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REPORT

The 'Future Uses' Dilemma: Secondary Uses of Data and Materials by Researchers and Commercial Research Sponsors

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The ability of researchers and sponsors of clinical research to use information, tissue, and other specimens collected during a primary research study for future unspecified research purposes has become a matter of increasing debate, particularly since the effective date of the final privacy regulations promulgated under the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA has highlighted existing confidentiality concerns in sponsored research and is forcing new dialogue between research sponsors, investigators, institutions, and the institutional review boards (IRBs) charged with reviewing and approving research. These parties in the research enterprise have been forced to rethink the adequacy of the privacy provisions contained in informed consent documents provided to research subjects and in research agreements governing the exchange and use of the data collected during a primary research study.

Is Consent to Future Uses Legal and/or Ethical?

The basic federal research regulations, known as the ''Common Rule,'' 45 C.F.R. Part 46, Subpart A, as well as Food and Drug Administration (FDA) regulations governing IRB review and informed consent in clinical studies subject to FDA jurisdiction, 21 C.F.R. Parts 50 and 56, require documentation of informed consent from each subject enrolled in a research study. The informed consent document (as well as the process that culminates in a signed document) must meet the standards set forth in those regulations, including the requirement that the prospective subject be given sufficient information to permit the subject, or the subject's legally authorized representative, to consider whether or not to participate. One of the basic required elements of informed consent is ''a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.''[1] The specificity implied by this requirement is in obvious tension with a consent form that seeks permission from potential subjects for future unspecified uses of their information or specimens in future research protocols that have yet to be developed. At the same time, there is nothing in the Common Rule or FDA regulations that expressly prohibits consent to future uses, and the practice of using information and materials in databanks for research purposes, with or without the subjects' knowledge, is widespread.

There are two opposed ethical arguments at play here: on the one hand, an argument that subjects cannot agree to a future research project about which they have not been, and cannot be, informed; on the other hand, an argument that refusing to allow subjects to agree to such future uses of their tissue and/or data would deprive subjects of the right to ''donate'' their own tissues and data for future uses. Caught between

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[1] 45 C.F.R. § 46.116(a)(1); 21 C.F.R. § 50.25(a)(1).

these two imperatives, IRBs considering the appropriateness of an informed consent form that proposes future unspecified research purposes generally have tried to craft case-by-case compromises by allowing some measure of consent to future unspecified uses but requiring some level of detail with respect to the categories or types of uses to which the information or specimens will be put, and emphasizing the confidentiality protections for the identified data and tissue involved. Among the questions IRBs and institutional officials have asked are: Who will have access to the information for future research purposes? What identifiers, if any, will remain associated with the information or specimens after the primary research study is completed? How will any abuses of that information be prevented? What limits (*e.g.*, in time or purpose) are being placed on future use of the data and tissue? What ability do subjects have to revoke their consent to future uses and how, logistically, will that revocation be honored? Are the subjects being given sufficient information to allow them to appreciate the scope of their consent?

The National Cancer Institute (NCI), after examining these issues in regard to the research it funds and conducts, settled on a series of three questions in a template informed consent form, by which a subject is able to consent to the banking of tissue.[2] The NCI formulation has the benefit of treading a line between being inaccurately specific and impermissibly vague. Under the NCI's approach, a subject is asked, at the end of the description of the primary study, to answer ''yes'' or ''no'' to three propositions:

1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.
2. My tissue may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
3. Someone may contact me in the future to ask me to take part in more research.[3]

Many IRBs have followed a similar formulation in approving consents to the banking of tissue collected during a primary study.

IRBs and institutional officials who approve research, including those that have approved some variant of the NCI approach to a general future consent, have been able to take some comfort in the fact that any specific future uses of identified data and human biologic materials by the primary researchers or by their colleagues within a research institution would at least remain under the oversight and jurisdiction of the IRB and the institution itself. Thus, IRBs have sometimes reasoned, if consent forms were defective or if future uses defy professional ethics, the IRBs at least would be able to remain aware of these future uses and could intervene as necessary to halt or modify them. Indeed, most medical centers, medical schools, and other medical research institutions are signatories to federalwide assurances (FWAs) with the federal Office for Human Research Protections (OHRP), by which these institutions have agreed that their researchers will undertake human subjects research only if consistent with the ''Common Rule,'' 45 C.F.R. Part 46, Subpart A. The IRBs' view that they should retain jurisdiction over databases and tissue repositories, and that no future specific research uses of those data or tissues may proceed without IRB approval, is fully consistent with the only substantial recent OHRP guidance on the topic.[4]

In recent months, however, the ''future uses'' dilemma has become even more complicated, as IRBs, institutional officials, and researchers have faced demands from private commercial research sponsors—primarily pharmaceutical, medical device, and biotechnology companies—that research consent or HIPAA authorization forms include permissions that run in favor not of institutional researchers, but instead, in favor of the sponsors themselves. Research sponsors have sought that these permissions from subjects allow the sponsors to be able to conduct a full and unspecified range of secondary uses of the identified data and tissue gathered during a primary study and sent to the sponsors by the investigators, as required by protocols and clinical trials agreements. Alarmingly to many IRBs, such activities—unlike the research activities of the medical staff over which the IRB and its institution have authority—fall outside continuing IRB oversight, and outside the restraints imposed by FWAs and Common Rule principles. These IRBs are correct in one aspect of their suspicions: in any secondary uses of these data and tissues, commercial sponsors, their internal researchers, and their contractors are in almost all cases not signatories to FWAs, are not subject to the Common Rule, and if they do not use research results to support FDA applications, not even subject to FDA research regulations.

Aside from obligations arising from industry ethics and general common law principles, these private sponsors may be restrained in these secondary research activities only by a few very limited, state-specific research statutes. Otherwise, once research sponsors are given identified tissues and data by the primary researchers they fund, they are—IRBs and institutional officials fear—unbound by requirements of specific informed consent and continuing IRB or other external oversight. The few meaningful restraints on sponsors' future uses would be those to which sponsors have vol-

[2] National Cancer Institute, Protecting Participants in Clinical Trials: Simplification of Informed Consent Documents, Appendices 6 and 7 (Dec. 30, 1999, updated March 5, 2004), located at http://www.nci.nih.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page3.

[3] The third proposition in the NCI informed consent for tissue banking raises the extremely complex issue of whether and how research subjects might be contacted if secondary testing on identified specimens, or secondary analysis of identified data, yields clinically meaningful information about their or their families' health. The issue of recontacting subjects in secondary research looms large here, especially since some secondary research uses undoubtedly will produce meaningful information. One very competent discussion of recontacting subjects with clinically meaningful information derived from genetic testing in secondary research may be found at I. Hedenfalk, *et al., Gene Expression Profiles in Hereditary Breast Cancer,* 344 *New Engl. J. Med.* 539, 546-7 (Feb. 22, 2001). Vigilant IRBs will raise the issue of recontact prospectively, at the time of considering primary research that includes a data or tissue banking component, and will consider whether primary study subjects should be offered the choice of being contacted in the future with any clinically significant secondary research test or data results.

[4] Office for Protection from Research Risks (now OHRP), Department of Health and Human Services, *Issues to Consider in the Research Use of Stored Data or Tissues* (Nov. 7, 1997), located at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm.

  MRLR ISSN 1539-1035

untarily agreed in clinical trial agreements (CTAs) or research grant contracts. When IRBs have begun to focus on the CTA terms that their academic and hospital grants offices have negotiated with commercial research sponsors, they have been dismayed to discover that these CTAs traditionally have contained very few restraints on sponsors' future uses of data and tissue of research subjects. In fact, in years past, few CTAs have even contained requirements that commercial sponsors receiving subjects' private medical data protect the privacy of those data and use the data only for research and scientific purposes.

One prime example of this, even today, is that most template CTAs offered by commercial sponsors to researchers and their institutions do contain ''confidentiality'' clauses; however, those clauses in most cases define ''confidential data'' as being limited to commercial and proprietary information of the sponsor about the product being tested and, in relation to that information, impose confidentiality obligations not on sponsors, but on researchers and their institutions. In our experience negotiating research agreements, subjects' medical information rarely is included in the CTA template's definition of ''confidential data,'' and CTAs tend to impose no specific obligations on sponsors to safeguard subjects' private medical information. There seem to be no ill intentions at work here; it is simply that a sponsor's primary and very understandable concern has been one of safeguarding the sponsor's valuable commercial information, and few seem to have realized, at least until recently, that the concerns of subject privacy need to be addressed as well. In retrospect, over the past years, massive quantities of subjects' data and biologic materials have been handed over to commercial sponsors that are largely unrestrained by contract or by regulation from doing with these data and tissue as they will—and they may even be free, from a legal perspective, to use subjects' data for market surveys and direct patient marketing.

These are among the fears and apprehensions of IRBs and medical centers that host research. Fortunately, of course, these fears have not been realized, since most commercial sponsors of research, even if unconstrained by contract or regulation, appear to have acted quite responsibly in their secondary uses of research data and tissues. Industrial research sponsors have a direct and understandable interest in these secondary uses. They need, for example, to be able to combine subjects' data from many trials of the same drug compounds, and to analyze those data over time and in innumerable ways; they need to be able to use collected tissues for a full range of laboratory testing, to assess efficacy and safety; and they need to be able to collect data from trials of different drugs and devices that have been tested on subjects with similar medical conditions, in order to determine promising new approaches to drug and device development. That industrial sponsors of research be able to conduct such activities without fear of legal liability is a decided good for the development and refining of drugs and devices, and thus very much in the public interest.

The risks perceived by some IRBs are, though remote, real. Eli Lilly and Co., for example, in an apparent technological mistake, unwittingly unveiled the identities of thousands of patients taking a new form of a psychotropic medication, resulting in a Federal Trade Commission investigation of Lilly's data practices.[5] Cases have been brought against pharmacies for the unconsented sale of patient data for direct drug marketing purposes.[6] Although not occurring in the context of ''research,'' these incidents have highlighted the potential for abuse of medical information, and of mass unconsented disclosure caused by technology coupled with lack of technological prowess. And in a world in which the public often remains suspicious of the implications of human genetic testing, many commercial sponsors of research appear to be engaged, in the course of their secondary uses, in many variants of genetic testing, using both validated and research genetic testing methods.[7]

This, then, is the set of issues facing IRBs and institutional research officials: to what extent should secondary uses of data and tissues be allowed? Should secondary uses, if allowed, be reserved for researchers under IRB and institutional control, or should secondary uses properly belong also to commercial research sponsors? What contractual constraints should be imposed on sponsors relating to their secondary uses? To what extent may or should subjects in a primary study consent to these secondary uses, by institutional researchers or by commercial sponsors?

Subjects' Rights Relating to Commercialization of Data and/or Materials Collected During a Research Study

A distinct, but related, question is whether it is ethical or legal for researchers, research institutions, or research sponsors to use the informed consent form as a vehicle for securing a waiver of subjects to future commercialization of the subjects' information or material collected during a research study. The legal question of what ownership rights patients and research subjects have in their biologic materials and their medical data is itself exceedingly ambiguous. In 1987, a study by the Office of Technology Assessment reviewed the available legal, ethical, and scientific literature relating to this issue, but concluded that there was no certain answer to the questions of ownership and control.[8] The OTA report appropriately pointed out that biologic materials themselves have little use or value, until and unless scientists manipulate and use the materials to develop cell lines, products, or useful data. One therefore can argue that the vast majority of the value of human tissues resides in the contributions of researchers

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[5] Federal Trade Commission, No. 012 3214. The consent agreement with the FTC may be viewed at http://www.ftc.gov/os/2002/01/lillyagree.pdf. The original FTC complaint may be viewed at http://www.ftc.gov/os/2002/01/lillycmp.pdf.

[6] *Anonymous v. CVS Corp.*, 728 N.Y.S.2d 333 (Sup. Ct. N.Y. Co. 2001); *Weld v. CVS Pharmacy Inc.*, 10 Mass. L. Rptr. 217 (Super. Ct. 1999).

[7] Commercial research sponsors (and/or their laboratory contractors) may in fact be subject to state genetic testing and disclosure laws, some of which require informed consent for genetic testing or disclosure of genetic testing results but contain no ''research'' exceptions. Understanding the application of these state laws and their application to research sponsors requires a case-by-case and state-by-state assessment. *See, e.g.,* N.J. Stat. Ann. §§ 10:5-45, 46, 47; N.Y. Civ. Rights Law § 79-L(2); Tex. Lab. Code § 21.403.

[8] Office of Technology Assessment, *New Developments in Biotechnology: Ownership of Human Tissues and Cells* (March 1987).

rather than in the original raw biologic material. The OTA report identified a variety of unresolved legal and ethical conundra relating to tissue ownership and control. These included: (1) the rights of patients/subjects to the commercialization of their tissues; (2) patent rights extending beyond inventors to research subjects when the subjects have donated tissues for research that eventuates in intellectual property; (3) the right to buy and sell human tissues; (4) the possible public domain status of cell lines; (5) the wisdom of the exemption in the Common Rule for the collection and study of ''existing'' pathological or diagnostic specimens, shielding such studies from IRB review; and (6) the legality of including commercialization ''waivers'' in research informed consent forms. In short, the OTA report, far from reaching certain conclusions about these issues, reflected a great confusion and vast gaps in relevant legal and ethical guidance.

Since the OTA report was released, law on these issues has developed less from considered changes in federal and state regulations than from courts considering and deciding cases that present various aspects of these issues. Four court proceedings in particular have highlighted the uncertainty of rights and responsibilities in the area of ownership, control, and future uses of data and tissue gathered during research. All of these cases suggest, although under differing theories, a possible movement toward holding research institutions, investigators, and possibly sponsors responsible for failing to obtain consent from subjects prior to using the subjects' information for purposes not outlined in the consent form.

The *Greenberg* and *Moore* Cases

In May 2003, in *Greenberg v. Miami Children's Hospital*,[9] the U.S. District Court for the Southern District of Florida handed down a decision permitting the plaintiffs—a group of individuals who provided genetic material for medical research into Canavan's disease, a genetically transmitted progressive neurological disease affecting children—to proceed with their claim for unjust enrichment against the principal investigator of the study and the research institution, Miami Children's Hospital. The researcher and research institution had obtained a patent on the genetic sequencing results of the research study (results were derived using plaintiffs' genetic material and accompanying data), allegedly without the knowledge or consent of the plaintiffs. The plaintiffs also had brought claims for breach of informed consent, breach of fiduciary duty, fraudulent concealment, conversion, and misappropriation of trade secrets, all of which were dismissed by the court as failing to state a cognizable legal claim. With respect to the breach of informed consent claim, the court held that although medical researchers have a duty of informed consent in certain circumstances, the court would not extend that duty to require disclosures to subjects of a researcher's economic interests in the research. The decision appears to have been partly due to the court's judgment that the plaintiffs were better characterized as ''donors'' of the genetic materials than as objects of human experimentation.

Interestingly, the *Greenberg* court reached these conclusions—conclusions that would seem very much to cut against any notion that the subjects in a study retain any ''property'' rights in their data or tissue harvested by the researchers—despite the fact that a 2001 Florida genetic testing statute designated all ''results of . . . DNA analysis'' as ''the exclusive property of the person tested.''[10] The court, in odd reasoning, found that the ''rights'' recognized in that Florida statute related only to consent for genetic testing and disclosures of testing results, and not to a right to the tissue itself and discoveries flowing from it.

Regarding the plaintiffs' ''unjust enrichment'' claim, however, the court held that the compliant alleged more than just a donor-donee relationship and had stated an appropriate legal claim: namely, that the plaintiffs would not have donated their genetic material if they had known of the researcher's goal of financial gain from the results of the research, and that due to the subjects' ignorance of the researcher's intentions, the researcher and his hospital had unfairly gained a financial benefit. Over the centuries of Anglo-American jurisprudence, such circumstances have been recognized as creating for the aggrieved party a claim known as ''unjust enrichment.''

The decision in the *Greenberg* case elaborates the principle, set forth by the Supreme Court of California in its 1990 decision, *Moore v. Regents of the University of California*,[11] that unconsented research uses of human tissue (in that case, the plaintiff's splenetic tissue) to develop commercial products from which contributors of the tissue will not benefit can give rise to a cause of action against the developer of the commercial products. In *Moore*, the cause of action recognized by the court was for breach of fiduciary duty and lack of informed consent, as opposed to the unjust enrichment claim recognized in *Greenberg*. The parties to the *Greenberg* case reached a confidential settlement effective Aug. 6, 2003, that allows the researcher and hospital to retain the patent at issue but that requires them to license the use of the patent to other Canavan's disease researchers without charge. Notwithstanding the settlement, however, the *Greenberg* decision, especially when read together with the *Moore* decision that preceded it, has potential ramifications with respect to the sufficiency of consent for secondary uses of tissue and data collected during the course of a research study.

The *Catalona* Case

A recent noteworthy case that has not yet been the subject of any definitive court rulings involves a complaint filed by Washington University against a researcher and nationally prominent urologist, Dr. William Catalona.[12] This case highlights the current legal uncertainty over who owns or has rights to information and tissues collected from patients or research subjects and maintained for possible future uses. Washington University has alleged that Dr. Catalona, a former Washington University faculty member, improperly asserted ownership rights in a tissue repository maintained at the University containing specimens collected from patients and research subjects at the University. In its complaint, the University is seeking a declaration by the federal district court that the University is the sole owner of the tissue samples. Part of the University's

[9] 2003 WL 21246347 (S.D. Fla. May 29, 2003).

[10] Fla. Stat. § 760.40(2) (2004).

[11] 51 Cal. 3d 120 (Cal. 1990).

[12] *Washington University v. Catalona*, Case No. 4:03CV01065-SNL (E.D. Mo., filed Aug. 4, 2003).

   ISSN 1539-1035

support for this claim includes the fact that tissue samples for the repository were collected from patients and research subjects with their informed consent. In particular, the University alleges that patients undergoing surgery or otherwise receiving treatment signed a consent form stating that the patient ''consent[s] to the disposal, use or examination of any bones, organs, tissues, fluids or parts which it may be necessary to remove.'' Research subjects, according to the complaint, frequently signed research informed consent forms including the following language: ''By agreeing to participate in this study, you agree to waive any claim you might have to the body tissues that you donate. Participation in this research means you waive the right to any new material or process developed through research involving your tissues.''

According to the complaint, Dr. Catalona improperly contacted prior research subjects and patients, without the University's permission, seeking their consent to transport their samples (and presumably, attached data) with him to a new position he accepted at Northwestern University's Feinberg School of Medicine. The University also is seeking a declaration that any ''consents'' of Dr. Catalona's former patients and research subjects obtained by Dr. Catalona to the transport of the materials are invalid, and is asserting that Dr. Catalona's contacting his former patients and research subjects to secure these consents was an illegal practice under HIPAA. Dr. Catalona, on the other hand, is arguing that the patients and subjects retained control over their samples and information even after they had donated them to the repository, and that therefore it is not within the University's power to prohibit the patients and subjects from authorizing Dr. Catalona to take the material from Washington University to Northwestern.

Depending on its resolution, this case potentially could have serious ramifications for the ''future use'' issue and could undermine institutions' assumption that once material has been ''donated'' to their keeping for future uses, the material is the property of the institution, whether or not the institution has an ethical and/or legal obligation to seek informed consent to any future uses of the materials. Although a court ruling would pertain only to Missouri law (in the same way that the holdings in *Greenberg* and *Moore* pertain only to Florida and California law, respectively), any interpretation of the right of patients and subjects to revoke this prior consent and to assert control over the information or material's ultimate custodian and uses could have a significant national impact on how databases and repositories are created, maintained, and used.

The *Havasupai* Cases

In February and March 2004, two related lawsuits filed by the Havasupai tribe against Arizona State University (ASU), the ASU IRB, the Arizona Board of Regents, and three researchers alleged that tribal members' blood samples and handprints, which were purportedly collected as part of a study of diabetes affecting the Havasupai tribe, were mishandled and ultimately used in studies of schizophrenia, inbreeding, and population migration without the tribal members' consent to such future uses.[13] The researchers' project was approved by the Havasupai tribe's seven-member tribal council, allegedly with the understanding that the study would involve diabetes research only. At the same time, however, it appeared that some written consents had contemplated certain future uses of the data and tissue for general population research (''to study the causes of behavioral/medical disorders''), while most subjects had been consented only verbally, or with informed consent forms that over time had been misplaced. The factual record, as related by experts hired by ASU, reflected great confusion as to whether the informed consent process for all subjects, and the pre-research consultations between the researchers and tribal leaders, included mention of the possibility that tissue from the subjects might be used in later research on topics not related to diabetes. Future studies using the tissue gathered during the primary study indeed focused on topics far beyond diabetes, such as trans-Bering Straits population dispersal, DNA typing in North American Indians, genetic analysis of dopamine receptor genes, and reproductive failure among the Havasupai. Alarmingly to the tribal members, at least some of the research seemed to support migration theories that conflicted with the Havasupai tribe's apparently autochthonous view of its own origins. Some tissues from the primary study were distributed to researchers at other institutions beyond ASU, where they were used for additional studies, but attached to those samples were only unique identifiers, with the code held only by ASU.[14] In short, the primary study generated tissue and data that were used for multiple secondary uses, while the written consents either were vague on such future uses or were missing altogether, their content unknown and unknowable. Moreover, in such a limited, discrete population of roughly 600 tribal members, any use of specimens, even if anonymized or de-identified, nevertheless yielded results that could be ascribed to most or all individuals within the group. One thinks here of the analog of studies done among limited populations affected by rare diseases or tumors, and of the possibility that ''de-identification'' of data and specimens in such small insular populations may offer only a phantom protection to subjects.

The complaints, one filed by the Havasupai tribe itself and the second filed by 52 individual tribal members, seek damages under various theories: (1) breach of fiduciary duty and lack of informed consent; (2) fraud and misrepresentation/fraudulent concealment; (3) intentional infliction of emotional distress; (4) conversion; (5) civil rights violations; and (6) negligence. As in the *Catalona* case, the outcome of these two law-

[13] *Tilousi v. Arizona State University*, Case No. CV2004-0115 (Ariz. Super. Ct. Coconino Co., filed Feb. 25, 2004); *Havasupai Tribe v. Arizona State University*, Case No. CV2004-0146 (Ariz. Super. Ct. Coconino Co., filed March 12, 2004).

[14] The expert report is inexact in some of its discussion of the process and implications of anonymization of the specimens, and seems to regard coded specimens, even when distributed to entities and researchers with no access to the code match, as ''identified'' specimens. Thus, the report in some cases appears to assume that a study conducted by a person holding coded specimens must constitute human subjects research, even though that person has and will have no access to the code and could not truly identify any specific research subject. This may reflect some misunderstanding of research standards in regard to the sharing of anonymized data or specimens with researchers at other institutions. *See* Office for Protection from Research Risks, *Engagement of Institutions in Research* (Jan. 26, 1999), located at http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm.

suits may help further to delineate research subjects' rights to object to unconsented future uses of data and specimens provided in the context of a narrowly defined research study, conducted among a narrowly defined population. At the least, the dissatisfaction of many Havasupai with the future uses of their tissues and data suggests that a lax, non-specific approach to consent for categories of future research uses may well result in later second-guessing of authority to engage in future research or to publish research results.

Can Subjects Waive Commercialization Rights?

After *Greenberg* and *Moore,* and of course, pending any relevant legal rulings in the Catalona case, research institutions, investigators, and sponsors will need to determine whether, in commercializing products derived from any identified data or tissue, there is any legal method by which subjects' informed consent can insulate researchers and research entities from a subject's possible future claim of unjust enrichment or deficient informed consent. This is a particularly vexing issue not only because of these court rulings, but also because federal regulations prohibit any language in a consent form that could be interpreted as waiving the subjects' rights in any way, or that releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.[15] In a 1996 Guidance on Informed Consent, the Office for Protection from Research Risks (OPRR, now OHRP) gave examples of *unacceptable* ''exculpatory language'':

- ''By agreeing to this use, you should understand that you will give up all claim to personal benefit from commercial or other use of these substances.''
- ''I voluntarily and freely donate any and all blood, urine, and tissue samples to the U.S. Government and hereby relinquish all right, title and interest to said items.''
- ''By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research.''

OPRR stated that *acceptable* language in a research informed consent form would include the following:

- ''Tissue obtained from you in this research may be used to establish a cell line that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.''
- ''By consenting to participate, you authorize the use of your bodily fluids and tissue samples for the research described above.''

The FDA also has given guidance on this issue in a 1998 Question & Answer appended to the FDA Information Sheets on informed consent. The question posed states: ''Is it acceptable for the consent document to say specimens are 'donated'?'' In response, the FDA states: ''It would be acceptable for the consent to say that specimens are to be used for research purposes. However, the word 'donation' implies abandonment of rights to the 'property.' 21 C.F.R. 50.20 prohibits requiring subjects to waive or appear to waive any rights as a condition for participation in the study.''

In contrast to the position taken by the FDA, a 1989 letter from the Director of the Division of Compliance of OPRR to the University of California responded to a question regarding the permissibility of a research subject's waiving his or her rights to materials collected in the course of a research study. The OPRR letter acknowledged that regulations prohibited the inclusion of language in the consent form waiving subjects' rights, but went on to state that the ''regulations are not intended to prohibit the informed subject from making a *legitimate donation*'' of his or her material. That 1989 OPRR letter continued, ''[t]herefore, an individual human subject of research may waive his or her rights, if any, in the commercial development of biological materials, or any products of biologic derived using them, taken from the subject in the course of a research activity conducted or supported by the Department of Health and Human Services and approved and conducted in accord with 45 CFR 46.'' It remains highly uncertain whether it is possible to read the 1989 official response from OPRR as being consistent with existing federal regulations and guidance from OHRP and the FDA.

The 1996 OPRR Guidance focuses on how the language in the consent form can be worded to avoid the appearance that consenting to participate in the study is in some way conditioned on the subject's waiving certain rights. However, the 1989 response letter appears to recognize that one of the subjects' rights *is* to make an informed donation of their materials or information for future purposes without expecting any financial reward in return. The right to make this type of altruistic gift to research is not expressly recognized by the FDA guidance, which expressly disapproves of the use of the word ''donation'' as implying the abandonment of property rights. One possible approach might involve language that focuses on a subject's consent to providing his or her material as a gift to the sponsor for future research uses with an express acknowledgment that the subject will not receive financial compensation in return. Although such language likely would not insulate a sponsor from a future claim that the subject has a financial interest in the product derived from his or her material, it hopefully would serve as insulation to a claim of lack of informed consent. Yet even this is uncertain because, as described above, the current regulatory regime is at best utterly confusing and at worst completely self-contradictory. The issue of waivability by subjects of economic and commercial interests in data and tissue awaits resolution by OHRP, the FDA, and the courts. The current confusion benefits no one, and undermines vital public interests in advancing science and medicine.

HIPAA's Requirements Regarding Future Uses

HIPAA and its implementing privacy regulations have imposed on all ''covered entities'' (which include almost all hospitals, group practices, and clinical investigators) a new layer of responsibility for assuring medical information privacy and limited uses of medical information.[16] As a general rule, entities that are covered by HIPAA may not use or disclose an individual's ''protected health information'' (PHI) for research purposes

[15] 45 C.F.R. § 46.116; 21 C.F.R. § 50.20.

[16] The definition of ''research'' under HIPAA is the same as under the Common Rule: ''a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.'' 45 C.F.R. § 164.501. Entities that are covered by HIPAA are limited to health plans, health care clearinghouses, and health care providers that transmit any health information in electronic form in connection with certain covered transactions (*e.g.*, any health care provider that bills electronically).

  MRLR ISSN 1539-1035

without the individual's express written authorization, except in a few limited circumstances, for example, when an IRB or ''privacy board'' waives or alters the authorization requirement.[17] PHI is information that relates to the past, present, or future physical or mental health or condition of an individual, or the provision of care to an individual, or the past, present, or future payment for the provision of health care to an individual, and that identifies the individual or with respect to which there is a reasonable basis to believe the information can be used to identify the individual. HIPAA's definition of what constitutes ''identified'' information is broader than how that term historically has been understood under the Common Rule. For example, health information that includes a discharge date, but no other identifying information, would qualify as ''PHI'' and would be subject to the requirements of HIPAA's privacy regulations, but under Common Rule analysis likely would have seemed to most IRBs to have constituted ''anonymized'' information for the use of which no subject informed consent would be needed.

To the extent data are ''de-identified'' under HIPAA's more rigorous standards, they fall outside of the HIPAA regulations and may be used or disclosed by a covered entity for research purposes without restriction. An intermediate category of data, known as a ''limited data set,'' may be used or disclosed for research purposes without individual authorization, but the recipient of the data set must execute a ''data use agreement'' with the covered entity, restricting the recipient's ability to use the data for other non-research purposes. A limited data set must be stripped of all direct identifiers, but is permitted to contain certain indirect identifiers, such as birth date and treatment date. A covered entity may only use or disclose limited data sets for research, public health, and operational purposes.

The federal government has made it clear, both in commentary to the final HIPAA privacy regulations and subsequent guidance on HIPAA and clinical research, that the mere creation and maintenance of databases or other specimen repositories meet the definition of ''research'' under the HIPAA regulations. Therefore, the use or disclosure of PHI by a covered entity for these database or tissue repository maintenance purposes is impermissible absent individual authorization or a waiver of the authorization requirement by an IRB or privacy board. One implication is that in a primary study, in the course of which identified tissue or data are to be collected and placed into a research database or repository, a second authorization is required, by which subjects permit the use of primary study data for these banking and repository purposes.[18] Additionally, any specific future research study using material maintained in a database or repository is considered also to constitute a separate research activity and thus requires a subsequent individual authorization or IRB/privacy board waiver, specific to the particular study. Under federal guidance, it is insufficient, and impermissible, to obtain a blanket authorization from subjects authorizing the use and disclosure of the subjects' PHI for unspecified future research purposes.

As discussed more fully below, research sponsors (themselves almost never covered by HIPAA) have in some cases begun to demand that a primary study's authorization include some form of consent to a sponsor's future unspecified uses of identified subject data. One such demand, put forward in the context of a template CTA offered by a commercial sponsor, is the following:

> [T]he institution . . . will obtain a valid HIPAA Privacy Rule authorization, as prescribed in 45 C.F.R. § 164.508(b) from each individual participating in the Study permitting disclosures from the Institution and/or the Principal Investigator to the Sponsor and any and all other clinical trial service providers of the individual's ''protected health information'' (as defined in HIPAA) as required by and in accordance with the Study, which *such authorization will permit the Sponsor's use of such protected health information for the purposes of monitoring the accuracy and completeness of the research data, performing clinical and scientific research, and medical product development.* (Emphasis added.)

Acceding to this demand, however, may threaten the validity of the primary study authorization, since research authorizations may be combined with other research permissions *only for that single study*, not for future unspecified studies.[19]

Another significant complication of HIPAA in regard to databases and tissue repositories that include identified data is that a subject under HIPAA is always able to revoke his or her authorization, even in the context of a research study. If maintenance of databases and tissue repositories is research and is thus subject to these

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[17] A ''privacy board'' is an independent board similar to an IRB, but that is charged solely with evaluating the privacy risks of a given research study and determining whether the study is eligible for waiver of the individual authorization requirement. A privacy board does not evaluate the risks and benefits of the research generally and does not have the authority to approve or deny research under the Common Rule. Institutions are permitted to use either an IRB or a privacy board to perform this function.

[18] According to NIH HIPAA guidance issued in January 2004:

> A single Authorization can cover uses and disclosures of PHI for multiple activities of a specific research study, including the collection and storage of tissues for that study. In addition, where two different research studies are involved, such as where a research study collects information for the study itself and also collects and stores PHI in a central repository for future research, the Privacy Rule generally would permit them to be combined into a single, compound Authorization form. However, a compound Authorization is not allowed where the provision of research-related treatment, payment, or eligibility for benefits is conditioned on only one of the Authorizations, and not the other. See section 164.508(b)(3)(iii) of the Privacy Rule. For example, a covered entity that conducts an interventional clinical trial that also involves collecting tissues and associated PHI for storage in a central repository for future research would not be permitted to obtain a compound Authorization for both research purposes if research-related treatment is conditioned upon signing the Authorization for the clinical trial. Any compound Authorization must clearly specify the different research studies covered by the Authorization so the individual is adequately informed. [located at http://privacyruleandresearch.nih.gov/pdf/research_repositories_final.pdf]

[19] 45 C.F.R. § 164.508(b)(3)(i) states that ''an authorization for the use or disclosure of protected health information for a research study may be combined with any other type of written permission *for the same research study*, including another authorization for the use or disclosure of protected health information for such research or a consent to participate in such research.'' (Emphasis added.)

HIPAA requirements, then a revocation of authorization by a subject presumably would require the custodian of the database or repository to discard the data and the identified specimen of that subject.[20] This is not dissimilar to a subject's withdrawal of informed consent from such a database ''study,'' which also would require that the identified data and/or tissue be discarded. The possibility of revocation, the trouble and expense of discarding data and tissue, and the possible bias inflicted on a database provide some incentive for researchers to purge data and tissue of all identification elements, consistent with HIPAA de-identification standards. Once data and tissues have been irrevocably de-identified, withdrawal of consent or authorization would require no action on the part of the database custodian. Importantly, as in other research requirements, the obligations of database and tissue repository custodians to honor subject withdrawals and revocations extend only to entities and research staff covered by the Common Rule or by HIPAA. At least under federal research and HIPAA regulations, commercial research sponsors have no obligation in regard to the databases and repositories they hold to honor subjects' withdrawals of consent or revocations of authorization.

In regard to intra-institutional secondary research uses of identified data and tissue, institutions and investigators have been left to struggle with how to continue to create, develop, and then use these resources of information and specimens without violating HIPAA's requirements. Most institutions with robust HIPAA compliance programs have created a process by which individual authorization is obtained from subjects for the purposes of collecting and donating information or materials to a bank or repository. Under such a process, assuming the regulatory HIPAA waiver of authorization criteria are met, investigators seeking to use that information or material for a future research project may seek and obtain from the IRB or privacy board a waiver of the authorization requirement for the subsequent specific research study. This presumes that the individual subjects also had given *informed consent* to have their information or material maintained and accessible for future unspecified research purposes at the time of the original study and that the IRB approved that consent form as appropriate.

The situation is more confusing in regard to how HIPAA authorizations may be made consistent with expectations that identified data, either alone or attached to tissue, will be handed over to a commercial research sponsor during the course of a study, and then used for multiple secondary purposes, primarily research. On the one hand, the HIPAA standards require that the authorization inform the subject of the purposes of the intended uses and disclosures, and that for research, those purposes be specific to a study. On the other hand, the investigator knows that the very reason why the subject is signing the authorization in a single study is to allow the investigator to hand over identified data to a sponsor, so that the sponsor in turn may use and disclose the data for multiple, unforeseeable future purposes. At the same time, IRBs and investigators are mindful of research regulations, which, as described above, demand some degree of specificity in consent documents, and which disfavor broad and undefined purposes. HIPAA requires effectively that subjects be afforded the right (and informed of the right) to revoke participation in databases and tissue repositories, while federal law does not require that databases and tissue repositories held by sponsors honor such requests.

This, then, is the box into which HIPAA, assisted by research regulations, has backed IRBs and investigators: they are required to be specific about uses, disclosures, and purposes that are unknowable at the time the consents and authorizations are acquired, and required to inform subjects of a right to revoke their authorization, while knowing full well that the bulk of ''future use'' databases maintained by sponsors need not honor any such request. The task of synthesizing HIPAA's new requirements with pre-HIPAA concerns about consenting to future uses is complex, and requires (i) reexamining the information that is presented to potential research subjects in the consent form; (ii) determining whether two separate authorizations are needed, one for the primary study and one for ''banking'' for future research use; (iii) explaining in detail the limits of subjects' ability to revoke authorization; (iv) determining how best to ensure consistency between the information provided in the consent form and any information provided to the potential subjects in the HIPAA authorization that they also must be asked to sign; and (v) carefully reviewing how the informed consent form and HIPAA authorization relate to the terms of any CTA between the sponsor of the original research study and the research institution collecting and maintaining individuals' identified data and tissues for future research purposes.[21]

Clinical Trial Agreements Among Research Sponsors, Investigators, and Institutions

The legal cases described above come at a time of growing concern in the research community that the terms of the CTA struck between the research sponsor and the institution do not comport with the information provided to the research subjects. This disconnect raises critical ethical concerns and may increase the liability risk that sponsors, institutions, and investigators face in conducting human subjects research. In light of existing concerns over the propriety of seeking informed consent from research subjects to future uses of their information—highlighted and complicated by HIPAA's prohibition on individual authorization to use and disclosure of PHI for future unspecified research—

[20] Although HIPAA permits researchers to continue to use and disclose PHI obtained prior to the time the individual revoked his or her authorization to the extent the researcher has ''acted in reliance'' on the authorization, it is unlikely that this exception would preserve a covered entity's ability to maintain the individual's PHI in a database intended for future unspecified research. The ''reliance exception'' in 45 C.F.R. § 164.508(b)(5) has been interpreted by the federal government to permit the continued use and disclosure of PHI ''as necessary to maintain the integrity of the research study,'' for example ''to account for a subject's withdrawal from the research study, as necessary to incorporate the information as part of a marketing application submitted to the FDA, to conduct investigations of scientific misconduct, or to report adverse events.'' Commentary to the Final Privacy Rule, 67 Fed. Reg. 53182, 53225.

[21] Under HIPAA, the informed consent document required by the Common Rule and FDA regulations may be combined with the research authorization form required by HIPAA; however, many institutions have elected not to do so for various policy purposes.

  MRLR ISSN 1539-1035

institutions, researchers, and sponsors should take a closer look at the terms of their research agreements and compare those terms with the information provided to subjects through the informed consent and authorization process.

As a preliminary matter, since the HIPAA privacy regulations' compliance date on April 14, 2003, there has been much confusion expressed by both institutions and research sponsors regarding their relationship to one another for HIPAA purposes. As discussed above, HIPAA impacts this relationship because the institution or researcher (generally a ''covered entity'' under HIPAA) must disclose certain PHI to the research sponsor, in the form of data, results, or subject records for monitoring and auditing of the research study. These uses and disclosures are all for ''research'' purposes and, under HIPAA, require express authorization from the individual subjects or the applicability of one of the exceptions to the authorization requirement. Institutions subject to HIPAA have become increasingly aware of their obligation to protect the privacy of the information they collect from research subjects. In an attempt to honor the privacy of this information, and to define their relationship to research sponsors in HIPAA terms, many institutions have erroneously sought to bind research sponsors as ''business associates.''[22] Yet research sponsors are almost never the business associates of institutions or investigators because the sponsor is not performing any function, activity, or service for or on behalf of or for a covered entity. To the contrary, the covered institution or investigator is the one that has been ''hired'' by the sponsor to perform an activity on behalf of the sponsor.[23]

In addition to not meeting the definition of a business associate, research sponsors are most often themselves *not* covered by HIPAA and are only indirectly affected by HIPAA's requirements on the institutions and investigators that sponsors hire to conduct research. Covered institutions and investigators therefore are left with uncertainty as to how to ensure that research subjects' PHI is appropriately protected by the sponsors of the research. Technically, under HIPAA, once PHI is disclosed by a covered entity to a non-covered third party such as a commercial research sponsor, the information is no longer subject to HIPAA's requirements. A statement to this effect must be included in any research authorization form signed by a research subject permitting the use and disclosure of his or her PHI for the purposes of a research study. Research subjects are thereby put on notice that if they authorize the covered institution or investigator to disclose their PHI to a third party who is not covered by HIPAA—for example the sponsor of the research study—the law provides no protection to that information once it is in the hands of the non-covered party. Notwithstanding the limitations on HIPAA's reach, institutions, investigators, and research sponsors are ethically, and potentially legally, bound to honor the terms of the informed consent document, in addition to the information provided in the HIPAA research authorization. And of course, most informed consent document templates promise a general ''confidentiality'' of study information, even though researchers and their institutions by now should be well aware that most sponsors, which are receiving identified subject data from the researchers, have no such privacy obligations, unless those obligations are imposed by the institution through the CTA or by individual states' laws.

Future uses of information by research sponsors generally are not within the control of the research institution or the IRB, or of the investigator who disclosed the medical information to the sponsor during the primary study. Also as noted earlier, commercial research sponsors are not in the same position as covered entities with respect to future uses, because sponsors have no technical legal obligation to secure subjects' authorizations, or to gain IRB/privacy board waivers of authorization, in order to conduct secondary research on material or information already in their possession. The only time HIPAA reaches a non-covered third party is when the third party qualifies as a business associate of a covered entity (which, again, research sponsors generally do not) and is required to sign a business associate agreement, or in the event the third party recipient of data receives a limited data set from the covered entity and is required to execute a data use agreement.

An option that some institutions and investigators are using is to include terms in their research agreements with sponsors that define the sponsors' ability to use the information or specimens provided to them in the course of the research study as consistent with the uses and disclosures contemplated in the protocol and informed consent form. Some sponsors are negotiating use language that is acceptable to the research institutions, but some other sponsors have objected to restrictions on the ground that as funders, they are paying for the data or specimens and should not be required to limit in any way their future uses of those materials. This ''push-back'' should signal to institutions and investigators that there may be an inconsistency between what the research subjects are being told by investigators and what the sponsor's intentions are with respect to future uses of data or materials. If subjects cannot, or do not, expressly consent to some measure of future uses of their data or biologic materials, the terms of the CTA should bind the research sponsor accordingly. Furthermore, under the terms of the CTA, the sponsor should be required to ''pass through'' and ''downstream'' any CTA restrictions on its own future uses of data and tissue to its agents (*e.g.*, a contract research organization, data management company, or clinical laboratory).

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[22] Under HIPAA, a ''business associate'' is an entity or individual that performs a function or activity on behalf of a covered entity (for example, data analysis), which function involves the use or disclosure of PHI, or is an entity or individual that provides certain services to the covered entity (for example, legal services), which services require the use or disclosure of PHI. A covered entity is permitted to disclose PHI to its business associates without individual authorization, however the covered entity must bind each business associate to protect the confidentiality of that information through a ''business associate agreement'' that meets the regulatory requirements set forth in HIPAA's privacy regulations.

[23] The fact that the research sponsor is hiring a covered entity to conduct research on the sponsor's behalf also does not create a business associate relationship because the research sponsor generally is not directly subject to HIPAA. In other words, the function, activity, or service being performed by the research institution or investigator for or on behalf of the research sponsor is not a function, activity, or service being performed for or on behalf of a covered entity.

Reaching Middle Ground Among Sponsors, Institutions, IRBs, and Investigators

The scope of research subjects' privacy rights in the future use of their information remains unclear, notwithstanding recent cases suggesting that institutions, investigators, and possibly sponsors have an obligation to inform research subjects of any intended future uses and obtain their consent to those uses. The principles set forth in HIPAA (including the right to revoke authorization to participate in a database or tissue repository) also suggest an increase in the control that individuals have over their data and what is done with those data, either during the trial or at some later time. For now, institutions and sponsors are left with some options for structuring their research relationships to avoid incurring any added liability for improper future use of subjects' data or tissues. These options, described below, are designed to permit legitimate and necessary information flow to and uses by sponsors, while still respecting a research subject's right, under the Common Rule, FDA regulations, and now HIPAA, to give informed consent to that use and to limit the purposes to which their identified information may be put.

Specify Future Uses and Clarify Future Duties Through the Clinical Trial Agreement. To the extent research sponsors will be receiving identified data from institutions or investigators (as is generally the case in clinical research), the research sponsors might be limited in their permitted uses, both now and in the future, according to the terms of the informed consent document signed by the subjects and approved by the IRB overseeing the study. In order to require a sponsor to handle data consistent with the terms of an informed consent, the CTA must include appropriate restraints or pledges by sponsors in regard to their future uses of identified data and tissue. Ensuring consistency between the informed consent document and the CTA would prevent claims by research subjects such as the plaintiffs in the *Greenberg* case, who were aggrieved by commercialization of their data and tissue when, they alleged, they never had been told about any such possibility.

Restraints imposed on a sponsor's future uses can take multiple forms, but a common formulation in recent CTA negotiations would require the sponsor to pledge to use identified data of subjects only for purposes of the study, analysis of the test drug or device, research on the medical condition(s) of study subjects, internal company operations, and interaction with regulatory authorities. Such CTA provisions also often include promises by sponsors to use ''best efforts,'' ''reasonable efforts,'' or ''commercially reasonable efforts'' to safeguard subjects' privacy. At the very least, CTAs should include pledges by the sponsor to use reasonable efforts to safeguard identified data and not to use identified data for direct marketing or for contacting subjects or their families. A sponsor that will not agree to that simple promise, and a research site that does not care enough about the terms of research to demand such a promise, likely should not be involved in funding or conducting research.

Any future uses or disclosures by covered entities of PHI maintained *by the covered entity* for future research uses will require a subsequent authorization by the research subjects whose information is being used, or waiver of the authorization by an IRB or privacy board. As described above, research sponsors not covered by HIPAA would not be required to obtain subsequent authorization or waiver of authorization to use information or materials received from covered entities. The sponsors would, however, be bound by the terms of the CTA, which should track the scope of the subject's original consent to participate in the research.

Disclose a Limited Data Set. Research sponsors that receive not identified information but only a limited data set from the covered entities conducting research will be required by the covered entities to execute a data use agreement that limits the sponsors' ability to use the PHI beyond the terms of that agreement. Specifically, the data use agreement may not authorize the limited data set recipient to use or further disclose the information in a manner that would violate the requirements of HIPAA if done by the covered entity. Institutions and investigators would need to consider, however, whether the fact that data or tissues provided to research sponsors are stripped of direct identifiers obviates the need to inform subjects from whom the data or materials were collected that the data or tissues would be so used. Given the uncertain rights of subjects in the use of their medical information, it would be prudent to describe the limited data set practice in the informed consent form, along with some indication of how such data sets might be used.

Another strategy that has been used (and publicly described) by Merck and some other commercial sponsors has been to receive identified data from research sites but then to place the identified data into an internal company database from which only limited data sets may be drawn by company researchers. This approach has been utilized even though research sponsors are not covered by HIPAA rules. The theory, however, is that if in regard to HIPAA-covered entities the government allows research uses of medical information contained in a limited data set without subject authorization, then in regard to non-HIPAA-covered entities the restraints on secondary research uses should be no greater.

Assuming that appropriate pledges are made in CTAs by a sponsor, this approach has the benefit of allowing the sponsor to have access to identified primary study data (which may well be necessary for adverse event reporting, data analysis, and research integrity), but then preventing nearly all risk of abuse by limiting the data given out within the company for secondary research uses. In order to assess whether this is a realistic alternative, a sponsor would need to be sure that its secondary researchers would be satisfied for all purposes with a limited data set, and research institutions would need to be satisfied that such pledges by a sponsor are verifiable and enforceable.

Disclose Only De-Identified Data. If research sponsors are able to monitor their research and in the process record only data de-identified according to HIPAA's standards, then covered entities may disclose these data to the sponsors without first seeking individual authorization or waiver of the authorization requirement. Again, the fact that HIPAA does not restrict the covered entity from sharing these data with the research sponsor does not answer the question of whether research institutions themselves should be able to use this information for future research, including by disclosing it to research sponsors who seek access to the data for that purpose, without having informed subjects in the primary study consent process about the in-

   ISSN 1539-1035

tent to craft such a data set for these secondary uses. Yet the less identified the data are, the less risk to subjects, and the less scrutiny an IRB is likely to give informed consents in regard to future uses. Further, deidentified data and tissues cannot by definition be affected by a subject's revocation of his or her participation in a database or repository, and the deidentified nature of the tissue and data render lingering ownership or property claims of subjects tenuous at best.

Conclusion

The principle of autonomy underlying informed consent requirements in human subjects research would seem to support the idea that a research subject should be able to consent to future uses of his or her information or identified specimens for future secondary research. Like any donation for altruistic purposes, research subjects should be permitted to allow research institutions and research sponsors to bank their information or material and use it at a future date. There is potential for abuse of such gifts, which an IRB reviewing research with any future use component should carefully assess. Research sponsors should not consider themselves absolved from all obligation toward the medical information and identified tissues they receive in the course of a research study. HIPAA aside, sponsors have an ethical, and possibly a legal, obligation to abide by the terms of the informed consent form signed by the subject, and it would be unduly risky for sponsors to use or disclose subjects' information or tissues in contravention of the terms agreed to in that form. If, as will be the case in most clinical research, the research sponsor is receiving identified data and biologic materials from the institution conducting the research, the institution and investigator should ensure that the clinical trial agreement binds the sponsor to some level of care and limits the sponsor's future uses in a way consistent with the subjects' understanding of what will happen to their data and tissues, and consistent with the sponsor's need to understand research, to develop future research, and to interact with government authorities. Regardless of how, legally, ownership rights in data and specimens are defined in the courts and state legislatures, the encouragement of continued participation in research and the donation of information and materials to support future research endeavors depends upon forthright representations by investigators, IRBs, and sponsors in regard to the true scope of subjects' participation in a research study and all that comes after it.