PATIENT REGISTRIES: PATIENT CONSENT WHEN CHILDREN BECOME ADULTS

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I. INTRODUCTION

Patient registries are now a widespread and valuable feature of the medical landscape. Registries are an enormously useful resource for information about the clinical course of diseases, treatment safety and efficacy, care quality, and comparative effectiveness of interventions. They collect data from both patients and their medical records, sometimes only at a single point in time, but often on a continuing basis. For many registries, data will be coded but individual identities will be preserved so that the coding could be reversed in appropriate circumstances for clinical care or for research. Registries serve to identify less frequent events and events that may only appear over time. They also may be used as a complement to or even replacement for the randomized clinical trial as a basis for studying drugs, devices, or other medical interventions. They are particularly useful in patient populations such as children who cannot give their own consent to inclusion in interventional clinical trials or pregnant women who are typically excluded from these studies.

Many registries involve diseases that manifest in infancy or early childhood, at a point before patients can be expected to give assent or consent. Children are included in such registries with parental permission. Permission may be given on the basis that the aim of the registry is to continue to learn about the condition and treatments for it or on a more open-ended basis, depending on the purpose of the registry. This permission includes data sharing on an ongoing basis, a process that is rendered increasingly seamless with electronic medical records. However, even when registries may continue to collect data from the records of identifiable patients, efforts may not be made to inform or to re-consent patients at the time they reach adulthood. Thus, patients may be unaware that data about them rest in and are used by — or even continue to be shared with — registries.

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Such proliferation of registries poses potential concerns. These include poor security practices, data-repurposing, data linkages that enrich information available about individuals and may enable re-identification of data without identifiers, and re-contacts that patients find distressing. Even when individuals are not directly affected, they may be indirectly affected by registry findings or uses. Patients with a particular disease may be greatly benefited by research from registries, even if they are not in the registries themselves. Or, patients may be stigmatized by registry findings if they are part of a group about whom inferences are drawn — reasonably or unreasonably — whether or not they are part of the registry. Thus, patients arguably have interests in knowing that they are included in registries, as well as what registries are doing with the information they hold.

This essay begins with a very brief overview of privacy laws and regulations applicable to registries. It then presents a sketch of some of the types and likely features of registries involving conditions manifest in infancy or early childhood. The account includes a description of the amount and kinds of data found in some registries, the uses made of the data, ongoing collection practices, policies about data sharing, and opportunities for data linkage. It is not a comprehensive survey, but an overview of some relevant registry features. The essay then continues with a description of a variety of adult notification or consent processes currently in use, either about data already collected or about ongoing data collection processes. The essay concludes by recommending transparency about registry practices for data collection and use and a requirement for re-consent when data are used in ways that do not fall within the original purpose of the registry. For registries that do not collect further information after children become adults but that continue to use or disclose data to other researchers, it recommends efforts to contact participants who have become adults and offer an opt-out possibility to the extent practicable, under clear standards for practicability. Registries that collect information on an ongoing basis should be required to re-consent patients after they have reached adulthood. As this is an exploratory essay, these recommendations are offered for further study, both about registry practices and about the ethical principles and regulations that should apply to them.

II. APPLICABLE LAWS AND REGULATIONS

Depending on their purpose, data contained, and location, registries may be subject to a complex mix of privacy and confidentiality laws and regulations. These rules are highly technical and not always consistent; this summary presents aspects of the rules that are most relevant to the problem of information concerning children. Most important are the federal rules regarding research with human subjects, the Health Insurance Portability and Accountability Act (HIPAA) privacy rule governing protected health

information, the Federal Trade Commission (FTC) Act, and state privacy and confidentiality laws. This section provides a very brief overview of the most relevant provisions of each. Although many registries are international in scope, this discussion is limited to United States law only.[1]

The federal rules governing research with human subjects apply formally to registries used for research concerning drugs or devices and research that is federally funded.[2] These rules are for the most part consolidated into the "Common Rule."[3] Importantly, some registries may not themselves involve the systematic collection of data for generalizable knowledge but instead function as umbrellas collecting patient information that researchers then may use for research; in such cases the individual studies are research, but the registries themselves are not and thus do not come under the Common Rule. Under the Common Rule, human subjects are only living individuals from whom information is collected directly or about whom identifiable information is collected.[4] In addition, research is exempt if data are collected from records identifying individuals in such a manner that subjects cannot be identified directly or through linking identifiers.[5] Individual informed consent is required for inclusion in human subjects research unless consent has been waived or altered by the relevant Institutional Review Board (IRB).[6] Consent may be waived if an IRB finds that the "research involves no more than minimal risk to the subjects," the "waiver . . . will not adversely affect the rights and welfare of the subjects," "the research could not practicably be carried out without the waiver or alteration," and if "appropriate the subjects will be provided with additional pertinent information after participation."[7] This provision is commonly interpreted by IRBs to permit waiver of informed consent for the creation of large limited data sets, for studies involving chart review of completed care, and increasingly for other studies involving existing information without any contact with the persons it concerns.[8]

1. For a proposal for international standards, see Edward S. Dove et al., *An Ethics Safe Harbor for International Genomics Research?* 5 GENOME MEDICINE 99 (2013).

2. *See* REGISTRIES FOR EVALUATING PATIENT OUTCOMES: A USER'S GUIDE 3, 167 (Richard E. Gliklich et al. eds., 2d ed. 2010) [hereinafter USER'S GUIDE].

3. 45 C.F.R. pt. 46 (2013). The scope of this section can be found at 45 C.F.R. § 46.101 (2013).

4. 45 C.F.R. § 46.102(f) (2013).

5. 45 C.F.R. § 46.101(b)(4) (2013).

6. 45 C.F.R. § 46.116(c) (2013).

7. 45 C.F.R. § 46.116(d) (2013).

8. *See* U.S. DEPT. HEALTH & HUMAN SERVS., SUBPART A SUBCOMM., SECRETARY'S ADVISORY COMM. ON HUMAN RESEARCH PROTECTIONS (SACHRP), RECOMMENDATIONS REGARDING THE PROVISIONS FOR WAIVER OR ALTERATION OF THE INFORMED CONSENT REQUIREMENTS UNDER DEPT.

For children involved in research funded by HHS, the Common Rule requires parental (or guardian) permission and, if appropriate, assent from the child.[9] For minimal risk research — which registries typically are — consent from one parent suffices;[10] thus, in circumstances in which parents are separated or do not communicate, one parent may be unaware that the other has entered a child into a registry. The regulations also require assent if the children's age, maturity, and psychological state so warrant; although this determination is left up to individual IRBs, it is unlikely that assent will be needed from children who have not yet entered elementary school.[11] In addition, the exemption for data collected from records in such a manner that subjects cannot be identified directly or through linking identifiers applies to research involving children.[12] The provisions for waiver or alteration of informed consent also apply to parental permission and child assent. The regulations are not explicit about whether there is need for consent at the point a child participating in a study becomes a legal adult in the jurisdiction in question. Guidance from the Office for Human Research Protection (OHRP), however, states that children becoming adults should be re-consented for any continuing interactions (including data collection) as well as for continuing data uses that would meet the criteria for human subjects research, unless a waiver is granted.[13] Some IRBs specifically follow this guidance in their own policies.[14] This is guidance, not formal regulation,

HEALTH & HUMAN SERVS. (HHS) REGULATIONS AT 45 CFR 46.116(D), *available at* www.hhs.gov/ohrp/archive/sachrp/mtgings/mtg07-07/present/WaiverConsentDocSAS.doc.

9. 45 C.F.R. § 46.404 (2013).

10. 45 C.F.R. § 46.408(b) (2013).

11. *See* 45 C.F.R. § 46.408(a) (2013) (stating that assent by children can be waived based on age and maturity level). As an example, the Penn State IRB cites an NIH panel in suggesting as guidelines a simple oral explanation and verbal assent from children age 6-7, a more complete oral explanation and documented verbal assent from children ages 8-12, and written assent thereafter, if the method is suitable to the child's level of development. *See* PENN. ST. UNIV., OFFICE OF RESEARCH PROTECTIONS, IRB GUIDELINE I, PARENTAL CONSENT AND CHILD ASSENT (2007), *available at* http://www.research.psu.edu/policies/research-protections/irb/irb-guideline-1. Other IRBs provide written consent form templates for different ages. *See*, *e.g.*, N.Y. UNIV. LANGONE MEDICAL CENTER, INSTITUTIONAL REVIEW BOARD, PROTOCOL / CONSENT / ASSENT / AUTHORIZATION TEMPLATES (2014) *available at* http://irb.med.nyu.edu/consent. Still others provide a single assent template. *See* UNIV. OF UTAH, INSTITUTIONAL REVIEW BOARD, HEALTH SCIENCES FORMS TEMPLATES (2014), *available at* http://irb.utah.edu/forms/health-sciences.php.

12. 45 C.F.R. § 46.401(b) (2013).

13. *Research with Children – FAQs*, U.S. DEPT. OF HEALTH & HUMAN SERVS, http://answers.hhs.gov/ohrp/categories/1570 (last visited Apr. 23, 2014).

14. *See* UNIV. TEXAS, OFFICE OF RESEARCH SUPPORT, SECTION 12: VULNERABLE POPULATIONS, *available at* http://www.utexas.edu/research/rsc/humansubjects/policies/section12.html#section_12_4 (last visited Apr. 25, 2014). *See also* UNIV. OF UTAH, INSTITUTIONAL REVIEW BOARD, INVESTIGATOR GUIDANCE SERIES: ASSENT, *available at* http://irb.utah.edu/_pdf/IGS%20-

however. Moreover, IRB willingness to grant waivers may vary and many registries are not within the formal scope of the federal regulations in any event.

HIPAA requires patient authorization for release of protected health information.[15] For purposes of this essay, protected health information can be understood to include individually identifiable health information, about living individuals or individuals who have died within the past 50 years, collected by a health care provider or payer.[16] De-identified data are not protected under HIPAA[17] and limited data sets may be released without authorization provided a data use agreement is in place.[18] With approval from an IRB or a Privacy Board, HIPAA permits authorization to be waived for protected health information to be used in research.[19] Criteria for a waiver include that the research is no more than minimal risk, that adequate protections of the information (including its destruction) are in place, that the research cannot practicably be conducted with if authorization is required, and that the research cannot practicably be conducted without the protected health information.[20] One argument that the research cannot practicably be carried out if authorization is required is selection bias.[21] HIPAA authorizations also are not required when protected health information is released to public health authorities as authorized by state law;[22] state cancer or immunization registries are examples. Once granted, HIPAA authorizations remain in effect until revoked in writing unless action has been taken in reliance on them such as the use of the data in already-conducted research.[23] Although authorizations must specify an expiration date or event, authorizations for research may be for the duration of the research.[24] An important difference between Common Rule consent and HIPAA authorization is that the former can be for quite general purposes whereas the latter requires more limited purpose specification; thus HIPAA authorizations may limit subsequent uses of registry information when the

%20Assent.pdf (last visited Apr. 25, 2014). Utah specifies that a protocol amendment is required if adult consent forms were not included in the original research submission. *Id.*

15. *Authorization Use & Disclosure*, U.S. DEPT. HEALTH & HUMAN SERVS., http://www.hhs.gov/hipaafaq/use/264.html (last updated Mar. 14, 2006).

16. The full definition of protected health information can be found at 45 C.F.R. § 160.103 (2013).

17. 45 C.F.R. §§ 164.502(d)(2), 164.514(a) (2013).

18. 45 C.F.R. § 164.514(e)(1) (2013).

19. 45 C.F.R. §§ 46.116(c)-(d) (2013).

20. 45 C.F.R. §§ 46.116(d)(1)-(4) (2013).

21. USER'S GUIDE, *supra* note 2, at 185.

22. 45 C.F.R. § 164.512(b)(2) (2013).

23. 45 C.F.R. § 164.508(b)(5)(1) (2013).

24. 45 C.F.R. § 164.508(c)(1)(v) (2013).

Common Rule does not.[25] The HIPAA privacy rule defers to state law on identification of personal representatives[26] and contains certain limits on disclosures of records of minors to their parents or guardians, but otherwise is silent on what happens to authorizations when children become adults. The HIPAA rules apply only so long as data are in the possession of a covered entity or its business associates; data collected by or transferred to registries outside the scope of HIPAA will not be HIPAA-protected even if it is individually identifiable, highly sensitive health information.[27] Some such data, such as data in a limited data set, may continue to be protected by data use agreements; these are contractual arrangements and little is known about how they are monitored or enforced. One technical possibility is to meta-tag each element of disclosed data so that each particular disclosure can be identified; this would permit data to be traced in the case of a breach.

The FTC Act prohibits unfair or deceptive trade practices by entities engaged in interstate commerce.[28] It is a deceptive trade practice to give people false information about data collection practices or uses, including privacy and confidentiality policies. Increasingly, the FTC is scrutinizing data security and privacy practices that might expose individuals to significant risks against which they cannot readily protect themselves as unfair trade practices.[29] Registries operating in the private sector are subject to these rules.

Finally, a variety of state laws are relevant to privacy and consent to participation in registries; HIPAA sets a minimum floor and permits state laws to set more stringent privacy standards. These include state privacy laws such as California's Online Privacy Protection Act that would apply to registries collecting information directly from patients residing in California.[30] In Maryland, HIPAA authorizations may last for a maximum of one year only.[31] In general, state statutes governing the power to consent to

25. USER'S GUIDE, *supra* note 2, at 182. This is a concern of the advance notice of proposed rulemaking concerning the Common Rule. *See* Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44,512, 44,523 (July 26, 2011) (to be codified at 45 C.F.R. pts. 46, 160, 164 and 25 C.F.R. pts. 50, 56).

26. 45 C.F.R. § 164.502(g) (2013). *See* Leslie P. Francis, *Skeletons in the Family Medical Closet: Access of Personal Representatives to Interoperable Medical Records*, 4 ST. LOUIS U. J. HEALTH L. & POL'Y 371, 380-81 (2011).

27. USER'S GUIDE, *supra* note 2, at 173.

28. 15 U.S.C. § 45(a)(1) (2012).

29. TRENDnet, Inc.; Analysis of Proposed Consent Order to Aid Public Comment, 78 Fed. Reg. 55,717, 55,718 (Sept. 11, 2013).

30. CAL. BUS. & PROF. CODE § 22575 (West Supp. 2014).

31. MD. CODE ANN., HEALTH-GEN. § 4-303(b)(4) (West 2013).

medical treatment also extend to the power to request medical records, and so these statutes would be relevant to information collected for registries when patients continue to be treated. These statutes authorize access to medical records, however, and do not also include provisions about whether an earlier authorization would need to be re-negotiated when a child reaches adulthood.

III. PATIENT REGISTRIES

Patient registries are a widely used source of information about the clinical course of diseases, treatment safety and efficacy, care quality, and comparative effectiveness of interventions. This section presents a snapshot of some of the most relevant features of the ever-growing number of registries currently in existence and involving children. In 2010, the Agency for Healthcare Research and Quality published the second edition of their best practices User's Guide for registries, a resource that contains a quite helpful discussion of models for registry design and implementation.[32]

A. Registry Purpose

Specification of a registry's purpose is a primary recommendation of the User's Guide.[33] Purpose specification is critical to defining the scope, duration, and data collection practices of a registry. Purpose specification is also a long-recognized fair information practice principle, requiring that data subjects be informed about the uses to which identifiable data will be put and that significant changes require consent.[34]

Registries have many stated purposes. Some registries are primarily umbrellas that can serve to identify potential participants for research studies but do not themselves conduct research. These registries then may approve particular research proposals and contact eligible registry participants to ask their permission to share contact information with the researchers. An example is the National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy, which contacts patients who are likely a candidate for approved studies about their interest before sharing

32. USER'S GUIDE, *supra* note 2, at iii.

33. USER'S GUIDE, *supra* note 2, at 23.

34. A seminal formulation of purpose specification reads: "There must be a way for an individual to prevent information about him obtained for one purpose from being used or made available for other purposes without his consent." U.S. DEPT. HEALTH, EDUC. & WELFARE, RECORDS COMPUTERS AND THE RIGHTS OF CITIZENS: REPORT OF THE SECRETARY'S ADVISORY COMM. ON AUTOMATED PERSONAL DATA SYSTEMS 41 (1973). For a useful history of Fair Information Practices see Robert Gellman, *Fair Information Practices: A Basic History*, BOBGELLMAN.COM (Nov. 11, 2013), www.bobgellman.com/rg-docs/rg-FIPShistory.pdf.

information with researchers.[35] Some registries, such as the Childhood Arthritis and Rheumatology Research Alliance juvenile rheumatoid arthritis registry, pool data from many individual researchers or clinicians to enrich the power of possible research.[36] Some registries will share data for approved research in de-identified form, as limited data sets, or under waivers of informed consent and HIPAA authorization. Some of these registries defray costs in part by charging approved researchers for use of registry data.[37] Some registries, such as the Cystic Fibrosis Foundation patient registry — now over 40 years old — are maintained by organizations devoted to particular diseases and may provide patient support, information about treatment and efficacy, and data for ongoing research.[38] Others may collect data only about a particular intervention at a given point in time, such as a registry for children and adults undergoing cardiac catheterization[39] or a registry for antiretroviral therapy during pregnancy.[40] Still others are aimed to improve public health, such as state immunization registries. Some are designed to improve the health of children generally, such as Rhode Island's KIDSNET which collects information on a wide range of characteristics of children's health.[41] Registries have also been constructed to detect adverse events from the use of a variety of drugs or devices, such as the use of antiretrovirals in HIV-positive pregnant women or the use of Celebrex in children.

35. *See Frequently Asked Questions*, UNIV. ROCHESTER MED. CTR., NAT'L REGISTRY FOR MYOTONIC DISTROPHY (DM) & FACIOSCAPULOHUMERAL DYSTROPHY (FSHD), www.urmc.rochester.edu/neurology/national-registry/about-us/faq.cfm (last updated Feb. 21, 2014).

36. Marc D. Natter et al., *The Childhood Arthritis & Rheumatology Research Alliance Network Registry: Demographics and Characteristics of the Initial 6-Month Cohort*, PEDIATRIC RHEUMATOLOGY, July 13, 2012, at A57. Some of these registries defray costs in part by charging approved researchers for use of registry data.

37. An example is the non-profit National Birth Defect Registry for Children. *See Research Data Project*, BIRTH DEFECT RES. FOR CHILD, INC., www.birthdefects.org/research/dataproject.php (last visited Apr. 8, 2014).

38. *See* CYSTIC FIBROSIS FOUND., 2012 PATIENT REGISTRY ANNUAL DATA REPORT 4-5 (2012), *available at* www.cff.org/UploadedFiles/research/ClinicalResearch/PatientRegistryReport/2012-CFF-Patient-Registry.pdf.

39. *See, e.g.*, *IMPACT Registry*, NAT'L CARDIOVASCULAR DATA REGISTRY, https://www.ncdr.com/webncdr/impact (last visited Apr. 8, 2014) (collecting data about children and adults with congenital heart disease undergoing diagnostic catheterizations).

40. *See Who We Are*, ANTIRETROVIRAL PREGNANCY REGISTRY, www.apregistry.com (last visited Apr. 8, 2014). The registry collects information about the child at birth; however, it is unclear from information available online whether information is collected about the child after the perinatal period. The Registry is located in North Carolina and can be contacted at 800-285-4263.

41. *KIDSNET*, R.I. DEPT. HEALTH, www.health.ri.gov/programs/kidnet/index.php (last visited Apr. 8, 2014).

B. Data Collection and Use

One important distinguishing feature is the extent to which a registry collects information that could be used to identify individuals. Privacy and confidentiality laws historically have addressed only information that could be used to identify individuals. Thus the Privacy Act of 1974 places disclosure limitations on "records" containing identifying particulars,[42] HIPAA applies only to "health information" relating to individuals,[43] and the Common Rule governing research considers human subjects only to include private information gained directly from or identifying living individuals.[44] Current controversy abounds over whether de-identification can ever be effectively protected, especially for types of information such as genetic information or when data sets are combined.[45] Commentators argue that even if data remain de-identified, information about groups may be problematic to individual group members.[46] It thus seems fair to say that the line between identifiable information and de-identified information is increasingly blurred.

Although some registries collect only de-identified information, registries are far more useful if they contain information about patient identifiers sufficient to allow record linkages, contact information about patients for follow up, and residence location for geographic comparisons.[47] Because specific diseases or interventions define many registries, risks of re-identification from registry data are thought to be higher than with other types of de-identified data.[48] Depending on the purpose of the registry, the User's Guide recommends collection of such information as sexual history, reproductive history, overseas travel and citizenship, and other sensitive social history information, thus posing risks if individually identifiable information is released.[49] Registries typically maintain such information in coded form, however, so that direct access to the registry will not reveal information about individual patients. When registries share information with others — for example, by giving researchers permission to use data in the

42. 5 U.S.C. §§ 522a(a)(4), 522(b) (2012).

43. 45 C.F.R. § 160.103 (2013)

44. 45 C.F.R. § 46.102(f) (2013).

45. Melissa Gymrekh et al., *Identifying Personal Genomes by Surname Inference*, 339 SCI. 321, 321 (2013); Jordan Robinson, *States' Hospital Data for Sale Puts Privacy in Jeopardy*, BLOOMBERG TECH. (June 4, 2013), http://www.bloomberg.com/news/2013-06-05/states-hospital-data-for-sale-puts-privacy-in-jeopardy.html.

46. Mark A. Rothstein, *Is Deidentification Sufficient to Protect Health Privacy in Research?*, 10 AM. J. BIOETHICS 3, 5 (2010).

47. USER'S GUIDE, *supra* note 2, at 108.

48. *Id.* at 147.

49. *Id.* at 111.

registry — they typically also only share de-identified or limited data sets[50] under agreements that the researchers will not attempt to re-identify individuals. Nonetheless, the increasingly blurred deidentification/ identification line means that privacy concerns about registry data in all of these forms cannot be ignored.

Data in registries may be collected from many sources: patients themselves, family members, electronic medical records, insurance claims, and pharmacy records, among other sources.[51] The increasing availability of information in electronic form makes information flow far more readily and seamlessly than when registry development depended on provider reporting from records maintained in paper form. The capability to submit data to immunization registries is a Meaningful Use Stage 1 menu objective,[52] and the capability to submit data to state cancer registries is a Stage 2 menu objective.[53] The result will be that registries will be able to gather impressive amounts of data from patient electronic health records, thus enabling these records to be used for purposes different from their original creation for patient care, and raising questions about the fair information practice principle of purpose specification if these data are compiled without patient consent.

Data in registries may be linked in two different ways that are critically different from a privacy perspective. Horizontal linkage aggregates data by characteristics — for example, an immunization and subsequent seizure.[54] Publication of aggregate statistics such as the percentage of children receiving particular immunizations and having subsequent seizures does not pose enhanced risks for identifying individuals. Vertical linkage, by contrast, links data to individuals — for example, a patient's medical record with physician prescribing information with administrative data about pharmacy claims that would show whether the patient filled a prescription. Vertical linkage presents far greater privacy concerns than horizontal linkage, as a

50. A "limited data set" is defined under HIPAA to mean a data set that includes no identifying information except date of service, town or city, state, and ZIP code. *See* 45 C.F.R. § 164.514(e)(2) (2013).

51. USER'S GUIDE, *supra* note 2, at tbl. 8.

52. *Eligible Professional Meaningful Use Menu Set Measures: Measure 9 and 10*, CTRS. MEDICARE & MEDICAID SERVS., http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/downloads/9_Immunization_Registries_Data_Submission.pdf (last updated April 2013).

53. *Stage 2 Overview Tipsheet*, CTRS. MEDICARE & MEDICAID SERVS., http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/Downloads/Stage2Overview_Tipsheet.pdf (last updated Aug. 2012).

54. Michael Gold et al., *Use of the Australian Childhood Immunisation Register for Vaccine Safety Data Linkage*, 28 VACCINE 4308, 4309 (2010).

vertically linked data-base will contain more information about each individual than the data bases independently.[55]

C. *Sponsorship*

Primary funding sources for registries are state public health agencies, academic medical centers and other treatment groups, non-profit organizations devoted to particular conditions, or commercial entities interested in drug or device development. Immunization registries, cancer registries, and a variety of registries concerning children's health are maintained by public health agencies. Pittsburgh Children's Hospital maintains a registry devoted to research on diabetes in children, for example.[56] The Cystic Fibrosis Foundation is one of many disease-based non-profits maintaining a registry aimed to improve treatment and conditions for patients with the disorder of interest.[57] The Children's Cardiomyopathy Foundation maintains a registry in cooperation with the National Heart, Lung, and Blood Institute.[58] Genzyme, a company with commercial interests in developing therapies for genetic diseases, sponsors registries for the lysosomal storage diseases Fabry,[59] Gaucher, [60] and Pompe.[61] Pfizer maintained a registry to study the long-term safety of treatment with its nonsteroidal anti-inflammatory Celebrex that included children ages 2-17; the registry was terminated after changes in treatment recommendations.[62]

55. USER'S GUIDE, *supra* note 2, at 147.

56. *Children's Hospital Diabetes Research Center Registry*, CHILD. HOSP. PITT., http://www.chp.edu/CHP/Diabetes+Research+Center+Registry+Study (last updated Mar. 7, 2014).

57. *See* CYSTIC FIBROSIS FOUND., PATIENT REGISTRY ANNUAL DATA REPORT (2012), *available at* www.cff.org/UploadedFiles/research/ClinicalResearch/PatientRegistryReport/2012-CFF-Patient-Registry.pdf.

58. *Patient Registry,* CHILD. CARDIOMYOPATHY FOUND., http://www.childrenscardiomyopathy.org/site/registry.php (last visited Apr. 15, 2014). One can contact the Foundation and its registry through Nicole Turcotte at 617-972-3045.

59. *Fabry Registry*, FABRY COMMUNITY, http://www.fabrycommunity.com/en/Healthcare/Registry.aspx (last visited Apr. 15, 2014).

60. *Understanding Gaucher Disease*, GAUCHER REGISTRY, https://www.registrynxt.com/Gaucher/Pages/Home.aspx (last visited Apr. 15, 2014).

61. *Treating and Researching Pompe Disease*, POMPE REGISTRY, https://www.registrynxt.com/Pompe/Pages/Home.aspx (last visited Apr. 15, 2014).

62. *Naturalistic Safety Registry Of Celecoxib (CELEBREX(R)) and NSAIDs in Juvenile Idiopathic Arthritis (SINCERE),* CLINICALTRIALS.GOV (May 6, 2014), http://clinicaltrials.gov/show/NCT00688545.

IV. PERMISSION AND CONSENT PRACTICES

Registries represent very different approaches to parental permission and implementation of assent or consent requirements as children age. Some registries simply cease to collect data after the age of legal adulthood, but may continue to allow use of previously collected data. Some registries require adult consent for continued participation. Other registries apparently allow parental permission to ongoing collection of data without re-consent when the child becomes an adult.

At one end of the spectrum are registries that require adult consent for continuing participation in the registry. An example is the registry of children diagnosed with cancer maintained by the Children's Cooperative Oncology Group.[63] This registry contains the records of 37,629 patients diagnosed with cancer as children; 96% of the patients were treated at cooperating institutions since full inception of the registry in 2007.[64] The registry follows children long-term and is an impressive resource for longitudinal outcome data. At the point patients in the registry reach 18, they are contacted for consent to continued participation in the registry; if they cannot be reached or if they decline continued participation, their data are no longer made available to researchers.[65] Another example of a registry reportedly requiring re-consent is the National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy; adults who refuse continued participation thus are not contacted by this umbrella registry to request their interest in participating in any further studies.[66] Some IRBs have explicit policies requiring re-consent to continuing participation in studies at the point of adulthood, unless a waiver is approved.[67] Others require re-consent (absent waiver) for ongoing data collection or other interventions but apparently not for research with data collected during minority.[68] A draft white paper for a proposed third edition of the User's Guide reports that the federal OHRP interprets the federal regulations to require re-consent at the point of adulthood for ongoing registry participation.[69]

63. *Childhood Cancer Research Network (CCRN) CCRN – Considering Registration*, CHILDREN'S ONCOLOGY GROUP, http://www.childrensoncologygroup.org/index.php/childhood-cancer-research-network-ccrn (last updated Aug. 21, 2013).

64. *Id*.

65. *Id*.

66. Yaffa R. Rubinstein et al., *Informed Consent Process for Patient Participation in Rare Disease Registries Linked to Biorepositories*, 33 CONTEMPORARY CLINICAL TRIALS 5, 7 (2012).

67. The University of Texas re-consent policy follows the ORHP guidance explicitly. *See* UNIV. OF TX., *supra* note 11.

68. UNIV. UTAH, INSTITUTIONAL REVIEW BOARD, INVESTIGATOR GUIDANCE SERIES: ASSENT, *available at* http://irb.utah.edu/_pdf/IGS%20-%20Assent.pdf (last visited Apr. 21, 2014).

69. U.S. DEPT. HEALTH & HUMAN SERVS., AGENCY FOR HEALTHCARE RESEARCH AND QUALITY, INFORMED CONSENT FOR PATIENT REGISTRIES: DRAFT WHITE PAPER FOR THIRD EDITION OF

At the other end of the spectrum are registries that continue data collection activity after the age of legal adulthood, operating under parental permission and authorization without any apparent requirement for re-consent. The Partners HealthCare registry for its Down syndrome patients would appear to be an example. The goal of the registry is to understand what conditions co-occur with Down, as patients with this condition are living far longer lives. Permission to participate in the registry lasts for the child's lifetime or until the parent chooses to withdraw the child or the child chooses to withdraw.[70] The consent form is explicit that data may be collected from past, present, and future medical records; will be identifiable; and may be shared with participating researchers.[71] There is no indication that patients will be re-contacted or re-consented at the time they reach adulthood, although the study is quite clear that data will continue to be collected as long as patient is treated at a participating institution. Another example of apparently open-ended permission is the type one neurofibromatosis registry at Washington University, which allows parents to authorize release of their children's medical information "until end of study."[72]

With the advent of biobanks linking tissue samples, genetic information, and patient records, research has attempted to ascertain patients' attitudes towards re-consent to participation at the point of adulthood. One study assessed patients' attitudes towards a hypothetical scenario involving the continued use of samples and data stored in pediatric biobanks.[73] The study finding was that two thirds would not be concerned about the use of their samples and data after they reached adulthood.[74] Almost half (46%) believed that their consent should be obtained; three quarters of these would be moderately or highly willing to give consent when asked.[75] Just over one-quarter would not be willing to have their data used without their

"REGISTRIES FOR EVALUATING PATIENT OUTCOMES: A USER'S GUIDE" (2011), *available at* http://www.effectivehealthcare.ahrq.gov/ehc/products/423/975/Informed-Consent-for-Patient-Registries_DraftReport.pdf.

70. PARTNERS HEALTH SYSTEM, PARENT TEMPLATE: DOWN SYNDROME PATIENT REGISTRY RESEARCH CONSENT FORM 2 (2010), *available at* http://www.massgeneral.org/children/assets/pdf/down-syndrome-registry-consent-form.pdf.

71. *Id*.

72. WASHINGTON UNIV. SCH. MED. IN ST. LOUIS, AUTHORIZATION RELEASE OF MEDICAL INFORMATION, *available at* https://nf1registry.wustl.edu/graphics/Authorization-for-Release-of-Medical-Information.pdf (last visited Apr. 1, 2014).

73. Aaron J. Goldenberg et al., *Pediatric Biobanks: Approaching Informed Consent for Continuing Research after Children Grow Up*, 155 J. PEDIATRICS 578, 578-83 (2009).

74. *Id*. at 579.

75. *Id*.

consent.[76] Interestingly, only 16% thought that de-identification of data made a difference as to their need for or willingness to give consent.[77] African-Americans were 2.7 times more likely to be concerned about the use of their data than white respondents.[78] As this study involved not only data but also biological samples, it may over-represent the likelihood of concern about the use of data collected during childhood. Another potential limitation of the study is that it involved a hypothetical scenario; it was not an assessment of the attitudes of patients whose samples had actually been included in biobanks. The authors of the study conclude that these findings may reflect the desire to participate in decision-making about research, rather than objection to the research itself.[79] Nonetheless, the fact that one-quarter of patients would not want their information used without their consent should give pause about continuing data use into adulthood. Other studies indicate that patients are more concerned about commercial uses of data than about public health or research uses.[80]

V. RECOMMENDATIONS

This section presents recommendations for further study and consideration about re-consent of patients in registries when they reach adulthood. It recommends transparency about registry practices for data collection and use and re-consent when data are used in ways that do not fall within the original purpose of the registry. For registries that do not collect further information after children become adults but that continue to use or disclose data to other researchers, it recommends efforts to contact participants who have become adults and offer an opt-out possibility to the extent practicable, under clear standards for practicability. Registries that collect information on an ongoing basis should be required to re-consent patients after they have reached adulthood.

The User's Guide emphasizes transparency as a means of fostering trust.[81] In some cases, it states that public disclosure of registry activities, such as when a section on a registry web page gives patients information about registry activities, may serve as an alternative to forms of consent.[82]

76. *Id*. at 580.

77. *Id*.

78. Goldenberg et al. *supra* note 73, at 581.

79. *Id*. at 579. *See also* REBECCA SKLOOT, THE IMMORTAL LIFE OF HENRIETTA LACKS (2010). Of note, the data for this study were collected in 2002-2003, while *The Immortal Life of Henrietta Lacks* was published in 2009.

80. Evette J. Ludman et al., *Glad You Asked: Participants' Opinions of Re-Consent for dbGaP Data Submission*, J. EMPIRICAL RES. HUM. RES. ETHICS, Sept. 2010, at 9, 14.

81. USER'S GUIDE, *supra* note 2, at 189.

82. *Id*. at 190.

For patients who are aware of the existence of a registry and the possibility that their information may be included in it, these websites may serve to alert them to possible data uses. In addition, it may provide them with information about disease discoveries, possibilities for participation in research, and patient support opportunities that might be of value to them. As an example, the University of Pittsburgh diabetes registry lists all active studies on its website.[83] Many disease-based registries such as the Cystic Fibrosis Foundation list a wide variety of information for patients and patient supports on their websites.[84] If use of data from individuals creates any obligations of reciprocity to those whose data are used — as arguably it does — then such transparency about potentially beneficial registry activities may be ethically required.

Registries that no longer collect information but that continue to allow data to be used should contact participants who have become adults and offer an opt-out possibility to the extent practicable, under clear standards for practicability, as recommended by the OHRP. This should include opting out for future uses of data, as well as for re-contact for consent to participate in future studies. Because registries may be highly valuable, arguably when participants cannot be contacted their data may continue to be used under circumstances in which IRBs grant waivers of consent. However, these waivers may be granted only if the research cannot practicably be conducted with consent or without the data and there should be clear standards for what practicability requires. "Practicably" is a technical legal term that means more than just costly or difficult. In contract law, obligations are voidable for impracticability, which requires changed circumstances that could not reasonably have been anticipated at the time the contract was made, that undermine a basic assumption of the parties, and that make performance unreasonably expensive or difficult.[85] Applied to registry participation, this would require subsequent changes in understanding that could not reasonably have been anticipated at the time of registry initiation, that alter needs for data collection and use, and that make re-consent or elimination of the data unreasonably expensive or difficult. An example might be important new research with registry data when sampling bias would be introduced by exclusion of participants who cannot be located for re-consent.

83. *Type 1 Diabetes Clinical Studies*, CHILD. HOSP. PITT., http://www.chp.edu/CHP/type+1+diabetes+clinical+trials (last visited Apr. 1, 2014). *See also Type 2 Diabetes Clinical Studies*, CHILD. HOSP. PITT., http://www.chp.edu/CHP/type+2+diabetes+clinical+trials (last visited Apr. 1, 2014).

84. *Patient Registry Report*, CYSTIC FIBROSIS FOUND., http://www.cff.org/livingwithcf/qualityimprovement/patientregistryreport (last visited Apr. 9, 2014).

85. RESTATEMENT (SECOND) OF CONTRACTS § 261 (1979).

Re-contact may be troubling for some registry participants. In addition to not knowing about their inclusion in the registry if their parents did not inform them, participants may not even know that they had the condition that identified them for registry entry. Or, they may regard this as a closed chapter in their lives that they wish never to remember. If re-contact is not conducted with great care, others may become aware of the registry participation or condition when the patient would not wish them to be so informed.

Finally, any continued data collection for registry use clearly requires re-consent on the part of competent adult participants in the registry. In order to continue to acquire medical information, the registry must perforce have contact information from the patient through his/her provider obtaining the information. To minimize distress, this re-consent should be the responsibility of the provider of the medical information.

VI. CONCLUSION

Registries are an enormously valuable resource for research, healthcare, quality measurement, comparative effectiveness measurement, public health, adverse event surveillance, and other purposes. Many registries concern conditions manifest in childhood and include participants who were entered without their knowledge on the basis of permission from their parents or guardians. Data in these registries may pose risks or concerns to participants and to the extent practicable they should be re-consented at adulthood for continuing registry participation. As registry participants are living longer and data sets are enriched, these risks may only increase. Further study of how registries work and how re-consent practices might be implemented is warranted.