologist confirms compliance with current health care practices, diagnostic standards and best practices.

At BioIVT, we believe that having the right tissue at the right time is essential to your success. Our team of **Board Certified Pathologists** with over 100 combined years of clinical practice experience, confirm diagnosis on an individual tissue specimen level and confirm consistency with clinical data provided. In addition, for cancer related HBS, they determine parameters such as percent tumor, necrosis, inflammation, and normal regions within each tissue block.

10 Does the HBS provider have an independent individual review clinical data?

HBS with supporting clinical data are a vital component of research integrity. Ensuring that these data are accurate and come from verifiable sources is crucial. A HBS provider should have dedicated internal staff conducting Case Report Form (CRF) data monitoring and certified medical record review. Any inconsistency or discrepancies should be flagged immediately for resolution with the SPN collection site. If inconsistency or discrepancies cannot be resolved, the HBS should be quarantined and addressed according to nonconforming material procedures.

BioIVT has staff dedicated to closely reviewing information supplied in each CRF to ensure the subject's social and medical history is adequately and consistently defined, recorded and curated to support research needs. If necessary, they will reach out to the SPN member site to confirm supplied information or request additional documentation to support the clinical diagnosis. Importantly, **BioIVT's clinical data team** independently verifies tumor staging for all ASTERAND Human Tissue specimens. Providing confidence to researchers that the specimens are appropriate and fit for their research purpose.

11 Does the HBS provider have the ability to customize collections but at the same time maintain regulatory requirements and quality standards?

Criteria for HBS collections have become more specific as research has become increasingly targeted. Previously, order requirements may have been for type 1 diabetes subjects but now, subject requirements may be type 1 diabetes with a specific genotype and on a certain type of medication. The HBS provider should be able to source this material from an IRB-approved investigator's site and support this collection with appropriate medical data. An optimal way to meet clients' needs is to have a large, established supplier network capable of collecting specifically to client requirements. Client requirements should be defined in a specific project protocol to communicate with the supplier. The supplier should receive training for each client project to ensure specimens and data needs are met.

For meeting increasingly specific project-specific HBS requirements in line with personalized medicine interest, at BioIVT we maximize our strong relationships with the sites in our extensive IRB approved HBS collection network. This allows us to acquire biospecimens to our specific standards, but with the flexibility that our clients require – making us your go to **"customerization"** partner. We work with you to understand your collection needs to procure fit-for-purpose specimens for downstream analysis, advising to best practices and feasibility for delivery. We offer on-going educational webinars, white papers, case-studies and more.

12 What challenges has the HBS provider overcome for clients?

Understanding an HBS provider's previous special project accomplishments and ability to overcome challenges is important, as it provides the client a level of assurance and comfort when presented with a proven track record. The previous experience, efficiency and accuracy for sourcing HBS helps determine if project-specific timelines can be met. Clients should be able to trust their HBS provider with challenging projects, including situations where plans change, for example last minute changes in inclusion or exclusion criteria, sample processing procedures, shipping instructions/locations. These tend to be frequent, and an experienced, flexible HBS provider is equipped to deal with such challenges.

While BioIVT's name is new, our core business units have been in operation for **over 35 years** as providers of high quality biospecimens and related services, including human and animal biofluids and tissues from both normal and diseased donors. Our experience across all types of biospecimens means we can source the right specimen with the right data at the right time. Sourcing certain human biomaterials for research is not always easy, but with the breadth of clinical sites in our network, dedicated personnel for ethical sourcing, quality control, auditing and project management, underpinned by our strong quality management system – we can ensure our clients have confidence in our ability to appropriately source those hard to get, essential research resources.

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".[3] Furthermore, the College of American Pathologists (CAP) has initiated a Biorepository Accreditation program.[4] This program, "designed to improve the quality and consistency of facilities that collect, process, store and distribute biospecimens for research"[2], 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.

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About BioIVT

BioIVT, formerly BioreclamationIVT, is a leading global provider of high-quality biological specimens and value-added services. We specialize in control and disease state samples including human and animal tissues, cell products, blood and other biofluids. Our unmatched portfolio of clinical specimens directly supports precision medicine research and the effort to improve patient outcomes by coupling comprehensive clinical data with donor samples. Our PHASEZERO® Research Services team works collaboratively with clients to provide target and biomarker validation, phenotypic assays to characterize novel therapeutics, clinical assay development and in vitro hepatic modeling solutions. As the world's premier supplier of ADME-Tox model systems, including hepatocytes and subcellular fractions, BioIVT enables scientists to better understand the pharmacokinetics and drug metabolism of newly discovered compounds and the effects on disease processes. By combining our technical expertise, exceptional customer service, and unparalleled access to biological specimens, BioIVT serves the research community as a trusted partner 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) 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

(3) HTA, Human Tissue Authority, https://www.hta.gov.uk

(4) CAP Biorepository Accreditation Program http://www.cap.org/web/home/lab/accreditation/biorepository-accreditation-program