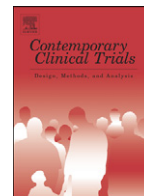




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Editorial letter

Informed consent and patient registry for the rare disease community: Editorial

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Informed consent is a fundamental ethical requirement in most clinical research. Much has been written about the benefits and barriers of research-related informed consent from patients prior to participating in medical research studies. Consent templates and examples exist and are widely available for use by organizations or individual investigators. Appropriately designed templates provide the required elements as mandated by federal regulations and international standards. Nonetheless, research consent forms are often long and complex and not always useful to participant understanding.

In order to initiate, conduct and complete meaningful studies on rare diseases in an appropriate time frame, it is necessary to identify and locate patients with rare diseases who may be dispersed over large geographical areas. Patient registries are becoming an important tool and resource to accelerate patient recruitment into clinical trials and other medical studies designed to evaluate diagnostics and therapeutics with the hope of eventually effectively treating or curing the millions of people suffering from rare diseases.

As more and more patient registries are being developed by patient advocacy groups, research investigators, industry, and other organizations, they are faced with the challenge of the appropriate process for obtaining consent from patients to include their medical histories or donated biospecimens in the patient registries. Importantly, obtaining consent for including patient information and specimens in a registry can be different than obtaining consent for clinical trials or other medical studies that registry patients might ultimately be invited to enroll in. Whether and how extensively federal regulations, such as those found in the Common Rule or HIPAA apply to the establishment of a patient registry will depend on the context in which medical information and

specimens are collected, how they will be stored, and other related factors.

The literature and guidance regarding obtaining consent for participation in patient registries are evolving. Organizations and patient advocacy groups involved in the process of establishing patient registries may be faced with uncertainties regarding the necessary elements and content of informed consent documents. One of the challenges is ensuring that participants receive the information they need to make an informed decision about participating in the registry.

Although the information provided and the requirements for obtaining consent from participants when establishing a patient registry may not be as stringent as consent for participating in a clinical research study, efforts should be made to develop a consent process that adequately informs patients about the purpose for joining the registry, how the registry will be used, and how the confidentiality of their information will be protected.

There is an urgent need in the rare disease community for further discussions among the various stake holders about the process of obtaining consent for participation in a patient registry. Stake holders should work together to develop sets of recommendations for informed consent language and processes that can be adopted by the many different developers of patient registries. As is true for consent forms for individual clinical research studies, informed consent for participating in a patient registry is dependent upon the intended uses for data gathered and analyzed in the patient registry. One consent form cannot fit all the different registries being developed by different entities.

In addition, the consent form is only part of the process of consent. For many rare diseases, adequate information may not exist and may need to be developed and provided to patients (and their family members as appropriate) as part of an ongoing consent process. Providing additional information beyond what can be presented in a written consent form may be essential in order to obtain meaningful consent from participants. The rare diseases community should work together to address these issues and develop templates and recommendations for obtaining the informed consent of patients, facilitating participation in patient registries, and adequately protecting the information provided.

Guidance and recommendations regarding points to consider and information to include in developing a consent process and the consent form would be very helpful to rare disease patient advocacy organizations and others when establishing patient registries. In addition, development and utilization of common templates would facilitate global harmonization necessary to exchanging, sharing, and aggregating de-identified patient medical information from patients around the world for future studies which is so desired by the rare disease community.

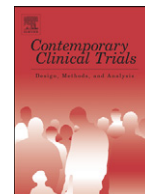
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Discussion

Informed consent process for patient participation in rare disease registries linked to biorepositories[☆]

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1. Executive summary

As plans are moving ahead to establish the Global Rare Disease Patient Registry and Data Repository (GRDR),^{2,3} 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-identified⁴ patient medical information linked to their biospecimens,⁵ using voluntary patient identifiers. 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.

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 participants focused on developing recommendations on the informed consent process which included: 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; 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; writing a short document that is easily understood.

Participants agreed that to obtain meaningful informed consent, additional information beyond what can be

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² Creating a Global Rare Disease (Patient) 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.

³ The case for a global rare diseases registry. Forrest CB, Bartek RJ, Rubinstein Y, Groft SC. *Lancet* 2010 Aug. 2 193: 5–7.

⁴ 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.

⁵ Biospecimens is a collective term for tissues, body fluid or any sample taken from the body.

presented in the written consent form may be needed and useful; in cases where the registry is linked to a biorepository, a separate consent form should be used to address issues specific to specimen donation.

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.

2. Workshop proceedings

2.1. Introduction

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. Following few key Speakers⁶ workshop participants gathered for group discussion.

3. Session I: informed consent for patient participation in a registry

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 subject 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)^{7,10} definition of the term “research” was discussed.

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 toward 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.

4. Required elements of informed consent

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

⁶ Full presentation of the speakers will be posted on the GRDR website.

^{7,10} Code of Federal Regulations Title 45 <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>.

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 re-consent 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).

5. Optional elements for informed consent

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.

6. Session II: informed consent for patient donation of biospecimens

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.

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. 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 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 are 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. 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.

7. Elements to be considered in informed consent for patient donation of biospecimens

- 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.

8. 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.

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. 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. 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 the US-EU collaborative activities on rare diseases are expected to increase. Dr. Rubinstein thanked the attendees for their participation and adjourned the workshop.

9. Recommended elements for informed consent process for participation in rare disease patient registries linked to biorepositories⁸

9.1. The informed consent process

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 consent form helps to both protect participants and inform investigators about how participants' data and samples can be used.

To obtain meaningful informed consent, additional information beyond what can be presented in the written consent form may be needed and useful. For example, a shorter consent form may be supported by background material. For this reason, it might be advisable to consider two distinct but complementary parts in the consent process: Part A: Background and supplementary material and Part B: Presentation, review and signing of the consent form. The background/supplemental material can also include additional details and further explanation on regulatory elements⁹ that are part of the requirements for the informed consent form.

One can envision a number of different approaches to providing such background information. It could be provided by posting on a group's website, by mail, orally, by audiotape or by other media. The information could be provided individually in the potential participant's personal environment or doctor's office, or in a group venue, for example during a support group meeting. If the potential participant's language is other than English, translation and interpretation should be available.

Part B of the consent process, presenting, reviewing and signing the consent form, is usually described as "obtaining informed consent." A printed hard copy consent form is traditionally used; an electronic consent form and signature may be acceptable in some situations and states. Whether in hard copy or electronic format, the consent form should be short, simple, clear and written at an 8th grade level. All consent elements required by Federal regulations must be present. The process should include the opportunity for potential participants to have their questions answered before signing. If the registry will include minors, provisions should be made for obtaining their assent, if appropriate. Accommodations should be provided for those with

⁸ Although these recommendations are for participating in a rare disease patient registries linked to biorepositories associated with GRDR, they can be used for patient participation in any patient registry. This is not a recommendation for informed consent to participate in a research study.

⁹ 46.116 General requirements for informed consent: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116>.

disabilities, for example, for the blind, the illiterate or the hearing-impaired. If the registry will include incapacitated adults who cannot provide their own consent, procedures for obtaining legal proxy consent along with assent of the incapacitated individual, if appropriate, should be put in place.

Listed below are sets of recommendations for consenting patients¹⁰ to participate in registries associated with biorepositories where patients' medical information is linked to their biospecimens using voluntary unique patient identifiers. However, these recommendations may also apply to any patient registry or biorepository. Any plans for the registry/biorepository to share and exchange de-identified patient information with other entities for research purposes should be indicated in the informed consent form.

9.2. Recommended elements for supplemental material (part A)

Listed below are key elements that are recommended to be included in the supplemental material that is provided to the patient/participant prior to signing of the consent form, as applicable.

1. Definition of patient registries/biorepositories; Define what a patient registry/biorepository is (as applicable) and explain what they do, and why they are important.
2. Purpose and the goal of the registry/biorepository. Explain the purpose of the registry/biorepository for which the participant is being asked to consent.
3. Recruitment, enrollment and participation: Describe the methods for recruitment and registration to participate in a registry (mailing, phone, internet etc.) and/or donate biospecimens. Describe the eligibility criteria for participants; describe the actions expected from participants. Describe the chain of contact, who may contact the participant and types of contact that may be expected. Explain what happens if patients/participants register in more than one registry/biorepository.
4. Updating medical information: Explain the importance of having the correct and current medical information and the need for participants to update their information on a defined basis.
5. Duration of the registry/biorepository: Describe how long the registry/biorepository intends to keep the participant's data/biospecimens and how long the registry/biorepository will exist. Describe the legacy plan in the event the registry/biorepository undergoes transition and/or is shutdown, including what will happen to the collected data/biospecimens and whether it will be destroyed or transferred to another entity.
6. Governance/oversight structure for the registry/biorepository: Include information about how the registry/biorepository is governed, how processes/policies are developed, who supports and owns the registry/biorepository and the oversight mechanisms in place. State how the registry/biorepository is funded and whether any costs will be incurred by participants. Describe occasions, if any, when the registry/biorepository may remove participants.
7. Confidentiality and privacy: Describe how the registry/biorepository maintains the confidentiality and protects the privacy of participants. As applicable, define the term "de-identified" as it relates to the collection, use and distribution of submitted information/samples and describe the relevant rules, regulations and laws that exist.
8. Voluntary participation/withdrawal from participation (opt in, opt out): Describe the voluntary basis for participating in the patient registry/biorepository. Describe the right to withdraw from the registry/biorepository at any time with no consequences to the participant's normal health care, including steps related to removal/return of data/biospecimens in the event the patient decides to withdraw.
9. Alternatives to participation: Describe alternatives to registry/biorepository participation, as available. Describe the right to refuse participation in the registry and/or not to donate specimens to the biorepository with no consequences to the participant's normal health care.
10. Access and sharing of registry data and biospecimens: Describe processes for sharing de-identified data/biospecimens, including the categories of individuals who may access the data/biospecimens and the acceptable purposes. Inform participants that they are free to participate in research opportunities outside the registry/biorepository.
11. Return of research results and incidental findings: As applicable, describe processes related to return of individual and aggregate results and incidental findings, including what type of information would be returned (if any), who will be responsible to report the results and to whom results would be returned. Describe findings that would not be returned through the registry/biorepository, i.e. results from external research studies.
12. Policies regarding participant requests: Describe the processes to handle requests from participants that their medical information and/or biospecimens be used only for a specific study or project.
13. Anticipated benefits: Describe anticipated benefits from participating in a patient registry or by providing a biospecimen.
14. Foreseeable risks: Describe risks associated with participating in a patient registry/biorepository including release of genetic information. Explain the GINA¹¹ law and its limitations. As applicable, describe physical risks associated with collecting a biospecimen(s). (For this reason, a registry consent form should separate from a repository consent)
15. Assent for minor and competency-impaired individuals: Describe the assent and consent process for minors and individuals not competent to provide informed consent, including the difference between consent and assent and the process to obtain valid consent on behalf of incapacitated subjects, as applicable.
16. Re-consenting enrolled minors at age of majority: Describe the process related to whether consent will be sought from minor participants at the age of majority. Explain the process for re-contact when the participant reaches adulthood, as applicable.

¹⁰ Due to different preferences by different organizations, "patient" and "participant" are interchangeable in this document.

¹¹ The Genetic Information Nondiscrimination Act of 2008 (Pub.L. 110-233, 122 Stat. 881, enacted May 21, 2008, GINA) http://www.ornl.gov/sci/techresources/Human_Genome/publicat/GINA/may2008.pdf
<http://www.genome.gov/10002077>
<http://www.hhs.gov/hop/policy/gina.html>.

17. Understanding the content of the consent form: Explain and emphasize the importance of understanding the content of the consent form, the meaning of the participant's signature and the need for the participant to confirm his or her consent when signing the form or submitting an informed consent form.
18. List of important acronyms and terminology: Terms may vary according to individual registries/biorepositories.
19. List of frequently asked questions (most useful for website users). Suggested topics may include the following: no

guarantee that participation in a clinical trial or research study will be offered, no requirement to participate in external research opportunities, how participants will be kept informed, ability for participants to access the information collected, anticipated timeframe when participants may access the collected information, ability for multiple family members join (or for multiple people to access the information), who to contact with questions, other resources that might be helpful for understanding rare disease and research.

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