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Target Article

Broad Consent for Research With Biological Samples: Workshop Conclusions

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Different types of consent are used to obtain human biospecimens for future research. This variation has resulted in confusion regarding what research is permitted, inadvertent constraints on future research, and research proceeding without consent. The National Institutes of Health (NIH) Clinical Center's Department of Bioethics held a workshop to consider the ethical acceptability of addressing these concerns by using broad consent for future research on stored biospecimens. Multiple bioethics scholars, who have written on these issues, discussed the reasons for consent, the range of consent strategies, and gaps in our understanding, and concluded with a proposal for broad initial consent coupled with oversight and, when feasible, ongoing provision of information to donors. This article describes areas of agreement and areas that need more research and dialogue. Given recent proposed changes to the Common Rule, and new guidance regarding storing and sharing data and samples, this is an important and timely topic.

Keywords: biomedical research, informed consent, regulatory issues, research ethics

Biological samples (also referred to as biospecimens, human biological materials, or samples) have been collected and stored from individuals in both clinical and research settings for decades, and billions of samples are now in storage (Secretary's Advisory Committee 2011). Valuable studies have been conducted with these biospecimens, including, for example, identification of prevalence estimates and clinical outcomes for the hepatitis C virus

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(Alter et al. 1999; Seef et al. 1992), characterization of different types of dengue virus (Lewis et al. 1993), estimation of the relative efficacy of tamoxifen for *BRCA1* versus *BRCA2* breast cancer chemoprevention (King et al. 2001), and many others.

Investigators use variable processes and practices to obtain consent for the future research use of biospecimens. These include obtaining consent at the time of specimen collection for a specific use, with re-consent for any subsequent uses, selection of permitted studies on a checklist, and, in some cases, no consent at all (Edwards et al. 2014). Reliance on different approaches necessitates keeping track of the type of consent that was used for particular biospecimens and handling them accordingly, with the potential to increase the costs of research and decrease its scientific value. Confusion and uncertainty about consent can also result in decisions to not use certain specimens for research and consequent loss in related public benefit from research. Some have proposed a policy of broad or general consent as a way to address these concerns (Wendler 2013) We define "broad consent" as consent for an unspecified range of future research subject to a few content and/or process restrictions. Broad consent is less specific than consent for each use, but more narrow than open-ended permission without any limitations (i.e., "blanket" consent).

A broad consent approach has been endorsed by recent and projected changes to the regulatory process for research with biospecimens. The Advanced Notice of Proposed Rulemaking, issued in July 2011 by the U.S. Department of Health and Human Services (DHHS) Office of Human Research Protections, proposed that written consent would be required for the research use of any specimen, including those collected through clinical encounters, but that such consent could be obtained by use of a "brief standard consent form agreeing to generally permit future research." The proposed rule went on to recognize that such a brief standard consent could allow individuals to say yes or no to categories of research that might raise unique concerns (e.g., creating a cell line, reproductive research, or studies of concern to indigenous populations) (Office of Human Research Protections 2011).

Similarly, the 2013 amendments to the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule no longer require research authorizations to describe a study-specific research purpose, but allow authorization for use and disclosure for future research purposes, as long as participants are provided with sufficient information to make a reasonably informed decision (Department of Health and Human Services 2013). In addition, the NIH Genomic Data Sharing Policy released in August 2014 (NIH Genomic Data Sharing Policy 2014) expects investigators submitting genomic data to the NIH to provide documentation of participants' informed consent to broad sharing of genomic and phenotypic data for future research purposes. Each of these regulatory proposals supports the use of broad consent for the research with biospecimens, an idea that has been echoed by some scholars (Wendler 2006; Hansson et al. 2006).

These endorsements of broad consent raise a critical need to consider whether it is ethically permissible for research using biospecimens and, if so, to identify the optimal implementation of such an approach, given expanding opportunities for research with biospecimens, an increasing number of biobanks, and changing regulatory proposals. This requires understanding of what broad consent entails, how it compares to alternative approaches of consent, and whether and why it may be the optimal approach.

In September 2013, the NIH Clinical Center Department of Bioethics convened a group of subject-matter leaders with diverse perspectives to debate the merits of broad consent for research with biospecimens (see Appendix 1). The group was asked to consider the ethics of broad consent for collection of biospecimens in clinical or research settings to be stored and used for future research, what broad consent should entail, and how it compares to other approaches. The goals of the workshop were (1) to consider the ethical justifications for broad consent and alternative approaches, (2) to develop an approach that could be adopted across diverse sites and studies, and (3) to identify areas of consensus and disagreement, as well as challenges in need of future research. The focus was specifically on informed consent at the time of collection of biospecimens—either in a clinical or research setting—and not on research with existing samples, community consent, incidental findings, or other important and related issues. The workshop focused on the kind and degree of information provided to the donor as part of consent, recognizing that decisions about the content of this information are crucial and independent of whether prospective donors are presented with a decision to opt in or opt out of donating a biospecimen.

This article proposes a view of broad consent as an ethically appropriate way to obtain consent for future research use of biospecimens when coupled with ongoing oversight of such research. While the contours of this approach were endorsed by most of the workshop participants, the article highlights areas of agreement and disagreement, as well as areas where future research and dialogue are needed to optimize the use of broad consent.

THE ARGUMENT FOR CONSENT FOR RESEARCH WITH BIOSPECIMENS

Many options exist for obtaining consent for the future research use of biospecimens, a range defined by the extent to which donors[1] are informed about and able to decide whether their samples are used for research purposes (Table 1). Identifying the best approach among this range involves first considering the reasons to obtain consent at all.

1. In this article, we use the term *donor* as opposed to "source" or other terms, since "donor" implies that consent to donation is sought and given.

TABLE 1. Participant Demographics

Less burden, less control	Type of consent	Description
	No consent	Do not obtain donor consent
	Blanket	Consent to future research with no limitations
	Broad*	Consent to future research with specified limitations
	Checklist	Donors choose which types of future studies allowed
More burden, more control	Study specific	Consent for each specific future study

*Framework proposed here couples initial broad consent with oversight and the possibility of ongoing communication.

At least five positive reasons support obtaining donors' consent for research with biological samples. First, obtaining consent shows respect for donors. Second, it allows them to control whether their samples are used for research purposes. Third, it allows them to decide whether the risks and burdens of research are acceptable to them. Fourth, it allows donors to decide whether to contribute to the goals of research, thus protecting and possibly promoting their fundamental values and nonwelfare interests. Lastly, obtaining consent makes transparent decisions about donating and researching biospecimens. Such transparency can promote public trust, and the ongoing viability of research with stored samples.

These considerations suggest a strong ethical rationale for obtaining donor consent for the future research use of biospecimens. Identifying the best approach requires also estimating the costs and burdens of obtaining consent. The costs include burdens on donors' and investigators' time, as well as the resources needed to obtain consent. In addition, there can be considerable cost and burden related to maintaining systems that record and honor individual choices, or to later seeking donor re-consent. Further, requiring consent raises the possibility that donors may decline, possibly diminishing the potential for future research.

This analysis suggests that at the level of policy, there is a presumption in favor of requiring consent in most circumstances, assuming that it is possible to obtain consent at the time of biospecimen collection in a way that is not overly burdensome. Importantly, in some cases, this proposal entails a greater degree of consent than is currently required under U.S. regulations. Under current guidance, stored biospecimens can be used for research purposes without consent or oversight as long as identifying information is removed or coded and the identity of the donors is not shared with the researchers. As such, researchers can use deidentified specimens that were collected in a clinical setting without research consent, as the subsequent research projects using these specimens are not considered human subjects research under the Common Rule (Office of Human Research Protections 2008).

Although the analysis thus far suggests that consent should typically be obtained when collecting biospecimens for future research use, it does not provide a clear reason to prefer any particular type of consent. One way to determine what is required for valid consent is to adopt a reasonable person standard, which holds that the information provided to donors should be based on what a reasonable person would want to know to decide whether to donate his or her samples. Empirical studies involving more than 100,000 individuals from around the world have surveyed patients, research participants, family members, religious leaders, and the general public about their views on future research use of stored biospecimens (Brothers et al. 2011; Chen et al. 2005; Mezuk et al. 2008; Simon et al. 2011). Overall, respondents indicate that they want to decide whether or not their biospecimens are used for research. In study after study, however, the majority of individuals say that their willingness to donate specimens is not affected by specific details of the future research, such as the disease being studied, the technology used (e.g., enzyme-linked immunosorbent assay [ELISA]), the study target (genes or white cells), or the product (treatment or prevention) (Hoeyer et al. 2004). These results are consistent across time in different populations in various countries and despite the methodology or the wording of the surveys, although some groups may be insufficiently represented.

Taken together, these studies suggest that, after initial consent, most individuals are not concerned about the vast majority of studies for which their samples might be used. Exceptions that have been identified involve: research involving human cloning, research involving indigenous peoples, and possibly commercial or for-profit research (Stegmayr et al. 2002; Tupasela et al. 2010; Gaskell et al. 2013; Brothers et al. 2012; McCarty et al. 2008). The empirical data thus support the claim that reasonable persons are willing to provide broad consent for future research with their biospecimens, provided that important exceptions are taken into account.

Simon and colleagues found, for example, that U.S. survey and focus-group participants wanted to give initial consent, but most commonly preferred broad consent because, among other reasons, "the research would help others," "I would only have to sign the paper or be asked about the research once," and "broad consent allows for research in the future that might not have been considered yet" (Simon et al. 2011). Studies have also found that a minority (4–40%) of individuals would not provide consent for future unspecified research use of their biospecimens (Kettis-Lindblad et al. 2006; McQuillan et al. 2006; Treweek et al. 2009; Wang et al. 2001). Some studies suggest that older individuals are more comfortable with broad consent than those who are younger (Trinidad et al. 2012), and that

certain populations may be less accepting of broad consent than others (Moodley et al. 2014).

In addition to the empirical data, there are more general reasons to think that broad consent is reasonable. In particular, it allows individuals to control whether their samples are used for research and avoids the potential burden for researchers and donors of asking individuals to consider and make a decision for each new study. Assuming that donors are aware of any general limitations on future studies and these limitations are implemented effectively, broad consent protects donors' interests, including their interests in supporting valuable research. Studies also show that individuals are reassured that their interests will be protected when oversight mechanisms are in place to review proposed research (Botkin et al. 2014). Finally, basing the consent process approach on the views of the majority of individuals shows respect for their views, and helps to ensure the public acceptability and long-term viability of research.

Broad consent may be problematic for the minority of individuals who are willing to have their samples used only for a few types of studies. However, those who are not in favor of their samples being used for unspecified future research can exercise their right not to donate their biospecimens for research. In the majority of cases, this is likely to be only a very small percentage of sample donors. However, there may be some populations for which the refusal rate to broad consent may be as high as 40%.

Ethical analysis and available empirical data provide support for obtaining broad consent at a minimum. In addition, the costs of maintaining a system of broad consent should be relatively low, although there may be significant infrastructure and start-up costs. This raises the question of whether any of the consent approaches that offer more information and specificity of choice and hence more control to donors are better than broad consent.

As indicated in Table 1, as the level of control offered to donors increases, the costs and burdens of the approach to consent also generally increase. The costs of checklist and study-specific consent are higher than the costs and burdens of broad consent. The higher costs associated with requiring consent for each subsequent study or following a complex menu of choices include the need to track and monitor compliance in any reuse. These methods may also preclude the subsequent use of biospecimens because of restrictions or ambiguity in the initial consent, especially if the limitations are vaguely worded or wide-ranging. For example, if donors were to specify a limit on using their samples only for "HIV-related" research, researchers and review bodies might struggle with whether this limitation allows or precludes research related to weight loss or cancer, which are common comorbidities in HIV, or studies related to white-cell dynamics or other retroviruses.

In contrast, the added benefits of these approaches compared to broad consent seem minor, at least for the majority of donors, especially if there is sufficient oversight to ensure that the subsequent use of samples is for purposes that do not conflict with donors' values. Allowing donors to decide the specific studies for which their samples will or will not be used appears to give them some level of increased control. Neither the donor nor the researcher might know, however, at the time of collecting the sample the range of possibilities for future research use, including research that could have substantial social value (Eriksson et al. 2011). Given the low risks to donor welfare and the uncommon circumstances in which research might conflict with donor values, this increased control contributes little value.

PROPOSAL FOR BROAD CONSENT

Workshop participants agreed that broad consent for research use of biospecimens[2] is ethically permissible and, in many cases, optimal, especially when it includes the following three components: (1) initial broad consent, (2) a process of oversight and approval of future research activities, and (3) wherever feasible an ongoing process of providing information to or communicating with donors. These features promote the ethical acceptability and scientific value of future research with biospecimens and demonstrate respect for donors' contributions. The participants also agreed that there might be cases in which broad consent is not appropriate, especially circumstances where it might be ethically appropriate and consistent with governing regulations to use samples without any consent, and circumstances where donors should be able to limit future research to specified studies. An example of the former type might involve a national pandemic or institutional outbreak that requires obtaining the widest number of samples possible. An example where more specific consent might be appropriate would be for donors with specific concerns regarding future uses, such as samples collected from an indigenous population.

Initial Consent

Consent serves to alert persons considering donating their biospecimens about the broad spectrum of research that could be undertaken and to promote their individual reflection on the risks and benefits of donation. To facilitate prospective donors' decisions, the initial broad consent form should advise about possible future uses of the samples and the processes of oversight that will be used to review specific studies. Workshop participants had diverse opinions on what information should be included in this initial consent. Most agreed that the consent form should briefly describe that the samples will be stored, that samples may be shared with a wide range of researchers and institutions and the conditions under which sharing would be allowed, that general health information accompanies the biospecimen, the possibility of commercial or therapeutic applications, the oversight process that will review

2. Workshop participants agreed that initial consent for donation of samples for research use should not be contingent on whether or not identifiers will be retained or used in the research.

proposed research, the potential for re-contact or ongoing communication, and the possibility of donors opting out of further research on their stored biospecimens in the future.

Some participants felt that prospective donors should be told that any research was possible unless specifically limited in the consent form or overruled by the oversight body. Others thought it would be helpful to include a broad but nonexhaustive description of possible research topics, including the possibility of genetic analyses and keeping cells for indefinite periods, as well as other techniques to be developed. For example, donors might be informed that biospecimens could be used in research about their disease or unrelated diseases that are designed to learn something that might help future patients. Some workshop participants felt strongly that donors should be informed that certain kinds of sensitive or controversial research might be conducted and that examples should be provided. Others felt that specimens from donors who gave broad consent should not be used for controversial research without further safeguards, such as oversight and sometimes re-consent. Current and potential future donors could play a pivotal role in designing these consent forms and processes, as could further empirical data.

Specific limitations included in the initial consent should be based on data showing that certain types of research are objectionable to a large number of people or to certain populations. The most prominent examples identified to date in this regard are certain types of reproductive research such as human cloning, or developing human embryonic stem cells from frozen embryos (Shepherd et al. 2007; McCarty et al. 2008). There may be reasons to include additional limitations for certain donor groups. For example, a group of donors with a rare disease might want to specify in the consent that the limited supply of their biospecimens be used only for studies related to their disease. For other groups, detailed preferences about long-term disposition of samples after death might be appropriate in order to respect culturally grounded values. Certain groups might find specific research topics to be controversial or sensitive, for example, studies of human evolution or genetic ancestry.

Broad consent is sufficiently flexible to allow specific limitations to be decided based on the site circumstances and donor population. Attention to formulating sufficiently clear and implementable descriptions is important. Individuals who feel that the limitations are not sufficient or are still uncomfortable with the research that might be allowed can choose not to donate their specimens.

Independent Oversight

A process for approving and overseeing the future research uses of stored samples will help to ensure the ethical acceptability and scientific value of such research, especially given the limitations of relying on the consent processes for achieving these goals. Oversight adds further protections, since future research uses cannot all be explained, predicted, or known, and donors consent to entrust research institutions and biobanks to make reasonable decisions about future research on their behalf (Mongoven and Solomon 2012). Such oversight goes beyond the scope of review currently required by the U.S. Common Rule with respect to deidentified or coded biospecimens, as well as beyond the requirements included in the proposed revisions to the Common Rule.

Some might worry that such oversight will be too onerous. Workshop participants envisaged a possible two-step oversight process to minimize burden. An investigator would briefly describe the proposed study and apply for release of stored samples, and (1) the oversight body designee would review the application and either approve it or (2) refer the application for further independent review based on whether it triggered a criterion for further review, as described below. This process could be tailored to the specific research and governance characteristics of individual institutions or biobanks.

Where feasible, existing oversight bodies, such as the institutional review board (IRB) or in some cases a data access committee (DAC), may be used or adapted to provide oversight (Pulley et al.2010), especially for research use of samples retained by investigators or institutions. As already described, a designee of this body would provide the initial and in many cases only review, referring the application for further review only in certain cases. Establishing an additional oversight body might be appropriate for large biobanks, and instructive lessons can be drawn from presently operational review mechanisms for some biobanks (Bedard et al. 2009). While the specifics vary, common and desirable criteria include broad-based membership with the capacity to assess proposals' scientific and ethical acceptability. These will likely include experts in law, ethics, and science (Bedard et al. 2009). Community representation is also important on the oversight body itself, including in the form of a community advisory board that provides a check on supported research (Mongoven and Solomon 2012; Lemke et al. 2010). More extensive donor or community involvement may be warranted where there is a case that raises group-specific issues, as may be the case with samples from patients with rare or highly stigmatized diseases (Terry et al. 2007).

Criteria for Further Review

Further review of proposals for research with stored samples would be prompted if the initial reviewer has concern regarding (a) the scientific value or rationale of the proposed research, (b) whether the risks are more than minimal, (c) whether the research is inconsistent with specified limitations in the initial consent, or (d) whether the research might conflict with the values of the donors (Tomlinson 2013). Research that might conflict with the values of donors beyond those specified in the initial consent limitations may be difficult to identify but could include, for example, research proposing to create gametes from induced pluripotent stem cells, research that proposes to identify genes associated with criminality, or research of

which the results could stereotype, stigmatize, or undermine socially identifiable groups. Specific re-consent may be required for such studies.

Importantly, individuals' nonwelfare interests are not set back simply when their samples are used for research that they may not have chosen. For example, if in the future donors' specimens are used for research that they would not have prioritized but otherwise would not object to, this does not seem bad for them. In contrast, when donors' samples are used for research that is inconsistent with their fundamental values, arguably this might set back donors' interests. Empirical research could help to identify controversial research topics and practices, including their acceptability among diverse groups of potential donors.

Ongoing Communication With Donors

While there are certain settings in which ongoing communication between the specimen donor and researchers or biorepository is not possible, workshop participants stressed the importance of a commitment when feasible to periodically informing donors about research activities and emphasizing the donors' right to withdraw from further distribution of their biospecimens. The structure and processes for such communication are likely to differ according to technological capacity, donor characteristics, and so forth. One approach is the creation of a website that is regularly updated to identify and seek donor comments on research projects for which the samples are being used (Kaye et al. 2012). Where feasible, these information technology (IT) systems or websites could also integrate mechanisms for donors to withdraw their consent for future use of their biospecimens, if they disagree with the particular research topics or practices for which samples have been released or used.

Establishing such processes has the additional benefit of allowing researchers and biobanks to learn from donor actions. For example, a large number of donors withdrawing consent after approval of a type of research might signal that such research conflicts with donors' values or expectations, and may suggest adding that category to the list of triggers for further independent review. A robust system for ongoing communication mirrors in some respects "dynamic consent" models but without asking participants for new consent for each new study (Wee et al. 2013; Kaye et al. 2014).

Enforcement and Evaluation

Ensuring the ongoing acceptability of research involving stored biospecimens requires more than merely a process for initial review. Mechanisms for promoting and enforcing ethical research practices also are important. A code of ethical conduct for researchers obtaining stored biospecimens could help inform them about their ethical obligations (e.g., see NIH 2010), such as not using the specimens beyond permissible research projects or adhering to commitments not to reidentify donors. Biobanks should develop systems for monitoring those who are accessing data, and develop explicit sanctions and dispute resolution strategies (Joly et al. 2011). This proposed system of initial consent and review also would benefit from systematic collection of information on the kinds of studies that are being conducted, rejected, or modified in the review process. Such information could be helpful in predicting problematic or publicly unacceptable research, as well as ensuring that the process has not become unduly burdensome or inefficient.

NEED FOR FUTURE RESEARCH AND DEBATE

Workshop participants acknowledged the need for further research on the adoption and implementation of broad consent for future research with biospecimens, including but not limited to research on donor attitudes and communication, the contours of the oversight process, and the applicability of this proposal to international sample collection or engaging certain donor groups, such as donors with rare or highly stigmatized disorders, or indigenous groups. The initial consent and oversight process depend on understanding potential donors' views on research topics and practices, including identifying those that would affect willingness to participate or to which potential donors would object. Also, more work is needed to specify the information that donors want to know regarding possible future research projects, and how they regard the oversight process for vetting future research. As consent forms are developed in accordance with our proposed broad consent model, research should be done on how donors respond to examples of research topics and practices, such as commercial applications. Data on the experiences of oversight bodies in developing principles and criteria for review and the circumstances that trigger wider review or modification of requests would also be useful.

Further research also is needed to explore the practical challenges of implementing broad consent for future research in clinical settings (Edwards et al. 2014). Research is needed to evaluate ethical and practical differences of opt-in and opt-out consent strategies. Another area is further exploration and dialogue regarding any ethical, practical, or policy grounds for distinguishing consent for research with health information or data from consent for research with stored biospecimens, particularly given the sensitivity of, for example, some epidemiological data.

CONCLUSION

Broad consent allows donors control over the use of their biospecimens while minimizing the costs to and burdens on donors and researchers. Further, broad consent is consistent with the views of the majority of persons who have responded to surveys about research use of biospecimens. Participants in a workshop to consider consent for collection of biospecimens for research use agreed that broad consent is ethically appropriate, and preferable to lack of

consent and more detailed consent for the majority of biospecimen collections. The proposed framework for acceptable broad consent includes initial consent, oversight of future research projects, and, when feasible, mechanisms for maintaining contact and communication with donors.

DISCLAIMER

The views expressed are those of the authors and do not represent the official policies or positions of the Department of Health and Human Services, NIH, or the Public Health Service.

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