

Managing Global Biospecimen and Data Collection & Placement Programs

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I. TRENDS DRIVING GLOBAL EXPANSION OF BIOSPECIMEN AND DATA COLLECTION AND PLACEMENT PROGRAMS

A. *Global Variability in Disease Incidence*

The legal landscape in the United States offers numerous challenges for those entities that undertake management of biospecimen and data collection and placement programs. These challenges can be amplified when such programs operate on a global scale. Global biospecimen management programs can take many forms, each of which presents unique issues that can impact the way principles of informed consent, privacy, ownership, and control of specimens are implemented. Many global biospecimen programs face these issues at the original sites of collection, which may be located in multiple countries.

Many future genomic studies will likely demand that a global population be represented in the applicable biorepository. Many scientists assert that emphasizing the differences or diversity of genomes of various groups of people may reveal information about why certain populations are more susceptible to diseases than to others.¹ Likewise, insight into the resistance of certain groups of people to diseases may lead to diagnostics

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¹ Joan L. MacGregor, *Population Genomics and Research Ethics With Socially Identifiable Groups*, 35 J.L. MED. & ETHICS 356, 359 (2007).

or therapeutics based upon those differences. For example, one may use the global variability in the incidence of type I diabetes in children and adolescents to demonstrate the need for representation of a diverse global population to support research into novel therapeutics and diagnostics. Almost twenty-five percent of new children and adolescents diagnosed with type I diabetes are from South East Asian countries.² In contrast, the Western Pacific region has a significantly lower number of new cases of type I diabetes, despite the fact that the relative total population of children and adolescents is greater than in South East Asia.³ Individual researchers seeking biomarkers for type I diabetes may find that the factors driving such variability among global populations cannot be adequately represented by even the most diverse regional populations, such as those found in United States urban medical centers. By failing to account for such regional differences, researchers may overlook key elements of disease risk, progression, treatment, and outcome. Therefore, the ultimate utility of biospecimen collections for medical research may hinge on the ability to assemble a global specimen database that is capable of detecting and controlling for regional-scale variations.

B. *Divergent Global Standards of Care*

A second trend that drives expansion of biospecimen and data collection programs to multiple regions and countries derives from variability in the standard of care. Health care, when viewed from a global perspective, is rampant with inequity. This can have a significant impact on the quality, integrity, and utility of biospecimens and data collected from any particular region. One can see the impact of such variation by examining the use of biospecimens in prostate cancer research, where the availability of early cancer screening may result in biospecimen samples that are too small to withstand certain quality analyses and research uses.

In the United States, the controversial Prostate Specific Antigen (“PSA”) test is widely available.⁴ This test has been credited with driving advances in the early detection of prostate cancer.⁵ Since diagnosis occurs early in disease progression, many United States-based patients then have multiple treatment options, ranging from radical

² Ismail Kola & John Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?*, 3 NATURE REV.: DRUG DISCOVERY 711, 711-15 (2004); see also Jamol P. Mathew et al., *From Bytes to Bedside: Data Integration and Computational Biology for Translational Cancer Research*, 3 PUB. LIBR. SCI. ONE: COMPUTATIONAL BIOLOGY e12 (2007) (providing an overview of technologies that generally involve the analysis of human biological materials, such as protein extraction and analysis, digital biological images, and creation of microarrays).

³ INTERNATIONAL DIABETES FEDERATION, DIABETES ATLAS, SECOND EDITION 16 (2003); see also Diabetes Atlas - Incidence, <http://www.eatlas.idf.org/Incidence> (last visited Jan. 4, 2009).

⁴ Lauran Neergaard, *How to Help Patients Make Wiser Health Choices*, ASSOCIATED PRESS WASHINGTON, Feb. 9, 2009; see also Thomas A Stamey et al., *The Prostate Specific Antigen Era in the United States is Over For Prostate Cancer: What Happened in the Last 20 Years?*, 172 J. UROL. 1297 (2004) (criticizing the use of PSA tests).

⁵ Gabriela De Angelis et al., *Twenty Years of PSA: From Prostate Antigen to Tumor Marker*, 9 REVS. UROL. 113, 121-23 (2007) (this article discusses the development of the PSA test, and notes that its wide use over the last ten years has resulted in changes to the epidemiology regarding prostate cancer); see also AMERICAN UROLOGICAL ASS’N, PROSTATE CANCER: GUIDELINES FOR THE MANAGEMENT OF CLINICALLY LOCALIZED PROSTATE CANCER 5-6 (2007) (discussing the evolution of prostate cancer diagnosis over the last 20 years), available at <http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/proscan07/content.pdf>.

prostatectomy to radiation to seed radiation to active monitoring.⁶ Only radical prostatectomy results in a surgical intervention involving the removal of diseased and normal tissue, and subsequent availability of surgical samples that may be dedicated to research. Pathological specimens acquired through radical prostatectomy are also often used to determine the presence of various prognostic indicators that provide information about the disease status and progression.⁷ Hence, prior to any research use, the tissues removed during radical prostatectomy may first be required to obtain information about the patient's prostate cancer.

However, between early detection of smaller tumors (though PSA testing) and the use of specimens for pathological analysis following radical prostatectomies, a small amount of tissue may remain for use in research.⁸ Aside from radical prostatectomies, prostate tumor biopsies may offer another alternative for acquiring prostate cancer specimens, but tend to leave even less tissue for research use, as such biopsies are performed with a needle (as opposed to surgical intervention).⁹ Smaller, earlier stage tumors do not demand the removal of extensive tissue in comparison to larger, later stage tumors. Extracting tumor tissue from small biospecimens to use for quality and integrity analysis (e.g. RNA integrity number ("RIN") or Agilent Bioanalyzer® analysis) may compromise a small biospecimen to the point where its value for research is minimized. In such instances, it may even be necessary to forego such quality and integrity analysis.

In order to locate biospecimens presenting adequate tumor percentage and homogeneity, a researcher may examine regions or countries where radical prostatectomy is a more common mode of treatment, or where diagnosis of prostate cancer generally occurs at a later stage of disease progression. This may require a researcher to collaborate with medical centers located in economically disadvantaged areas, which in turn presents complications regarding ethical treatment of the applicable patient population. Such disparities in treatment among various regions are marked, even within the United States.¹⁰

Since most biospecimen and data collection programs do not operate in a manner that impacts the ordinary standard of medical care, such programs may escape more contentious conflicts arising from involvement of patients subject to a lower standard of care.¹¹ Most surplus surgical biospecimen recovery programs impact only the processing of tissue deemed superfluous to the patient's treatment, and thus do not affect the treatment itself in any manner. Still, biospecimen management programs must always

⁶ Jeffery H. Burkhardt et al., *Comparing the Costs of Radiation Therapy and Radical Prostatectomy for the Initial Treatment of Early Stage Prostate Cancer*, 20 J. CLINICAL ONCOLOGY 2869, 2869-75 (2002).

⁷ See generally A. Desai et al., *Complete Embedding and Close Step-Sectioning of Radical Prostatectomy Specimens Both Increase Detection of Extra-Prostatic Extension, and Correlate With Increased Disease-Free Survival by State of Prostate Cancer Patients*, 5 PROSTATE CANCER & PROSTATIC DISEASES 212 (2002) (providing an overview of how various processing techniques may impact the usefulness of samples acquired through radical prostatectomy for diagnosis).

⁸ AM. UROLOGICAL ASS'N, *supra* note 5, at 3.

⁹ *Id.*

¹⁰ See generally Benjamin A. Spencer, *Variations in Quality of Care for Men With Early Stage Prostate Cancer*, 26 J. CLINICAL ONCOLOGY 3735 (2008) (noting the regional differences in the United States in treatment of early stage prostate cancer).

¹¹ David Wendler, Ezekiel J. Emanuel, & Reidar K. Lie, *The Standard of Care Debate: Can Research in Developing Countries Be Both Ethical and Responsive to Those Countries' Health Needs*, 94 AM. J. PUB. HEALTH 2048, 2048-49 (2004).

remain sensitive to the patient population to ensure that the autonomy of all prospective research subjects is honored, such as by drafting informed consent forms tailored to the reading level and language of the applicable patient population.

C. Regional Localization of Biospecimen Management

A third trend that drives the expansion of global biospecimen and data collection programs is the increase in regional or institutional biorepositories designed to support specific research endeavors. For instance, numerous institutions have created biospecimen and data collection programs in order to support designation as National Cancer Institute Specialized Program of Research Excellence (“SPORE”) centers of excellence.¹² Many other institutions have created such programs in order to support their own institutional research and development initiatives, perhaps to increase the intellectual property (and thus assets and reputation) of the applicable medical institution.¹³ To the extent that such institutions may have previously or concurrently provided biospecimens and data to other local researchers or commercial entities, the supply of biospecimens and data from that institution may be diverted and thus diminished. In a similar vein, many commercial entities—especially those with multiple research and development centers across the world—may attempt to acquire biospecimens from the applicable local region but rely on global programs to fill deficits in the regional supply. Certain types of research demand a regionally located supply of biospecimens, particularly research involving fresh tissue samples.¹⁴ Where a regional supply is not available, researchers utilizing fresh tissue samples must ensure that their external supply of fresh tissue samples is organized in a manner that minimizes loss of tissue integrity during transit. Such tissue placement activities often require sophisticated (and often expensive) coordination between many parties, including qualified couriers.

II. EXPANSION OF BIOSPECIMEN AND DATA COLLECTION PROGRAMS TO MULTIPLE SITES

In the United States alone, multiple laws, regulations, and guidance documents may impact the methods by which biospecimen and data collection programs are managed. Among these are the Health Insurance Portability and Accountability Act

¹² SPOREs, <http://spores.nci.nih.gov> (last visited Jan. 4, 2009) (giving a comprehensive list of current participants in the SPORE program).

¹³ The instances of regional biobanks are too numerous to list comprehensively. Here, a few noteworthy examples are included. For example, the Mayo Clinic recently announced plans to build a significant population based biobank at its Minnesota facility. *Mayo Clinic to Build “Biobank” from DNA of Local Volunteers: IDS Linked to Medical Records for Study*, ST. PAUL PIONEER PRESS, Dec. 21, 2008. According to this Article, the Mayo Clinic anticipates that the biobank may represent up to 20,000 individual patients. Another noteworthy endeavor is that of Kaiser Permanente, which was a recent recipient of an award of \$8.6 million to build a biobank. *See Kaiser ‘biobank’ lands \$8.6M grant*, S.F. BUS. TIMES, Dec. 17, 2008, available at <http://www.bizjournals.com/sanfrancisco/stories/2008/12/15/daily78.html>.

¹⁴ Wilfrido D. Mojica, Leighton Stein, & Lesleyann Hawthorne, *An Exfoliation and Enrichment Strategy Results in Improved Transcriptional Profiles when Compared to Matched Formalin Fixed Samples*, 7 BMC CLIN. PATHOL. 7, 18 (2007). (Certain studies on pharmaceutical compounds (e.g., ADMET) are best performed on viable tissues. In addition, viable fresh tissues generally yield RNA with high integrity).

(“HIPAA”);¹⁵ 45 CFR Part 46 (the “Common Rule”); Office of Human Research Protections Guidance on Research Involving Coded Private Information or Biological Specimens;¹⁶ FDA Guidance regarding in vitro diagnostics;¹⁷ and many highly variable laws existing at the state level. The State laws that impact such programs are worthy of closer examination. Many of these laws arise either from antiquated objectives dealing with the proper disposition of human remains upon death and are likely having an unintended effect of precluding research; or, alternatively, were intended to address specific scenarios, such as clinical genetic testing, but are written broadly enough to impact ancillary research endeavors, such as genetic research to identify novel biomarkers. The lack of harmonization among these different laws, which is seen clearly at the state level, may impede expansion of biospecimen collection programs within the United States.

A. *Variability of Definitions in State Laws*

For example, there is a significant amount of variability at the State level in determining the definition of items likely to have implications for biospecimen and data collection programs. This is illustrated in the deceptively simple terms “genetic information.” The State of Arizona defines genetic information as “information about genes, gene products and inherited characteristics that may derive from the individual or a family member, including information regarding carrier status and information derived from laboratory tests that identify mutations in specific genes or chromosomes, physical medical examinations, family histories and direct analysis of genes or chromosomes.”¹⁸ The State of Delaware, in contrast, defines “genetic information” as “information about inherited genes or chromosomes, and of alterations thereof, whether obtained from an individual or family member, that is scientifically or medically believed to predispose an individual to disease, disorder or syndrome or believed to be associated with a statistically significant increased risk of development of a disease, disorder or syndrome.”¹⁹ While these definitions have many commonalities, they also have material distinctions. Since many States regulate disclosures of genetic information, variability in definitions from State to State may have a significant impact on biospecimen and data

¹⁵ Health Information Portability and Accountability Act of 1994, Pub. L. No. 104-91, 110 Stat. 7 (codified in scattered sections of 18, 26, 29, and 42 U.S.C.).

¹⁶ *See generally*, OFFICE OF HUMAN RESEARCH PROTECTIONS, U.S. DEPT. OF HEALTH AND HUMAN SERVICES, GUIDANCE ON RESEARCH INVOLVING CODED PRIVATE INFORMATION OR BIOLOGICAL SPECIMENS (2008), available at <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm> (The Guidance explains OHRP’s views regarding when research involving coded private information or biological specimens qualifies as human subjects based research as defined under 45 C.F.R. 46, and sets forth exceptions to this qualification).

¹⁷ *See generally*, U.S. DEPT. OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR SPONSORS, INSTITUTIONAL REVIEW BOARDS, CLINICAL INVESTIGATORS AND FDA STAFF: GUIDANCE ON INFORMED CONSENT FOR IN VITRO DIAGNOSTIC DEVICE STUDIES USING LEFTOVER HUMAN SPECIMENS THAT ARE NOT INDIVIDUALLY IDENTIFIABLE (2006), available at <http://www.fda.gov/cdrh/oivd/guidance/1588.pdf> (The FDA set forth its guidance regarding the necessity of informed consent when human specimens are used for FDA regulated in vitro diagnostic (“IVD”) device investigations. A key part of this guidance was the FDA’s statement that it would not object to the use, without informed consent, of remnant (i.e. surplus surgical) specimens for certain types of IVD investigations, provided certain privacy protections were applied to the specimens.).

¹⁸ ARIZ. REV. STAT. ANN. § 20-1051(4) (West 2009).

¹⁹ DEL. CODE ANN. tit. 16, § 16-1220 (West 2009).

collection programs. Entities that conduct such programs in multiple States may have a higher administrative burden as they ensure compliance with each applicable State Law.

B. *Additional Regulation Arising From State Law*

Examination of State laws is also helpful in demonstrating other legal principles that may impact biospecimen and data collection activities. The Federal Policy for the Protection of Human Subjects, popularly known as the “Common Rule,” is limited by the fact that it solely regulates federally funded research involving human subjects.²⁰ Hence, the Common Rule’s reach generally does not expand to the numerous commercial entities that engage in biospecimen and data collection programs, such as pharmaceutical companies and commercial biorepositories. Such commercial entities are generally not engaged in biospecimen research for federally funded research.

In addition, according to the Office of Human Research Protections Guidance on Research Involving Coded Private Information or Biological Specimens,²¹ specific types of biospecimens are exempt from the definition of “human subjects.” While at the federal level, commercial entities can run biospecimen and data collection programs and conduct research with minimal formal oversight, State laws and oversight may bind them to the federal standard regardless.

To illustrate this point, it may be useful to revisit the State of Delaware. The State of Delaware indicates that “no person shall obtain genetic information about an individual without first obtaining informed consent from the individual.”²² On its face, this statute would appear to require that even if an entity were not bound by the Common Rule, and even if the applicable research use did not technically involve “human subjects” as defined by the OHRP,²³ the collecting institution would still be required to obtain informed consent from the research subject before it may access the results of genetic tests in donor medical records, or perform its own genetic research.

Delaware’s law does provide exceptions to this requirement. In particular, if the genetic information is “for anonymous research where the identity of the subject will not be released,” no informed consent is necessary.²⁴ Here, the term “anonymous” may introduce ambiguity. The OHRP requires that “anonymous” samples be severed from all identifying information regarding the original donor of the tissues and data, whether by (a) coding the samples and data and destroying the “Key” linking such codes to the original donor; or (b) entering into a legal agreement precluding the end user of the tissues and data from obtaining such identifying information.²⁵ Notwithstanding, nothing precludes States from interpreting the term “anonymous” in a manner more stringent than

²⁰ 45 C.F.R. § 46.101 (West 2009).

²¹ *Id.*

²² DEL. CODE ANN. tit. 16, § 16-1221(a) (West 2009).

²³ Human Subjects means any living individual about whom an investigator (whether professional or student) conducting research obtained (1) data through intervention or interaction with the individual, or (2) identifiable private information. 45 C.F.R. § 46.102(f). OHRP provides further clarity about how the definition of human subjects may be applied to biorepositories in its Guidance document. Office for Protection from Research Risks, Issues to Consider in the Research Use of Stored Data or Tissues (1997), available at <http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm>. The OHRP guidance discusses the OHRP’s expectations for IRB review and oversight, tissue usage agreements and informed consent requirements. 45 C.F.R. Pt. 46.

²⁴ DEL. CODE ANN. tit. 16, § 16-1221(b).

²⁵ *Id.*

that supported by the OHRP. After all, the OHRP guidance uses the term “anonymous” to determine whether the applicable research involves human subjects. Delaware is, in contrast, setting standards for the disclosure of genetic information. Since States have freedom to enact additional requirements for biospecimen and associated data collection programs that may otherwise not be subject to such oversight, expansion of collection programs throughout the United States can add complexity to the expansion of biospecimen collections.

C. *Going Global: Examining European Directives*

This complexity is further enhanced when biospecimen and associated data collection programs are expanded not only within the United States, but also into other countries. Expansion of collection programs into multiple countries inevitably introduces a plethora of novel laws with which to ensure compliance. For example, the European Data Directive²⁶ is a legislative directive that is likely applicable to global collection programs seeking to expand into Europe. While the Directive itself is not immediately binding on the citizenship of Member States in the European Commission, each Member State has adopted or is in the process of adopting data protection legislation to conform with the Data Directive. The European privacy protection scheme is very different from those adopted in the United States, although the objectives of the HIPAA Privacy Rules appear to overlap to some extent with the objectives of Directive 95/46/EC. Under Directive 95/46/EC, personal data must be processed in accordance with certain practices and guidelines, including those governing informed consent. Directive 95/46/EC defines personal data as “any information relating to an identified or identifiable natural person; an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.”²⁷

For comparison, the HIPAA Privacy Rule defines protected health information as individually identifiable health information, held or maintained by a covered entity or its business associates acting for the covered entity that is transmitted or maintained in any form or medium (including the individually identifiable health information of non-U.S. citizens).²⁸ Furthermore, HIPAA sets forth a safe harbor rule listing eighteen identifiers that, if stripped from the applicable data, would render it de-identified²⁹ and thus not subject to the HIPAA Privacy Rule. It is noteworthy that HIPAA applies only to covered entities. Covered entities generally include health plans, health care clearinghouses, and health care providers that electronically exchange health information in connection with any transaction for which the HHS has adopted standards.³⁰ As such, many of the entities performing global biospecimen and data collection efforts would not necessarily be covered by HIPAA. Many pharmaceutical research and development laboratories, commercial biorepositories, and biospecimen storage companies will likely fall outside the scope of the HIPAA Privacy Rule. Notwithstanding, such entities may adopt HIPAA’s de-identification guidelines as a business practice, in order to facilitate

²⁶ Directive 95/46/EC, 1995 O.J. (L 281) 31 (EC).

²⁷ Directive 95/46/EC, art. 2, 1995 O.J. (L 281) 31 (EC).

²⁸ 45 C.F.R. § 160.103.

²⁹ 45 C.F.R. § 164.514.

³⁰ 45 C.F.R. § 164.501.

partnerships with covered entities. Still, it is unclear whether compliance with HIPAA's Privacy Rule would automatically qualify an entity for compliance under Directive 95/46/EC.

The European Commission, as the executive arm of the European Union, influences many Member States that have become increasingly attractive locations for clinical trials and biospecimen and data collection programs. Last year, biotechnology and pharmaceutical companies spent approximately \$58.8 billion on research and development, with forty percent of such budgets dedicated to clinical trials. Research involving biospecimens and associated data can precede such clinical trials (e.g. identification of novel biomarkers) or run in tandem with such studies (e.g. biospecimen analysis to explain clinical trial findings).³¹ In order to reach appropriate patient populations and, arguably, to minimize already exorbitant costs, many of these biotechnology and pharmaceutical companies are increasingly looking to Eastern and Central European countries to conduct these trials. The number of multi-center clinical trials conducted in such countries has grown at significant rates in recent years.³² Biospecimen and data collection programs, being closely linked with the success of many clinical trials, will likely follow similar trends regarding expansion in Eastern and Central European countries.

However, while the European Commission has put forth Directive 2001/20/EC to harmonize clinical trials performed in European Union Member States,³³ the Commission has not set forth specific guidance regarding biospecimen and data collection programs. Rather, it has concentrated on the performance of Phase I through IV clinical trials. Directive 2001/20/EC sets forth standards regarding the composition and authority of independent ethics committees. Further, Directive 2001/20/EC contains standards that mirror the U.S. Common Rule in that they address protection of human subjects participating in clinical trials.

However, without OHRP-like guidance, there will likely be considerable variability among independent ethics committees regarding: (a) whether collections of biospecimens and data from living subjects falls within their authority for review; and (b) what kind of informed consent standards are appropriate for biospecimen and data collection programs, particularly surplus surgical collections that require no prospective surgical intervention with the applicable subject. Each independent ethics committee operates in a local manner. Given the daunting number of regulatory authorities and rules to consider when conducting multi-national biospecimen and data collection programs, entities may decide to exercise considerable caution and resign themselves to extensive and exhaustive informed consent forms and patient information booklets. However, such entities may still find themselves facing challenges from independent ethics committees that deem extensive informed consent language regarding privacy protections, coding and linkages to identifying information, and genetic privacy risks, as inappropriate for the applicable population.

³¹ Carolyne R. Hathaway et al., *Looking Abroad: Clinical Drug Trials*, 63 FOOD & DRUG L.J. 673, 673 (2008).

³² *Id.* at 673.

³³ Clinical Trials Directive, 2001/20, 2001 O.J. (L 121) 34 (EC).

D. Collection Program Type Influence on Multi-national Transfers of Biospecimens and Data

Several different types of general biospecimen and associated data collection programs have emerged, each carrying with it unique regulatory and legal implications. The first type of collection program is an archive collection. Archive collections generally involve the use of biospecimens and data collected for a purpose other than the instant research use. Archive collections include biorepositories of specimens originally acquired during surgical interventions for pathology examination and confirmation of diagnosis. The American College of Pathologists recommends that such paraffin embedded pathology specimens be retained for up to ten years after the date of collection.³⁴ After that time, many U.S. based institutions discard their pathology archive biorepositories as medical waste. In addition, many university departments may maintain archive collections from earlier studies.

Archive collections may present technical challenges. For example, a considerable amount of controversy exists regarding the viability of samples stored for extensive lengths of time for certain research uses.³⁵ However, these archives can offer a unique opportunity to acquire a specimen characterized by a set of longitudinal data. In the U.S., archive collections generally appear to qualify for waivers of informed consent provided the applicable researchers can demonstrate: (1) the research involves no more than minimal risk to the participants; (2) the waiver of informed consent will not adversely affect the rights and welfare of the participants; (3) the research could not practicably be carried out without the waiver; and (4) if applicable, that participants will be provided with additional pertinent information after participation.³⁶

The second type of collection program is interventional. This type of collection program will inevitably require intervention with a living donor in order to at least acquire medical information and informed consent. Common interventional programs involve acquisitions of surplus surgical biospecimens and biofluids. Interventional collection programs generally have the closest resemblance to classic clinical trials, including the prevalence of comprehensive informed consent forms.

The third type of collection is post mortem collection. This collection type is well suited to demonstrate the variability in regulatory schemes that can impact biospecimen research. The regulations, directives, and statutes addressed thus far largely arise from

³⁴ See American College of Pathologists, Recommendation and General Policy, <http://home.ncifcrf.gov/ccr/lop/intranet/PolicyManual/GeneralPolicy/CAPCLIA.asp> (last visited Jan. 4, 2009).

³⁵ A number of researchers have tackled the question of whether storage time, as defined in months or years, impacts the quality and integrity of the RNA extracted from formalin fixed paraffin embedded ("FFPE") samples. This particular study is representative of conclusions being drawn from such studies. Given the variability between biorepositories in collection and storage methods, one would expect to see vast divergence in results among biorepositories. Alfredo Ribeiro-Silva et al., *RNA Extraction From Ten Year Old Formalin-Fixed Paraffin-Embedded Breast Cancer Samples: A Comparison of Column Purification and Magnetic Bead-Based Technologies*, 8 BMC MOLECULAR BIOLOGY 8, 23 (2007). In addition, researchers recently published results of a study examining how refinement in biobanking techniques impacts sample quality over time. R.O. Barnes, *Influence of Evolution in Tumor Biobanking on the Interpretation of Translational Research*, 17 CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION 3344, 3344-50 (2008).

³⁶ 45 C.F.R. § 46.117(c).

clinical trials, human subjects' protection, and data privacy landscapes. Post mortem collection programs present unique challenges. In contrast to other collection programs, post mortem collection programs are often subject to regulations, directives, and statutes that govern anatomical gifts upon death, transplantation, creation of biologics, and disposition of bodily remains. This is because post mortem collection programs often acquire tissue for research as a by-product of allograft procedures. To examine these challenges, it is illustrative to review the regulations addressing collection of biospecimens from decedents in the United States and the United Kingdom.

In the United Kingdom, the activities of such entities are regulated by the Human Tissue Authority in accordance with the Human Tissue Act (2004).³⁷ The Human Tissue Authority published Codes of Practice regarding Consent, Post Mortem Examination, and Import and Export of Human Bodies, Body Parts, and Tissue.³⁸ In comparison to the United States' post mortem scheme described above, the United Kingdom has a fairly centralized method of overseeing recovery of post mortem tissues for research use, involving one regulatory body.

It is essential for many entities to be able to freely transfer biospecimens internationally for research use. UK HTA Code of Practice on Import and Export of Human Bodies, Body Parts, and Tissue (hereinafter, "Code of Practice 8"), Section 23 indicates that "as good practice, importers should therefore satisfy themselves that, in the countries in which they seek to import tissue, the gaining of consent for the purpose to which the tissue is subsequently put is part of the process by which the material is obtained."³⁹ In the United Kingdom, the Human Tissue Act makes it a criminal offense to analyze an individual's DNA without prior consent.⁴⁰

In contrast, many United States-based post mortem collection programs are geared toward the primary transplantation use. The applicable informed consent forms utilized by institutions that conduct post mortem collection programs often note that only non-transplantable tissues will be dedicated for research use and do not explicitly address genetic research in much depth, if at all.⁴¹ It is unclear whether such United States-based post mortem collection programs would be deemed to meet the requirements of Code of Practice 8.

The National Disease Research Interchange (NDRI) provides an example of a United States based (and federally funded) organization devoted to acquisition of human biomaterials through collaboration with such post mortem collection programs. In November 2008, the NDRI announced that the National Institutes of Health (NIH) had awarded a \$7.6 million grant to enable the NDRI to continue to expand its collection and

³⁷ Human Tissue Act, 2004, c. 30 (Eng.).

³⁸ Human Tissue Auth., Code of Practice No.1, Consent (2006); Human Tissue Auth., Code of Practice No. 3 Post Mortem Examination (2006); Human Tissue Auth., Code of Practice No. 8 Import and Export of Human Bodies, Body Parts and Tissue (2007).

³⁹ Human Tissue Auth., Code of Practice No.8, Import and Export of Human Bodies, Body Parts and Tissue 9 (2007).

⁴⁰ Human Tissue Act, 2004, c. 30, § 45 (1) (Eng.).

⁴¹ Harvard Brain Tissue Research Center, Post Mortem Authorization for Brain Donation <http://www.brainbank.mclean.org/consent.htm> (last visited Apr. 3, 2009). For comparison, the UK Human Tissue Authority has posted its model post mortem consent form at http://www.hta.gov.uk/guidance/model_consent_forms.cfm (last visited Apr. 3, 2009)

placement of human biomaterials to research facilities in the United States.⁴² One component of the NDRI's initiative involves reliance upon eye banks to support eye disease research in retinopathy, glaucoma, macular degeneration, retinitis pigmentosa, and other eye diseases.⁴³ Whole eyes, posterior poles and retinas are useful to the study of these diseases, and must be acquired from post mortem collection programs.⁴⁴

Eye banks do not submit all research protocols to IRB, since the applicable donors are deceased, and thus fall outside the scope of the definition of "human subjects" under the Common Rule.⁴⁵ Rather, eye banks operate in accordance with accreditation standards promulgated by the Eye Bank Association of America (EBAA); FDA and State Laws. The FDA's oversight of eye banks is limited to the scope of the FDA's authority, such as compliance with the Good Tissue Practices, which focuses on the use of eye banks to support cellular and tissue based products for use in humans.⁴⁶ Hence, the FDA does not exercise oversight authority over *in vitro* research use of tissues originating from eye banks. State oversight generally appears to originate with State departments of public health. California and New York are examples of the many States that license eye banks as part of their public health governance.⁴⁷ Consent forms developed to ensure compliance with the FDA regulations, EBAA accreditation standards and State public health laws governing post mortem collection will inevitably have distinct differences from those developed for living human subjects. Such differences add another layer of complexity for Designated Individuals trying to ensure compliance with Code of Practice 8. How should such Designated Individuals "satisfy themselves that, in the countries in which they seek to import tissue, the gaining of consent for the purpose to which the tissue is subsequently put is part of the process by which the material is obtained?" Should Designated Individuals have discretion to enforce multiple standards based on the type of collection program? The answers to these questions will need to be resolved for United Kingdom based entities to collaborate with entities in other countries with ease and consistency.

Moreover, Code of Practice 8 may present import challenges for entities acquiring tissues, regardless of whether post mortem or otherwise, under an opt-out scheme. For example, in Iceland, the Iceland Biobank Act provides for a presumption of consent for storage and further research use for biospecimens and data acquired from donors pursuant to clinical tests or medical treatment, but provides patients the ability to rebut the presumption of consent by opting out of participation in national biobanking efforts

⁴² Press Release, National Disease Research Interchange, NDRI Awarded \$7.6 million Grant from NIH for the Next Five Years to Fund Core Initiatives, (November 18, 2008), *available at* http://www.ndriresource.org/Newsroom/Newsroom/23/vobId__395/.

⁴³ *Id.*

⁴⁴ Christine A. Curcio, *Declining Availability of Human Eye Tissues For Research*, 47 INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCI. 2474, 2747-49 (2006).

⁴⁵ 45 C.F.R. § 46.102(f) (definition of "human subjects").

⁴⁶ Current Good Tissue Practice for Human Cell, Tissue and Cellular and Tissue Based Product Establishments; Inspection and Enforcement; Final Rule; 69 Fed. Reg. 68612 (Nov. 24, 2004) (codified at 21 C.F.R. Pt. 16, 1270, 1271).

⁴⁷ See N.Y. PUB. HEALTH LAW § 4364 (West 2009) (indicating that a license is needed for the procurement of tissue or non-transplanted organs and listing considerations that should be examined prior to granting a license, and that none of these considerations pertains to the *in vitro* research-only use of the tissues procured or stored by the applicable bank); see also CAL. HEALTH & SAFETY CODE § 1639.1-1641.1 (West 2009) (addressing licensing of tissue banks by the State of California).

unless affirmative consent is provided.⁴⁸ To the extent the UK HTA requires affirmative consent for DNA analysis, UK-based researchers may express reluctance to import tissues from those foreign institutions that recognize opt-out rights as opposed to affirmative consent. This variation in approach may have a preclusive effect on multinational efforts to perform research.

Many States in the United States enable the donor's next of kin or legal representative to provide informed consent for research donation via witnessed and recorded telephone consent. The State of Maine sets forth this method as follows:

Consent for an anatomical gift by a recovery agency [sic] must be documented in writing or, if secured in a telephone conversation, in a suitable recording, must disclose in plain language the specific tissue, organ or body part being donated and the purpose for which the anatomical gift will be used and must comply in all respects with rules regarding consent requirements for anatomical gifting [sic].⁴⁹

While this practice is recognized in the United States, it may not be acceptable in a country where all tissue donations for research must be set forth in writing and signed by the donor or his next of kin or legal representative.

The above situations demonstrate the importance of acknowledging the distinctions between different types of collection programs when arriving at a unified institutional policy for biospecimen management. As institutions that operate globally seek to comply with the myriad requirements in the countries in which they operate, they must remain cognizant of the differences between different types of collection programs. Institutional level policies are only the first step in resolving the aforementioned challenges in multi-state and multinational biospecimen and data collection efforts.

The most immediate solution to the aforementioned challenges may be to engage an international harmonization effort akin to or perhaps even under the authority of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.⁵⁰ Human biospecimens and associated data are increasingly being used not only for pre-clinical research and target evaluation, but also to demonstrate quality, safety, and efficiency of pharmaceutical products.⁵¹ As such, international harmonization, whether through an accreditation body or through other organizations is imperative to ensure donor privacy, adequate consent processes, and free transfer of biospecimens and data pursuant to multi-national research collaborations. However, the success of international harmonization efforts depends upon the ability of each individual country to exercise appropriate authority to develop a consistent legal approach to biospecimen and data collection programs. As biotechnological research moves swiftly into the era of genomics and proteomics, the failure to address these inconsistencies (at the local, national, and international levels) will inevitably impede the development of new diagnostics, prognostics, and therapeutics.

⁴⁸ Act on Biobanks (Act No. 110/2000), Sec. 111, art. 10 (Ir.).

⁴⁹ ME. REV. STAT. ANN. tit. 22 § 2950(4) (West 2008).

⁵⁰ See International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, The ICH Process for Harmonization of Guidelines, <http://www.ich.org/cache/compo/276-254-1.html> (last visited Mar. 28, 2009).

⁵¹ Tony Kennedy, *Managing the Drug Discovery/Development Interface*, 2 DRUG DISCOVERY TODAY 436, 436-44 (1997).