§46.408 **Permission by Parents or Guardians**

- Parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children).
- Appropriate mechanism for protection is substituted, taking into consideration:
  - nature and purpose of the research activities
  - risk and anticipated benefit
  - subjects’ age, maturity, status, and condition.
- Not inconsistent with federal, state, or local law.

**Documentation of permission by parents or guardians**

see §46.117(c) above

§46.408 **Assent of Children**

- The capability of some or all of the children is so limited that they cannot reasonably be consulted,
  OR
- There is a prospect of direct benefit to the child that is available only in the context of the investigation.

Even if the subjects are capable of assent, the requirement may be waived if §46.116(d) criteria (above) are met.
Do People Care What’s Done with Their Biobanked Samples?

The increasing efficiency and sophistication of techniques in genetics, proteomics, mass spectrometry and other fields has made it possible to use archived biological samples to conduct large-scale and long-term epidemiological, genetic, and other research that previously could not have been done. Research on large collections of representative samples promises very significant advances in better understanding the frequency, distribution, and causes of a variety of illnesses, providing the scientific foundations for new diagnostic, preventive, and therapeutic approaches.¹

The materials in these “biobanks” can be collected under a variety of circumstances. Regarding their initial diagnostic, therapeutic, or research uses, there are generally well-understood standards requiring the individual’s informed consent to the collection and use of his or her biological samples. But what about all the possible future research studies that might use these materials?

When people donate their deidentified biological samples or medical information to a biobank for use in health research, do they care how their donations might later be used? This is an important question because these donations are usually made under a broad consent approach, in which permission is given in advance for any future research uses, with no opportunity provided to later control how one’s donated materials are used. The ethical justification for this practice is that, with deidentified samples, the donor is no longer exposed to any risk from the research and doesn’t need the further ethical protection that would be provided by specific consent to each project using his or her materials.²

We know, however, that when considering the research uses of their biological samples, people are concerned about things other than risks to their welfare or confidentiality. They are concerned as well about the purposes of the research using their samples, and its ethical and social implications.³ These might include concerns about research that they would find ethically troubling, such as research into prenatal diagnostic testing that could prompt decisions for selective abortion or research involving cloning.⁴ Donors may also have a deeply felt interest in protecting their group’s identity, even when the likelihood that they will personally suffer the effects of group harms is low. For example, one study indicated that some Jewish people would be significantly less likely to consent to future possible research uses of their biological samples when that research may be studying traits like frugality and homosexuality that could reinforce stereotypes about Jews.⁵ And other studies suggest that some people may have moral concerns regarding the ways that financial gains from research using their medical information are created or distributed, quite apart from any personal interest in financial reward. For example, one study reported that some respondents would be reluctant to have their deidentified medical information used in research sponsored by drug or insurance companies, and all insisted that researchers not personally profit from research done with their information.⁶

We call the sorts of interests described above the “nonwelfare” interests that individuals continue to have about the ways their biological samples and medical information are used even when the materials have been deidentified. A “nonwelfare interest” regarding research exists when someone has a concern about participation in, or donation to, research concerning some matter that will not harm the individual or otherwise affect his or her welfare. It is important to note that included among donors’ nonwelfare interests are not just worries like those described above but also hopes


²IRB: Ethics & Human Research

³IRB: Ethics & Human Research

⁴IRB: Ethics & Human Research

⁵IRB: Ethics & Human Research

⁶IRB: Ethics & Human Research
for the contributions their donations might make to medical progress.

So how might nonwelfare interests affect people's willingness to donate their biological samples under a broad consent approach? This question has not been previously investigated. We therefore conducted an empirical study designed to answer it, along with these four related questions: How widespread is reluctance to contribute biological samples that might be used for research projects that may violate some respondents' nonwelfare interests? How much do descriptions of research projects that explicitly lay out nonwelfare concerns reduce people's willingness to donate, compared with descriptions that do not explicitly raise these concerns? How are these concerns about donation distributed among different racial, ethnic, and socioeconomic groups? What kinds of attitudes affect willingness to donate?

Pilot Interviews and Internet Survey

We performed a face-to-face-interview pilot study, followed by an Internet survey. The Social Science Institutional Review Board (IRB) at Michigan State University (MSU) approved both studies. Participants in the pilot study gave written informed consent. Due to its low risk, the online survey was determined to be exempt from the federal regulations governing research; documented informed consent was thus not required.

*Pilot Study.* The pilot interview study consisted of face-to-face interviews with 50 respondents between August 4 and October 1, 2010. It was designed for two purposes: to find out if respondents could understand the relevant facts about biobanks and donations to them and to help us decide which of five initial hypothetical research projects to use in the later Internet survey. Respondents were recruited in person and with flyers posted in the East Lansing, Michigan, area. The interviews were conducted mostly in offices at MSU, although some were held elsewhere for the convenience of the subject (e.g., at a restaurant or a subject's home). Interviews took 40 to 60 minutes, and respondents were given a $20 gift card from a major grocery store that was also a one-stop shopping center in the Great Lakes states.

The content and format of the pilot interviews were very similar to the Internet survey, described in more detail below. Results from the pilot study led to the selection of three Problematic Projects—to be used in the later Internet survey—that had the strongest effects on interview respondents' willingness to give broad consent for research with their biological samples. Results from the pilot interview indicated that willingness to provide biological samples for research under a broad consent approach varied depending on the nature of five hypothetical research projects described to interview participants. When participants were presented with no prior information about research projects or with just the three morally unproblematic projects described in Table 1 (found, along with all the tables for this article, on the IRB: Ethics & Human Research website), 94% said they would provide a biological sample under a broad consent approach. We later refer to these three projects as Positive Projects. Respondents' willingness to provide a biological sample for research dropped slightly—from 90% to 86%—for other research projects we refer to as Problematic Projects (Table 2).

However, interviewees responded differently to the expanded versions of some of these projects. For two of the five initial projects, only 4% to 6% were less inclined to donate than when presented with the expanded version. By contrast, 20% were less inclined to donate when given the expanded version of the cystic fibrosis project, and over 30% were less inclined to donate when given the expanded versions of the mental illness and diabetes projects. These three Problematic Projects were then selected for use in the Internet survey.

**Internet Survey Methods.**

- **Participant Recruitment.** Survey participants were recruited with flyers posted at various locations throughout the state of Michigan, including county health departments and clinics. We also distributed email solicitations, including emails to MSU alumni. Recruitment also took place in person at two community centers in low-income neighborhoods in Lansing, Michigan. It was not possible to consistently determine response rates for these methods of recruitment since we did not know how many people received solicitations.

Recruitment materials instructed those interested to contact the research team at the email address provided. As an incentive, individuals who took the survey were given a $10 gift certificate, redeemable from an online gift certificate distribution company. To guard against potential duplication of participants, the survey was not accessible on an open link. Email
addresses and Internet protocol (IP) addresses were collected from participants and compared against a list of those from previously completed surveys. Five surveys suspected to be duplicates were removed from the full dataset.

- **The Survey Instrument.** The survey opened with information about biobanks, the medical research performed with biological samples donated to them, and about the deidentification of the samples. Five true-false questions were embedded in the presentation of this information (Table 3). These were designed both to help motivate attention to the written material and to check comprehension of it. After each response, participants were either informed that their response was correct or were given the correct response. Survey participants were next presented with a hypothetical scenario in which their doctor asked them whether they would be willing to donate blood left over from a screening test, along with deidentified medical information to the fictional biobank MedCytics. They next read about three Positive Projects previously conducted by MedCytics, projects that had benefited many people and were also unlikely to raise ethical concerns (Table 1). They were then asked whether they would donate their deidentified biological sample and medical information to the fictional MedCytics biobank.

- **Key Dependent Variables.** Willingness to donate was measured with two questions. The first was a yes-or-no response to the following: “My deidentified tissue samples and medical information may be given to MedCytics and used for any research study that it allows, without further consent from me.” The second asked, “Please indicate... how sure you feel about your choice” on a scale from 1 (very unsure) to 7 (very sure). The respondents who indicated that they would not donate or who were willing to donate but rated themselves at 5 or less on how sure they were about doing so were asked to explain their concerns.

Participants were next presented with three Problematic Projects, the description of each designed to raise a different nonwelfare interest. The mental illness project may raise concerns about the stigmatizing effects of being labeled as at risk for mental illness. The diabetes project may raise concerns about potential insurance discrimination against people at risk of diabetes. The cystic fibrosis project may raise concerns about increasing the likelihood of selective abortion. These are all concerns that could be held by prospective donors, even if they didn’t fear that they would be directly affected.

- **Experimental Variations.** Each respondent was presented with either the brief or the expanded description of each project. The expanded descriptions explain how the project might raise specific ethical concerns, while the brief descriptions omit that information (Table 2). The surveys were randomly varied in the following two ways: the order of presentation of the three Problematic Projects—all six possible orders were in the design—and whether the brief or expanded description of each project was presented. Each survey contained only brief or only expanded descriptions.

- **Comprehension Checks.** With the presentation of each project, participants were instructed, “We are not asking whether you would agree to have your tissue used in these specific projects... We are asking whether you would donate your tissue to MedCytics, knowing there is a possibility that your tissue might be used in future projects like these.” After presentation of each Problematic Project, they were again asked about their willingness to donate a biological sample—knowing that there was a chance that their sample might be used for a similar project. As with the Positive Projects, those who were unwilling to donate, or were uncertain, were asked their reasons.

After encountering the first Problematic Project, respondents were also asked, “What are the chances that your tissue will be used in this new project?” and were given these choices: a) “Will never be used,” b) “Some unknown chance of being used,” and c) “Will almost definitely be used.” The correct answer was b), and respondents were informed of this after giving their answer. Those who gave the wrong answer were given the opportunity to change their donation decision in view of the new information. Respondents were asked this question to ensure that they understood they were not being asked to donate to any specific project, including that one. Instead, in donating to the biobank, they would be taking some unknown risk that their biological sample might be used in that way. They could weigh this against the knowledge that they would also be supporting other medical research that they might think serves a valuable purpose.

After responding to the third Problematic Project, participants were asked another five true-false questions, to further check their understanding of biobanks. Each corresponded to one of the earlier true-false questions, but this time each question was phrased in the negative. The survey ended with questions about the respondent’s sociodemographic characteristics, attitudes
that might be related to willingness to donate, such as attitude towards abortion, and attitudes towards and experiences with medical research.

Internet Survey Results.

• Sample Characteristics. Participants responded between March 31, 2011, and February 2, 2012. Total sample size was 683, after removing suspect cases. The sample was 68.2% female. Of the 94% who gave their race, 87% identified themselves as white, 9% as black, and less than 4% as members of any other group. By comparison, in Michigan, in the 2010 census, 79% identified themselves as white, and 14% as black. Our sample's age ranged from 18 to 88, with a median of 30. In Michigan, the median age, among those who are at least 18 years old, exceeds 40.

Over 77% had graduated from college, including 41% who had advanced degrees. Only 25% of Michigan residents have graduated from college. While the sample over-represents the highly educated, its income distribution is fairly representative of Michigan. For the sample, the median reported household income was in the range of $40,000 to $60,000, while for the Michigan population, it is $48,400.

• Recollection of Material Presented. For the true-false questions immediately after presentation of the information about biobanks, 78.7% answered all five correctly, and 13.6% answered four correctly. After going through most of the survey and being asked slightly reworded versions of these questions, 67.1% answered all five correctly, and 20.9% answered four correctly. Thus, we can conclude that most respondents understood the information given to them about biobanks. In response to the question “What are the chances that your tissue will be used in this new project?,” 82.2% correctly answered, “Some unknown chance of being used?” 5.5% said, “Will never be used”; and 12.3% said, “Will almost definitely be used.” The great majority of participants therefore understood that they weren’t being asked to give specific consent to the projects presented in the survey.

• Key Dependent Variables and Data Transformations. After presenting each project, we asked both a dichotomous question as to whether respondents were willing to donate and a question as to how sure they were about their decision. These two variables were combined into a nondichotomous Willingness to Donate variable by multiplying the dichotomous variable (1 = Yes; -1 = No) by the “sureness” to produce a variable that ranged between -7 (very sure about not donating) and 7 (very sure about donating) prior to the transformations described below. Henceforth, we use the term “Willingness to Donate” to refer to these nondichotomous variables associated with each project. When we are discussing the dichotomous variable, it will be so labeled.

The nondichotomous variable gives a more refined sense of the respondent’s attitude than does the dichotomous variable. It permits distinguishing between being certain that one is willing to donate from leaning in that direction but having less certainty. The nondichotomous variable is also more amenable to multivariate statistical analysis than the dichotomous dependent variable. This is because valid statistical inference using the linear model requires that residuals be approximately normal (i.e., that they can be represented by what resembles a bell-shaped curve). The structural equation modeling reported in the Appendix assumes multivariate normality.

Like the Willingness to Donate “sureness” variable, Trust in Medical Research had most responses at the high end of the scale, with a very small number at the low end. Therefore, both of these variables had distributions that were highly abnormal. To approximate normality, these variables were transformed so as to stretch the distances between the largest absolute values (e.g., 6 and 7) relative to the distances among the smallest values (e.g., 1 and 2). We use these transformed variables as the dependent variables for most of our inferential analyses and for causal modeling.

• Effects of Experimental Variables and Positive Projects on Response to Problematic Projects. Our factorial design consists of one within-subject variable (the identity of the three Problematic Projects) and two between-subject variables (the Order in which these projects are presented and Description Type—Brief versus Expanded). A repeated measures analysis of variance shows that the effect of Order is not significant (F[5, 646] = .76). Moreover, for each of the Problematic Projects, there is no significant difference in willingness to donate between the order conditions in which
that project was listed first and the other order conditions. Hence, we combine results of all orders in further analysis.

Prior to introducing the Problematic Projects, all respondents were given information about three Positive Projects and then asked about their willingness to donate their tissue; 93.2% were willing to donate. To compare responses to the different projects and different descriptions, we examine Tables 4 and 5. The data in those tables consists of the 653 cases that have responses to the Positive Projects and to all three Problematic Projects.

As shown in the left side of Table 4, with either the brief or the expanded description, the overwhelming majority was still willing to donate after being presented with any of the three Problematic Projects. In fact, with the brief descriptions, the percentages of people willing to donate after hearing of either the mental illness or the cystic fibrosis projects did not differ significantly from the percentages of those willing to donate after hearing only of the Positive Projects. However, when presented with the diabetes project, the dichotomous willingness to donate was modestly, but significantly, less than for the Positive Projects (McNemar’s test \( p = .017 \)). With the nondichotomous variable (right side of Table 4), we can reject the null hypothesis that the four sets of projects induce the same willingness to donate in our larger population of interest (\( F[3,320] = 3.25, p = .02 \)). However, none of the three Problematic Projects induces significantly different willingness to donate than the Positive Projects.

With the expanded descriptions, over 85% of respondents were still willing to donate. However, the percentage unwilling to donate was approximately twice as large as for the Positive Projects. For both the dichotomous and nondichotomous measures, the willingness to donate following presentation of any of the Problematic Projects differed significantly (\( p < .001 \)) from willingness to donate following presentation of the Positive Projects. For the expanded descriptions, when we use the dichotomous measure of willingness to donate, the identity of the different Problematic Projects makes no significant difference in people’s willingness to donate. However, when we use the transformed nondichotomous measure (Table 4), we find that the identity of the specific Problematic Project had a modest, but significant, effect on willingness to donate (\( F[2,328] = 3.26, p = .04 \)). With the expanded descriptions, respondents were least favorable to donating after hearing of the diabetes project and were most favorable after hearing about the cystic fibrosis project. The difference between these projects was significant (\( p < .05 \)).

Table 4 shows that people are less willing to donate when presented with the expanded descriptions than the brief ones. But do those who are still willing to donate feel less certain about this decision after seeing the expanded descriptions? In Table 5, we look only at those who are willing to donate. For all projects, the sample data shows less certainty among those who read the expanded description. For both the diabetes and mental illness projects, these differences between the certainty of brief and expanded versions are highly significant (\( p < .001 \)).

• Serious Diseases, Medicine, and Medical Research and Race, Socioeconomic Status, and Trust. Out of all participants, 18.5% had experienced at least one of eight serious diseases listed, 8% indicated that either they themselves or a family member had participated in medical research, and 19% were health care professionals. Over 83% rated the usefulness of medical research as a 6 or 7 (on a scale with 1 being “Totally Harmful” and 7 being “Totally Beneficial”). There was less trust, however, that medical researchers would protect the rights and well-being of their research participants. Only 59.6% gave a rating of 6 or 7 (on a scale with 1 being “Don’t trust at all” and 7 being “Completely trust”). Whether or not a participant was a medical professional, had a serious disease, had participated in medical research, or had a family member who had participated in it had no significant effect on trust in medical research or on willingness to donate.

Controlling for type of description, black respondents had slightly (standardized regression coefficient = -.079) but significantly (\( p < .05 \)) lower trust in medical research than others. However, with the same control variable, the effect of race is not significant on the average willingness to donate after hearing about each Problematic Project. Neither income nor education had significant effects on trust or willingness to donate. Moreover, none of the interaction terms involving these variables or description type had a significant effect.

• Abortion Attitudes and the Cystic Fibrosis Project. Abortion attitudes were measured by asking respondents to select among a range of policy options. At one end was “By law, abortion should never be permitted.” At the other was “By law, a woman should always be able to obtain an abortion as a matter of personal
choice.” Two options separated these poles. With the brief descriptions, 87.5% of those who were totally opposed to abortion were willing to donate after hearing of this project, while 96.2% of those who were totally prochoice were willing (a difference of 8.7%). However, with the expanded descriptions, attitude towards abortion had a much larger effect on donations. Only 61.7% of those who were totally opposed to abortion were willing to donate after hearing of this project, while 93.8% of those who were totally prochoice were willing (a difference of 32.1%).

- Causal Modeling. We used structural equation modeling to test and estimate a causal model predicting attitudes towards donating biological samples; full details are in the appendix. Five conclusions emerged from this analysis: 1) the two trust items are measuring a single theoretical construct—Trust in Medical Research; 2) responses to the three Problematic Projects and the Positive Projects are all caused primarily by another theoretical construct—General Disposition to Donate; 3) General Disposition to Donate is causally affected by Trust in Medical Research; 4) seeing the expanded description directly affects the response to each of the Problematic Projects, and the size of these effects differs somewhat between Problematic Projects; and 5) Trust in Medical Research explains a great deal (over 40%) of the variance in General Disposition to Donate.

Discussion

- Problematic Research and Willingness to Donate. This study is the first to document the effect that individuals’ nonwelfare interests have on their willingness to donate biological samples to a hypothetical biobank under a broad consent approach. The results are reassuring but raise questions about the kinds of information that biobanks should provide to potential donors under a broad consent approach and about how potential donors use information regarding their nonwelfare interests in their decisions about donation.

A large majority of respondents, from all demographic groups examined, were still willing to donate after hearing about three Problematic Projects. In fact, for two of the Problematic Projects in their brief descriptions (the mental illness and cystic fibrosis projects), the dichotomous measure of willingness to donate showed survey respondents to be fully as willing to donate after hearing that their sample might be used for those projects as they were after learning about only the Positive Projects. Twice as many respondents who were given the expanded descriptions (which included explicit descriptions of possible negative implications of the research) were unwilling to donate as for the brief descriptions. And those willing to donate were somewhat less certain about their decisions than those who received the brief descriptions. This is not surprising, since many people would not have the background knowledge to imagine these implications on their own.

However, even when presented with the expanded descriptions, approximately 85% of respondents were still willing to donate. Our results are consistent with many previous studies reporting large majorities willing to give broad consent for research with their biological samples. More importantly, our results suggest that recruiting biobank donors using a broad consent approach will not be substantially undermined if they are provided with more information about nonwelfare interests.

Nonwelfare interests had only a modest effect on respondents’ willingness to donate biological samples to a hypothetical biobank.

- Donors Need Information about Nonwelfare Interests. The effect that the expanded descriptions had on willingness to donate and on confidence in that decision suggests that any efforts to accommodate nonwelfare interests among biobank donors will require informing them about more than the scientific objectives of research projects. They will also need information about the known clinical, social, or other practical implications of research projects. Without such information, very few donors will be able to discern how their moral concerns might be relevant to their decision. This information is not routinely provided by most biobanks, and developing it may require the involvement not only of health researchers, but also of bioethicists, social scientists, and others.

However, our study does not suggest what form such information should take. We presented selected examples of specific projects that had previously been conducted by our fictional biobank. Donors might instead be given information about types of nonwelfare interests that might be affected by future research (e.g., research that might increase insurance discrimination), without mention of any particular study. Or they might be pointed to a website cataloging all the research proj-
fects supported by the biobank. Information relevant to nonwelfare interests might be included in each project description, but it would be the responsibility of the prospective donor to ascertain whether any are of concern. How to best provide information about nonwelfare interests is an important policy question that our study does not resolve.

- **Ethical Balancing.** The fact that presentation of nonwelfare interests had only a modest effect on willingness to donate has two possible explanations. First, it is possible that some people think that each Problematic Project has greater potential for doing good than for doing harm. This result may also be due to the ethically complex decision the donor faces. A decision not to donate means that the donor avoids the risk of contributing to research projects that he or she finds morally troubling in some ways. But it also means that the donor is not contributing to medical progress, a goal the donor may strongly support. We deliberately built this tension into our survey by first presenting our respondents with three Positive Projects and then reminding them of these as we presented each Problematic Project. We have little doubt that the initial presentation of morally exemplary research, and repeated emphasis of it, may have reduced the negative impact of the problematic projects on participants' decisions.

An opposite problem would have plagued a design that reversed the emphasis. The choice is a methodological quandary. We favored the positive emphasis for two reasons. First, we believe that the vast majority of biobank research using biological samples raises no concerns for anyone. If so, a presentation that emphasizes such research is true to the facts and is appropriate to use in recruiting donors. We also believed from the start that a decision about donation was inherently a moral one that required trade-offs between the donors' hopes and their fears about how their biological samples might be used. We intended, then, to implicitly confront our respondents with the challenge of balancing these opposing considerations. Our results suggest that although the risk to their nonwelfare interests is taken to be relevant, their final decisions often favor contributing to medical progress.

A particularly striking example of this phenomenon is the effect of respondents' attitudes towards abortion. Where the relationship to abortion is made clear (in the expanded description of the cystic fibrosis project), the respondents' attitude towards abortion had a moderately large effect on the dichotomous Willingness to Donate variable. But even with the expanded description, over 60% of those who regard abortion as never acceptable are still willing to donate after learning of this project. Perhaps they are willing to take a risk of indirectly contributing to the number of abortions for the sake of the good their donations will otherwise do. Whether this "ethical balancing" hypothesis is an adequate explanation for the modest effects of nonwelfare interests on the decision to donate is a question for future research, including an analysis of the qualitative data that we gathered but do not report here.

- **The Importance of Trust.** The variable that most affects willingness to donate is trust in medical research. Other studies have also found that trust affects the willingness to participate in medical research. It is striking that the effect of trust on willingness to donate overshadows the effect of being presented with potentially problematic uses of biological samples, regardless of how those are described, and overshadows other plausibly relevant factors like education, income, and race.

Our proposed causal chain assumes that race affects trust in medical research, which, in turn, affects general disposition to donate. This helps explain the fact that, although the slightly lower level of trust among black participants in our study than among other participants is statistically significant, black participants were not significantly less likely to donate to the fictional biobank. This is because the imperfect correlation between trust and disposition to donate attenuated the initially small effect of race on trust to the point where it was not statistically significant.

As indicated earlier, our sample under-represented blacks and those of low education. However, we found that these variables had very small effects on willingness to donate. Hence, the fact that our sample was not representative of the Michigan population should not have substantially affected our conclusions.

Our results suggest that biobanks that do a good job of cultivating trust among their donors can afford to disclose more of the potential downsides of some research projects without significantly affecting the successful recruitment of donors. Methods for building trust include such things as increasing public transparency about biobanks' operations or creating forms of public accountability, such as community advisory boards. However, presentation of potentially problematic uses in the expanded descriptions does appear to modestly reduce people's trust in the integrity and
value of medical research. This is not surprising if such
trust is commonly based in an unambiguously rosy
view of the research enterprise and its effects. Biobanks
will need to keep this potentially corrosive effect on
trust in mind when providing information relevant to
donors' nonwelfare interests to avoid inadvertently
suggesting that a large proportion of biobank research
projects have morally troubling implications. It may be
important to place this information in the context of the
full spectrum of research being supported, as we did by
presenting the Positive Projects.

Our research shows that disclosure of information
relevant to donors' nonwelfare interests can modestly
reduce their willingness to donate to a biobank under a
broad consent approach. We do not yet know how
donors interpret and process this information. Do some
take these projects to be emblematic of all research,
which becomes tainted by association? Do some see
them as only remote possibilities and, hence, irrelevant
aberrations? Do some interpret them as a risk to be bal-
anced against some set of benefits to their participation
in the biobank? These questions are worthy of future
research.

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Tables and Appendix

All tables and the Appendix for this article are available at the
IRB: Ethics & Human Research website.

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Ethics and Regulatory Complexities for Pragmatic Clinical Trials

Some patients do not receive the best care possible, either because research to support clinical decision making with high-quality evidence is lacking or because evidence-based practices are not routinely implemented. Pragmatic clinical trials (PCTs), which include patients in routine clinical practice settings and typically incorporate comparative effectiveness research (CER)—that is, comparing the safety and effectiveness of diagnostic, therapeutic, or delivery system options—can help overcome these challenges. The advent of research methods that use cluster randomization and leverage patient data from electronic health records (EHRs) to increase the sample size of trials at much lower costs is enabling major national initiatives to generate the data needed to improve care. These include the Health Care Systems Research Collaboratory and the Patient-Centered Outcomes Research Network (PCORI).

As evidenced by recent controversy, research that evaluates elements of usual medical practice may encounter ethical and regulatory challenges. But unless significant progress is made toward efficient functional approaches to these issues, the evidence gap for clinical practice will remain. Based on our experiences with the NIH Collaboratory and PCORI, we describe 10 complexities that must be unraveled in ways that enable vital research while also protecting the rights, interests, and welfare of research participants.

Consent
In CER and PCTs that test established interventions for which there are minimal incremental risks and burdens compared with usual clinical care, obtaining conventional written informed consent may be not only ethically unnecessary but may render such research impracticable because of logistical burdens and may introduce selection bias. Proposed alternatives include notification, opting out, and truncated consent, but there is little information regarding patients’ attitudes toward these largely untried approaches. Moreover, modifications of consent practices for research entail important regulatory considerations and usually require a determination of “minimal risk.” They also necessitate agreement on the specific approach among institutional review boards (IRBs) and regulators.

Risk Determination
Although federal regulations provide seemingly straightforward definitions of minimal risk research, making these decisions can prove complex. Experts and IRBs may disagree, especially about whether risk should be judged relative to a healthy person or to the condition under study. These issues are often heightened in pediatric research. Guidance is clearly needed. Meanwhile, investigators should articulate a clear rationale for risk determination and work closely with IRBs to facilitate review.

Nature of interventions
Interventions that are the focus of CER and PCTs may present risk and consent issues similar to those in traditional clinical research; however, interventions directed at clinicians and systems can be categorically different. For example, testing a reminder system for clinicians or changing bathing procedures across hospital units involve interventions for which patients are not typically engaged directly. Instead, professionals are targeted for the interventions as mediators of risk, thereby complicating their ethical assessment. As these issues are addressed, it will be useful to assemble descriptions of “solutions” so that others may learn from them.

Identifying Research Participants
In CER and PCTs, it is essential to identify both direct and indirect participants in research. For example, although an intervention may be directed at clinicians or the environment, outcomes may be measured among patients and risk or benefit may extend beyond the immediate target of the intervention. When interventions are directed at the environment, staff and visitors may be affected as well. Additional evaluation and guidance regarding these complexities are needed.

Regulated Products
Unlike traditional clinical research, CER or PCTs that evaluate an off-label use for an approved product would not necessarily be conducted under a US Food and Drug Administration (FDA) Investigational New Drug application because the research is not intended to support a new labeling indication. In this scenario, sponsors and IRBs, and regulators may face challenges stemming from confusion about appropriate regulatory authority. Moreover, except in very limited circumstances, FDA regulations require written informed consent. Consequently, there is a need for a functional regulatory approach that encourages vital research, offers protection to participants, and appropriately controls medical product use.

Institutional Review Boards
Conducting CER and PCTs across multiple health systems may involve myriad IRBs in review and oversight. Although IRB oversight must account for local conditions that affect the rights and welfare of research participants, harmonizing determinations about risk, consent, and related issues is crucial for ensuring the integrity of CER and PCTs. Models such as central IRBs, reciprocity agreements, and shared review have been implemented in large-scale multicenter research; however, acceptance at local levels varies substantially. Thus, demonstration projects involving alternative review models should be encouraged.
Research and Quality Improvement

Comparative effectiveness research and PCTs can share attributes with quality improvement (QI), including cluster randomization, interventions directed at clinicians and the environment, secondary uses of EHR data, and uncertainty about whether consent is necessary and, if so, what type it should be. Further, ethical oversight of QI is usually truncated, thereby expediting implementation. On one hand, to evade being labeled as research (thus triggering burdensome oversight), QI initiatives may avoid using rigorous methods such as randomization or complex multivariable statistical analysis. Instead, they may be conducted in a manner unsuitable for drawing reliable conclusions to inform practice and may have design shortcomings (inadequate power due to small sample sizes, inadequate historical controls, and before-and-after-use designs). On the other hand, CER researchers could label their work as QI in an attempt to avoid regulatory scrutiny. Such tactics are not acceptable. Alternative approaches that match the degree of oversight to risk rather than relying on arbitrary "research vs QI" distinctions have been proposed.6 There is concern about individuals deciding for themselves if a particular initiative represents QI and whether the initiative does not require scientific scrutiny and regulatory review and oversight, because practice changes made based on the results of QI can have serious consequences for patients.

"Vulnerable Subjects"

The current regulatory model identifies many classes of "vulnerable subjects" (ie, research participants) who receive additional protections, such as limitations on the types of research that can be conducted and complex consent provisions. These regulations may thus create a barrier to the efficient conduct of CER and PCTs, because modified or waived consent and the enrollment of large numbers of people in clusters do not allow opportunities for intensive individual engagement at enrollment or during the study. These potential barriers should be considered as current regulations are revisited.

Data Monitoring

Data monitoring plans, which may include data monitoring committees, are now common in research. Many are predicated on the notion that data are being regularly collected for research purposes and can be analyzed centrally to assess safety and efficacy. However, PCTs often use routine clinical data aggregated at the end of the trial; thus, no interim data are available for review. Nevertheless, given the real possibility that interim data might provide signals of safety or efficacy suggesting that a trial should be modified or stopped, data monitoring plans sensitive to these concerns should be developed.

Gatekeepers

In some circumstances, representatives with authority to speak on a group's behalf have been approached for permission to conduct research involving the group. Although ethical issues associated with gatekeepers have been addressed for some international research and cluster randomized trials,7 such issues within health care systems are not well described. Nevertheless, gatekeepers can enhance or forestall the possibility of conducting research. For example, health system administrators may be opposed to research that might demonstrate a weakness in their delivery systems. Such roles raise questions about authority, legitimacy, and conflicts of interests and obligations—issues that will become especially important to a successful transition to learning health systems.

Moving Forward

Widespread availability of EHR data, further development of CER and PCT methodologies, and new levels of patient engagement raise the possibility of improving health outcomes. However, this also brings into sharper focus the uncertainties and operational inconsistencies in current ethics and regulatory paradigms. Early lessons drawn from the NIH Collaboratory point to the benefits of involving multiple stakeholders in shared conversations about proposed research.2 Further discussion is needed to allow these issues to be explicitly addressed through policy guidance, scholarship, and empirical research. These essential tasks must be undertaken to realize the potential of a national learning health system—one capable of producing the volume of high-quality evidence needed to support recommendations and therapeutic decisions for patients and populations.

REFERENCE


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Getting ahead of the wave: MOOC's and human subjects research

by Rebecca D. Armstrong, DVM, PhD, director of research subject protection, at the University of California, Berkeley and a member of PRIM&R's Education Committee

In early June, I was invited to attend a multi-day convention, The Asilomar Convention for Learning Research in Higher Education, co-hosted by Stanford University and the Massachusetts Institute of Technology to share my IRB expertise. The event, which was largely supported by the National Science Foundation, tackled the issue of massive open online courses (MOOCs), educational research, and, by extension, human subjects research and IRB review. Knowing next to nothing about MOOCs, what I learned was fascinating.

There is now software that can track an online learner’s every move throughout the learning process, and researchers are hungry to analyze the "big data" that is generated by the more than 50,000 course enrollees from around the world, with the goal of improving learning. Educational researchers are getting data from commercial companies that host MOOCs, such as Coursera and edX, or from their own in-house courses that utilize similar platforms. Typically, at the beginning of a course, enrollees accept (i.e., click on) a basic user agreement, but they may not realize that included in that agreement is language that allows for the use of their data in a research field referred to as learning analytics. This lack of awareness is somewhat akin to the recent Facebook study controversy. MOOCs, and the abundance of data that results from these courses, are likely to have a significant impact on research in the learning sciences. Those of us involved with the IRB can either be a hinder or facilitate research in this new domain. IRB professionals and institutions need to consider what is “normal” educational practice per 45 CFR 46.101 (b)(1). Where do data domains such as log files and text data fit? What are distance/online learners’ expectations of how their data will be used? Is this research exempt? What about when a learning experience is modified based on real-time analysis of learning data? Does this intervention require the learning experience (and research study) to undergo expedited level review? How should the educational databanks that result from MOOCs be managed? And, how do institutions view those participating in MOOCs? Are they seen the same as students who attend on-campus courses? And, if so, what are the implications of that decision with respect to the protections afforded under the Family Educational Rights and Privacy Act? Do the same rules apply to on-campus courses that utilize MOOCs to generate data that can be analyzed (e.g., key strokes, use of resources, sequence of learning activities, etc.) to improve learning?

In much the same way that attendees at the Asilomar Convention did, those of us in human subjects research compliance need to start thinking about the aforementioned questions and many more. Institutions' IRBs will need to be proactive and promote collegial science as this field moves forward, while still finding ways to respect privacy and the voluntary participation of learners. To begin this discussion at your institution, I encourage you to review the two-page principles document that was developed by the attendees at the Asilomar Convention. Several of the agreed upon principles are informed by The Belmont Report. In closing, stay tuned! It's going to be an interesting ride in the realm of educational research, learning analytics, and technology whether at a distance or in your local higher education classrooms.