

# Informed Consent Process for Patient Participation in Rare Disease Registries Linked to Biorepositories

## Summary:

As plans are moving ahead to establish the Global Rare Disease Patient Registry- Data Repository (GRDR),<sup>1,2</sup> contributing registries are in need of guidance on the informed consent process for patients whose information will be included in a registry. One of the GRDR goals is to aggregate de-identified<sup>3</sup> patient medical information linked to their biospecimens,<sup>4</sup> using voluntary patient identifiers, for research purposes. The aim of the GRDR is to provide a resource for research that will improve the quality of life of those with rare diseases, develop therapeutic interventions and, ultimately, find cures. Since biospecimens are essential resources for medical research and the understanding of the mechanism and the pathogenesis of different diseases and conditions, individual patient registries are strongly encouraged to create biorepositories, where registrants can voluntarily donate their biospecimens to be stored along with their registry medical information.

Contributing registries will need to inform their participants, as part of the informed consent process, that their de-identified information will be shared with the GRDR. One of the challenges in obtaining consent is ensuring that participants receive all the information and background material necessary to make a fully informed decision and understand what his/her signature means, including all the regulatory elements in the consent form, and yet writing a short document that is easily understood. In addition to a well-written consent form, much thought and attention need to be given to the consent process itself. The GRDR process may be helped by having a common template for an informed consent form and common consent processes that can be adopted by the rare disease registries that will be part of the GRDR.

An international workshop entitled, *Informed Consent Models/Templates for Rare Diseases Registries Linked to Biorepositories*, was held in Bethesda Maryland on December 13-14, 2010. The workshop discussed the informed consent process for participating in a patient registry that is linked to a biorepository. The workshop participants focused on developing recommendations

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<sup>1</sup> Creating a Global Rare Disease (Patient)t Registry Linked to a Rare Diseases Biorepository Database: Rare Disease-HUB (RD-HUB). Rubinstein et al. *Contemporary Clinical Trials*. 2010 Sep;31 (5):394-404

<sup>2</sup> The case for a global rare diseases registry. Forrest CB, Bartek RJ, Rubinstein Y, Groft SC. *Lancet* 2010 Aug. 2 193: 5-7

<sup>3</sup> De-identified data refer to coded data or information where all 18 elements that could be used to identify the individual have been removed but the link to the individual has been preserved. [http://privacyruleandresearch.nih.gov/pr\\_08.asp](http://privacyruleandresearch.nih.gov/pr_08.asp)

<sup>4</sup> Biospecimens is a collective term for tissues, body fluid or any sample taken from the body

on the informed consent process. Participants agreed that to obtain meaningful informed consent, additional information beyond what can be presented in the written consent form may be needed and useful. There was consensus among workshop participants that, in cases where the registry is linked to a biorepository, a separate consent form should be used to address issues specific to specimen donation.

## **Workshop proceedings:**

On December 13-14, 2010, the Office of Rare Diseases Research (ORDR) and the Office of Dietary Supplements (ODS) of the National Institutes of Health (NIH) held an international workshop entitled “Informed Consent Models/Templates for Rare Disease Registries Linked to Biorepositories.” Participants included experts in ethical and legal issues from the private sector, academia, patient advocacy groups, and the Federal government.

ORDR Director Dr. Stephen Groft explained that the workshop follows the January 2010 conference on the establishment of a Global Rare Disease Registry (GRDR). Dr. Groft described the GRDR as a data base for aggregating de-identified (coded) patient medical information from existing and newly established rare disease registries as a resource to accelerate medical research and the development of new treatments for rare diseases. Dr. Groft noted that registries, which are becoming essential to research, can help increase the number of clinical trials moving forward and facilitate researchers’ access to data and biospecimens. The GRDR will be able to link to biorepositories using a voluntary unique patient identifier. The GRDR can also serve as a resource for investigators to recruit patients for clinical research and to obtain specimens for basic research studies. Minimal Common Data Elements (CDEs) that can be used for any rare disease patient registry have been developed to harmonize captured data to be aggregated in the GRDR.

Following Dr. Groft’s remarks, Dr. Yaffa Rubinstein, ORDR, tasked the workshop participants with deliberating the issues and developing recommendations for an informed consent template for participation in patient registries, rather than for participation in specific clinical studies. Workshop participants were asked to consider: (1) what information should be provided to patients before consenting; (2) what elements should be included in an informed consent form; and (3) what existing template(s) or model(s) for short, simple, and clear informed consent forms, for patient participation in registries, should be evaluated for guidance in developing the appropriate informed consent. Dr. Rubinstein noted that the complex issues to be considered at this workshop were complicated by the many organizations and individuals with diverse approaches and concerns, including international patient registries and registries developed by academia, industry, the private-sector, and patient advocacy groups. Added to these complex issues are other concerns related to registering patients who are not affiliated with any advocacy group and patients with undiagnosed diseases.

Dr. Barbara Karp, Chair of the NIH Intramural Combined Neuroscience Institutional Review Board, chaired the first day of the workshop and explained that this day of the workshop will feature presentations and discussion.

**Dr. Richard Moxley, M.D.**, University of Rochester, gave the first keynote presentation on “*Opportunities and challenges of registries and biorepositories*”. The Scientific Core of the University of Rochester Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center (MDCRC), which receives NIH funding, includes the National Registry of Myotonic Dystrophy (DM) and Facioscapulohumeral Muscular Dystrophy (FSHD) Patients and Family Members and a separate tissue biorepository. The intent of this registry is to collect de-identified clinical information, assist in patient recruitment, and educate patients, family members, physicians and other researchers about these diseases and potentially improve standards of care. Dr. Moxley described enrollment in the registry, which includes an open consent process through which patients provide consent for the analysis and reporting of anonymous data in unknown future studies. He also detailed the restricted consent process for recruitment into clinical studies. Staff members identify potential patients who fit study criteria and send the study notifications and contact information to eligible members of the registry. The potential patients are sent descriptions about research studies from the investigators who have received approval to use the registry. Patients contact the investigators if they choose to participate or would like additional information. Consent is provided for each specific study directly by the investigators at the particular site(s) involved. The consent process for these specific studies is entirely separate from the consent to participate in the registry.

Because participating in the registry imparts minimal risk to subjects, its Institutional Review Board (IRB) does not require that consent be obtained in person. This process makes it less costly to enroll patients throughout the country and increases the likelihood of enrolling a diverse group of patients. The registry is able to provide consent forms online. There are some possible problems with obtaining consent remotely, however, including: (1) patient misunderstanding of participation risks and benefits; (2) receiving applications with missing, incomplete, incorrect, or expired application forms; (3) receiving materials from vulnerable populations who require special consideration; and (4) receiving information from ineligible patients.

The registry receives IRB review to avoid problems, including unintentional breaches of confidentiality. The Department of Health and Human Services (DHHS) provided a Certificate of Confidentiality that adds protection to the collection of personal and genetic information and helps the staff avoid involuntary disclosures of data as part of legal actions. The staff reviews the medical records and curates the data entered into the system.

Dr. Moxley identified a number of challenges associated with linking registries to biorepositories: (1) developing guidelines for counseling patients; (2) developing standardized methods for collecting, storing, and analyzing tissue biospecimens; (3) ensuring privacy and de-identification; (4) linking to clinically meaningful outcomes; and (5) developing and ensuring standardized clinical exams.

Following Dr. Moxley’s presentation, Dr. Clement McDonald of the National Library of Medicine (NLM) noted that some IRBs allow for obtaining consent electronically. Dr. Moxley explained that Web-based and other electronic means of entering consent information can be effective, but validation can be challenging. Dr. Julie Kaneshiro, DHHS Office for Human Research Protections (OHRP), noted that the regulations typically provide two options for allowing the use of electronic resources for informed consent. One provision permits the use of

an electronic signature on a consent form. In such cases, there is no waiver of documentation of consent and legally effective informed consent is obtained with documentation. Researchers have to defer to local law to determine whether electronically-signed consent is considered valid within their particular jurisdiction. The second option allows electronic submission or an on-line process to be used if the IRB of record has waived the requirement for written informed consent in accordance with regulations. Dr. Karp noted that determining whether written consent should be waived is an issue for further discussion.

Dr. Karp asked what information the registry provides back to patients whose diagnosis does not qualify them for inclusion. Dr. Moxley explained that the registry has a comprehensive diagnostic classification system, and in these cases, patients are told that the registry is currently unable to have them join as either an unaffected family member or a person with DM or FSHD. These patients are informed that the registry would reconsider, if their medical information changes, helping clarify their diagnosis. Often in these situations, patients are encouraged to undergo a neuromuscular evaluation.

In response to a question, Dr. Moxley indicated that the National Registry includes children and re-consents them when they become adults. Dr. JeanHee Moon of the Children's Hospital of Philadelphia asked about providing follow-up information to registry patients regarding initiatives that are ongoing or that have been completed. Dr. Moxley explained that members are provided an annual update that contains information on all projects that have been pursued through use of the registry's resources, as well as a list of publications related to these studies. He encouraged workshop participants to suggest ideas on how to partner effectively with registry patients to provide them additional information and emphasized the need for registries to develop stronger communities and build trust with patients.

The second keynote speaker, **Dr. Clement McDonald, M.D.**, Director, Lister Hill National Center for Biomedical Communications, National Library of Medicine gave a presentation on *“Challenges concerning public access to de-identified patients with rare diseases”*. Dr. McDonald explained that the term “de-identification” is defined in the Health Insurance Portability and Accountability Act (HIPAA) regulations. For protected health information to be considered “de-identified,” 18 specific identifiers must be removed, including information that identifies the patient or relatives, employers, or household members of the patient. The regulation also forbids “any other information that could be used alone or in combination with other information to identify the individual.” The HIPAA Privacy Rule specifically prohibits month and day for all dates directly related to an individual, and permits years only for individuals 89 or younger. De-identification is not the same as anonymization.<sup>5</sup> HIPAA regulations accept that de-identification is close to anonymization (breaking the link between the patient and his information) but not the same. In general, the goal of de-identification is to avoid situations in which private information would be provided to a third party about a specific patient beyond what they already know.

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<sup>5</sup> De-identified data refer to coded data or information where the link to the individual has been preserved, versus anonymized where the link between the data and the individual has been broken.

Different types of problems arise with de-identifying different types of data. Structured data [information stored in a structured database with fixed columns and fixed (non-free-text)] is easier to de-identify than narrative data, such as data found in dictated discharge summaries and operative notes, because the structured database fields known to contain HIPAA identifiers can be removed. Dr. McDonald cautioned that the data should always be checked to ensure that free text was not inadvertently inserted into a field meant to be numerically valued. Tools do exist for de-identifying narrative reports, including open source software and at least one commercial package. These tools attempt to remove names, dates, and other identifiers, but this removal process is more difficult than the de-identification of a fully-structured database and often requires review and operation by a human being. Very rare diseases present extra challenges to de-identification. The mere fact that an individual has a particular very rare disease, even after known identifying information has been removed, may enable others to identify the patient, particularly when biomedical repository data is combined with repository demographic information such as the state where a patient lives, which is permitted in de-identified data, or the first 3 digits of the zip code, which are sometimes permitted.

Dr. McDonald described biobank registry databases that presume a linkage between DNA (and possibly other biological material) and other information in the database. Biospecimens were not regarded as personal health information in the original HIPAA regulations (as long as the biospecimens were not associated with any identifiers). However, policymakers are currently reconsidering this issue. Dr. McDonald suggested that rare disease registries de-identify all information, and only provide public access to very limited and well considered subsets and statistical summaries of the database. “Limited use data” are data sets that allow for dates and some location information beyond what is in a HIPAA de-identified data set. With appropriate IRB review, researchers who sign a specified use agreement can use limited data sets for research purposes. Deceased patients represent a special category and historically there were no usage restrictions on data from deceased persons. With the last round of HIPAA regulations, however, some restrictions were placed on the use of data from deceased individuals.

Dr. McDonald indicated that consent forms will likely be required under almost any circumstance to make reasonable scientific use of a biobank. He suggested that registries have a stratified consent document that includes stepwise approvals for research, with specification of whether the consent includes one or more of the following: (1) permission to contact; (2) permission to access all of the data but not to contact; (3) permission to access de-identified data; and (4) permission to access the biospecimen and/or biospecimen data.<sup>6</sup>

Dr. Maurizio Scarpa of the University of Padova in Italy emphasized the importance of de-identification of biospecimens and data. In his experience, it is not easy to de-identify data from patients who have very rare diseases. Some registries he works with contain a great deal of data in narrative form, and as noted by Dr. McDonald, aggregating these comments and de-identifying them is challenging. He suggested keeping a code to re-identify patients to simplify work when using the data. Dr. McDonald commented that with very rare diseases that have such small numbers of patients, the risk of being identified is greater, such that consent is probably the

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<sup>6</sup> Additional information on how can covered entities use and disclose protected health information for research and comply with the privacy rule is available online at: [http://privacyruleandresearch.nih.gov/pr\\_08.asp](http://privacyruleandresearch.nih.gov/pr_08.asp).

only option. Having a patient care relationship between the researcher and the patient can be helpful.

Dr. Karp asked if the participants were in agreement on the use of the terms “de-identified” and “anonymized.” These definitions have traditionally been problematic for researchers and IRBs. There was general agreement among participants that the term “de-identified” means there is a code to link back to the identifying information. Dr. McDonald cautioned that the term “de-identified” is built into regulation and existing laws. Dr. Karp noted the importance of informing patients of exactly what data will be released about them and whether any link back to the data will be retained. Dr. Domenica Taruscio of the National Centre for Rare Diseases in Italy said that it would be helpful if workshop participants could reach consensus on the definitions of these terms to clarify matters moving forward. Very often, these terms are misused by researchers. Dr. McDonald reminded participants that this subject has been addressed by many experts outside of this workshop and that it may be more effective to define the issues and then take the information to those who specify these distinctions.

Next Dr. **Dominca Taruscio, M.D.**, the National Centre for Rare Diseases in Italy, gave a presentation on EPIRARE: the “*Development of Rare Diseases Epidemiological Data From Patient Registries (EPIRARE)*.” She explained that EPIRARE is a 30-month project funded by the European Union (EU) Commission starting in the spring of 2011. EPIRARE is intended to build consensus and synergies for the EU platform of rare disease patient registries. The National Centre for Rare Diseases at the Italian National Institute of Health will coordinate the project. This organization presented the EU Commission with an application to establish the EPIRARE project for a number of reasons. In Europe, as is the United States, there is great interest in rare diseases among the research community, and many registries—mainly promoted by academicians—exist. The EU Council Recommendation on Rare Diseases (adopted by member states in June 2009) recommends the implementation of registries and databases for epidemiological purposes. Regulations on personal data protection present several challenges for data collection and exchange in Europe.

EPIRARE will operate under the principle that the development of guiding reports, including the legal and organizational framework for the registration of rare disease patients, is strategic to building up an evidence base for community, public health policies, health service management, clinical research, and the assessment of orphan drugs’ effectiveness and appropriateness of use. Through an agreement between the central state and regions, regional registries send a common agreed-upon data set to the National Registry every 6 months. Each data set includes: (1) patient identification code; (2) live-death date; (3) diagnosis of rare disease; (4) region/hospital that made the diagnosis; (5) diagnosis date; and (6) orphan drug used. This model has been proposed as the framework for the EPIRARE project. Dr. Taruscio concluded her remarks by emphasizing the need for European and American research collaboration to develop common ground, share data elements, and coordinate rare disease initiatives.

Dr. Frederick Kaskel, Children’s Hospital at Montefiore in New York City, asked whether the national registry in Italy has opportunities for investigators to determine where biospecimens are stored or can be stored for use in collaborative studies. Dr. Taruscio indicated that in Italy, aggregate data are available at the regional level, and that there are opportunities for

collaborative efforts. Dr. Groft was interested in how differences in language and dialects across Europe will be reconciled into a uniform lexicon. Dr. Taruscio acknowledged the language challenge. EPIRARE partners communicate in English, the official language of the scientific community. For many of the European projects, reports and other documents are translated into English or into the language of each EU member state.

Gretchen Navidi of the National Institute of Mental Health asked about the use of unique patient identifiers and whether patients could be tracked, regardless of the institution that collected the data, and whether there was a need to follow the patients longitudinally. Dr. Taruscio explained that in Italy, the data are encrypted and there is no way to link back to identifiable information. For data collection at the European level, however, additional possibilities are being explored. Dr. McDonald noted that there is a hash mechanism being used in France that allows certain identifiers to be used to develop the code. This approach might make future research efforts easier. Ms. Navidi noted that the National Database for Autism Research uses a global unique identifier (GUID). The GUID is generated from identifying data that are fed into a software package. The identifier is encrypted into a one-way hash code so that it cannot be re-identified. The GUID offers the advantage that the same code will be generated from the same set of identifiers, so that data can be identified as coming from a single unique individual, regardless of the location at which data were collected.

Following Dr. Taruscio's presentation, Dr. Barbara Karp and Dr. Richard Moxley co-chaired a panel on informed consent for patient participation in a registry. The session began with a discussion of the definition of human subjects research and the circumstances requiring informed consent. Informed consent would not be needed if the formation and operation of a registry do not involve "human subjects" research. In light of that, the Common Rule (Title 45 CFR 46, Subpart A)<sup>7</sup> definition of the term "research" was discussed. The regulatory definition of research is "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities." It was noted that registries which collect data in addition to simply registering people appear to meet the definition of research under the US federal regulation. Therefore, informed consent would be required unless it could be waived by an IRB under the regulations.

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<sup>7</sup> Code of Federal Regulations Title 45 <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

Next, workshop participants discussed consent-related issues, such as required and supplemental elements of informed consent; the process (approaches and methods) of informed consent; ongoing consent; right of withdrawal, special populations (e.g., minors, adults without consent capacity, others); documentation of informed consent, and future communication especially for clinical trial recruitment. The definitions of the different types of patient registries were provided in a handout to the participants and were discussed.

Patient registries are organized programs for collection, storage, retrieval, and dissemination of a clearly defined set of data collected on identifiable individuals for a specified purpose. Registries can be characterized by the types of uses and information collected and their purpose. The two types most frequently utilized are contact registries and clinical registries. Contact registries are used for administrative purposes. Contact registries may include listings of other specific contact registries, such as registries for investigator use, for biorepositories, and so forth. A contact registry can be a way of identifying potential candidates for clinical trials. The data on the patients are entered and curated to be used as a source of information to recruit participants from the membership for clinical studies or other studies. Clinical registries collect information included in contact registries along with detailed medical information, including family history. The data are entered by health care providers or patients, or the data may be obtained and entered from the electronic health record on behalf of patients. Data entered by other than the health care providers are curated for accuracy and validation.

Following the panel discussion, **Frederick J. Kaskel, M.D., Ph.D.**, Children's Hospital at Montefiore, gave a presentation on ***“Emphasizing the potential for discovery of new information while ensuring trust in the informed consent process”***. Dr. Kaskel first addressed the problem of broken trust between researchers and patient groups. He gave several examples such as the Tuskegee experiments on African-American males, the Willowbrook hepatitis studies, and the Havasupai Indian Tribe case.

With regard to informed consent related to biospecimens, Dr. Kaskel noted that questions remain regarding what constitutes adequate informed consent for biospecimens that are collected for specific research, as well as specimens stored and used later for unrelated studies. Case law states that biospecimen donors do not retain property interests in biospecimens collected and used in accordance with properly obtained informed consent. In addition, research on previously collected identifiable biospecimens may be permitted if the IRB waives informed consent, for example when: (1) there is minimal risk to participants; (2) patients' rights or welfare are not adversely affected by the waiver; (3) the research could not practicably be carried out if new informed consent were required; and, (4) the research provides a mechanism for giving participants additional pertinent information when appropriate. The OHRP states that informed consent for the use of identifiable biospecimens should include a clear description of the specific types of research to be conducted. Dr. Kaskel commented that what constitutes adequate informed consent for research on stored biospecimens has both ethical and legal ramifications.

Approaches to obtaining informed consent for research on stored biospecimens include:

- Specific consent: Research participants are re-contacted and asked to consent for each new use of their biospecimen or for information that is outside the scope of their original consent.
- Tiered consent: At the time biospecimens are collected, research participants are presented with a “tier” or menu of options for use of biospecimens from which to choose. Choices often include unrestricted permission for future use, consent only for future uses related to the original study topic, consent for future uses unrelated to the original study topic, or a requirement that the investigators must obtain specific consent for any future use that differs from that in the original study.
- Unrestricted permission: At the time biospecimens are collected, research participants are asked to permit any and all future uses that a qualified ethical review board or biorepository board determines to be scientifically meritorious and ethically defensible.
- Presumed consent (also known as passive consent): At the time biospecimens are collected, research participants are informed that their biospecimens will be used in future research unless they expressly deny permission.

Dr. Kaskel identified issues to consider when selecting an informed consent approach.

- Does unrestricted permission for future research constitute meaningful informed consent? With genomic data, there is the potential for a breach of confidentiality that, since an individual may be identifiable from his/her genetic profile, may not be entirely avoided by either irreversibly removing identifiers or labeling biospecimens with code numbers and storing links to identifying information separately.
- Does removing donors’ identifying information from biospecimens eliminate the ethical dilemma related to the potential for identification? The rationale is that the analysis of biospecimens may not involve risk at present, but that the risk may change as future projects utilize new technologies. This information should be captured in the consent form and emphasized when communicating with patients.

Dr. Kaskel reminded participants that people have a right to control the use of their bodily tissues. The donation of biospecimens for research represents a contract in which the participant agrees to donate biospecimens and the researcher agrees to abide by the conditions set forth in the consent process regarding their collection and use. Many consider allowing donors to grant unrestricted permission for future use as ethically acceptable, but others are concerned that the use of even anonymized biospecimens for purposes beyond the agreed use would not be ethical unless new informed consent is obtained. He described his institution’s “best practice” for informed consent, noting that the first step is to determine what the research participants want. Surveys and previous research have shown that the majority of the public finds unrestricted permission acceptable; however, there are individuals who desire specific consents for new uses, especially if genomic information is obtained. Dr. Kaskel noted also that participants should be told that the biorepository will allow research aimed at curing a certain disease or improving human health, although this may not be sufficient to ensure trust.

Dr. Kaskel believes that the tiered consent offers the best consent method for respecting patients’ choices and assuring permission for research use of biospecimens. He provided examples of language that can be used in tiered informed consent documents, adapted from the National

Cancer Institute's informed consent template for cancer treatment.<sup>8</sup> In discussing informed consent as it relates to community engagement, Dr. Kaskel emphasized the need for researchers to ensure that the patients' perspectives are addressed and respected. He suggested that the community and advocacy groups be consulted first to identify potential areas of concern, and that flexible partnerships be developed with the community, the patients, their families, and other involved parties as appropriate. Information obtained from research on the biospecimens should be provided to the community in language that allows the community to understand and appreciate the value obtained from their contribution. Researchers also need to maintain ongoing communication and transparency of goals.

Dr. Kaskel used the example of the PedsHome study to highlight a number of issues related to informed consent. He mentioned that in working with the community stakeholders, researchers developed a comprehensive informed consent form that incorporates the points emphasized earlier in the presentation and noted that the informed consent for the genetic testing can be most challenging to develop, especially when new genes might be identified after the study had begun. Because of the comprehensive informed consent process and consent form, study subjects do not need to be re-consented as these genetic studies progress.

The following statements, taken from the genetic testing component of the informed consent form that PedsHome has developed, may serve as sample language:

- Genetic means having to do with information that is passed on in families from parents to offspring through genes.
- Researchers and doctors know some of the genes that cause disease, but they do not know all of them. Your participation in this study may help identify genes that are related to high blood pressure in adolescents, which in turn, may help in the diagnosis and treatment of high blood pressure.
- Tests conducted under this research study may reveal genetic information.
- You may wish to obtain professional genetic counseling prior to signing the informed consent. A genetic counselor is a person qualified to provide information about what the results of this type of test may mean to you and your family. You or your insurance company will be responsible for the cost of genetic counseling services.
- Because the significance of these tests is not known, we will not disclose the results of the genetic testing.

The biobanking component of the the PedsHome informed consent document includes the following information for patients:

- In addition to the research you are consenting to under this research study, researchers at this or other institutions may wish to study the biospecimens in future research, including genetic analysis. These biospecimens, taken from your body, would not be linked back to you. No one will know your name or protected health information.

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<sup>8</sup> National Institute of health, Informed Consent Template for Cancer Treatment Trials, <http://www.cancer.gov/clinicaltrials/education/simplification-of-informed-consent-docs/page3>

- At this time, the researcher does not know what the future studies will be. Your biospecimens may also be submitted to a tissue/cell/DNA bank. The biospecimens may be kept for a long time and may exceed 50 years.
- In some research using human blood or tissue, the biospecimens and their parts may enable researchers to develop medical tests or treatments that have commercial value. You will not receive any money that may result from any such commercial tests or treatments. Your biospecimens may be used for future research, even though the purpose of the future research is not known at this time.

Dr. Kaskel noted that to date, all PedsHome Study participants have given consent for their biospecimens to be used in future research studies.

In a response to a question about Dr. Kaskel's presentation, Dr. Sara Hull of the National Human Genome Research Institute noted that tiered consent involves a complicated set of options and tradeoffs. If the purpose of the registry is to maximize research opportunities, the tiered consent approach can work against these efforts, if patients choose more restrictive options. There is a tradeoff between maximizing the research potential and enrolling exactly the right patients in the registry. Some raised concerns that parts of the population may not be well informed, and use of the term "research" in the consent form may dissuade potential participants from enrolling in a registry. Dr. Hull noted, however, that care must be taken not to mislead enrollees, so it is questionable whether or not the term "research" can be avoided in consent forms.

Dr. Moxley asked about what can be done to educate communities, some of which may use English as a second language or may for another reason be unaffiliated with the health care system, with regard to the informed consent process. Dr. Hull noted that there is an increasing emphasis on community-based participatory research to determine and understand the requirements for different types of populations and reminded workshop participants that there is no one single rare disease community. Consent should be part of an ongoing conversation rather than a one-time signature on a document; consent should be treated as a continuing process. Having the right to withdraw is important; patients retain the right to change their minds at any time.

Dr. Rubinstein asked how researchers can engage with patients to ensure that they understand the consent form and know what they are signing. Dr. Miriam Kelty of the National Institute on Aging commented that this is an important issue and relies on effective, ongoing communication with the patient. Dr. Kaskel noted that his team of researchers, and many others in the pediatric research field have approached the family with the material, explained what the study was about, and gave the family adequate time to digest the information before presenting the consent form.

Dr. Devin Oglesbee of the Mayo Clinic noted that his group has included an assessment at the end of some consent forms as a tool to identify areas in the consent that are particularly important for the participant to understand but may not have been fully grasped. This assessment, a series of questions about key points of the study and participant rights, is used in person as well as online, via telephone, and through the mail. He also noted that advocacy groups are crucial to recruitment into registries. Ms. Liz Donohue of the Sanford Children's

Health Research Center emphasized the importance of training for the research team and the research coordinator or other individuals who have face-to-face contact with patients. Ms. Camp echoed Dr. Kaskel's earlier comments about the importance of trust between the research community and the public. She noted that in Texas earlier this year, the state destroyed 4 million residual dry blood spot samples collected from neonates at the time of birth because some families felt that they were not appropriately informed about the collection and future use of their biospecimens. Trust can help minimize future loss of such valuable research material.

Following Dr. Kaskel's presentation and ensuing questions and answers, workshop participants resumed their discussion on informed consent for patient participation in a rare disease registry and the elements of a consent document. Dr. Karp identified several process-related issues for consideration: (1) ensuring that patients fully understand the consent process and the information included in the consent document; (2) developing and providing background information related to the consent form; (3) establishing how consent is to be obtained (e.g., written, oral, or electronic), where it is to be stored, and who provides oversight; and (4) developing a list of frequently asked questions. Also discussed were the elements to include in assent forms for both minors and capacity-impaired patients (i.e., adults who, because of cognitive limitations, cannot legally provide their own consent). Consent forms and procedures are additionally needed for individuals with disabilities, such as those who are blind, non-verbal, illiterate, or deaf. Assent forms generally are geared towards the age range of the minor population to be included, which may require multiple assent forms (e.g., one for 7-12 year olds, another for 12 years and older). It was agreed that adult consent forms should be written at an eighth grade reading level. The development of an assent form may be difficult, as there are no regulatory requirements for what should be included in an assent form. There was consensus that minors should be re-consented once they reach adulthood.

Dr. Karp summarized the following required elements of informed consent as in Title 45 CFR 46 and how they might be applied to consent forms for a patient registry:

- *Purpose Statement*—the purpose statement should inform patients that the information collected will be used to identify potential research subjects and that the registry also has a research component, as the registry will likely use collected information as research data to help understand disease. Although separate consent will be needed for secondary research, patients should be told that another purpose of the registry is to refer them to secondary studies. Defining who owns or sponsors the data also should be included. Workshop participants decided that it was unnecessary to include in the purpose statement language indicating that the registry would not be used to guide or develop treatment, although clinical trials may be developed using the registry. Such a statement could appear elsewhere in the informed consent document.
- *Voluntary Basis*—the informed consent form should explicitly state that patients are participating in the registry on a voluntary basis, that there will be no penalty in choosing not to participate, and that they will not be denied any rights or benefits to which they are otherwise entitled.

*Reasonably Anticipated Benefits*—the document should include a statement on reasonably anticipated benefits. Patients should be made aware of the fact that there likely will be no direct personal benefits associated with their participation in the registry. Secondary benefits, which some workshop participants suggested could be mentioned in advance of the “no direct benefits” statement to reflect a more positive overall message, should be included. A phrase such as “joining the registry may give you the opportunity to participate in research studies” could be included.

- *Foreseeable Risks*—Foreseeable risks that patients should be informed of include the potential loss of confidentiality caused by misuse of data, misconduct, hacking and so forth, loss of autonomy if they will not be able to direct specific future use of their data or biospecimens, and the chance of information about a family member possibly being divulged. Steps the registry is taking to protect data should be provided; e.g., storing data on a secure server, providing registrants with a registration number, de-identifying and/or coding data, and controlling access to the data.

*Right of Withdrawal*— Patients should be informed that they can withdraw from participating in the registry at any time after they register and make no further submissions. Attendees discussed whether participants should be offered the ability to have previously submitted data removed. Consensus was reached that information already in the database should not be destroyed once it is collected. Workshop participants discussed what would happen to the data if the patient withdraws. Current registries use various approaches ranging from removing or destroying data to stopping all ongoing and future use of the data to permitting any data previously collected to continue to be used in both ongoing and future research. Regardless of how the registry plans to address this issue, the consent form should inform participants of what will be done with their data if they withdraw. The consent form should also indicate if the registry is intended to exist indefinitely. Patients should be informed of what will happen to their records should the registry cease to exist.

- *Procedures*—The procedures listed in the informed consent document should clarify what will occur once a patient enrolls. For example, procedures may include: (1) steps for data entry; (2) submission of medical records; (3) allowances for participation by a patient surrogate (when applicable); (4) provision of updates to patients; (5) methods of future contact from staff; (6) access to data by researchers; (7) the use and sharing of the data for research; and (8) information on or options for future uses. The procedures should be in language that is as clear and as informative as possible to help patient understanding. The consent should be written as generally as possible, to avoid having to obtain reconsent for minor changes in the registry in the future.
- *Contact for Questions*—Each registry and consent form should identify a contact for questions, both during the consent process and later during participation. For patients who have an advocacy group, the group’s registry coordinator could serve as a preliminary contact for consent or registry-related questions. For the GRDR, an individual will be needed to manage questions or inquiries from patients who have a disorder that does not have an advocacy group or who would prefer not to proceed

through an advocacy group. Therefore, two contacts may need to be listed on the consent form (an advocacy group contact as applicable, and a GRDR contact).

Workshop participants also discussed a number of optional elements for informed consent as applicable, including:

- A statement indicating that participation in the registry does not pose a risk to pregnant women or fetuses.
- Circumstances under which a subject or the subject's data may be removed from the registry without consent (e.g., for submitting false information or an incorrect diagnosis). Language for this optional element should not be accusatory in any way.
- Information on cost to participants, there is usually no cost for participation. However, there may be some costs associated with obtaining and submitting copies of medical records. Participants should be informed of the possible expense and if the registry will reimburse the cost.
- Informing subjects of significant new findings emerging from research using the registry regarding their particular disease.
- A quiz or comprehensive assessment indicating an understanding of consent may be included at the end of the consent form.

Workshop participants also discussed whether a single consent form could be used for participation in a registry which includes a biorepository, or whether a separate consent form to address the biorepository would be needed. Dr. Karp suggested that if two consents are needed, consistent language is needed to make clear that patients' data in the registry and their biospecimens will be linked. There may be cases in which a patient is willing to contribute data to a registry or provide a biospecimen, but not both.

The last keynote for the workshop was given by **Dr. Steven Hirschfield, M.D., Ph.D.**, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH entitled: "***An Integrated Approach to Data and Biospecimen Sharing for Vulnerable Populations: The National Children's Study as a Case Study.***" Dr. Hirschfield discussed a new paradigm for considering the relationship of the public and the research enterprise in an integrated systems approach being used as part of the study. Study researchers plan to collect not only biospecimens but also environmental specimens on and around children. During his presentation, Dr. Hirschfield touched on key points such as harmonization, standardization, respect shown to the participants as well as respect for their data and biospecimens, developing trust among stakeholders, and the informed consent process. These are all relevant issues for registries linked to biorepositories

The above study will follow pregnant women (and a subset of women prior to pregnancy), their fetuses, and children born into the study. It is expected that these children will be followed through 21 years of age. The plan is to collect not only biospecimens but also environmental specimens (e.g., house dust, soil samples, air particles, water samples, etc.) from different places in and around children.

Dr. Hirschfield presented a flowchart depicting the interplay between the health care delivery system and research. Summarizing the flowchart, he explained that there is a framework in which an education process occurs and is followed by a permission process—informed consent—and then a data acquisition process followed by a transitional return to the health care delivery system (almost immediately for the person, and hopefully, eventually for the data). Dr. Hirschfield mentioned that part of the informed consent process, which was also touched earlier during the workshop, should include a description of what happens to patients. For example: (1) once they volunteer to enroll in a registry or research project; (2) once that project or registry comes to an end; and (3) if they decide to withdraw from the registry or research project. Then, Dr. Hirschfield posed a number of questions: Should research results be returned to patients if requested? Is there any opportunity for returning the data or biospecimens after the study has concluded? And how does a patient return to the system after he or she has withdrawn? He explained that once data/specimens are donated by an individual, they are stored at an individual level and then pooled for a study as aggregated data and biospecimens. To leverage aggregated data, he indicated that data and biospecimens should be collected in a standardized way to produce meaningful outcomes. The analyses then inform new levels of research and the development of practice, guidelines, and policy.

This new paradigm views data as an extension of the individual volunteers, meriting the same protection and respect, and views privacy and security as complementary aspects of protecting the individual. This new paradigm also acknowledges that this research process will be optimally functional when there is adoption of interoperable standards and processes. This approach divides the research experience into the permission phase, data acquisition phase, and transition phase with a particular focus on the transition phase, both in terms of the transition of the individual and of the data (and how these data move through a larger system). The planning, protections, and oversight need to extend to these transitions as well as to the mechanisms for enrolling a patient in the study. This approach will only be practical if there is regulatory agreement and harmonization.

Next, Dr. Hirschfield explained that the term “harmonization” can be defined as the capacity to integrate processes and operations and to leverage infrastructure and data acquisition investments. Harmonization necessitates consideration that there is a much larger universe than just the research project in which the data and the biospecimens will initially be included. He discussed the advantages of using data standards, harmonization, and partnerships, and then focused on the National Children’s Study engagement process.

Dr. Hirschfield echoed Dr. Kaskel and others, emphasizing the need to develop trust between the participants, their families, the community and the investigators. For that purpose, the National Children’s Study has developed a multi-stage education process. The study utilizes a general informed consent process that emphasizes flexibility (subjects can enter or leave the study at will, and can opt in or opt out of any given question, assessment, or biospecimen donation). Subjects are provided with assurances that access to the data is only through a formal data access process controlled by a committee that acts as their surrogate protectors. The Children’s National Study uses a visit information sheet when assessments are conducted. This sheet provides information on what will happen at each visit and asks subjects if there are any study-related activities in which they do not want to participate.

Dr. Hirschfield concluded saying that an integrated systems approach provides the quality, sustainability, and affordability required for pediatric research to continue and develop. The major operational components should be harmonized, and standards that are thoughtfully designed and implemented should be used whenever possible. The interface between ethical, technical, and process issues must be addressed, and the process considered from a comprehensive and integrated view.

In a response to a question regarding when assent is obtained from children, Dr. Hirschfield said that the current thinking is that when children are ready to read, it may be the appropriate time to broach the assent question. The age of consent will depend on the patient's jurisdiction. Dr. Rubinstein commented on the importance of informing the patients and that it seems easier to obtain permission in the setting of a health care provider's office. She asked Dr. Hirschfield about how patients are educated and how permission is obtained when this process does not take place face-to-face. Dr. Hirschfield commented that there are several approaches to educating and obtaining permission. The National Children's Study utilizes three tactics: (1) the "knock on the door" approach that involves face-to-face meetings, (2) referrals from clinics and physicians' offices, and (3) direct-to-public approaches using the media and public events. In general, the consent process is carried out in person through a staged approach.

When asked about collaborating with international partners and whether consideration has been given to harmonization of the consent process and the quality of that process, Dr. Hirschfield explained that the research team has been engaged in informal conversations with national cohorts in Japan, Germany, the United Kingdom, Germany, Norway, and other countries. The team participates in the International Childhood Cancer Cohort Collaboration and engages in formal, structured data sharing (largely retrospective analyses). Through the WHO<sup>9</sup>-sponsored International Pediatric Regulators Network and other activities, discussions have begun on at least having common elements in the consent forms. Following these comments, Dr. Rubinstein thanked everyone and adjourned the first day.

### **Day two of the workshop:**

The second day of the workshop began with the third keynote presentation given by Dr. Jerry **Menikoff, M.D., J.D.**, Office for Human Research Protections. Dr. Menikoff spoke on "*Adequately informed open-ended consent*", noting that his comments were from his personal perspective, not from an official viewpoint. He explained that a person can say "yes" to a vague statement, for example; "I will let the researchers use the materials in the biorepository for approved studies." No details are provided in a given consent form about what such research might involve. He asked: Is it ethical to not provide any information about what the research might involve? Is the consent in this instance informed consent? Clearly, the person consented to something, but did the person really understand what he or she was agreeing to? Dr. Menikoff noted that there may be special concerns regarding whether broad, open-ended consent is adequately informed and he used examples from clinical care and research to emphasize this point.

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<sup>9</sup> WHO-World Health Organization

Dr. Menikoff described a case involving an 18 year old patient whose father wanted her to undergo a hysterectomy to increase her chances of survival without her knowing the details. He commented that this is a good example of a scenario in which a person appears to be consenting to something without knowing all the details. Should the doctors agree to this? Would the consented patient be informed? Saying “yes” to something open ended can be uninformed if the person does not fully appreciate what it includes.

He noted that there are similarities between this case and the issues related to the use of tissue or other biospecimens in research. What might someone consenting to open-ended use of their biospecimens not know about—and that they might object to if they did know about it? Cloning and GWAS or whole-genome sequencing are additional examples in which these issues come into play. Dr. Menikoff emphasized that open-ended consent does not mean that researchers can do whatever they want with the data. Creating a cell line is another example of a procedure that people might not understand might be done when they give unrestricted consent.

When a consent form that is many pages long contains one sentence about what will be done with the biospecimen, can one be sure that patients who say “yes” understand what they have agreed to? Dr. Menikoff suggested that empirical research could help clarify this. For example, one could ask participants presented with open-ended consent language whether they knew what they were consenting to and whether they had any concerns.

Dr. Menikoff ended his talk by noting that there are a variety of ways to address these issues, including: (1) recognizing that certain types of research are not covered by open-ended consent; (2) conducting targeted discussion on these issues so that subjects know specifically what they are permitting; and (3) offering the opportunity to “opt in” to specific types of research. He added that, in particular, consent related to research that might lead to the development of cell lines should include information on what this means.

During the question and answer period, Dr. Hirschfield reported that at a recent meeting, the head of the United Kingdom Biobank, when asked if there were any restrictions on the use of tissues donated to the biobank from approximately 504,000 individuals and whether there were any restrictions on creating cell lines from these tissues, said there were no restrictions on the use of the tissues and that cell lines could be created. The possible scenarios that appear to be surfacing are that: (1) people do not know what the possible future uses of their biospecimens may be and should be educated; (2) if they are educated, it may be that their education is based on a newspaper article that presented one point of view rather than the full spectrum of options; or (3) there is an intermediary group that ascertains responsible use of the data and patients agree to have an independent party serve as their surrogate.

Dr. Menikoff indicated that one option may be to grandfather existing biospecimens and provide more complete information to patients moving forward. Although there are different levels of understanding and different ideas about what can be done with biospecimens, the research community is not prevented from informing patients about biospecimen use, either on the consent form or on a list of frequently asked questions. Many of these issues boil down to the extent to which individuals trust the entities involved in the research and consent process.

Because there are many unknowns about public attitudes toward these issues, creating a system the public will trust is a work in progress.

Dr. Hull noted that increasingly, researchers are interested in creating induced pluripotent stem cell lines, which can be done using stored somatic adult cells. This raises questions about whether re-consent is needed to create these types of cell lines. Dr. Hull's group is obtaining re-consent for these types of issues and erring on the side of over-informing patients. They also are conducting some empirical research to gauge patient's attitudes towards this type of research. She also noted that the consent process can play an educational role in helping patients to understand these issues.

Dr. Rubinstein commented that in general, the more patients are informed, the more they are willing to participate. It is possible that by not providing detailed information on potential future research, a part of the population that would be willing to participate is not agreeing to do so. Dr. Oglesbee added that patients with rare diseases have added motivation to participate in research and are more likely to agree to open-ended research possibilities. They are also typically more trusting of the organization or researcher seeking to obtain consent.

Following Dr. Menikoff's presentation and discussion, Ms. Julie Kaneshiro and Dr. Nicole Lockhart, National Cancer Institute, NIH, led a panel on informed consent for patient donation of biospecimens. Ms. Kaneshiro opened the session by describing similarities and differences between biorepositories and registries as they relate to informed consent. The issues of purpose, procedure, and duration, which were discussed during the previous day regarding registries, also apply to consent for biorepositories. One of the goals of the GRDR is to ensure patient consent for the linkage of patient clinical data (medical information) with patient biospecimens. With regard to biorepositories, it is likely that a clinician is involved in the collection of the biospecimen for research purposes. In some cases, the clinician treating the patient is also an investigator collecting biospecimens for research. At the time consent is given, it is often difficult to anticipate for which research projects biospecimens may be used. There is a tension between the need for specificity in the informed consent document and the need for flexibility with regard to future use. In other words, consent specificity may lead to the need for re-consent if the scope of the research changes. Cultural concerns overlay these issues as well. Different issues may be sensitive to different populations. Also, there are some in the rare disease community who would welcome open-ended consent, while others would not. The fact that there are researchers engaged in obtaining empirical evidence on these topics is encouraging, but there are many unknowns. It appears that many in the rare disease community may not be particularly concerned about specificity in consent because of their desire to accelerate research on rare diseases.

Ms. Kaneshiro noted that the issues regarding biorepositories are more complex than those regarding registries. Unlike data, biospecimens are a finite resource—there is only so much of a biospecimen that can be given to researchers, leading to the question of whether patients should be given the opportunity to limit the use of their biospecimens to only specific projects or types of research. Allowing patients to specify the types of research for which their biospecimens can be used adds to the complexity of the consent document. Ideally, the consent process should be designed to limit the need to obtain additional consent for future research.

Specifying the patient opt-out/withdrawal process for collaborative projects should also be included in the consent. Both registries and biorepositories allow for the right to withdraw consent and for patients to stop submitting data or providing biospecimens. Challenging issues arise when considering whether the data in the registry or the biospecimens in a biorepository should be destroyed following withdrawal of consent and whether already-collected data/biospecimens may be used in current and future research projects.

In terms of risks and benefits, Ms. Kaneshiro explained that in some cases there may be physical risk associated with the process of collecting a biospecimen. Although research with biospecimens may be more likely than research with registry data to generate personally meaningful results, patients should not participate with the expectation of direct personal benefit. Patients providing biospecimens may be more likely to expect to be provided with the results of research, either in aggregate or in individual form. If results are to be provided to subjects, the timing and format of the return of results are important considerations. Ms. Kaneshiro also noted that a wide range of biospecimens could be collected by a biorepository (cheek swabs, blood samples, tissue samples, etc.) and that patients should be informed about the collection process associated with these various biospecimens.

Dr. Kaskel reminded participants that workshop attendees had agreed that the oversight of the registry should be included in the purpose statement of the consent form. The same holds true for biorepository consent forms. Dr. Lockhart commented that, as is the case with registries, those rare disease patients who do not have representative patient advocacy groups with biorepositories and want to donate a biospecimen must be considered. It was noted that patient advocacy groups are not as involved in patient donations of biospecimens as they are with patient participation in registries.

Ms. Kaneshiro commented that the biorepository consent document should contain explicit information regarding any costs to participants, similar to the consent document for participation in a registry. If it is anticipated that the biospecimen will be linked to a registry, this should be made clear to the patient, as well as information about who will have access to the links.

Dr. Lockhart added that moving forward, the ORDR should strongly consider how best to link with existing biorepositories. Dr. Rubinstein agreed and emphasized that building collaborations and linkages with existing biorepositories/registries is especially important in the rare disease field. If biospecimens are shared through collaborative projects, the biorepository consent form should clearly identify who controls the biospecimens and what would happen to the biospecimens if the biorepository ceases to exist.

Dr. Lockhart reminded the group that the elements recommended for inclusion in a biorepository consent form would need to be customized based on the individual policies of the biorepository. She also noted that collecting biospecimens from minors and then obtaining consent at the age of majority is a topic of great debate. Specific research using biospecimens obtained from assented minors may need to provide a plan to retain the biospecimens until the child reaches the age of majority. Currently biorepositories associated with different patient advocacy groups develop their own policies, thus making a specific recommendation difficult. Nevertheless, certain issues

must be addressed, such as: (1) Will consent be required at the age of majority and, if so, how will it be handled? and (2) How will patients be tracked?

Dr. Hull asked if a biospecimen obtained from a child is being stored and has not been sought by investigators, does the biorepository have to obtain consent just for the continued storage? Dr. Taruscio noted that in Italy, consent for continued storage is required. Dr. Gipson explained that consent in this scenario depends on how the provisions in the original IRB-approved protocol and consent form, under which the samples were obtained or donated, are written. Consent for continued storage of biospecimens may not be needed if the original biospecimens were collected with permission from the parents or consenting adult—with or without assent depending on the age of the child—and the consent form indicated that biospecimens would be collected and stored for future use, unless the participant or parent/guardian requested removal. Dr. Scarpa noted that it is not uncommon for a child with a rare disease to die before reaching the age of consent. Dr. Gipson commented that many parents want their deceased child's biospecimens to be used in research rather than stored, not used, or destroyed. Another participant said, however, that some parents want closure after the death of a child, and it can be traumatizing to be contacted about using biospecimens after a child is deceased. Dr. Lockhart noted that discussing expectations with parents or consenting adults, and planning ahead with IRBs prior to biospecimen collection, can help resolve or prevent some of these issues.

Dr. Rubinstein highlighted the importance of specifying what is meant by the term “biospecimen” in the biorepository consent document. There was general agreement that biospecimens are biological samples from a person and that images (e.g., x-rays, MRIs, retinal scans, dental records) are a type of data. Removing identifiers is as important with biospecimens as with data. One must also be careful that identifiers are not in some way embedded in or associated with the data, for example, when pictures of faces are included. Access to images that identify individuals (e.g. full facial images) should be based on scientific need and carefully controlled.

Dr. Lockhart commented that an area that needs to be addressed is whether biorepository participants can complete a web-based consent form if they are collecting their own biospecimens. Regardless of whether consent is obtained in person or electronically, the biorepository will have to make staff available to answer questions and serve as a resource.

Additional discussion points included:

- Cultural concerns overlay consent issues and differ according to the culture. These sensitivities need to be taken into account when designing biorepositories.
- An important issue that has not been resolved is when and how research results of clinical importance to the individual participant should be provided to the patient.
- Oversight is required and leaders in the field from institutions, agencies, and advocacy groups should be represented in an open and transparent process. Such participation could help speed the process
- Policies and regulations regarding biospecimen collection at the international level need to be considered.
- The definition of the term “biospecimen” should be included in consent materials.

- Early IRB involvement in the development of biorepository policies and procedures should be encouraged.
- A glossary or definition of terms for the public may be helpful. Similarly, some type of educational effort will be required, such as developing a brochure or Web site with information on informed consent.

During the working lunch session **Dr. Maurizio Scarpa, M.D., Ph.D.**, University of Padova, Italy presented “**Informed Consent for Children and Teenagers Turning Adults in Rare Disease Registries: A Clinical Point of View**” He described the 2006 Biannual International Symposium on Mucopolysaccharide and Related Diseases that was held in Venice, Italy. There are more than 50 lysosomal storage diseases that result from a functional defect in a lysosomal hydrolytic enzyme or membrane transport enzyme. Roughly half of lysosomal storage disease patients have an associated neuropathy that is progressive. To treat the neurological disease, therapies must cross the blood-brain barrier. Dr. Scarpa described a group of scientists and clinicians, referred to as “Brains for Brain,” who work with biotechnology companies to stimulate and collaborate on research focused on pediatric neurodegenerative disorders, in particular lysosomal storage diseases.

Dr. Scarpa described efforts to build registries of patients who have lysosomal storage diseases. He also described three governance issues associated with registries, including: (1) the need for independence from industry; (2) informed consent; and (3) preventing multiple registries duplicating efforts.

He explained that outcome surveys are used to try to improve patient care and patient outcomes in rare diseases. The objectives of these surveys are to understand the long-term effectiveness and safety of treatments, enhance understanding of the natural history of rare diseases, and provide high-quality data and analysis to support clinical decision making. Dr. Scarpa noted that informed consent is not a single event or a simple form to be signed. Rather, it involves an educational process that occurs between the investigator or other resource person and the prospective patient. The basic elements of the consent process include full disclosure of the nature of the research and the patient’s participation, adequate comprehension on the part of the prospective patient, and the patient’s voluntary decision to participate. Documentation of legally effective informed consent generally involves the use of a written consent form that is signed by the subject or the subject’s legal representative. The consent form, he continued, is a documentation of informed consent and does not in and of itself constitute informed consent. Furthermore, the fact that a subject signed a consent form does not mean that he or she understood what was being agreed to or truly gave voluntary consent. Dr. Scarpa described elements of the informed consent documents used in lysosomal storage disorder registries, many of which have been discussed during the workshop.

Dr. Scarpa added that the consent issues discussed at this workshop are particularly important for vulnerable populations. There are federal regulations in place that give specific protections to pregnant women and fetuses, as well as children participating in human subjects research. IRBs expect investigators to provide additional information regarding cognitively impaired individuals and others likely to be vulnerable to coercion or undue influence. A large proportion of the data in the lysosomal storage disorder registries are related to children, and he explained that adequate

provisions are made to secure permission from the parents or guardians of each child. For minimal risk research or research with direct benefit, the IRB may allow permission from one parent; for higher risk research without direct benefit, permission from both parents is required. Dr. Scarpa listed topics covered in a teenage information and consent form. He also described general progression of consent activities. Children should be informed about the trial commensurate with the child's understanding. Teenagers (13-18 years) should be informed about the trial to the extent compatible with the child's understanding and, if capable, should sign and date the written informed assent form. Once majority age (18 years) is reached, the adult consent form should be signed.

In conclusion, Dr. Scarpa reminded participants that rare diseases are good models for discussing ethical issues that the development of new therapies for rare diseases requires data collection and analysis, and that patients must understand why data collection is needed before participating in research activities. Informed consent must be handled by professionals who are able to answer any question. Additionally, informed consent must include all information regarding the registry, a plan for assent from minor patients.

In response to a question about data ownership in his institute, Dr. Scarpa explained that prior to publication, data are available only to specific working groups of physician experts and boards that are examining the data for correctness. The physicians own the data for their respective patients, and the only data in the registries are those entered by the physicians, who can access data on their own patients.

Dr. Rubinstein asked about how different terminology is handled when data are collected from different hospitals, particularly when the diseases have different forms and different severities. Dr. Scarpa explained that his group has written papers defining certain diseases (e.g., MPS 1) with common terms for classification. He did acknowledge that ensuring consistent use of terminology across registries and among investigators from different countries is a difficult challenge.

### **Workshop summary:**

Dr. Karp reminded participants that informed consent and the elements that should be included in the informed consent form and the process of informed consent were the focus of the workshop. She indicated that it is likely that two consent forms will be needed, one for registry participation and one for biospecimen use, which will include some common elements and some different ones. Dr. Karp mentioned that in some cases, during analysis of a biospecimen, an investigator may come across an interesting and important observation that may create an opportunity to participate in a clinical trial or that may affect the patient's health. In these cases, there may be a need to link back to identifiers so that the patient could be contacted. That link might best be through the treating physician.

Given the limited availability of biospecimens, biorepositories may want to limit the types of research that would be permitted utilizing the biospecimens. For both biorepositories and registries, there is a need to address what control patients maintain over their data and/or biospecimens once they are submitted, and the consent should explicitly indicate those rights.

For instance, will patients be able to direct their use, limit their use, withdraw their use, and for biospecimens specifically, will they be able to withdraw the specimen and have it returned? The opportunity to opt in/opt out should exist for both registries and biorepositories.

Biorepositories should not continue to distribute biospecimens once a subject has withdrawn consent; however, once a biospecimen has been analyzed, the data should not be removed from previous data sets. For patient registries, one unresolved issue is whether a registry can continue to distribute data that was collected prior to withdrawal of consent. Consent information should include information on where the control and responsibility for the collected data and biospecimens resides and for how long a registry or biorepository is expected to exist, for example, if it is likely to be indefinite. How to address the consent process for minors also remains unclear, given the variation in laws across the country and in other countries. The issue of whether consent will be obtained once patients reach adulthood is also an issue of differing opinion.

For a biorepository, consent background language should address how and under what circumstances the biospecimen will be obtained as well as who is paying for the collection. The biorepository and registry consent documents should discuss the sharing of an individual's information and data between them; i.e, data obtained from analysis of a biospecimen from the biorepository will be transferred and included in the registry data for that individual. Additional procedures include careful planning and information for participants on how the biospecimens or data are accessed, the types of research projects that will utilize biospecimens and/or registry data and the governance structure for the biorepository or registry. This information will help patients understand how their biospecimens and data will be used. When biospecimens are used for testing purposes, physicians should discuss the results with their patients. Patients should be aware that some tests may need to be repeated and may require additional costs.

In terms of risks, patients should be informed of the potential for a loss of confidentiality and autonomy as well as the possibility that knowledge could be obtained that has implications for their family members. These risks apply to both biorepositories and registries. There are additional risks associated with biorepositories, such as the potential use of biospecimens for sensitive or objectionable research and the possibility of exhausting a limited research resource. There may be less of a possibility that information of direct personal benefit to the patient will be gained from registry data than from analysis of biospecimens, but the consent form for biorepositories should emphasize that there will likely be no direct personal benefit to the patients, although their biospecimens may help researchers better understand the disease. It is also important to mention that biospecimens may not be analyzed in a CLIA-certified laboratory (Clinical Laboratory Improvement Amendments Program) and therefore the results obtained may not be usable for clinical purposes. Patients should be informed that data generated from research might need to be validated before results can be shared with them. The consent form should clearly indicate whether patients will receive individual research results or aggregated results.

The consent process itself— whether in person or electronically, and how minors, disabled persons, and capacity-impaired adults are consented—should be spelled out as well as having steps to ensure that subjects are fully aware of what they are consenting to and that they have the

opportunity to ask questions. Combining personal contact with electronic methodologies may be an effective approach. Procedures for maintaining privacy and confidentiality need to be explained, and the IRB of record should be identified for both biorepository and registry consent.

The workshop ended with a reminder of the overall goal put forth by Dr. Groft, who noted that US and EU experts recently met in Iceland and decided to follow up with a meeting in the United States to increase future work in this area. US-EU collaborative activities on rare diseases are expected to increase. Dr. Rubinstein thanked the attendees for their participation and adjourned the workshop.