Recontacting participants for expanded uses of existing samples and data: a case study

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| Purpose: | Facilitating genomic research may require the use of samples and data collected via consent processes that did not include specific descriptions of secondary uses. We explore whether a waiver of consent with notification and the option to withdraw (WNOW) is a viable alternative to written informed consent for secondary uses of samples and data. |
| Methods: | We developed a retrospective case study of a rare-disease protocol involving 1,978 participants that implemented WNOW for genomic data-sharing activities. We analyzed institutional review board and investigator records and conducted in-depth semistructured interviews with key staff members. |
| Results: | WNOW was largely successful at achieving its goals in this case, although the recontact effort, relative to proceeding with a waiver, decreased participation in genomic data sharing by 13.8% (n = 253), primarily because 224 letters were returned as undeliverable. A small number of participants responded (n = 89), and some of them expressed confusion and frustration. In the pediatric arm of the study, the research may have been practicable without a waiver, given the relationship between the pediatric clinicians and families. |

**INTRODUCTION**

Repositories of human biospecimens and data are a valuable resource for genomic research, especially in the context of rare diseases for which widespread sharing of samples and data is needed to facilitate research addressing the critical lack of diagnostics and interventions. It is often desirable to conduct ongoing analyses of samples and data using new techniques, such as genomic sequencing, that were not available when samples were originally collected. However, this can present challenges with respect to informed consent, given that previous consent documents are highly variable in their content and are unlikely to have described genomic sequencing research. What should researchers do when the original consent form was not broad enough to encompass newly proposed research?

There is a range of possible approaches for ongoing use of valuable samples and data for genomic research when prior consent documents did not address the generation and broad sharing of genomic sequencing data. Recontacting the original donors to obtain prospective written informed consent (i.e., “reconsent”) may be most appropriate when new plans are clearly outside of the scope of the original consent. In other instances, prospective written informed consent may not be required, and institutional review boards (IRBs) may instead grant a waiver of informed consent, sometimes coupled with a plan for notifying subjects about new research projects and reminding them about their ability to withdraw. Although seeking written reconsent arguably respects participants' autonomy in the most robust manner, some contend that it is often not required and that being recontacted unnecessarily could be an intrusion upon participant privacy. Furthermore, research teams may find it burdensome and difficult to locate the participants. The possibility of a waiver of informed consent exists under the Common Rule in the following situations:

1. The research involves no more than minimal risk to the subjects
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects
3. The research could not practicably be carried out without the waiver or alteration
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation

Genomic sequencing and data sharing in secure databases are generally considered to be minimal-risk research activities that fulfill the first requirement. Requirement 4, which is relevant primarily to deception research, does not apply in the context of genomic research. Therefore, for genomic sequencing and data sharing, criteria 2 and 3 are more variable and require greater scrutiny.

Waiver requirements 2 and 3 depend on characteristics of the specific research activities proposed as well as the study.
cohort, and although neither requirement is clearly defined in the Common Rule, some guidelines have attempted to provide clarification. Regarding the rights and welfare requirement, the National Bioethics Advisory Committee suggested that “IRBs should be certain to consider a) whether the waiver would violate any state or federal statute or customary practice regarding entitlement to privacy or confidentiality, b) whether the study will examine traits commonly considered to have political, cultural, or economic significance to the study subjects, and c) whether the study’s results might adversely affect the welfare of the subject’s community.”

This analysis is relevant to evaluating the interests of both individuals and groups in the context of genomic research with biospecimens. In practice, however, it may be difficult to know the significance of specific research topics to participants without formally surveying them or providing them with updated information about research being conducted using their specimens and data over time.

The Secretary's Advisory Committee on Human Research Protections (US Department of Health and Human Services) has suggested that the “practicability” criterion be based on whether “(1) scientific validity would be compromised if consent were required; (2) ethical concerns would be raised if consent were required; (3) there is a scientifically and ethically justifiable rationale why the research could not be conducted with a population from whom consent can be obtained [and] (4) it is not determined solely by considerations of convenience, cost, or speed.” Accordingly, research requiring rich data sets with uncommon characteristics, such as research on rare diseases for which each sample is extremely valuable, could be impracticable to maintain longitudinally, particularly if the cohort is too large or too geographically dispersed for reconsent to be obtained from the majority of participants.

How waivers are implemented in practice could affect both the rights and welfare and the practicability criteria. For example, when waiving informed consent could potentially adversely affect the rights or welfare of participants (e.g., per National Bioethics Advisory Committee criteria), coupling a robust notification process with the waiver could reduce the potential adverse impact of a new study and be practicable for the research team to carry out. This approach, which we refer to herein as “waiver with notification with option to withdraw” (WNOW), is similar to what some have referred to as a “thick opt-out” recontact policy, whereby participants are recontacted and given an explicit opportunity to withdraw if they object to ongoing research. Such an approach requires that participants be made aware of potential new research uses of their samples and receive a genuine opportunity to withdraw from research if they object. WNOW provides an intermediate option between written informed consent and a waiver of consent that may advance the rights and welfare of enrolled participants while still permitting research to proceed.

We used a retrospective case study to examine the feasibility of the WNOW approach and whether it appropriately balances the continuation of research with the interests of enrolled participants, focusing on a rare-disease protocol at a research hospital that used WNOW to inform enrolled participants of new plans to deposit genomic data into the database of Genotypes and Phenotypes and other secure databases.

The study cohort consisted of 570 patients (both children and adults) with extremely rare conditions, and 1,384 family members, enrolled between 2008 and November 2014. All patients and most family members contributed a sample to the study for genetic analysis within that time frame.

The WNOW effort for this study was prompted by the investigators’ desire to go beyond the minimum requirements of the National Institutes of Health genomic data-sharing policy to deposit into various large-scale repositories genomic data generated from samples collected before 2015. Their goal was to maximize the scientific benefits of broad sharing, but they were unsure whether the consent forms signed by the participants were sufficient. Specifically, they were concerned about whether privacy and confidentiality risks associated with broad sharing of genomic sequencing data needed to be disclosed explicitly to enrolled participants, through either a written consent process or other form of notification, and whether failing to do so would adversely affect the rights and welfare of those participants. Different versions of the consent forms had been used throughout the study for affected individuals and family members. Not all versions of the consent form explicitly mentioned broad data sharing or an attendant increase in privacy risks, although they did state that the samples may be de-identified and “sent elsewhere” or sent “to experts at other centers” (Table 1). The IRB ultimately approved the WNOW proposed by the investigators.

This cohort is relevant to study because its members have rare disorders that are underrepresented in most repositories. Through this case study, we aimed to assess whether WNOW is a viable alternative to seeking informed consent, not only for genomic data sharing but also for other research activities involving no more than minimal risk. In particular, we focused on whether the WNOW approach protected or adversely affected the participants’ rights and welfare, and whether the research would have been practicable without the waiver.

**MATERIALS AND METHODS**

We used a qualitative descriptive approach to develop a comprehensive description of the WNOW effort and how the individuals involved perceived it, drawing from multiple sources of data. First, we reviewed IRB minutes to reconstruct how the IRB came to adopt the WNOW. Then we reviewed records kept by the investigators to assess quantitative outcomes of the recontact effort. Finally, we contacted nine research team members and interviewed five who had interacted with participants or reflected seriously about the recontact effort: the principal investigator, two pediatric nurse practitioners, one genetic counselor, and one administrative nurse. We conducted in-depth semistructured interviews, lasting on average 30 min, focusing on the responses they received from patients and whether their reflections about (i) the participants’ rights and
Table 1 Evolution of language about genomic data sharing in protocol consent forms

| Date            | Original Language                                                                                     | Additions                                                                 |
|-----------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 11/06/2008      | “We may send your (your child’s) samples elsewhere for analysis.”                                       |                                                                          |
| 11/20/2010      | “In the case of the cell lines (fibroblasts and iPSC cells) generated from the skin tissue biopsy...”    |                                                                          |
| 02/21/2013      | “Sometimes it will also be beneficial for us and for the medical community to submit your genetic data, |                                                                          |
| 09/10/2014      | “We will also obtain research data from you through this study. If you withdraw from this study, the   |                                                                          |

Table 1: Evolution of language about genomic data sharing in protocol consent forms

IRB minutes and past consent forms

On what basis did the IRB accept the WNOW approach? First, it examined the various consent forms used between 2008 and 2014. The earliest version contained a single sentence about data sharing, stating that “we may send your (your child’s) samples elsewhere for analysis,” in contrast to later versions with more detail: “sometimes it will also be beneficial for us and for the medical community to submit your genetic data, consisting of the sequence of millions of DNA bases, to a public database.”

RESULTS

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To facilitate broad data sharing, the investigators requested a waiver of informed consent, along with a letter notifying participants about the expanded data-sharing activities and providing them with options to withdraw. Because WNOW is not explicitly described in any existing regulatory category, it is not obvious how the notification letter factors into regulatory approval of a waiver of informed consent. Could the IRB approve the proposal only if a waiver without notification met the regulatory requirements? In this case, the IRB seems to have approved the waiver on the basis of the entire proposal, including the notification letter. First, the IRB determined that the data-sharing activities involved no more than minimal risk. Second, the IRB reasoned that the waiver would not adversely affect the rights and welfare of the subjects because their privacy interests would be protected by “careful security measures that have been appropriately vetted.” In addition, expanded data sharing would probably not contradict the participants’ basic goals for participating in the study, because they had previously consented to some amount of sharing data and they would have the option to withdraw under the WNOW. Third, the IRB deemed the research impracticable without a waiver because many participants would have moved or otherwise been lost to follow-up, and the absence of their data would reduce “the potential value of this dataset from an extremely rare disease population.” The last criterion, requiring that “whenever appropriate, the subjects will be provided with additional pertinent information after participation,” did not apply. The IRB also approved the text of the letter, which was sent in November 2014 under the principal investigator’s signature to 1,958 patients and family members.

Investigator records

A total of 1,978 participants were designated in the protocol database as living as of November 2014. However, because the database did not contain addresses for 20 participants, only 1,958 letters were mailed. According to the records kept by the investigators, 60 affirmative replies (3.0%) were received, including 4 from family members of participants who had died but whose deaths were not previously reported to the research team. Of these 1,958 participants, 1,645 did not reply. A total of
224 letters were returned as undeliverable, including those sent to 72 patients and 152 family members. In addition, 29 participants, including 11 patients and 18 family members, actively declined to participate. The data for those who actively withdrew, for whom there was no valid address, and whose letter was returned as undeliverable were not used in the expanded data-sharing activities ($n = 253$; 13.8%) (see Table 2).

**Staff interviews**

In addition to the principal investigator, three of the four interviewees agreed that providing participants with updated information had indeed been necessary, because the previous consent forms did not cover genomic data sharing sufficiently. Only one member of the research team felt that it might have been acceptable to assume that genomic data sharing was consistent with the values and interests of the cohort and proceed without any further notification. All staff members observed that individuals in this rare-disease cohort are generally "excited" to share their data not only to better understand their condition but also to help others with the disease. Nonetheless, all staff members indicated that they would have preferred written consent over the WNOW, at least as it was implemented in this study.

As implemented, the WNOW did not succeed in conveying information to the greatest possible number of participants. The protocol uses multiple databases that did not all have matching current addresses. In addition, some staff members maintained direct contact with the participants and could learn about an updated address informally—through a Christmas card, for instance. Not cross-checking the address information, which contributed to the return of 224 letters as being undeliverable, was described as not "satisfying" by some staff members (interviewees 1 and 2). The staff members were also frustrated because there was no way to know whether the participant actually received or saw the letter. One member of the team expressed this vividly: "Put it this way, we could have stuffed all of [the envelopes], I could have pitched them into the garbage, and we would've known just as much as [we] know now" (interviewee 1). This suggests that staff members felt that the WNOW should be carefully designed to reach as many participants as possible, such that every participant should have the opportunity to be informed and withdraw if they so choose.

Although relatively few participants responded, some of those who did were confused. Specifically, they had the impression that the research team had individualized research results of relevance to them or their children. It was noted in the archival record that multiple patients had asked for their results. This misunderstanding may have stemmed from the language in the letter they received as well as the consent forms they had signed earlier. Each version of the consent forms had asked the participants to indicate whether they wanted to be contacted about "any important information about the diagnosis, possible treatment, related symptoms, associated risks, or genetic causes of your (your child's) disorder." For those who opted to be contacted and had faithfully updated the research team with their contact information as requested, the letter may have seemed to be the result of that choice.

### Table 2 Outcomes of recontact effort

|                | Presumed yes | Affirmed yes | No | Undeliverable | Total |
|----------------|--------------|--------------|----|---------------|-------|
| All            | 1,645        | 60           | 29 | 224           | 1,958 |
| Pediatric      | 824          | 19           | 16 | 118           | 977   |
| Proband        | 180          | 8            | 4  | 33            | 225   |
| Family member  | 644          | 11           | 12 | 85            | 752   |
| Adult          | 818          | 41           | 13 | 106           | 978   |
| Proband        | 277          | 22           | 7  | 39            | 345   |
| Family member  | 541*         | 19           | 6  | 66*           | 632*  |

*Those whose letters were deliverable and who did not reply were presumed to have agreed to the expanded data-sharing activities. *Seven unknown. *One unknown. *Eight unknown.

### Table 3 Staff interviews

| Theme          | Examples                                                                                           |
|----------------|---------------------------------------------------------------------------------------------------|
| Rights and welfare | Recontact was necessary for data-sharing plans because previous consent forms were not sufficient (except for genetic counselor).  
                     Affirmative consent was preferred.  
                     There was no verification that participants received, read, or understood the letter to exercise their autonomy to withdraw.  
                     Participants were confused about the availability of individual results, leading to disappointment and even anger in some cases.  
                     Participants were not concerned about privacy and confidentiality risks associated with genomic data sharing.  
                     Letters were sent to all participants, including multiple members of a single household, unaffected family members, and individuals who signed the consent form but did not return their DNA collection kit.  
                     The one-time letter that did not list their primary clinicians as contacts was unfamiliar.  
| Practicability | Pediatric clinicians had regular contact with families and felt that calling 180 families and obtaining affirmative written consent was not impracticable.  
                     One pediatric clinician estimated each phone call could last between 5–10 min.  
                     The genetic counselor thought phone calls would take too long.  
                     This was less practicable for adult patients because many live independently and communication with primary clinicians is less frequent.  

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Moreover, the letter stated that the investigators “would like to share your information (both the DNA sequencing data and the disease descriptions using a dictionary of medical terms) without identifying you” (italics added). This may have further misled the recipients to think that the investigators had information particular to their cases. In addition, one clinician pointed out that the letter referred to “the data” and “the genetic variants” without explaining that not all patients may have “data” or “genetic variants” to deposit into public databases. This vagueness may reflect the challenge of trying to create one letter for everyone who had participated in different capacities—from probands seen at the research institution to distant family members who mailed in a blood sample—over a period of 6 years.

When families that were confused learned that the letter pertained to a change in the research protocol, not to a personal finding, most nonetheless permitted the team to use and share their samples and data. However, the letter triggered some families’ frustration over the lack of progress on their cases and led them to withdraw. Two staff members remembered that one family with a child who had the disease not only withdrew from the expanded activities but also demanded that their research files and samples be returned. One clinician recalled, “We didn’t get an answer for them in what they felt was a reasonable time, and when they got recontacted with the letter, they were furious…because Mom’s interpretation of that letter was that we had withheld an answer specific to her child and then when she understood that we were just asking to share data in a database…that’s what broke Mom’” (interviewee 2). The staff members had an exchange either over the phone or via e-mail with the majority of participants who withdrew. According to their recollections, no participant withdrew on the basis of privacy concerns associated with genomic sequencing and data sharing involved in research.

Several operational aspects of the effort probably contributed to unintended negative effects on these few participants’ experience. First, there was a lack of coordination within the research and care team. Although the letter listed only the principal investigator and a patient coordinator as points of contact, many pediatric families called their primary clinician contacts on the research team, who were not prepared to answer their inquiries. In addition, the pediatric clinicians felt that they could have anticipated the patients’ reactions to the letter, such that some of the disappointment and frustration that the patients experienced might have been mitigated or avoided.

Second, the letter was sent to all study participants, including probands and multiple family members within a single household who were enrolled in the study. Some family members had never returned the DNA kit or participated in any other way, and there was no need to contact them. The pediatric arm comprised 224 probands and 745 family members—approximately 3 family members for each child. The research team’s records indicated that for several pediatric probands, the “mother called to say yes for [the] entire family.” Sending four letters instead of one in this case may have come across as impersonal while unnecessarily increasing the time and resources spent on the WNOW, particularly when all participants were part of the same nuclear family. In other cases, however, separate letters for each family member might better respect individual autonomy and be logistically simpler to implement. In making this trade-off, researchers should consider whether the participants are immediate family members or more distant relatives, among other factors.

With respect to practicability, interviews revealed an unexpected distinction between the pediatric and adult arms of the study. The pediatric clinicians felt that the research—genomic data sharing—would have been practicable without a waiver of informed consent. Each of the two clinicians could have called about half of the 224 families, explained genomic data sharing, and asked them to return a signed consent form. Given their experience with updating consent forms when new siblings were born, for instance, one clinician estimated that each phone call would take 5–10 minutes. By contrast, a genetic counselor who works with both pediatric and adult participants thought that calling the participants would “open the floodgates” to long conversations about unrelated topics. Phone-based consent in the adult arm would be more burdensome not only because the clinicians did not maintain such frequent contact with the participants but also because separate calls may be more appropriate for adult patients and their family members (see Table 3).

**DISCUSSION**

The goals of this specific recontact effort—to respect the autonomy of research participants by informing them of new research plans and reiterating their ability to withdraw—seem to have been largely accomplished. Sixty participants contacted the research team and affirmed their desire to participate, even if initially confused. In the absence of evidence to the contrary, one can assume that the 1,645 participants who did not respond at least received the letter, such that WNOW achieved its recontacting goal for 1,705 participants (86.2%). This is in line with another study that implemented WNOW, in which 985 of 1,178 (83.6%) participated.

The case study revealed, however, several important considerations regarding WNOW approaches. First, the research team needs a reliable channel of communication that is sensitive to the participants’ needs and in line with their expectations. This is essential to ensure that the WNOW does not adversely affect the rights and welfare of participants by inappropriately denying participants the opportunity to withdraw from the research or causing unnecessary distress. A one-time letter sent to members of a cohort not familiar with this method of contact may be disruptive. If clinicians communicate effectively with their patients through e-mail and update them regularly about findings and changes to the protocol, a WNOW by e-mail will be less likely to cause distress or have other unintended negative consequences. Clinicians can tailor the language to the characteristics of the cohort, including individual patients who may require additional attention. Indeed, such an implementation affords the participants a reasonable opportunity to ask questions and/or withdraw.
In addition, whether the research would be practicable without the waiver depends in part on how informed consent would be sought. For instance, contacting 224 families is much less burdensome than contacting 969 individual participants. Some opportunity costs will be associated with seeking informed consent, but the appropriate amount is mainly a question of judgment. One pediatric clinician in the rare-disease protocol, when asked about the burden of calling each family, responded, “but isn’t it [the research team]’s responsibility?” (interviewee 3). Whether WNOW is a viable alternative to informed consent cannot be determined in the abstract; different approaches of seeking informed consent will be more or less burdensome for different participant populations. Whether a waiver of informed consent is necessary and whether its goals will be optimally achieved depends, at least in part, on the implementation of the approach.

Conclusion

Facilitating the establishment and use of repositories of genomic sequencing data is scientifically valuable. Doing so with data generated from previously collected biospecimens raises challenging questions about whether and how to seek reconsent for ongoing uses. WNOW has been proposed as an approach that is less burdensome than written informed reconsent, while potentially advancing the rights and welfare of enrolled participants. As implemented in the case study described above, it seems to have been largely successful at meeting both criteria, although for a small number of participants it had unintended adverse consequences that might have been avoidable. In addition, pediatric clinicians suggested that genomic data sharing might have been practicable without a waiver of consent in the pediatric arm of the study. To determine whether WNOW is a feasible alternative to seeking consent for a study protocol, we recommend that research teams and IRBs consider three issues. First, the investigators, including primary clinicians and other staff members, should gauge the practicability of the research without a waiver. Primary clinicians may have insight into whether the participants are responsive or unlikely to return affirmative written consent forms. Second, the investigators should consider other alternatives to written informed consent, such as phone-based consent. Finally, if the research is considered impracticable without a waiver and WNOW is deemed the most appropriate alternative, it should be designed to avoid adversely affecting the participants’ rights and welfare to the extent possible. This can be accomplished by establishing a process in which the research team presents a detailed plan for IRB approval. The IRB can then evaluate and make recommendations about implementing WNOW in a manner that, although perhaps more burdensome for the research team to implement than a waiver, can avoid adversely affecting the rights and welfare of participants while still permitting investigators to proceed with valuable research.

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DISCLOSURE

S.C.H. was the IRB chair who presided over the IRB’s approval of the approach described in this manuscript. Consistent with National Institutes of Health policy, all IRB members were given an opportunity to decline to have their review documents used in this research project, and none objected. The other authors declare no conflict of interest.

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