JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 13, No. 8, August 2017 "Happy Trials to You"

Who Owns the Data from a Clinical Study?

By Leanne Tran

In a clinical study, "data" consists of any non-identifiable "study data," Protected Health Information ("PHI") ("Personal Health Information" in Canada), medical records, genetic data, and blood, tissue and other biosamples.

Data is at the core of the clinical research enterprise. It comes in many forms, with differences in ownership and protection that depend on the type of data. The clinical trial agreement ("CTA"), the protocol, the informed consent form ("ICF"), and HIPAA (the "Health Insurance Portability and Accountability Act" of 1996, as amended) authorization specify the rights of each party to the data. These rights affect important CTA provisions, such as those pertaining to intellectual property, publication, monitoring and auditing, subject injury, and indemnification.

Study Data

Study data consists of non-identifiable information resulting from or developed in the course of performing a clinical study. Study data is linked to a study participant's number, not to a name or other PHI (other than ICF signatures, birth dates, and visit dates, which are PHI). In industry-sponsored studies, study data is usually owned by the study sponsor, since the sponsor has authored the protocol and funded the study. Similarly, if a principal investigator ("PI") has authored the protocol and the site has funded the study, then the PI and/or the site owns the study data.

In general, CTAs for industry-sponsored studies prohibit sites and PIs from using study data for commercial purposes or from transferring the data to a third party for commercial purposes. Non-commercial purposes, such as internal reporting, research, education, patient treatment, and even academic inter-institutional sharing of data, are typically allowed. It is also becoming more common for study data to be used in internal investigations for research misconduct; however, the results of the internal investigation and even the existence of an ongoing investigation are considered the confidential information of the site. Some sponsors request that they be notified of a research misconduct investigation and that the results (including study data used) be provided to them as part of the debarment disclosure clause. Sites rarely agree to this request, on the basis that such results are for internal use only and confidential in nature. Universities and hospitals are also permitted to disclose study data and/or research results to study participants and/or their lawful representatives, sponsors, study steering committee (if one exists), institutional review board ("IRB") (research ethics board ("REB") in Canada) at the site and at other participating study sites, and regulators, if and when the PI, site and/or the IRB/REB deem disclosure necessary to protect the health of study participants. Such disclosures could be connected with the reporting of serious adverse events ("SAEs") to regulatory authorities. Disclosure to study participants and/or their lawful representatives is also necessary to obtain and maintain informed consent.

In a multicenter study, the PI may publish articles and present talks based on study data, including clinical research methods and results from his or her own site, but only after the sponsor's multicenter manuscript has been accepted for publication or, typically, 12 months after the completion of the study at all sites (i.e., data lock), whichever occurs first. The PI must first submit his or her manuscript(s) to the sponsor to allow the sponsor to protect its

confidential information and the patentability of any inventions disclosed in the proposed publication or presentation.

Normally, the sponsor will indemnify (i.e., contractually promise to pay) the PI and site for any future loss, damage, costs and expenses (including reasonable legal fees) of third-party claims to the extent that they result from several situations, one of them being the misuse by the sponsor (or someone acting on behalf of the sponsor) of the study data and results. However, the sponsor often imposes a carve-out to the indemnification and subject injury clauses so that the sponsor will have no obligation to indemnify a particular indemnitee to the extent that any injury or loss is caused by the site's or PI's failure to comply with applicable law, including privacy laws.

Protected or Personal Health Information (PHI)

PHI is information about a study participant (e.g., a participant's name, address, genetic test results, or biological samples) that, on its own or in combination with other information, can identify the participant.

Unlike non-identifiable study data, PHI is covered by HIPAA, the Health Information Technology for Economic and Clinical Health Act ("HITECH"), and the implementing regulations by the Department of Health and Human Services ("HHS") (collectively the "Privacy Rule") or the Personal Information Protection and Electronic Documents Act ("PIPEDA"), the equivalent privacy legislation in Canada. Moreover, there are state (and, in Canada, provincial and territorial) and local laws and regulations that govern the use and disclosure of PHI. Other governmental jurisdictions, notably the European Union, have their own rules for protecting PHI.

The EU's General Data Protection Regulation ("GDPR"), which will take effect May 25, 2018, is the most expansive and stringent data protection law to date, as it applies to personal information across all sectors (and not just the health sector, as in the U.S.) and strengthens the individual's rights to data protection by increasing the consent standards and decreasing the threshold for privacy breach reporting. For example, consent must be specific for each use and, therefore, broad consent might not be sufficient for future or secondary use of biosamples. Moreover, personal data may only be transferred to countries outside the EU when an adequate level of protection is guaranteed; the European Commission has deemed only a handful of countries, including Canada, as providing such adequate protection. For transfer of data from the EU to the U.S., the new Privacy Shield has replaced the U.S.-EU Safe Harbor Framework. The Privacy Shield provides strong protections for the personal data of individuals from the EU and allows such data to be exported to the U.S. only if the ICF and contractual clauses in the CTA state acceptable circumstances for the transfer. Although participation in the Privacy Shield is voluntary, once an entity agrees to comply with the Privacy Shield requirements, that agreement will become enforceable under U.S. law, with robust U.S. governmental oversight.

In the U.S., the HIPAA Privacy Rule generally requires participant informed consent and HIPAA authorization for use and disclosure of PHI for research purposes or an IRB/REB waiver of the authorization requirement. However, a HIPAA authorization is not required if the data has been de-identified by removing the 18 types of identifier information. In contrast, in Canada, the Personal Information Protection and Electronic Documents Act ("PIPEDA") states that, even if PHI will be de-identified, researchers still need consent from the participant to collect and use their data. Further, PIPEDA is not as prescriptive as HIPAA in how it defines PHI, in that it does not specify 18 identifiers for de-identification.

Study data and PHI are different concepts that need to be treated as such in a CTA. Therefore, even if sentences in a clause relating to study data and HIPAA compliance

provisions look similar, HIPAA language covers only PHI and does not cover non-PHI, such as some study data. This distinction is critical to cover any biological samples such as tissue (which is PHI because it contains genetic material) and any associated data appropriately. In such cases, the CTA needs to refer to the fact that the collection and use of biological samples is in accordance with the protocol and only in ways permitted by the ICF under which they were obtained.

Although study sponsors and contract research organizations ("CROs") usually do not perform HIPAA-defined activities on behalf of sites, the determination of whether a business relationship exists and a business associate agreement ("BAA") is required is becoming a more fact-based and individualized analysis that might require legal advice. Both the sponsor and the site can be the business associate to the other's covered entity in a BAA.

Some sites, erring on the side of caution, refer to study sponsors as business associates, requesting that a BAA be put in place or, alternatively, imposing PHI handling obligations on sponsors in CTAs that are the equivalent of BAA obligations. For example, a medical device company can be a business associate to the site (which is the covered entity) where the company helps de-identify PHI or review patient-specific images (i.e., data analysis or data processing in the radiology and pathology realms). On the other hand, certain medical device companies might be considered HIPAA-covered entities and, as a result, increasingly, the medical device study sponsor enters into a BAA with the site (the business associate), especially for multicenter studies.

In the U.S., BAAs, in addition to the CTA, further protect PHI in accordance with HIPAA guidelines. BAAs are not used at Canadian sites, but Canadian sponsors might enter into a BAA with a U.S. site. Moreover, in both the U.S. and Canada, biological samples must be collected and used in accordance with any applicable laws, including privacy laws. In addition to a provision that ensures general compliance with applicable laws and regulations, CTAs can also reference ethical standards, such as the Declaration of Helsinki[1], and the International Conference on Harmonization's Harmonized Tripartite Guideline for Good Clinical Practice ("the ICH GCP Guidelines").

Further, two liability approaches can be taken with PHI: (1) the sponsor indemnifies the institution and the PI from any liability arising from the sponsor's failure to comply with applicable privacy laws or (2) each party to the CTA will be responsible for damage, loss or cost to the extent arising from a breach of patient confidentiality or privacy. As insurance for privacy becomes more common, sponsors are seeing more requests for indemnification provisions that cover data breaches. However, the position that each party is liable for their own actions is still the most popular, given the increasing number of class action lawsuits for privacy breaches, which make sponsors hesitant to indemnify for claims made against sites or PIs.

Biosamples

Prior to any sampling, a person's blood and tissue belongs to that person. However, once that blood or tissue becomes a biosample, its ownership is governed by applicable laws, including contract and property law. It can be argued that biosamples (e.g., paraffin-blocked tissues) and the associated data (e.g., pathology reports), become part of the clinical medical record if the study participant is also being monitored by his or her usual physician as a patient. The pertinent laws, regulations, policies and procedures that govern access to clinical medical records are different than those for study data. In clinical care, leftover diagnostic tissues are generally considered to be abandoned by patients, and thus, the patient has relinquished any property rights to that material. In contrast, in clinical research, various laws, regulations and guidelines govern the ethical collection and use of biosamples. IRBs/REBs act as gatekeepers that review ICFs and protocols to ensure

compliance with research informed consent principles. The IRB/REB can exempt studies from informed consent if identification of the study participant is not possible (e.g., if only aggregate data are reported) or they can grant waivers or alteration of informed consent requirements. However, since there are no clear laws or regulations that define the ownership of human blood or tissue, this issue is guided by case law.

In several U.S. state cases, the courts have addressed the question of whether a patient retains any ownership in his or her excised tissue that would allow him or her to share in the profits of any commercialization of research, direct who controls the samples, or decide if and how the samples will be used in future research.[2] In most of these cases, the courts have decided that patients and research participants do not retain ownership rights of their excised tissue.[3,4] However, contrary decisions have been reached in cases where there was a clear understanding that the patient or study participant would retain ownership of the excised tissue, for instance, in *in vitro* fertilization (IVF) programs for freezing fertilized eggs, as it is clear that patients have a continuing use for the excised tissue. Depending on the ICF, some donor property-like rights might be retained, such as directing destruction of excised tissue if consent is withdrawn.

The originating case in this area was decided in 1990 in *Moore v. Regents of University of California*, 51 Cal. 3d 120; 271 Cal. Rptr 146; 793 P.2d 479 ("Moore"). The patient sued the institution after discovering that his cells had been used for research that resulted in economic gain without his knowledge or consent. The Supreme Court of California found that the patient did not have property rights to his excised tissue but could sue for breach of fiduciary duty due to the lack of informed consent. In this case, a distinction was drawn between property rights and the dignity and privacy interests that are based on informed consent principles. Moore later negotiated and came to a settlement agreement with UCLA that covered his legal fees on the basis that he had not been informed, nor had he agreed to the research. In 1991, the U.S. Supreme Court also rejected Moore's claim regarding the profit issues, stating that a hospital patient does not own rights to excised tissue, even if they are valuable through commercialization.

In *Greenberg v. Miami Children's Research Hospital Institute*, 264 F. Supp. 2d 1064 (S.D. Fla. 2003), the court found that the plaintiffs voluntarily gave tissue for research purposes without expecting return or economic benefit. Accordingly, the plaintiffs had no ownership interest in the tissue or the research performed using the tissue that resulted in the licensing of a new diagnostic test. The court opined that to have a contrary view would halt medical research, as it would provide a continuing right for donors to possess the results of any research undertaken by the hospital.

In *Washington University v. Catalona,* 490 F 3d 667 (8th Cir. 2007), Washington University refused to transfer tissue collected from research to another institution at the request of one of its investigators (and some tissue donors).[5] The court held that the donors had gifted their tissue and, therefore, did not have the right to direct their samples to be transferred to another site.

As a counterpoint to the above cases, in *York v. Jones*, 717 F. Supp. 421 (E.D.Va. 1989), a couple sought IVF treatment at a clinic in California other than the Jones Institute in Virginia ("Jones") that stored their frozen eggs. Jones, the initial IVF facility, refused to transfer the frozen eggs, arguing that, under their contract, the Yorks' property rights were limited to implantation, donation to another infertile couple, donation for approved research, or destruction. The court disagreed, stating that the consent form and other agreements repeatedly referred to the frozen eggs as the Yorks' "property." The court also noted that the contractual limitations on the Yorks' rights applied only if they no longer wished to commence a pregnancy.

In an Ontario, Canada case of medical malpractice, *Piljak Estate v. Abraham*, 2014 ONSC 2893, found that human tissue removed for medical testing is subject to rights of ownership and constituted personal property, and became the property of the hospital. The court's view was that, once possession and, thus, ownership of the tissue were transferred to the institution or hospital, then the tissue can no longer be owned by the patient who, at most, has "reasonable access" to it. This case involved an area of health law that had long been argued in U.S. jurisprudence but had not been adjudicated in Canada until 2014.

Thus far, the cases have generally rejected claims of patients and research participants to own their excised tissue. However, the law regarding donor control over biosamples is still evolving, especially when it comes to questions of future research use of tissue, such as in biobanking and data registries. As the law stands today, study participants must be advised of all intended uses for their biosamples. If samples are to be used in additional research later, participants must give additional informed consent for this new research, or samples must be de-identified. If the specific uses for the biosample were not originally intended or known, re-consenting the participant will likely be required, or else an IRB/REB may waive informed consent for the secondary project. However, it should be noted that an IRB/REB waiver is more likely if, at the time of biosample collection, the study participant consented to future research (i.e., a "broad consent" was given).[6,7]

Under the January 19, 2017 Common Rule revisions (scheduled to take effect on January 19, 2018), broad consent is still permitted (i.e., exempted from the Common Rule) for the storage and maintenance for secondary research use of biospecimens and individually identifiable data (i.e., biobanking and database registries), and for the use of such stored material for future unspecified research studies. Any secondary research might be exempt from the Common Rule if the broad consent was properly obtained and documented, and if an IRB determines that the secondary research is within the scope of the broad consent. Broad consent under the amended regulations of the Common Rule should contain the following elements: (1) if the biospecimens may be used for commercial profit, the participant must be informed of that potential use and state whether the participant will or will not share in any commercial profits; (2) if the possible research might include whole genome sequencing, that information must be disclosed to the participant; (3) the types of research that may be conducted with the biospecimens or identifiable data; (4) if biospecimens or identifiable data might be shared with other researchers or institutions the participant must be informed; (5) if biospecimens and identifiable data will be stored, the duration allowed for storage and maintenance (even if indefinite) and the time period that such information or biospecimens may be used for research purposes (even if indefinite) must be disclosed to the participant; and (6) a statement that the participant or legally authorized representative will not be informed of the details or results of any specific research studies that might be conducted using the participant's biospecimens or identifiable data, unless otherwise negotiated.

In the absence of any issues related to biosample ownership by the study participant, the study sponsor and site still need to define their respective ownership rights. This question is a contractual matter to be decided between the two parties. In most cases, the CTA grants ownership rights to the biosamples and accompanying data to the sponsor, if the sponsor authored the protocol and funded the research. If the PI authored the protocol and the site funded the study, the site might retain a portion of the biosamples for future research purposes as part of a biobank and data registry. However, in some cases of sponsor-funded research, especially when the site is a large academic medical center, it retains ownership of the biosamples and grants the sponsor a limited license to use the biosamples for specific purposes; most sponsors are reluctant to accept such terms.

In the absence of comprehensive statutes and regulations, the laws governing the use, distribution and disclosure of biosamples and genetic data are largely governed by case law,

which, to date, is neither comprehensive nor definitive. The Henrietta Lacks story, which is somewhat similar to the *Moore* case discussed earlier, illustrates some of the issues and, in fact, was a catalyst for the Common Rule revisions to broad consent.

John Hopkins Hospital in Baltimore, Maryland, treated Henrietta Lacks, an African American woman, for cervical cancer in 1951. As part of her medical care, Lacks' tissue was biopsied. This tissue became the source of the HeLa immortal cell line (i.e., a cell line that reproduces without dying) without her knowledge or consent, as was the practice at the time.

The HeLa cell line has been and continues to be one of the most important cell lines in medical and commercial research. For example, HeLa cells were used to develop the polio vaccine. Countless researchers around the globe have used HeLa cells for studying cancer, AIDS, gene mapping, cloning, IVF, effects of radiation and toxic substances, cosmetics, etc., There are almost 11,000 patents involving HeLa cells.

In the early 1970s, the fast-growing HeLa cells contaminated numerous other cell cultures, compromising many research projects, a problem that continues to this day.[8] To map HeLa genes in order to develop a DNA test for identifying HeLa cells, scientists contacted Henrietta Lacks' family for blood samples. Then, in the 1980s, another group of scientists published Lacks' family medical records without family consent.

In March 2013, German scientists published and posted in public databases the DNA sequence of a strain of HeLa cells. When these scientists later informed the Lacks family of the publication and the databases, the family objected, so the scientists pulled the paper, removed the sequence from the public databases, and apologized.

Meanwhile, a U.S. research group, working on a different HeLa cell line's genome using National Institute of Health (NIH) funding, had a paper in press in the journal *Nature*. As *Nature* mandated that authors make their data publicly available online, *Nature* met with the Lacks family. Separately, the NIH also reached out to some family members. In August 2013, the NIH reached an agreement with the Lacks' family that gave the family some control over access to the cells' DNA sequence (through two family members on a six-member committee determining access on a case-by-case basis) and acknowledgement in scientific papers. This agreement prohibited publication of the entire genome and limited its access to select researchers. The authors and publishers of both papers agreed to this controlled access to genomic data.

The Lacks family has not received any economic benefits from discoveries made with HeLa cells, and the NIH agreement did not include compensation. (The *Moore* case appears to have eliminated any financial rights they might have had.) As well, the June 13, 2013 U.S. Supreme Court ruling that naturally occurring genes could not be patented, limited the ability of biosample donors to derive financial benefits from their tissues.[9] Although the family's focus has largely been on privacy and respect thus far, the eldest son of Henrietta Lacks, as of February 2013, remarked publicly that he planned to sue John Hopkins University and potentially others to receive compensation, stating that he did not take part in the agreement with the NIH.

The Lacks story raises ethical questions about consent, privacy and patient rights that the law has yet to address. For example, do family members or descendants have the right to consent or veto consent akin to organ donation? If one researcher passes a cell line to a second researcher without a contractual agreement, what are their respective rights, obligations and liabilities to each other and to the original donor?

Genetic Data

Genetic data, especially DNA sequence data on its own or linked to other data, contains within it the potential ability to identify the donor and their descendants. In addition, certain physical characteristics (e.g., gender, hair color, and facial features) can be determined from certain genetic data, and this capability will only grow over time.

Since most biosamples contain DNA, they can be used to create genetic data. Genetic data and most biosamples thus constitute PHI. They can also both be very valuable for medical researchers, as seen in the Henrietta Lacks story. CTAs, ICFs and HIPAA authorizations thus typically treat genetic data and biosamples in the same manner.

Medical Records

A patient's medical record consists of paper-based or electronic documentation of healthcare provided by a healthcare provider and refers to the physical file as well as the information contained therein. It is generally accepted that these medical records are the property of the healthcare provider and are not the sponsor's data or the participant's data.

In a clinical study, medical records are part of the source documentation. However, since some information in a medical record constitutes PHI, the CTA typically grants the study sponsor limited access, for example, to site monitors and auditors for confirmation of eligibility, source data verification, validation of case report forms (CRFs), and analysis of SAEs.

Before medical records can be accessed, sites might also require sponsor representatives to sign a separate confidentiality agreement and/or take the site's privacy training, including on its electronic medical records (EMR) system. When the EMR system cannot restrict access just to the medical records of study participants, sites typically access the EMR on behalf of the site monitor or auditor and allow access to copies of the pulled medical records without providing the actual copies to sponsor monitors and auditors. There will usually also be a clause in the CTA stating that such information shall be appropriately protected by the sponsor against loss, theft, unauthorized access, copying, or modification, and shall be retained by the sponsor only as long as necessary for fulfillment of the approved purposes for which it was collected, after which time it shall be returned, destroyed, erased or made anonymous, and the sponsor shall take appropriate care in the disposal or destruction of the information to prevent unauthorized parties from gaining access to it.

In Canada, CTAs often state that medical records not only are the property of the site but also cannot be copied by the sponsor. If a site monitor can read medical records and make notes but not make copies, remote monitoring is more difficult, but not impossible. However, sites can deviate from their own policies and selectively make copies for the monitor. Remote monitors can directly access medical records electronically if there are software programs in place that do not allow for copying, although if one is technologically savvy, one can get around any such limitation. Hence, it is more likely that the legally imposed restriction on copying, rather than a technological one, will be relied on, and the consequences for not complying will be legal in nature (i.e., lawsuits).

If a site stores study data with a patient's EMR records, the distinction between clinical care records and study records can be problematic. Some hospitals use different EMR systems for clinical care and clinical research to maintain separation between the two types of data. Also, some EMR systems segregate study records to address this issue, protect patient privacy, and prevent clinicians from improperly using study data (e.g., research laboratory-developed test results), except in a "break the glass" emergency.

Conclusion

So, who owns the data? Well, it depends on the type of data, its source, its location, the legal jurisdiction, and the terms of the CTA, protocol, ICF, HIPAA authorization, and, possibly, previous documents signed by the study participant. Further, the law continues to evolve as relevant cases are tried in court. However, in most instances, the parties to a clinical trial can protect their appropriate rights to data through negotiation and contracts with clearly written and legally compliant CTA, ICF and HIPAA authorizations.

References

1. World Medical Association (WMA). WMA Declaration of Helsinki: ethical principles for medical research involving human subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (Accessed June 2017).
2. Allen MJ, Powers MLE, Gronowski KS, Gronoswki AM. Human Tissue Ownership and Use in Research: What Laboratories and Researchers Should Know. Clinical Chemistry 2010; 56:11:1675-82.
3. Kaiser J. Biomedical research: court decides tissue samples belong to university, not patients. Science 2006; 312-346.
4. Dry S. Who owns diagnostic tissue blocks? Lab Med 2009;40:69-73.
5. Andrews L. Who owns your body? A patient's perspective on *Washington University v. Catalona.* J Law Med Ethics 2006:398-407.
6. Glantz L, Roche P, Annas GJ. Rules for donations to tissue banks – what next? N Eng J Med 2008; 358:298-303.
7. Hakimian R., Korn D. Ownership and use of tissue specimens for research. JAMA 2004; 292:2500-5.
8. Lucey BP, Nelson-Rees WA, Hutchins GM. A Henrietta Lacks, HeLa cells, and cell culture contamination. Arch Pathol Lab Med. 2009;133(9):1463-7.
9. *Association for Molecular Pathology v. Myriad Genetics, Inc.*, *et al.,* 133 S. Ct. 2107 (2013).

Author

Leanne Tran, JD, MD, is a health lawyer and Principal at JD MD Solutions. Contact her at 416.613.1188 or leanne.tran@jdmdsolutions.com.

