

## **Informed Consent for Patient Registries**

### Draft White Paper for Third Edition of “Registries for Evaluating Patient Outcomes: A User’s Guide”

## **Introduction**

This paper identifies the best practices for obtaining informed consent for registry participation. It builds on some of the general ethical and legal principles discussed in the “Principles of Registry Ethics, Data Ownership, and Privacy” chapter,<sup>1</sup> specifically the application of the regulations governing human subjects research and the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.

The purpose of this paper is to provide an ethical framework for obtaining informed consent for registry participation and to distinguish registries from clinical research protocols. It is not designed to provide specific legal guidance, nor can it substitute for Institutional Review Board (IRB) review. Moreover, where law is discussed it is limited to U.S. statutes and, more specifically, to Federal as opposed to state regulations. Some states have guidelines governing the conduct of research involving human subjects or statutes addressing privacy, and an exploration of either area is beyond the scope of this paper. Likewise, analysis of the relevant international standards and laws is left to others.

## **Registries, Research, and Other Activities**

The purpose of this volume is to provide guidance for *registries used to evaluate patient outcomes*, such as efforts to describe the natural history of disease, determine clinical and/or cost effectiveness, assess safety or harm, and measure or improve quality of care. As a result, the focus of this paper is on informed consent issues that arise in registries used for research. Some registries used for research may have been developed initially for clinical purposes (e.g., a name/contact information registry of patients using a

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<sup>1</sup> Chapters referenced in this document can be found in the second edition of “Registries for Evaluating Patient Outcomes: A User’s Guide,” available at:  
<http://www.effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%202nd%20ed%20final%20to%20Eisenberg%209-15-10.pdf>.

particular treatment to facilitate notifications or recalls). Increasingly, however, registries are being used for research purposes even when initially developed for clinical purposes, and thus it is suggested that in all cases, consideration should be given to the informed consent issues, as well as HIPAA privacy requirements, discussed in this paper. The HIPAA Privacy Rule governs the use and disclosure of most individually identifiable health information (called protected health information or “PHI”) held by covered entities (health plans, health care clearinghouses, and most health care providers).

The Federal research regulations promulgated by the U.S. Department of Health and Human Services (HHS), as well as those developed by U.S. Food and Drug Administration (FDA), focus on clinical research involving human subjects. The FDA regulations apply to “all clinical investigations” regulated by the FDA—defined as “any experiment that involves a test article and one or more human subjects” (21 CFR 50.3(c)). The HHS regulations apply only to “human subjects research,” where “research” is defined as a “systematic investigation” and “human subject” as a living person about whom the investigator obtains either data through intervention or interaction, or identifiable private information (46 CFR 102 (d)- (f)). Thus, investigations that involve non-living individuals, or that do not collect data through intervention/interaction and do not collect identifiable information are not governed by the HHS regulations. Despite the apparent limitations of the regulatory language, institutions may choose to apply the frameworks more broadly (sometimes under an “assurance,” i.e., an agreement with HHS that the institution will apply the regulations to all research at the institution regardless of funding source). Even when the activity in question meets the HHS definition of research subject to regulation, a series of exemptions may apply (45 CFR 46.101(b)).

### ***Registry Research vs. Clinical Research***

It is worth noting some of the significant differences between registry research and clinical research. In particular, the use of a control group in a registry setting is often substantively different from the concept of a control group in a clinical research setting. Registry controls may be pulled from a general population—in some cases a population that may not have interacted with health professionals or a health institution. Unlike clinical controls, who may be exposed to placebos (and thus need to consent) or exposed to a standard treatment (and thus will already be involved in the treatment system), registry controls may be identified from an unaffected population. This raises ethical questions about the initial contact with an individual who may have no link to the registry topic area and who may view the contact

as an unwelcome intrusion or perhaps even an incorrect indication of problematic health status.<sup>2</sup> Furthermore, since a clinical research trial may involve double-blind procedures, “controls” may agree to participate because of the potential for direct therapeutic benefits or even the indirect therapeutic benefits that come from better attendant care. In other situations, controls may participate because they hope to help others suffering from their ailments (altruistic reasoning) or perhaps because they seek monetary compensation. In contrast, controls in a registry trial have no similar potential therapeutic (direct or indirect) or monetary benefits. While altruism may play a role in this context, its effects may be less than ideal. There is a great concern about the potential for selection bias in the creation of a control group for registry trials (there is also significant concern about the effect of bias in clinical trials). Those who may agree to participate in a registry may be qualitatively different from those who do not agree, which can threaten the external validity of research findings. Concerns about selection bias will be heightened for diseases with a low prevalence in the general population since there will be a greater possibility that the bias will affect the data. Developing consent requirements in such a way as to avoid selection bias will be extremely important in this setting.

Questions about adapting the regulatory requirements to research that does not fit the typical clinical model are not unusual. There are two other areas that have raised questions about the how the Federal regulations apply and that are particularly relevant to registry evaluations: public health activities and quality improvement/assurance (QI/QA).

### ***Public Health Activities***

The HIPAA Privacy Rule expressly permits the disclosure of Protected Health Information (PHI) to a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, including for activities related to disease, injury, or vital event reporting. Thus, a covered entity may disclose PHI, without individual authorization, for a registry maintained by a public health authority (or by an entity acting under a grant of authority from or contract with such public agency) for authorized public health purposes, such as, for example, immunization registries, state cancer registries, birth and death registries, and general disease reporting (although the latter is often anonymous). The HIPAA Privacy Rule also allows the disclosure of PHI to a person subject to the jurisdiction of FDA for FDA regulated product reporting.

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<sup>2</sup> David Casarett, et al., “Bioethical Issues in Pharmacoepidemiologic Research,” in Pharmacoepidemiology 593 (RL Strom ed., 4th Ed. 2005).

Public health activities may not be considered “human subjects research” under HHS or FDA regulations. Differentiating between public health practice and public health research activities can be challenging. According to the Belmont Report, on which the Federal research regulations are based, if any aspect of an activity constitutes “research” then the entire activity should undergo regulatory review. The Office for Human Research Protections (OHRP) interpretation of the HHS regulations implies that if any part of the activity falls under the regulations the entire activity is covered.<sup>3</sup> By contrast, according to the Centers for Disease Control and Prevention (CDC), an activity is only considered research if the primary intent is to contribute to or generate generalizable knowledge (CDC Guidelines 1999). Local IRB policies in this area vary; some focus on whether the primary intent of an activity is to gain generalizable knowledge, and others categorically exclude normal public health department activities.

To address confusion regarding what is considered a public health activity versus a research activity, the Council of State and Territorial Epidemiologists (CSTE) issued a report clarifying that public health practice activities are those for which: there is a specific or general legal authorization to conduct (e.g., state statutory cancer registries, or reports of newborn hearing screening to the state health department); the specific intent of the authority conducting the activity is to promote the health of, or prevent harm to, the individuals or communities involved (as opposed to research where the intent is to gather generalizable knowledge); and there are, in fact, health benefits to the individuals involved or to the target community.<sup>4</sup> Moreover, public health activities, unlike research, are not likely to involve experimental procedures or to have one (or more) individuals responsible for the development and conduct of the activity such as a primary investigator (PI), or entail individual randomization for access to interventions.

Alternatively, a public health activity may fit the definition of research, but fall into one of the various exemptions to covered research. For example, there are exemptions for research involving surveys, interviews, or observations of public behavior, provided certain requirements are met. (46.101(b)(2) and (3)). There is also an exemption for the collection or examination of existing data, if publicly available and information is recorded “in such a manner that subjects cannot be identified, directly or through identifiers.” (46.101(b)(4)).

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<sup>3</sup> U.S. Department of Health & Human Services. Text Version of OHRP Decision Charts. Available at: <http://www.hhs.gov/ohrp/policy/decisioncharttext.html>. Accessed August 18, 2011.

<sup>4</sup> Council of State and Territorial Epidemiologists. Public Health Practice vs. Research. May 24, 2004. Available at: <http://www.cste.org/pdffiles/newpdffiles/CSTEPHResRptHodgeFinal.5.24.04.pdf>. Accessed September 29, 2011.

### ***Quality Improvement/Quality Assurance Activities***

As with certain public health activities, HIPAA provides an explicit exception to the authorization requirements for the use and disclosure of PHI for “health care operations,” which are defined as certain activities of a covered entity, including “conducting quality assessment and improvement activities . . . , provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities.” 45 CFR 164.501. Individual authorization for disclosure of PHI in this context is not necessary, but individual consent is permitted if a covered entity chooses to obtain it.

The Federal research regulations do not have an explicit exemption for QI/QA activities. Many of the efforts in this area will: (a) not meet the regulatory definitions of “research,” (b) not involve “human subjects,” (c) fall under a delineated exemption, or (d) not be supported by HHS, involve an FDA regulated product, or otherwise covered by an assurance of compliance. Some local IRB policies have a categorical exemption for QI/QA activities, as they might for public health activities.

The application of the human subjects research regulations does not rest on whether or not a procedure is considered “standard” or part of the “standard of care;” rather, it rests on the purpose of the activity. Intent to publish the results of a QI/QA activity is not determinative of whether the human subjects regulations apply. Registries developed within an institution to implement a practice to improve the quality of patient care or to collect data regarding the implementation of such a practice are not considered “research” under the regulations. Nor are registries designed to collect provider performance data for clinical, practical, or administrative uses. Registries that involve existing data that is not individually identifiable may entail “research,” but do not involve “human subjects” as defined by the regulations. However, a QI/QA project that involves an untested clinical intervention (whether or not part of the standard of care) for purposes of gathering scientific evidence of efficacy (i.e., a systematic investigation designed to contribute to generalizable knowledge) would be governed by the regulations, although a specific exemption may apply (e.g., if it is part of the evaluation of a public benefit program).<sup>5</sup> Even if the regulations apply, waivers or alterations to the consent process may be approved as noted below.

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<sup>5</sup> U.S. Department of Health and Human Services. Office for Human Research Protections. Quality Improvement Activities – FAQs. Available at: <http://answers.hhs.gov/ohrp/categories/1569>. Accessed September 29, 2011.

## Current Challenges for Registries

### *Electronic Health Records*

The development of large-scale data registries raises a variety of regulatory questions, and this is nowhere more evident than in the discussions about electronic health records (EHRs). These issues are explored in detail in the “Interfacing Registries With Electronic Health Records” chapter. This paper focuses only on the relevant consent issues. There are currently few, if any, efforts to obtain individual consent for the creation of an EHR (or, for that matter, the creation of any health record). Yet, these databases have enormous research potential. For example, Kaiser Permanente, a leader in the use of health information technology, created and maintains one of largest private-sector EHR systems, collecting health information from over 8.7 million Kaiser members nationwide. Moreover, there are a number of efforts to develop (sometimes via state legislation) multi-payer claims registries to support comparative effectiveness research (CER). Various steps have been discussed to ensure the privacy and confidentiality of the individual health information gathered into these registries (e.g., the use of coded identifiers). Application of traditional consent models for the secondary use of these databanks for research may prove inefficient and may result in selection bias, impacting the usefulness of downstream analyses.

As the development of EHRs, claims registries, health information exchanges, and linkages between innumerable health databases moves forward, keeping records private becomes more difficult to manage. Personal health information may be accessed and shared in ways patients never imagined, often for the purpose of secondary analysis and often without patient consent. Although studies consistently indicate that Americans are generally supportive of EHRs and even secondary uses of the data, they want to be informed about how and to what extent their information will be shared and disclosed to others.<sup>6,7,8,9</sup>

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<sup>6</sup> National Committee on Vital and Health Statistics. Privacy and Confidentiality in the Nationwide Health Information Network. June 22, 2006. Available at: <http://www.ncvhs.hhs.gov/privacyreport0608.pdf>. Accessed September 29, 2011.

<sup>7</sup> A.F. Westin. How the Public views Privacy and Health Research. October 2007. Available at: <http://www.iom.edu/CMS/3740/43729.aspx>. Accessed September 29, 2011.

<sup>8</sup> Mark A. Rothstein. “Improve Privacy in Research by Eliminating Informed Consent? IOM Report Misses the Mark.” *Journal of Law, Medicine & Ethics* (2009): 507-512.

<sup>9</sup> Agency for Healthcare Research and Quality. “Final Report: Consumer Engagement in Developing Electronic Health Information Systems.” July 2009. AHRQ Publication No. 09-0081-EF. Available at: [http://healthit.ahrq.gov/portal/server.pt/gateway/PTARGS\\_0\\_1248\\_888520\\_0\\_0\\_18/09-0081-EF.pdf](http://healthit.ahrq.gov/portal/server.pt/gateway/PTARGS_0_1248_888520_0_0_18/09-0081-EF.pdf). Accessed September 29, 2011.

Despite apparent public unease with a system of open access to EHRs, the Institute of Medicine (IOM) in 2009 released a statement that informed consent for research using EHRs should not be required, with the justification that obtaining permission from patients is too burdensome for researchers and should be eliminated entirely.<sup>10</sup> This generated widespread concern that the IOM's proposal would undermine the trust that forms the basis of the patient-physician relationship and also more broadly increased concerns about patients' privacy and confidentiality protections. Given the strong arguments on both sides, establishing consensus on the topic has been slow.

In an effort to resolve the debate, additional work in this area should focus on striking the appropriate balance between providing patients with control over information and facilitating necessary research. Commentators have suggested a variety of different approaches, including recognition of public ownership of large electronic databases<sup>11</sup> or the creation of licensed data centers that would control access to information without individual consent.<sup>12</sup> It is not clear from the empirical evidence that patients want full consent protections in this context. One study, for example, found that patients were more likely to be comfortable with the research uses of their EHR information when they were asked about the use by a specific entity (e.g., universities, hospitals, or disease foundations) rather than when asked in the abstract, and that they fully supported public health uses of their data.<sup>13</sup> Public education about the scope of research uses may alleviate some patient concerns about the use of EHR data without consent.<sup>14</sup> Similarly, addressing underlying fears about unauthorized access to identifiable data or discriminatory uses of the information can also be helpful in increasing support for this type of research. Given the vast potential for using EHRs to conduct large-scale observational studies, development of an alternative to specific individual consent may be useful. On July 26, 2011, HHS and the Office of Science and Technology Policy (OSTP) published an advance notice of proposed rulemaking (ANPRM) entitled, "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing

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<sup>10</sup> Institute of Medicine. Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research. January 27, 2009. Available at: <http://www.iom.edu/Reports/2009/Beyond-the-HIPAA-Privacy-Rule-Enhancing-Privacy-Improving-Health-Through-Research.aspx>. Accessed September 29, 2011.

<sup>11</sup> Marc A. Rodwin. Patient Data: Property, Privacy & the Public Interest. *American Journal of Law & Medicine*, 36 (2010): 586-618.

<sup>12</sup> Fred H. Cate. Protecting Privacy in Health Research: The Limits of Individual Choice. *California Law Review* (2010): 1765-1804.

<sup>13</sup> D.J. Willison et al. Alternatives to Project-specific Consent for Access to Person information for Health Research: What is the Opinion of the Canadian Public? *Journal of the AMIA* 14(6): 706-712, 2007.

<sup>14</sup> FG Miller. Research on Medical Records Without Informed Consent. *Journal of Law, Medicine & Ethics*, 36(3): 560-566, 2008.

Burden, Delay, and Ambiguity for Investigators.”<sup>15</sup> A number of changes have been proposed to enhance protections of research participants, while facilitating valuable research and reducing burden among research investigators. Included in the proposal are suggestions that specifically address EHRs and large-scale electronic databanks.

### **Biobanks**

The increasing availability of electronic data repositories linked with biological samples (and biobank registries) raises additional concerns. In addition to the Federal regulations described below, there are also guidelines governing the creation of a data repository or biobank (see the “Principles of Registry Ethics, Data Ownership, and Privacy” chapter). In particular, IRBs are charged with reviewing protocols for obtaining, storing and sharing information; verifying informed consent; and protecting privacy and confidentiality.

The Secretary’s Advisory Committee on Human Research Protection (SACHRP) advises the Secretary of HHS on issues related to the protection of human subjects. SACHRP developed frequently asked questions (FAQs) to provide a framework for IRBs, institutions, and investigators to consider relating to the collection, use, and storage of biospecimens. One of the FAQs states that generally consent is necessary before moving excess identifiable clinical specimens to a centralized databank. In rare circumstances, an IRB may determine that the conditions for a waiver of consent have been met. Relevant factors to consider include: governance and oversight of bank; protections in place for confidentiality/privacy; policies regarding access to specimens; nature of research for which specimens used; ability to locate/contact subjects; risk of introducing bias into collection; potential anxiety/confusion for subjects; number of subjects; length of time since specimens first collected; and the likelihood subject would object to research use (SACHRP January 2011). While these are designed to address the use of clinical specimens, the issues raised are also applicable to the use of clinical data. Similarly, SACHRP suggests that an IRB determine whether a transfer of specimens to a new bank or institution is permissible under the initial consent—a relevant point for information transfers as well.

As with EHRs, there have been a variety of challenges to the use of biobanks for research without specific individual consent. Many long-standing biobanks were established either for non-research purposes (e.g., newborn blood spot banks) or under a general consent allowing the use of leftover tissue in hospitals.

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<sup>15</sup> Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 143 (proposed July 26, 2011). Available at: <http://www.gpo.gov/fdsys/pkg/FR-2011-07-26/html/2011-18792.htm>. Accessed September 29, 2011.

While more recent banks and repositories have been set up with a variety of consent protections, it is unclear what to do with existing repositories created without these protections, or how to manage access to archived data within the repositories where initial consent was either silent on the matter or significantly limits future research. At least one author has suggested the creation of a new regulatory oversight framework that would substitute for the necessary individual informed consent for the use of existing data or tissue samples.<sup>16</sup> Another suggests using broad initial consents to cover a variety of future uses.<sup>17</sup> Litigation in Texas and Minnesota regarding the use of newborn blood spots has highlighted this issue in the national dialogue, and development of additional regulations at the State level is likely. The ANPRM cited above includes among its proposed changes mechanisms to improve informed consent, including consent for the secondary use of pre-existing biospecimens and data.

Key unresolved issues relevant to both biobanks and large information data repositories include: obligations to return individually relevant research results, future unforeseen research uses, the need to recontact participants (some of whom may not wish to be recontacted or who are deceased), the financial burdens of recontacting, the limits on withdrawal of the sample or information, whether the sample/information can be kept indefinitely, whether commercial uses of the bank should be treated differently than non-commercial uses, and the implications of large-scale database research for socially identifiable groups. Moreover, as technology continues to progress, so will the ability to re-identify participants from data deposited into biobanks and large data repositories.

De-identification and aggregate reporting alone does not completely conceal identity.<sup>18,19</sup> For example, there is a considerable push to make de-identified, aggregate-level data from Genome Wide Association Studies (GWAS) publicly available in large repositories so that the data can be combined with other studies for more powerful analysis. However, an individual can be re-identified by assessing the probability that an individual or relative participated in a GWAS through composite statistics across cohorts (such as allele frequency or genotype counts). BioVU, the Vanderbilt DNA Databank, has taken

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<sup>16</sup> Henry T. Greely. *Breaking the Stalemate: A Prospective Regulatory Framework for Unforeseen Research Uses of Human Tissue Sample and Health Information*. *Wake Forest L. Rev.* (1999): 737-766.

<sup>17</sup> Dave Wendler. *One-Time General Consent for Research on Biological Samples: Is It Compatible With the Health Insurance Portability and Accountability Act?* *Arch Intern Med.* 166(14):1449-52.

<sup>18</sup> Homer N, Szelinger S, Redman M, Duggan D, Tembe W, Muehling J, Pearson JV, Stephan DA, Nelson SF, Craig DW. *Resolving individuals contributing trace amounts of DNA to highly complex mixtures using high-density SNP genotyping microarrays.* *PLoS Genet* 2008, 4:e1000167.

<sup>19</sup> Jacobs KB, Yeager M, Wacholder S, Craig D, Kraft P, Hunter DJ, Paschal J, Manolio TA, Tucker M, Hoover RN, Thomas GD, Chanock SJ, Chatterjee N: *A new statistic and its power to infer membership in a genome-wide association study using genotype frequencies.* *Nat Genet* 2009,41:1253-1257.

steps to diminish the risk of re-identification. BioVU is linked to a de-identified version of data extracted from an EHR in which all personal identifiers have been removed. Thus, there is no identifiable information attached to the records. The disadvantages or tradeoffs in such design are that it explicitly precludes both re-contact and linking with any information other than that contained within the original EHR. It also prevents the return of individual results—an issue that remains controversial even when the study design allows it.

The informed consent documents initially used for biobanking research either stated explicitly that no results would be returned to participants or remained silent on the issue. More recently, there is general agreement in the scientific community supporting the return of aggregate results to research participants. There is less agreement on return of individual results. Moreover, there is still debate regarding the most ethically appropriate mechanisms for returning results (e.g., when, how, and by whom-- physician or investigator). In 2010 a National Heart, Lung, and Blood Institute (NHLBI) Working Group released revised recommendations providing guidance on many of these issues, but the issue is far from settled.<sup>20</sup>

### ***Reconsidering the Ethical Framework Governing Research***

Perhaps the most challenging part of the shift to large database research and the current regulatory structure is the potential re-framing of the underlying ethical issues. The July 2011 HHS-issued ANPRM states that “[a]lthough the regulations have been amended over the years, they have not kept pace with the evolving human research enterprise, the proliferation of multi-site clinical trials and observational studies, the expansion of health services research, research in the social and behavioral sciences, and research involving databases, the Internet, and biological specimen repositories, and the use of advanced technologies, such as genomics.” The current Federal research regulations are based on the Belmont Report, which focused on the traditional clinical research context. The HIPAA Privacy Rule was put in place more recently to protect the privacy of individually identifiable health information and demonstrates the challenges with balancing individual privacy with the information needs of a comprehensive health system. The future focus on electronic data repositories and the potential for large-scale observational studies to replace some clinical trial data require consideration of whether the approaches used thus far should be adapted.

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<sup>20</sup> Richard R. Fabsitz et al. Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines From a National Heart, Lung, and Blood Institute Working Group. *Circ Cardiovasc Genet* 2010, 574-80.

For example, in discussing the possible use of the FDA's Sentinel System as a pharmacoepidemiological research database, Professor Barbara Evans identified three "novel challenges in applying familiar ethical frameworks."<sup>21</sup> The first is the possibility that with the shorter time period between research results and clinical application, the history categorization of research versus treatment (or even public health practice versus research) may be incorrect. Perhaps IRBs will need to consider both the potential direct medical benefits of an observational study, and potential participant health risks such as negative insurance coverage determinations or changes in physician prescribing patterns. Second, the creation of these massive databanks that span numerous states (and sometimes countries) raises issues about whether the "local context review" that forms the basis for the IRB system continues to be relevant. Although a detailed examination of state regulations is not part of this paper, it is worth emphasizing the challenges faced by multi-state registries, which may face different requirements for informed consent, different privacy protections, and even different definitions of "human subjects research" from state-to-state. This can add enormous burden to the regulatory oversight system and significant complexity to these endeavors. Finally, this type of research raises questions about the meaning of vulnerability and susceptibility to harm, and who should be identified as a "vulnerable" population in need of additional protections. It may be that the groups traditionally considered vulnerable in the clinical research context are not especially vulnerable in this context. Conversely, there may be groups particularly vulnerable to re-identification, or for whom re-identification poses unique risks of psychosocial or economic harms, but which would not usually be considered vulnerable in clinical research. In fact, the need to understand potential group harms highlights the limitations of the traditional ethical framework that assumes the focus should be on the individual. More work is needed to consider the ethical framework that should guide large-scale observational studies, but such exploration is beyond the scope of this paper. The challenges raised by these studies have implications for research more generally and may lead to broader regulatory changes such as those proposed in the ANPRM.

## Regulatory Consent Requirements

While a number of issues remain unanswered in this area, there is some clear guidance for registries that fall under the Federal research regulations. There are two primary sets of Federal regulations governing the conduct of human subjects research. HHS regulates research supported by Federal money or covered under an institutional "assurance of compliance" (see the "Principles of Registry Ethics, Data Ownership,

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<sup>21</sup> Barbara J. Evans. Appropriate Human-Subject Protections for Research use of Sentinel System Data. FDA Sentinel System Meeting Series Issue Brief: Legal Issues in Active Medical Product Surveillance. March 2010.

and Privacy” chapter for more detail). The FDA regulates research that will be used to support an FDA regulated product. Both sets of regulations largely have the same consent requirements; relevant differences are indicated below. The HIPAA Privacy Rule also contains individual authorization requirements for uses and disclosures of individually identifiable health information for research. Each of these Federal regulatory areas will be discussed in turn.

### ***HHS and FDA General Consent Requirements***

For activities covered by the HHS and FDA research regulations, eight basic elements of information must be provided to research participants:

1. 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;
2. A description of any foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or whether further information may be obtained;
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject; and
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. 45 CFR 46.116(a); 21 CFR 50.25(a)

In addition, the FDA announced on January 4, 2011 that informed consent forms for applicable clinical trials must include a statement that the trial information will be entered into the National Institutes of Health (NIH) clinical trial registry.<sup>22</sup> Both the HHS and the FDA regulations also require, where appropriate, additional elements of informed consent including:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
3. Any additional costs to the subject that may result from participation in the research;
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of research which may related to the subject's willingness to continue participation will be provided to the subject; and
6. The approximate number of subjects involved in the study. 45 CFR 46.116(b); 21 CFR 50.25(b)

The HHS regulations allow an IRB to authorize a waiver or alteration of the consent requirements for minimal risk research where the waiver or alteration will not affect the rights of the subjects, the research cannot be carried out without the waiver, and, when appropriate, subjects will be provided information after participation (45 CFR 46.116(d)). The FDA regulations do not allow waivers or alterations under these circumstances, but do allow for waivers in life-threatening situations and allow Presidential waivers

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<sup>22</sup> Informed Consent Elements; Final rule. 76 Federal Register 2 (4 January 2011), pp. 256-270. Available at: <http://edocket.access.gpo.gov/2011/pdf/2010-33193.pdf>. Accessed September 29, 2011.

for some military research (21 CFR 50.23). Both sets of regulations allow for waiver of consent requirements for research conducted in specific types of emergency situations (21 CFR 50.24).

### ***Documentation and Format of Consent***

There are varying requirements for documentation of the consent process. Both FDA and HHS regulations speak to the documentation of informed consent. 45 CFR 46.117; 21 CFR 50.27. Unlike treatment consents, research consents are usually written and the consent form functions both as documentation of the consent process, and in some cases as an aspect of the consent itself (since in long form the document contains all of the necessary consent disclosures and participants may be given the form to read as part of the consent process). HHS allows an IRB to waive the written documentation requirement in whole or in part when 1) the only record linking the subject and the research would be the consent document and the principal risk of the study would be potential harm resulting from a breach of confidentiality, or 2) the research involves no more than minimal risk of harm and involves no procedures for which written consent is not normally obtained in a clinical context. 45 CFR 46.117(c). In either case, the participant may still be provided a written summary.

Under certain conditions HHS and FDA regulations allow for the IRB to approve an oral consent procedure. 45 CFR 46.117(b); 21 CFR 50.27(b)(2). Oral consent is often used for research involving interviews conducted by telephone. The oral presentation of informed consent information should be accompanied by a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what has been presented orally. A witness to the oral presentation is required, and the participant (or representative) must be given copies of the short form document and the summary. The participant must sign the short form document and the witness will sign both the short form and the summary.

E-consents may be considered written documentation under either set of regulations and are within the scope of the IRBs' power to authorize as an alternation of written documentation requirements under the HHS regulations. HHS specifically allows electronic signatures on research consent documents, provided they are legally valid in the specific jurisdiction.<sup>23</sup> FDA also has provisions for e-signatures on electronic records, but does not speak directly to e-consent for research participation.<sup>24</sup> While the Federal Electronic

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<sup>23</sup> U.S. Department of Health and Human Services. Office for Human Research Protections. Can an electronic signature be used to document consent or parental permission? Available at: <http://answers.hhs.gov/ohrp/questions/7260>. Accessed September 29, 2011.

<sup>24</sup> Maria Donawa. New FDA Guidance on Electronic Records and Signatures. Medical Device Technology. Nov. 2001. 25-28, 25.

Signatures in Global and National Commerce Act (E-SIGN) attempts to provide some uniformity among state laws governing electronic transactions, there remain some variations.<sup>25,26</sup> The primary goals of e-signature laws are authenticating the signature and ensuring privacy and confidentiality of electronic information. Although there have been some suggestions for standardized electronic consent procedures, there is little focused specifically on the research area.<sup>27</sup>

### ***Informed Consent Form Revisions and Re-consent***

Changes to the informed consent document that require re-consent of patients may be necessary if there are changes in the scope of the registry—such as substantive changes to the protocol, addition of procedures not previously addressed in the consent, changes in data sharing or reporting procedures, or if there are identified errors or omissions in the original consent document. As noted below, re-consent may also be necessary if the participants were below the age of consent when initially enrolled but reach the age of majority when the registry is still active (see discussion *infra*). The decision to change the informed consent form and subsequently re-consent participants needs to be carefully considered due to possible challenges in obtaining the re-consent. For example, participants may be lost to follow up because they have moved or died. Challenges may be particularly evident for registries that have been in place for several years. These difficulties are what prompted the interest in broad general initial consents. In situations where the initial consent does not cover the change, registries may seek IRB waiver of re-consent requirements.

For studies in which re-consent is sought, registry developers should consider the potential effects of selection bias and the implications for external validity. Re-consented participants may be systematically different from non-re-consented participants. For example, participants that are not re-consented may have died or been lost to follow up for health related reasons, leaving an overall healthier group of participants. Additionally, even among those who can be contacted, individuals who agree to continue participation may be different from those who refuse to provide consent. As a result, one important requirement for studies that undertake re-consent may be to evaluate characteristics of the original study population as compared to the subset of patients that do re-consent and consider the implications for

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<sup>25</sup> Buchanan Ingersoll & Rooney PC. Electronic Records and Signatures in Healthcare and the Interplay of E-Sign, HIPAA and UETA. 1-7, 1. Available at: <http://library.findlaw.com/2001/Jan/1/126648.html>. Accessed September 29, 2011.

<sup>26</sup> Paterick, et al. Expanding Electronic Transmissions in the Practice of Medicine and the Role of Electronic Informed Consent. *Journal of Patient Safety*. Volume 4(4). Dec. 2008. 217-20, 219.

<sup>27</sup> Melissa Goldstein. Health Information Technology and the Idea of Informed Consent: The Effects of Health Information Technology on the Physician-Patient Relationship. *Journal of Law, Medicine & Ethics*. 2010. 27-35, 28.

research outcomes. The evaluation of whether re-consents are more common for particular populations should be done for any analyses that have comparative arms.

Minor changes to a consent document do not necessitate re-consent. Re-consent is necessary, however, where the terms of the study or the background pre-conditions have changed. In some long-term studies, re-informing participants, but not re-consent, may be necessary. Even where re-consent is needed, IRBs may waive requirements. Alternatively, data collection, sharing, and reporting for participants who cannot be re-consented could be maintained in accordance with the terms of the original consent. In those situations in which a re-consent process is implemented, participants should be told the reasons for the re-contact and provided a summary of consent form changes. Additionally, as with the original consent, documentation of the re-consent must be maintained as required by the registry, the IRB, and any relevant regulations.

### ***Applying the Federal Research Regulations to Registries***

Some of the regulatory requirements have less applicability to registries. For example, of the eight basic elements listed earlier, requirements 4 (alternatives) and 6 (compensation/injury) are crafted to address issues raised in traditional clinical trials, rather than registries. Other elements have aspects that clearly encompass registry research (such as basic elements 1, 2, and 7), but other parts that seem less applicable, since registries will not involve “experimental procedures” that must be identified, entail no physical “discomforts to the subject,” and do not pose a risk of (physical) “research-related injury”.

Other requirements may pose challenges for registries, such as basic element 8, which requires subjects to be informed about a right to withdraw. While registry participants may refuse to provide additional information about their medical status or care, withdrawing from a registry may undermine the data collection. In situations where the data have been anonymized, withdrawal will likely prove impossible. In many such cases, registry informed consents may contain language notifying subjects that in the event of withdrawal, data that was collected prior to the withdrawal may continue to be used and disclosed according to the consent in order to preserve the scientific integrity of the registry. However, even where data have not been anonymized, some argue that the registry must retain all records to be a valid information tool. The FDA explicitly requires the retention of identifiable data even after a subject withdraws from a study. HHS permits the retention of such data, but also permits the investigator to omit or destroy the data if retention is not required by FDA regulations or study integrity. OHRP suggests that IRBs provide guidance on documentation of participant withdrawal. Moreover, the OHRP guidance dated September 21, 2010 on this issue clarifies that once a subject withdraws, the investigator must stop

interacting with the subject to obtain data, and stop collecting identifiable private information from other sources (unless the subject specifically provides consent to the continued data collection).

## **HIPAA**

The HIPAA Privacy Rule also may apply to either the use or disclosure of health information into/from a registry, or the use of such information to create a registry, or both. Because the HIPAA Privacy Rule governs the use and disclosure of most individually identifiable health information held by covered entities, the Privacy Rule requirements may apply even if the human subjects research regulations do not. Moreover, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires all qualified entities with which it contracts to provide analyses of drug safety data, regardless of whether they are a HIPAA covered entity, to follow the minimal requirements of the Privacy Rule.<sup>28</sup> The “Principles of Registry Ethics, Data Ownership, and Privacy” chapter describes the general Privacy Rule framework in this context and the specifics of coverage. The Privacy Rule requires that a covered entity obtain written authorization for the use and disclosure of an individual’s PHI for research purposes unless the use or disclosure is permitted by another provision of the Rule (e.g., where a waiver of authorization is applicable). A subject’s informed consent to participate in research can be combined with a HIPAA authorization in one document. There are six core elements and three required statements for a HIPAA authorization:

### Core Elements

- A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner
- The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure
- The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure
- A description of each purpose of the requested use or disclosure

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<sup>28</sup> Pub. L. No. 110-85, 121 Stat. 823 (2007) (Codified in 21 U.S.C.).

- Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure ("end of the research study" or "none" are permissible for research, including for the creation and maintenance of a research database or repository)
- Signature of the individual and date. If the individual's legally authorized representative signs the Authorization, a description of the representative's authority to act for the individual must also be provided

### Required Statements

- A statement of the individual's right to revoke Authorization in writing, and either: 1) a description of how to do so, and the exceptions to the right to revoke authorization, or 2) reference to the corresponding section of the covered entity's notice of privacy practices.
- Whether treatment, payment, enrollment, or eligibility for benefits can be conditioned on the individual signing the Authorization, including research-related treatment, and consequences of refusing to sign the Authorization, if applicable.
- A statement of the potential for the PHI to be re-disclosed by the recipient and no longer protected by the Privacy Rule. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.<sup>29</sup>

Authorization is not needed for activities that are "preparatory to research," which may include scanning a patient database to determine feasibility for creating a registry. Before allowing an investigator access to PHI for such purposes, however, the covered entity must obtain from the researcher representations that: 1) the use or disclosure of PHI is sought solely for purposes preparatory to research, 2) no PHI will be removed from the covered entity during the review, and 3) access to the PHI is necessary for the research purposes. 45 CFR 164.512(i)(1)(ii). These preparatory activities may aid investigators in the

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<sup>29</sup> 45 CFR 164.508. For additional information on authorizations for research, see <http://privacyruleandresearch.nih.gov/authorization.asp>.

identification of potential research participants. Subsequent contact of potential research participants for purposes of obtaining authorization for the use or disclosure of the individual's PHI may be permitted under the Privacy Rule in a variety of ways depending on the relationship between the investigator and the covered entity. An investigator that is a workforce member of the covered entity is permitted to contact potential participants directly or through another person at the covered entity, such as a treating provider, to obtain authorization. Alternatively, a covered entity is permitted to hire a business associate – who may be an investigator – to contact patients to obtain authorization on behalf of the covered entity. Finally, a covered entity is permitted to provide contact information of potential research subjects to an investigator that is not part of the covered entity or a business associate, if the covered entity obtains documentation that an IRB or privacy board has waived the authorization requirement for the disclosure.

Additionally, uses or disclosures of decedents' PHI to a research registry or from a registry for research purposes do not require an authorization (as long as certain representations are provided to the covered entity that is providing the information) (45 CFR 164.512(i)(1)(iii)). Authorizations are also not required for uses or disclosures of de-identified data sets, provided the information has been de-identified in accordance with the Privacy Rule (45 CFR 164.514 (a)-(c)). Nor are authorizations required for uses or disclosures of "limited data sets," as defined by the Rule (so long as a data use agreement is in place with the recipient of the limited data set) (45 CFR 164.514(e)). See the "Principles of Registry Ethics, Data Ownership, and Privacy" chapter for more details.

In addition, an IRB or privacy board may waive or alter aspects of the HIPAA authorization requirements. Like the requirements for a waiver or alteration under the human subjects research regulations described above, these are limited to situations in which the research could not be practicably carried out both without the waiver or alteration and access to the PHI, and the use or disclosure information involves no more than minimal risk to privacy because there is: (a) an adequate plan to protect the identifiers from improper use or disclosure; (b) an adequate plan to destroy identifiers if possible; and (c) adequate written assurances that the PHI will not be reused or disclosed except as required by law, as needed for research oversight, or for other research in a way permitted by the Privacy Rule (45 CFR 164.512(i)(2)).

Finally, if a subject was enrolled in a research protocol prior to the compliance date of the Privacy Rule (for most covered entities, April 14, 2003) and pursuant to a valid informed consent, an authorization may not be required unless after the compliance date another informed consent is sought from the subject. 45 CFR 164.532. This may be especially relevant to registries that were created prior to the application of the Privacy Rule.

The HIPAA Privacy Rule also speaks to the issue of withdrawal from a registry. The Privacy Rule explicitly gives individuals the right to revoke their authorization for the use and disclosure of protected health information (the revocation must be in writing), except to the extent that a covered entity has already relied on the authorization. HHS guidance on the application of the Privacy Rule to research makes it clear that a covered entity that has disclosed PHI for research in reliance on an authorization is not required to retrieve information it disclosed prior to receiving the revocation, and may also continue to use and disclose PHI already obtained to the extent necessary to preserve the integrity of the study (e.g., as necessary to account for the subject's withdrawal). As noted above, FDA requires that the data gathered as part of research under their regulatory authority is necessary and must be retained; but even for those registries outside the scope of FDA oversight, HIPAA permits the continued use of data as necessary to protect the integrity of the research.

There is significant focus on coordination and harmonization of the HIPAA authorization requirements and human subjects research informed consent requirements.<sup>30</sup> While a HIPAA authorization may be combined with a research informed consent document (and elements already present in the research consent need not be repeated in the authorization), there are some situations in which an additional separate authorization may be necessary for a separate research activity or future research activity. The HIPAA Privacy Rule allows covered entities to condition the receipt of research-related treatment in a clinical trial on the individual signing an authorization for the use and disclosure of PHI for the trial, and also allows the use of a combined authorization/consent form in this context. However, the Privacy Rule does not currently permit a compound authorization in such circumstances that would also authorize the use or disclosure of the individual's PHI for a separate research activity that may not be conditioned on the individual receiving the research-related treatment, such as the use or disclosure of PHI to create or contribute to a separate research database or repository. Thus, a separate authorization would need to be obtained from the individual for the use or disclosure of PHI to the database or repository. Additionally, HHS has determined that HIPAA authorizations must be study-specific for purposes of complying with the Privacy Rule's requirement that an authorization must include a description of each purpose of the requested use or disclosure. Thus, for future uses or disclosures of PHI from a registry maintained by a covered entity, investigators must obtain a new authorization for a specific research purpose, obtain a waiver from the authorization requirements, or otherwise qualify for one of the limited exemptions to the

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<sup>30</sup> See, Institute of Medicine *Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research*. The National Academies Press; Washington, D.C.: 2009. See also, Mark Barnes & David Forster, SACHRP, Subcommittee on Harmonization (SOH) Update: July 20, 2011 (2011). Available at: <http://www.hhs.gov/ohrp/sachrp/mtgings/mtg07-11/soh.pdf>. Accessed September 29, 2011.

authorization requirement. The latter situation includes those uses or disclosures explicitly permitted by the Privacy Rule (e.g., of de-identified data, of limited data sets with a data use agreement, for public health activities, or for health care operations). HHS published a notice of proposed rulemaking on July 14, 2010, which proposed to both eliminate the prohibition on compound authorizations for conditioned and unconditioned research activities and allow authorizations to encompass certain future research, but these changes have not yet been codified.

### ***Special Consent Issues: Incapacitated Adults and Children***

In addition to the general requirements discussed above, there are also additional requirements for certain specific research populations. HHS has regulations that apply to pregnant women and fetuses, children, and prisoners. FDA has regulations that apply to children (which, for the most part, match the HHS regulations). Both also allow research to be conducted with adults lacking decisional capacity, although consent must be obtained by a “legally authorized representative,” who may be a guardian, proxy, or surrogate decision maker (the terms are defined by state law). Likewise, HIPAA also allows for authorizations from “personal representatives” (again, generally defined by state law).

Of particular interest to registries are the research regulations pertaining to children. Unlike research involving adults, research involving children must fit into one of four categories: minimal risk (404; 50.51), greater than minimal risk/prospect of direct therapeutic benefit (405; 50.52), minor increase over minimal risk/likely to yield generalizable knowledge about subject’s disorder or condition (406; 50.53), and research not otherwise approvable but authorized by the Secretary of HHS in consultation with an expert panel (407; 50.54). Most registry research is likely to fall into the minimal risk category. For these studies, permission must be obtained from at least one parent/guardian and assent obtained from the child, if capable of assenting. Waivers of both permission and assent are possible. Under HHS regulations, a waiver of parental permission is allowed under the same conditions that allow for a waiver of informed consent in adult populations (45 CFR 46.116); or when parental permission is not a reasonable requirement to protect the subjects (45 CFR 46.408(c)). FDA regulations do not allow for waivers of parental permission. Both HHS and FDA regulations allow a waiver of assent when a specific child, or all children, involved are not capable of providing assent; or when the research involves an intervention holding the potential for direct therapeutic benefit and is not available except through participation; or when parental permission is waived in accord with section 46.116.<sup>31</sup> (46.408(a); 50.55)

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<sup>31</sup> The FDA regulations do not allow waiver of consent by adults, but do allow a waiver of assent requirements if certain requirements are met (and those requirements are the same as the ones that HHS uses for waiving assent—and even waiving consent for adults). 21 CFR 50.55(d).

Both sets of regulations allow an IRB to determine that permission is only required from one parent, even when required from both under 406 or 407, in limited circumstances (408b). Where authorization must be obtained, the HIPAA Privacy Rule requires authorization from only one personal representative of the individual, such as one parent of a minor child, and does not require assent of the child.

OHRP has indicated that when the research in question involves a treatment for which the child would have legal authority to consent, the child's consent may suffice and parental permission may be unnecessary. The HIPAA Privacy Rule also generally provides that when a minor has legal authority to consent to a particular health care service without the involvement of a parent, the minor and not the parent has authority to act as the individual with respect to the PHI pertaining to that health care service. State statutes granting decision-making authority to minors vary. Many address issues such as treatment for sexually transmitted infections (STIs), access to contraception, and some even allow consent for mental health or substance abuse treatments. Registries involving these areas may be able to rely on the minor's consent, rather than the parental permission/assent framework. However, more specific legal guidance on the particulars of state statutory interpretation may be warranted in these situations.

Another important consideration is what to do when a minor who is involved in a registry reaches the age of majority. OHRP interprets the continuing consent standard to require that legal consent be sought from the participant upon reaching the age of majority. An authorization under the Privacy Rule, including one signed by a parent as the personal representative of a minor, remains valid until it expires or is revoked, even if such time extends beyond the child's age of majority. If the authorization expires on the date the minor reaches the age of majority, a covered entity would be required to obtain a new authorization signed by the individual in order to further use or disclose PHI covered by the expired authorization. Registries that involve children that will retain identifiable information past the child's age of majority will need to take steps to gain the appropriate consent and, if necessary, authorization for continued use. Less clear is whether investigators should seek a child's assent to continued participation when the initial consent was provided by parents at a time when the child lacked the capacity to play any role in decision-making.

## **A Proposed Framework for Registry Consents**

### ***Current Practices and Problems***

There are three current approaches to consent: opt-in, opt-out, and non-consent. An opt-in approach assumes that an individual will not be part of the registry until they have specifically consented to participation. An opt-out approach assumes that all individuals will be part of a registry, unless there is a

specific refusal to participate. Finally, a non-consent model does not seek or require individual consent or refusal, but includes all relevant individuals in a registry. The labeling of the approaches may vary in the literature, but the general concepts remain consistent. Additionally, some registries involve a mix of one or more approaches or a combined consent mechanism, where an opt-in approach is used for one aspect (access to a particular treatment) and non-consent for the other (listing in the treatment registry). This may also be referred to as “conditional access.”

### Opt-In

An opt-in procedure may involve a consent process similar to that used for clinical research protocols. It may be used separately for a registry, or it may be appended to a consent document used for a particular treatment (for example, individuals who consent to the use of a particular device may also be asked to participate in a registry for that device). While an opt-in approach has the benefit of assuring compliance with the Federal regulations, a number of the regulatory requirements are difficult to apply to registries (as discussed above). This has led many to suggest a modified opt-in approach—using elements of the clinical research framework but adjusting to fit the registry model. But, even with a modified model, there are concerns that the strict informed consent requirements of the clinical research consent will have negative effects on subject selection, resulting in biases that will undermine the validity and thus affect the usefulness of the registry. An analysis of the Canadian Stroke Network estimated that dealing with consent issues cost \$500,000 over the first 2-3 years of the registry, and the requirement to obtain written informed consent introduced significant selection biases undermining the usefulness of the registry.<sup>32</sup> Alternative consent approaches may need to be considered for large-scale observational studies.

### Opt-Out

An opt-out procedure shifts the presumption from one in which each individual must consent to participate, to one in which each individual must refuse to participate. There is a great deal of discussion about the usefulness of an opt-out model, particularly for registries (e.g., organ donation registries). To be a valid opt-out model, individuals must be fully informed about the existence of the registry and their rights to opt-out of participation. In many cases, the information requirements are the same as the information requirements for an opt-in procedure—the only difference is that instead of explicitly agreeing to participate, the person must take steps explicitly to refuse to participate. While the information requirements may not change, the psychological shift may be significant. If the expectation is that everyone will participate, people may be more inclined to acquiesce. There is evidence in other

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<sup>32</sup> Jack V. Tu et al., *Impracticability of Informed Consent in the Registry of the Canadian Stroke Network*, *New England Journal of Medicine* (2004) 350:1414-21.

areas of decision making that setting the default to participation results in greater inclusion than setting the default to non-participation, even when individuals are given an easy way to opt-in or opt-out.<sup>33</sup> While the Federal research regulations appear to assume an opt-in approach, in some circumstances an IRB could approve a modification that allowed a shift to an opt-out. In order for an IRB to approve an opt-out approach for non-exempt, HHS-supported human subjects research, they must document that the waiver of informed consent is appropriate for the research. An opt-out approach may be especially useful for registries. Nonetheless, Privacy Rule requirements will preclude this approach unless the situation fits within one of the delineated permissible uses without an individual authorization (e.g., with a waiver of authorization for research or for public health activities).

IRBs could consider the opt-out approach for research that meets the four criteria for a waiver or alteration of consent under the HHS guidelines: 1) the research involves no more than minimal risk to participants; 2) the waiver or alteration will not adversely affect the rights and welfare of participants; 3) the research could not practicably be carried out without the waiver or alteration; 4) participants will be provided with additional pertinent information after participation. For example, the Vermont Diabetes Information System (VDIS) is a quality improvement, registry-based decision support and reminder system targeted to primary care physicians and their patients with diabetes. With IRB approval, VDIS incorporated an opt-out consent process.<sup>34</sup> Patients are notified by mail of their eligibility and inclusion in the registry and given a mechanism to opt-out by calling a toll-free number.

### **Non-Consent**

Non-consent is not really a consent mechanism and thus will not be addressed here in detail.

Nonetheless, this approach may, and probably should, entail providing participants with information about the registry. The format and process of disclosure may vary. In some cases, general public notifications (perhaps listing on a website, or posting prominently in a place likely to be seen) will be sufficient. In other cases, individual notification may be appropriate. A non-consent approach is used currently for registries that fall outside the Federal research regulations such as state mandated public health reporting or quality improvement activities. One primary methodological advantage of the non-consent approach in no-risk and minimal risk studies is that it can function to reduce concerns about biases introduced by the consent process, such as those that occur when individuals who consent to participate in the registry systematically differ from those who do not or cannot consent. Besides debates

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<sup>33</sup> Richard Thaler and Cass Sunstein. *Nudge: Improving Decisions about Health, Wealth and Happiness*. Yale 2008.

<sup>34</sup> Littenberg, B. and MacLean, C. D. Passive Consent for Clinical Research in the Age of HIPAA. *Journal of General Internal Medicine*. 2006. 21: 207–211.

about when the use of a non-consent approach is acceptable (based on the level of permissible risk), most of the focus in this area should be on the type and extent of required notifications.

### ***Scope of Consent***

Consents may be broad or narrow. A so-called “blanket consent” approach asks for consent to a wide category of uses and assumes that consent will cover all uses, unless one is specifically excluded. Blanket consent should be distinguished from broad or general consent that does not necessarily imply “blanket” consent to all uses. In agreement with legislation, broad consent refers to use in biomedical research, not to other kinds of uses, such as for forensic use or for use by immigration authorities. A blanket consent model has historically been relatively common and still exists in some contexts. For example, patients entering a health institution or agreeing to a procedure sometimes have a notation at the bottom of the general consent form allowing the use of leftover tissue in any way deemed appropriate by the institution. Extremely broad blanket consents are not generally viewed as valid exercises of autonomy and thus may not truly be considered to be “informed consent.” At best, blanket consent may be viewed as a type of notification procedure, alerting individuals to the possible uses of their information. Neither the Federal human subjects research regulations nor the Privacy Rule permit extremely broad blanket consents. Some registries will have been created, with the use of a prior express legal permission from individuals, before the compliance date of the Privacy Rule, and additionally fall under an exemption to the human subjects research regulations; in these circumstances previously obtained broad blanket consent may be deemed sufficient.

The real issue related to the scope of consent is to what extent consent can and should authorize future unspecified uses. In other words, how broad a consent is permissible? The exercise of autonomy should include the ability to consent both to specific and to non-specific research participation. An individual who would like to give broad permission for the use of their data in any future registry (or for use in a particular registry, but include permission that the information may be shared with investigators for any future research query) is exercising a form of autonomy. As noted earlier, however, there are legal restrictions on the scope of these broad permissions. In addition, part of the issue is in determining whether a broad consent was truly informed. In the absence of specific details about the future uses, decision-making is necessarily less informed than if every future use is spelled out clearly. However, the ethical doctrine of informed consent does not require this level of detail. Moreover, requiring multiple consent dialogues may respect autonomy less than permitting broad consent if the individual does, in fact, wish to give broad permission and does not want continued re-contact. In some contexts, such as the donation of biological samples, broad consents are more acceptable (there is a long history of allowing

unrestricted tissue donations). It has become common to provide a menu of options in a consent form for biological or genetic databanking. These allow participants to specify any constraints they would like to place on the use of their samples, such as permitting use only for the specific study listed, or for all studies in a particular research area (e.g., heart disease), or for any future study in any area. Details regarding whether and under what circumstances the participant would like to be recontacted may also be collected. By contrast, in other areas such as consent to participate in a clinical trial, broad consents (e.g., “I give consent to participate in any clinical trial”) are insufficient on both ethical and regulatory grounds. For situations such as the use of medical information, the scope of a broad consent is less clear. The debates about the scope of consent are on-going. While investigators should be aware of regulatory constraints, there are likely some broad consents that contain all of the ethically relevant elements.

### ***Oversight and Community Consultation***

Consent is only one aspect of the protections in place for human research participants. The other part involves IRB review and oversight. Other chapters discuss the oversight roles for IRBs and registry governance boards. While the idea of community consultation usually appears in the context of discussions on human subjects research consent, there is no simple community analog to individual consent. Consent requirements for research arise from the principle of autonomy, and there is no corresponding principle at the community level. Thus, concepts such as “community consent” or “community authorization” can be incoherent, in part because there is no unitary concept of a community. Communities may be defined on social, biological, religious, racial, cultural, or geographic grounds. Most people belong to multiple, sometimes overlapping, communities. Some of these communities may have a designated spokesperson, but this individual may not represent the interests of all members of the community (consider, for example, the complex relationship between the Pope and Catholics in the United States). Other communities have no clearly identified spokesperson. It is inappropriate to consider community consultation as a replacement for individual consent. Rather than view community involvement as an aspect of consent, it should be considered as part of oversight (and an analog of IRB review).<sup>35</sup> Community involvement in the design and oversight of a registry may be particularly important when the registry involves socially identifiable groups that have been subject to historic discrimination or when it involves sensitive genetic information. In some cases, community involvement can enhance participant understanding for consent and, in turn, increase individual participation.

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<sup>35</sup> Marshall P, Berg J. Protecting Communities in Biomedical Research. 6(3) American Journal of Bioethics 28 (2006).

## Consent Guidance

Although general agreement has been reached about the required elements of informed consent for clinical research, this model may not be entirely applicable to informed consent for creation of and participation in registries. Risks to participants (and, when applicable, risks to groups and/or communities) should be balanced carefully with the public health benefits of registry development. The sensitive nature of information about participants and potential for broad data distribution highlight the importance of the informed consent process. Moving forward, informed consent elements and guidelines specific to registry research should be developed.

### *Special Considerations*

Given the nature of registry research, some elements of informed consent should be given special consideration, including: the scope of the use of registry data, potential for recontact, withdrawal, and information regarding the electronic data security and management to be employed.

### Scope of Use of Registry Data

Registries constitute a valuable resource since investigators often draw upon these to address questions extending far beyond those envisioned when the registries are first created. Therefore, informed consent for registry research that allows broad data sharing is optimal for promoting science. There may be instances, however, such as with respect to research on specific diseases (e.g., HIV/AIDS research), where more specific consent may be appropriate. Additional Federal level guidance on the appropriate scope of broad consent for future uses will be important. In the meantime, registry developers should not only provide clear parameters regarding the scope of use of registry data when first creating the registry, but should also develop a mechanism to consider how future, possibly unanticipated, requests for data access will be evaluated. The registry governance board can play an important role in this situation.

### Recontact

Individuals should be informed how their data/samples will be used at the point of entry into the registry. Whether and how participants will be recontacted should be established at the outset and included in the consent form. Exceptions should be considered specifically where data/samples were made irretrievably anonymous, since recontact would then be impossible. It is important to inform registry participants that the anonymization of their data will make withdrawal from the registry impossible.

### Withdrawal

Many issues governing withdrawing from a registry have been discussed in this paper. Consensus needs to be developed regarding whether withdrawal should be presented as an option to participants in the

initial consent, and, if it is an option, how withdrawal will be managed. While withdrawal from a traditional research study is a basic subject right, withdrawal of collected data, even from clinical trials, may be restricted. It is extremely important that registry creators develop initial rules and procedures for withdrawal and fully inform participants of these.

### **Electronic Data Security**

Given the public concerns about electronic data security, participants in the registry should be clearly informed as to the physical security of their data and/or biospecimens, including methods of coding and removal of identifiers, encryption techniques, potential for cloud computing, and quality assurance policies. As well, participants should be informed about the process of releasing and transferring data to future investigators as it relates to maintaining confidentiality. In some cases, this information will reassure participants, potentially increasing consent rates.

### ***Proposed Consent Form Elements***

The following is an outline of potential elements to consider when developing consent forms and engaging in consent dialogs for registry research. These elements were generated from the applicable HHS, FDA, and Privacy Rule requirements and include consent aspects particularly relevant to registry research. These are all issues that should be considered; there may be additional legal requirements (i.e., for a HIPAA authorization). The outline below should not be viewed as comprehensive or even applicable to all registries. Modifications will be appropriate for some registries, while others will follow a consent procedure similar to one used for traditional clinical trials. However, this outline provides a starting place for understanding the scope of informed consent for registry participation. It is important to note that the responsibility for obtaining and assuring appropriate informed consent rests on multiple parties, including sponsors, investigators, Protocol Review Committees (PRCs), and IRBs. Moreover, despite the multitude of elements listed below, every effort should be made to keep consent forms as short as possible and at approximately a 6<sup>th</sup> to 8<sup>th</sup> grade reading level.

1. A statement that the individual is being asked to take part in a registry (or a research study, if applicable)
  - a. The name of the specific registry for which consent is being obtained
  - b. An explanation of the purposes of the registry (why it was created, who will be included)
  - c. The expected duration of participation

- d. A description of the procedures entailed
    - e. The approximate number of subjects involved (if applicable)
  2. A description of any foreseeable risks or inconveniences (specifically risks related to any potential breach of confidentiality related to the data being collected);
    - a. When human genetic research is anticipated, information should include possible consequences of genetic testing (e.g., insurance risks, paternity determinations, potential risks to family and community) and other related confidentiality risks;
  3. A description of the types of research that the repository will support, and any benefits to the subject or to others which may reasonably be expected;
    - a. A statement about whether and how findings will be communicated to participants
  4. A statement describing the extent to which confidentiality of data/biospecimens identifying the subject will be maintained (including a description of the operations of the repository--how data/specimens will be stored and managed);
    - a. If applicable, a statement about whether registry result will be published
    - b. A statement about the impact of participation on the subject's access to his/her medical records (e.g., that access may be limited until all work on the Registry is completed).
  5. The conditions and requirements under which data and/or specimens will be shared with recipient investigators;
    - a. If applicable, a description that the data/specimens will be broadly shared and may be used for future research that is not yet identified;
    - b. The fact that the data/specimens may be transferred to other institutions and explanation of a data transfer security plan;
  6. A description of when recontact might be necessary, and how recontact will be handled.
  7. A statement of whether there are any costs to participation and/or any payment for participation

8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
  - a. The consequences of a subject's decision to withdraw from the research, including the possibility that the previously collected data will continue to be used, and procedures for orderly termination of participation by the subject.
9. Details on who to contact for answers to pertinent questions about the research and research subjects' rights.
10. As appropriate, any state-specific addendums