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Recontacting Participants for Expanded Uses of Existing Samples and Data: A Case Study

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Abstract

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 1978 participants that implemented WNOW for genomic data-sharing activities. We analyzed Institutional Review Board and investigator records and conducted in-depth semi-structured interviews with key staff members.

Results: WNNOW was largely successful at achieving its goals in this case, although the re-contact 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.

Conclusion: The practicability of conducting research on existing specimens without a waiver of informed consent, and whether WNOW is a viable alternative, depend on contextual factors, including a reliable way to communicate with participants.

Keywords

Research Ethics; Secondary Uses; Data-Sharing; Biospecimens Research; Biobank Research

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Disclosure/Conflict of Interest

The authors declare that no financial conflicts of interest. Sara Chandros Hull was the IRB chair who presided over the IRB's approval of the approach described in this manuscript. Consistent with NIH policy, all IRB members were given an opportunity to decline to have their review documents used in this research project, and none objected.

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INTRODUCTION

Repositories of human biospecimens and data are a valuable resource for genomic research,[1,2] 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.[3] It is often desirable to conduct ongoing analyses of samples and data using new techniques, such as genomic sequencing, that were not available at the time that 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 they did not write the original consent form broadly 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.[4,5] Recontacting the original donors to obtain prospective written informed consent (ie., “re-consent”) 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 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. [6,7,8,9] Although seeking written re-consent 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.[10] Furthermore, research teams may find it burdensome and difficult to locate the participants.[11] The possibility of a waiver of informed consent exists under the Common Rule when:

> (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; and
>
> (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.[12]

Genomic sequencing and data-sharing in secure databases are generally considered to be minimal risk research activities that fulfill the first requirement.[13,14] Requirement (4), which is largely relevant to deception research, does not apply in the context of genomic research. Therefore, for genomic sequencing and data-sharing, the criteria that are more variable and require greater scrutiny are (2) and (3).

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 (NBAC) suggested that:

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> … 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.[15]

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 with their specimens and data over time.

The Secretary's Advisory Committee on Human Research Protections has suggested 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) not determined solely by considerations of convenience, cost, or speed."[16] Accordingly, research requiring rich datasets 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 geographically dispersed to successfully obtain re-consent from the majority of participants.

How waivers are implemented in practice could have an impact on both the rights and welfare and the practicability criteria. For example, in cases when waiving informed consent could potentially adversely affect the rights or welfare of participants (e.g., per NBAC criteria), coupling a robust notification process with the waiver could reduce the potential adverse impact of a new study while not being impracticable for the research team to carry out. This approach, which we will refer to herein as "waiver with notification with option to withdraw" or WNOW, is similar to what some have referred to as a "thick opt-out" re-contact policy, whereby participants are re-contacted and given an explicit opportunity to withdraw if they object to ongoing research.[5] 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 employed WNOW to inform enrolled participants of new plans to deposit genomic data to dbGaP and other secure databases.[17] The study cohort consisted of 570 patients with extremely rare conditions and 1384 family members, enrolled between 2008 and November 2014, including both children and adults. All patients and most family members contributed a sample to the study for genetic analysis within that timeframe.

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The WNOW effort for this study was prompted by the investigators' desire to go beyond the minimum requirements of the NIH genomic data sharing policy[18] to deposit genomic data generated from samples collected prior to 2015 in various large-scale repositories. 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, either through 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 nor attendant increase in privacy risks, although they did state that the samples may be de-identified and "sent elsewhere" or "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.[19] 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 utilized a qualitative descriptive approach[20] to develop a comprehensive description of the WNOW effort and how 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 re-contact effort. Lastly, we contacted nine research team members and interviewed five who had interacted with participants or reflected seriously about the re-contact effort: the Principal Investigator, two pediatric nurse practitioners, one genetic counselor, and one administrative nurse. We conducted semi-structured, in-depth interviews, lasting on average 30 minutes, focusing on the responses they received from patients and whether their reflections about (1) the participants' rights and welfare and (2) the practicability of the research without the waiver converged with those predicted by the IRB. We developed an initial set of questions based on the criteria for waivers or alterations of informed consent, and we conducted and analyzed the interviews in a reflexive and interactive manner to accommodate new data and insights.[20] We shared emerging drafts with two interviewees as a form of member-checking to improve the accuracy and validity of the case study.[21] In consultation with the study team, we decided not to contact the participants directly, because it would likely present an additional burden and intrusion into their privacy. The NIH Office of Human Subjects Research Protections (OHSRP) determined this project was exempt from IRB review.

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RESULTS

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 datasharing, 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.[22] (Table 1) The investigators proposed to the IRB that “the scientific aims of the study would benefit significantly from greater collaboration and sharing of these data among researchers, especially given the rarity of the disorders involved and the value of pooling these data,” and explained that such sharing would not be possible because the various consent forms “have addressed the sharing of samples and data, but did not uniformly nor precisely address the mechanisms of sharing of data sufficiently to apply to [various specific repositories].”[23] These statements to the IRB were informed by precedent set by other similar studies as well as pre-submission consultation with the IRB chair.

In order to facilitate broad data-sharing, the investigators requested a waiver of informed consent, coupled 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 appears 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 likely 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.” And the last criterion, requiring that “whenever appropriate, the subjects will be provided with additional pertinent information after participation,” did not apply.[23] The IRB also approved the text of the letter, which was sent out November 2014 under the Principal Investigator’s signature to 1958 patients and family members.

Investigator Records

There were 1978 participants designated in the protocol database as living as of November 2014. However, the database contained no addresses for 20 participants, so 1958 letters were mailed. According to the records kept by the investigators, there were 60 (3.0%) affirmative replies, including 4 from family members of participants who had died but whose deaths

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were not previously reported to the research team. 1645 did not reply. 224 letters were returned as undeliverable, including 72 patients and 152 family members. In addition, 29 participants, including 11 patients and 18 family members, actively requested not to participate. The data of 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).[24]

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 may 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 it. 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 utilizes 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 224 letters being returned as 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 if the participant actually received or saw the letter. One member of the team illustrated 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.[24] 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.”[22] For those who selected 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.

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)

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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 six years.

When families who were confused learned that the letter pertained to a change in the research protocol and not 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 one pediatric family that 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 email with the majority of participants who withdrew. Based on 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 likely 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 may 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 other ways, and there was no need to contact them. In the pediatric arm, there were 224 probands and 745 family members: approximately three 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."[24] 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 unit. In other cases, however, separate letters for each family member may better respect individual autonomy and be logistically simpler to implement. In making this tradeoff, researchers should consider whether the participants are immediate family members or more distant relatives, among other factors.[25, 26]

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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 last between 5 to 10 minutes. In 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.

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 – appear to have been largely accomplished. 60 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 1645 participants who did not respond at least received the letter, such that WNOW achieved its re-contacting goal for 1705 (86.2%) participants. This is in line with another study that implemented WNOW, in which 985 (n=1178, 83.6%) participated.[27]

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 in a cohort not familiar with this method of contact may be disruptive. If a clinician communicates effectively with their patients through email and updates them regularly about findings and changes to the protocol, a WNOW by email will be less likely to cause distress or other negative unintended consequences. The clinician 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 to 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, rather than 969 individual participants, is much less burdensome. There will be some opportunity costs associated with seeking informed consent, but the appropriate amount is largely 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

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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 re-consent for ongoing uses. WNOW has been proposed as an approach that is less burdensome than written informed re-consent, while potentially advancing the rights and welfare of enrolled participants. As implemented in the case study described above, it appears to have been largely successful at meeting both criteria, although it had unintended adverse consequences for a small number of participants in ways that may have been avoidable. In addition, pediatric clinicians suggested that genomic datasharing may have been practicable without a waiver of consent in the pediatric arm of the study. In order 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 investigators as well as 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. Lastly, if the research is deemed 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Evolution of Language about Genomic Data-sharing in Protocol Consent Forms

	Data-sharing
11/06/2008	"We may send your (your child's) samples elsewhere for analysis."
11/20/2010 Additions	"In the case of the cell lines (fibroblasts and iPS cells) generated from the skin tissue biopsy or from other cells of your body, it is possible that these samples will be shared with other investigators for use in ethics committee approved general research projects other than those involving your disorder. Examples of future basic research uses include genetic modification of cells, large-scale genome sequencing, and patenting of scientific discoveries."
02/21/2013 Additions	"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. This carries the theoretical risk of revealing your identity. We consider this risk to be extremely low, because identifying an individual based on these data would be very difficult, and because there appears to be no reason for anyone to do this. The medical and research data that we obtain on you may also be shared with collaborating investigators. This will be done without identifying you or sending along identifying information."
09/10/2014 Additions	"We will also obtain research data from you through this study. If you withdraw from this study, the associated research data will also be destroyed, except for medical data that are contained within the official medical record and data that were deposited in a de-identified fashion within public databases."

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Table 2.

Outcomes of Recontact Effort

	Presumed Yes*	Affirmed Yes	No	Undeliverable	Total
All	1645	60	29	224	1958
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[a]	19	6	66[b]	632[c]

*Those whose letter were deliverable and did not reply were presumed to have agreed to the expanded data-sharing activities.

[a]7 unknown

[b]1 unknown

[c]8 unknown

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Table 3.

Staff Interviews

Themes
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, individuals who signed the consent form but did not return their DNA collection kit
➢ 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 minutes
➢ Genetic counselor thought phone calls would take too long
➢ Less practicable for adult patients because many live independently and communication with primary clinicians less frequent