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Research on informed consent conducted in wealthy countries has found that subjects’ understanding of research often is incomplete or, at times, inaccurate. Other studies reveal a subtler clouding of the distinction between treatment and research, whereby patients/subjects know they are in research, but view research as treatment for their disease. Such a misunderstanding may compromise meaningful decision-making about participation in clinical trials.

The minimal empirical research on informed consent that exists from developing countries suggests that trial subjects in the developing world encounter similar challenges. Research participants in resource poor regions may face additional barriers in informed consent related to language, education, culture, beliefs, and/or decision-making styles. For example, in a study in Haiti on HIV transmission, only three of 15 potential participants scored well enough on a true-false comprehension test to be enrolled, and investigators in The Gambia found that 90% of participants in a vaccine trial knew the purpose of the vaccine, but only 10% understood placebos.

Autonomous decision-making, a standard goal of existing national and international research ethics guidelines, may be especially challenging for research conducted in international settings. It is expected that autonomous decision-makers voluntarily agree to participate in clinical trials. Yet voluntariness can be compromised by a variety of factors, including poverty, limited access to medical care, and patterns of decision-making related to gender, socioeconomic status, or culture. The political and human rights context of studies can also compromise voluntariness.

Moreover, in some contexts, potential participants may feel they cannot say no to a professional’s recommendation that they enroll in a study. It has been well documented in both U.S. and international research that trust in researchers contributes significantly to participation in research, regardless of whether participants understand the study. Finally, concerns have been raised that financial or medical incentives may create undue influence to participate in research, although the degree to which inducements are problematic remains a matter of debate.

Given the limited empirical data documenting understanding and voluntariness in international research, we conducted a qualita-
tive pilot study to learn how participants in international clinical trials define research and why they enroll. We interviewed participants in three developing countries who were participants in six different randomized, controlled infectious disease trials. We hope future studies will lead to interventions to improve informed consent, research review, and policy.

**Study Methods**

- **Sampling Frame and Recruitment.** In-depth interviews were conducted with 26 research participants from six different randomized controlled trials studying a clinical intervention designed to prevent or ameliorate an infectious disease in developing countries. Trials spanned three countries, two in Africa and one in the Caribbean. Three trials were conducted in each country. Two studies tested drugs to prevent tuberculosis (TB) in HIV-infected populations, two tests interventions to reduce maternal to child transmission (MTCT) of HIV, one tested the efficacy of a vaginal microbicide in preventing heterosexual transmission of HIV, and one examined the efficacy of a malaria treatment for young children in a drug-resistant region. We deliberately sought interviews with participants in trials in different countries studying different infectious diseases in order to determine whether our findings transcended study topic and geographic region. We also deliberately chose randomized controlled trials (three were placebo-controlled) from which to recruit participants because the literature on randomization shows it is a difficult concept to communicate and understand. U.S. or European sources funded all the trials, which were collaborations with one of four different U.S. or European research institutions. All the trials were conducted at an established referral hospital or health center in the relevant country. These facilities served poor communities who generally lacked access to basic infrastructure such as running water and electricity. Access to regular, quality health care outside the study ranged from minimal to nonexistent.

Participants selected for this pilot study were enrolled in a clinical trial or had completed trial participation within the last year. Using convenience sampling, we asked research staff of the ongoing parent trials to refer participants to us who attended the research clinic on the days interviewers from our study were visiting. For completed trials, research staff from parent trials invited up to five former participants to be interviewed for this pilot project. Everyone referred to us agreed to participate and gave witnessed, oral consent. Interviews were conducted in the hospital or clinic setting where the six studies occurred. Participants were not paid to participate in the study. However, after the interview was completed they were given a small thank you gift such as barrettes for their children or a bar of soap.

- **Interview Guide Development and Interview Conduct.** We used a semistructured interview guide based on the general theme of motivations, understanding, and voluntariness. Interviewing began with general questions (such as “Tell me about a typical day for you”) and moved to increasingly specific questions about the research trial and the individual's participation. The interview guide outlined general topics for discussion (see Appendix); interviewers continued with probing follow-up questions as appropriate. We modified the interview guide as the study progressed and as new themes emerged during interviews. One or two study members (JA and/or NK) conducted interviews in a private room that generally lasted 30-40 minutes. All interviews were audiotaped for subsequent transcription.

- **Translation.** All participants spoke and responded in a local lan-

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**Appendix: Interview Field Guide**

- Tell me a bit about yourself. What do you do? Do you have children?
- Why did you come here today?
- Can you tell me about this activity/study/project?
- What is the goal of the activity/study/project?
- What is a research study?
- Who first talked to you about the study? What did they say?
- Did you consult with anyone (family or friends) before you decided to join this study?
- Why did you decide to join the study?
- What are the possible advantages/disadvantages of being in a study?
- Do family and friends know about your participation in this study? Did you tell them about it? Why or why not? How did they react?
- Do you feel like any person forced you to be in this study? If so, whom? How did they do that?
- Do you remember signing a form? Can you tell me what that was for?
- If you want to stop being in this study, do you think that is possible?
- Would you recommend to a friend of yours to join/not join a research study? Why/why not?
guage. In one country (two trials), the interviewer/investigator for this study spoke the local language and was able to conduct interviews in the local language. In this setting, interviews were audiotaped, and the investigator translated interviews into English. The English versions then were transcribed. In the other two countries (four trials), the staff of the parent trial provided a translator of convenience. A research nurse was a translator for one of the trials, a nonresearch nurse was a translator for two of the trials, and for the other trial the translator was a visiting relative of one of the research staff who was a university student and spoke English. For these four trials, the interviewer, the subject-responder, and the translator sat together in a private room. The interviewer from our staff asked questions in English, the translator repeated the question in the local language, the respondent answered in his/her local language, the translator repeated the answer in English, and then the next question was asked. Only English sections of audiotapes were transcribed for analysis.

**Data Analysis.** An inductive coding approach was used, whereby the coding scheme was developed from patterns and themes that emerged from the data. Data were segmented manually into categories or groups according to the coding scheme. In the final stage of analysis, a matrix was developed to compare major themes, patterns, and connections within and across interviews and across studies.

**Study Findings**

**Demographic and Background Information.** All but one of the respondents was female. We have demographic information for approximately half of respondents. Of these respondents, almost all had less than eight years of formal education, and about half had less than five years of education. About two-thirds were between 20-30 years old and about one-third were between 31-40. Of the 16 for whom we have employment information, five were unemployed, seven were street vendors, and four had domestic positions. About three-fourths were married and all had children.

**Major Themes in Data.** Five major themes emerged from the data, each of which will be described in greater detail below: 1) participants generally understood the purpose of the clinical trial in which they were or had been enrolled; 2) respondents generally did not understand randomization, treatment allocation, or that different trial participants would receive different interventions; 3) the opportunity to receive better medical care was a major incentive to participate in the clinical trials; 4) respondents often extrapolated from beliefs about their personal outcome to their beliefs about the outcome of the trial; and 5) most participants understood that joining the trial was voluntary, but several felt they could not leave the trial once enrolled. Of note, due to the iterative nature of the interview process, we did not ask every respondent every question. Where possible, we report the numbers of respondents with whom each topic was discussed as well as the general direction and range of responses within each theme.

**Study Purpose Generally Understood.** Twenty-five respondents were asked to define research and/or the activity in which they were participating. Nine explicitly stated that the research or activity was to learn about a new medicine, or to learn if a new medicine works. A woman in an MTCT HIV trial said, "They did give us something to drink so that our babies cannot be affected," and a woman in the microbicide trial said, "This research was about the product . . . like the gel that you put into the vagina if it can prevent STDs." Another three respondents appreciated that the activity was to learn about the condition in question, but never mentioned the testing of a particular intervention. One respondent in the MTCT HIV prevention trial initially said she could not explain research. When probed she said, "Research is great in learning about HIV." A woman whose child was in the malaria treatment trial said, "The researchers would like to know what's really causing malaria."

Nine respondents knew they were at the clinic or hospital because of a particular illness they had, but none mentioned anything about research, learning, uncertainty, or investigation. For example, a woman in the MTCT HIV trial said the activity is "for the baby to take the medicine"; another woman in the same trial said, "She is attending for HIV." A woman in the TB/HIV prevention trial said the project was for "medicines, things for health, to keep us alive." Five of these respondents, and four others, said they had no idea whatsoever what research was. One respondent said, "Research project? They build houses?" A translator for a woman whose child was in the placebo-controlled malaria trial explained, "She does not know what research is. She thought they have already done the research, and they are trying to implement the results of the research with these children."

**Treatment Assignment Not Well Understood.** Interviewers asked respondents whether all participants in the same trial get the same drugs. Only if a respondent answered no did we ask how researchers assigned treatments or interventions in the trial. It was typical for respondents across different studies to say they did not know how researchers decided to give which participants which treatment. Three specifically said all participants get the same drug, and four specifically said participants get different treatments. Another said
that, while she did not know, it would make sense to her that people with different amounts of malaria in their blood might get different interventions. Two women enrolled in the same MTCT HIV trial responded that women received different drugs. They believed this meant they were in different studies, however. Another thought the researchers selected the drug specifically for her because of her particular medical history. According to the translator, "She said they decided to give her AZT because she had had a miscarriage." Most of the mothers of children in the placebo-controlled malaria study thought all the children were receiving the same treatment. One mother told the translator the children "are getting the same kind of medicines because they were suffering from the same kind of malaria. She said they might be getting different amounts of the same medicine." Another woman from the malaria trial who referred to the consent form said she "is sure that they are all getting the same drugs because the paper says they are all given the same drugs." None of the respondents who were subjects in the three placebo-controlled trials mentioned the possibility that they had received a placebo or no treatment as part of the study.

- **Hope for Access to Treatment or Care Is Primary Motivation for Participation.** Seventeen of 18 respondents who provided reasons why they joined the research or activity cited the desire for help or for treatment. Most of the comments reflect the view that the primary motivation was to obtain medical care. Two respondents said they thought the treatment provided through research was **better** than the available medical care. Said one participant in a TB/HIV trial, "I thought that they would help us." Another trial participant told the translator, "She doesn't know any place [besides the study] that she could get help." A participant in a different TB/HIV trial said, "They work with you. Whatever illness you have, they help you . . . they gave you a whole bunch of medicine." She told the translator "if she hadn't been in the project she would have died already." A mother of a child in the malaria trial reported: "She came because her two kids were sick with malaria. So she went to the outpatient clinic and they referred her to come in." Among those who thought care in research was better than what they could obtain outside a clinical trial, we heard, "[Care is] better in the research than in the clinics" and "She signed the form because the medicines they are giving are new and it may be helpful." Two respondents, both in the microbiode trial, said their desire to be tested for HIV motivated them to join that study.

- **Extrapolating from Beliefs about Personal Outcome to Beliefs about Trial Outcome.** Six respondents volunteered a belief that the research intervention worked because they had experienced a positive outcome. For example, a woman in the placebo-controlled microbiode trial said she was "sure the drug worked because she tested HIV-negative." When asked if the gel will prevent STDs, she said "yes because she used it and was sure it was a good product." We asked, "How does she know it was a good product?" and were told, "Because when she used the product there was no problem with the product, and when it was given to the partner there was no problem."

- **Participants Did Not Feel Forced to Enroll in the Research Studies.** We asked all but three respondents whether their participation in the clinical trial was voluntary. One respondent said she did not remember; three did not directly answer the question. Of the remaining 19 respondents, all indicated they had participated voluntarily. Eight specifically said they had been told that participation was up to them and/or that no one had forced them to join. For example, the translator for a participant in a TB prevention study reported the woman said she "did not feel forced into the study. If you don’t want to enter you don’t have to." Ten respondents referred to the consent form as evidence that the choice to enroll was theirs. According to the translator for a participant from the malaria study, the woman "said the paper said she had a right to say no. After thinking about the situation with her child she decided to join." Another woman reported that she had signed the paper "to show the study she agreed to do the research . . . she only does that in this clinic, not the other clinics." The notion was that for regular medical care, there are no forms to sign, but in research, the papers are there to say one can refuse.

Four respondents said they did not realize they could quit the trial if they wanted to. Moreover, two suggested that because of the benefits the trial provided, it would be ridiculous to leave the study once enrolled. According to the translator for a participant in a placebo-controlled TB trial, "Nobody forced her into the project. She said she cannot leave at any time because it is bad. But that is because they give you the gift of life and, therefore, it is bad to leave."
Discussion

In interviews with 26 clinical trial participants from three countries, we found variation in their understanding about the purpose of the clinical trial and about the voluntariness of trial participation. Many of the respondents viewed research as a “learning” activity, though some were specifically aware that research is designed to test the effectiveness of a new product. In almost all cases, respondents knew that the trial in which they participated focused on a specific disease that they could name. Most seemed eager to have joined the trial in order to obtain benefits from participation. None reported being forced to participate.

Ten of the 26 respondents said that the consent form for the clinical trial symbolized to them that they could drop out of the study or activity. However, it is somewhat troubling that a few respondents said that once enrolled in a trial, they believed they could not withdraw from the study. This finding is consistent with other published accounts of trial participation in resource poor countries. For example, an investigation in Bangladesh revealed that 48% of research participants did not know they could withdraw after joining a trial, and in an HIV trial in South Africa, only 24% believed they could leave after enrollment.

Respondents generally knew that the clinical trial in which they were enrolled was a research study. However, there was no evidence across interviews that participants knew they were being randomized. Moreover, no participant in any of the three placebo-controlled trials mentioned the possibility of receiving a placebo, and no participant expressed uncertainty about whether the research intervention would work. When respondents were aware that different trial participants might receive different medications, they provided their own explanations to make sense of differences in allocation. Featherstone and Donovan have shown that research participants often make sense of difficult research concepts such as randomization or equipoise by developing detailed narratives. They further suggest that even providing seemingly clear and accurate information does not ensure accurate understanding of research concepts. Indeed, many studies have documented that research subjects do not understand randomization and placebos, even when research staff specifically explain these concepts and practices to them.27

There were limitations to this study. Although respondents were participants in several different clinical trials conducted in three resource poor countries, it is difficult to generalize our findings based on the responses from 26 individuals. Additional empirical research on informed consent in resource poor settings is needed to validate or refute our findings and recommendations, including studies that focus on individuals invited to participate in clinical trials who chose not to enroll. Our sample was limited to those who agreed to participate in a clinical trial; it is possible that those who rejected research participation would add important insights about motivation, understanding, and voluntariness.

A significant limitation of our findings is that, for the four studies in which we used translators of convenience, we were unable to validate the accuracy of translation. Particularly for qualitative research, where the exact quotes are themselves the data, accurate translation is critical to the validity of the conclusions drawn. While we asked all translators to translate verbatim, it is possible that, rather than doing so, some translators summarized the respondents’ answers in a way that did not accurately reflect their responses. Finally, two limitations exist in all informed consent research of this sort. First, we did not know what the research staff told respondents about the clinical trial in which they participated. Thus, if they misunderstood an aspect of the trial, we do not know whether this was due to how the research was described to them or to their inability to understand the information they were given. Second, since we conducted some of the interviews several months after respondents had enrolled in the study in question, what we interpreted as a lack of understanding may have been a problem of recall.

Recommendations

We recommend that future research examine creative approaches to improve understanding in international, resource poor settings. Furthermore, formative research should guide the development of such interventions, as well as assess how well participants understand the information ultimately provided. Perhaps most importantly, we recommend that a higher bar be used to judge research acceptability when conducting research where participants may not understand key research procedures, as well as the defining feature of clinical research. We offer specific recommendations along these lines.

1. Conduct more empirical research testing interventions to improve understanding of research conducted in resource poor countries. It is essential that scholarly work be conducted measuring the effect of creative interventions to improve participants’ understanding of research, particularly in settings where individuals are not very familiar with the concept of research and thus may conflate research with health care delivery. We are aware of no published studies documenting the effect of consent interventions in developing countries. In U.S.-based studies, requiring patients to verbalize risks and benefits themselves or having research staff provide "cor-
rected feedback” to participants has been shown to be effective. Use of simplified material and pictures improved understanding, and another study found patients preferred simplified consent forms. Two studies found that the use of video did not result in improvement of understanding but improved recall one to two months later. While these studies demonstrated improvement in certain aspects of research understanding, we are aware of no studies that improved understanding of the critical fact that clinical benefit and/or treatment allocation were uncertain. Creating and evaluating alternative means of communicating consent procedures is critical. U.S. Institutional Review Boards (IRBs) should remember that a variety of approaches, either in addition to, or instead of, written consent forms, can be legally acceptable means of educating participants and documenting consent. Alternative approaches seem particularly important in light of the finding from one published study that, where more than 80% of international participants are illiterate, 60% of investigators still use written consent forms.

2. Test participant understanding and engage in formative research. “Formative research” is a form of rapid ethnographic assessment involving target populations before a study is initiated, particularly in large or multisite trials. This approach can help identify appropriate terminology and locally relevant analogies to explain challenging concepts and generally highlight what participants find difficult to understand. Once a study begins, researchers should, as a matter of course, conduct informal assessments of participants’ understanding and why they enroll. Research staff can then engage in group and/or individual discussions to try to clarify misunderstandings. We know from previous work that, while 65% of researchers think it is desirable to build formal mechanisms to test participant understanding into a study’s design, only 16% of U.S. investigators working in developing countries do so. If investigators asked qualitative questions before or during a study to assess understanding, they could provide “corrected feedback,” ultimately improving understanding. Formative research in the planning stages of a study can also be invaluable in identifying what participants do and do not understand about research, both generally and in relation to particular protocols. Learning not only what participants find unfamiliar, but also what their beliefs are regarding health care, research, malaria, HIV, and other relevant conditions, may influence the content of informed consent materials. Formative research also can identify preferred methods for learning information, such as group sessions, involvement of family members, and use of peer educators.

3. Give more attention to risks and benefits when participants do not fully understand. Until further empirical research can suggest additional strategies to improve understanding, researchers will continue to conduct clinical trials even though participants may not fully understand the nature of research or that clinical benefit is uncertain. The normative question becomes whether researchers should continue to enroll participants under such circumstances, and/or what safeguards might be put in place. An incomplete understanding of research can raise concern in two ways. Conducting research with someone who fundamentally does not understand they are in research and/or that efficacy is uncertain is potentially exploitive, in that the researcher is using the participant to further the agenda of others without having obtained valid consent to do so. Second, without a full understanding of what research is about, participants may experience harms. Those who do not understand, for example, that a vaginal microbicide may not be efficacious, or that half the women get placebo, may be more likely to engage in unprotected intercourse. Mothers who mistakenly believe their child’s malaria has been cured may be less vigilant about seeking medical care when symptoms persist. Indeed, it was jarring to learn from our respondents who participated in the microbicide trial that they enjoyed sex more because they felt protected by the microbicide or that their husbands were happy because the women were using something to protect against HIV transmission when we knew that half of the women in the trial received placebo, and that trial results revealed that the microbicide increased the risk of HIV transmission.

However, while participants’ lack of understanding is prima facie ethically problematic, one should not conclude that incomplete understanding necessarily ought to forbid the conduct of all research, or that incomplete understanding is of equal concern in all types of research. Indeed, requiring full understanding might lead to the termination of the bulk of health research in all regions of the globe, rich and poor alike. Instead, we propose that to adequately determine how much understanding is necessary for particular studies to go forward, studies should be evaluated on a case-by-case basis, based primarily but not exclusively on the risks posed by lack of understanding. The determination should be what the effect of the risk of misunderstanding would have on the subject or the community and what the risks and benefits of the study are overall. High-risk studies demand careful assessments of participant understanding, greater demonstrated levels of participant understanding, and greater expectations of benefit than do studies that pose lesser
risks to research participants. If a misunderstanding could lead to potentially dangerous outcomes—as in the example of the microbicide trials or with HIV vaccine trials—researchers must always assess participant understanding. When individuals do not fully understand the critical components of a trial, they must be excluded from participation.

Conversely, for some lower risk studies, after first ensuring that investigators devote sincere effort to improving participant understanding, it may be appropriate for them to proceed even with the knowledge that some participants don’t understand they will receive a placebo or why the study is being conducted. The justification for going forward is that the research might produce important generalizable results without undue risk to trial subjects. In populations where it is questionable whether there is understanding of essential concepts, and thus whether valid consent is obtained, a more vigilant examination of risks and benefits must be undertaken.

4. Make careful distinctions between provision of benefit in research and coercion. Our respondents generally felt free to join or to refuse to participate in a clinical trial, and most viewed enrollment as being in their (or their children's) best interests. Indeed, several explicitly said they had nowhere else to turn for medical care, and a few said without the research intervention, they would have died. While respondents may have been correct in believing that joining would be to their benefit, the notion of voluntary "choice" inevitably is different in settings where there are few reasonable alternatives for medical care. Moreover, given that settings of deprivation are fertile ground for public health problems to be highly prevalent and severe—and thus will and ought to be the settings for public health research—they raise challenging moral questions about what are appropriate levels of benefit for those with so few health care or material resources. Researchers and IRBs are right to consider appropriate levels of benefit, or inducement, in research studies in resource poor settings. At the same time, it is critical not to conflate the provision of beneficial research in a community with few good alternatives for medical care with coercion. As always, it is incumbent on researchers and reviewers to examine the study's risks and the acceptability of all individual study procedures. The provision of benefit to participants is a good thing. No amount of benefit, however, can be used to justify unacceptably risky research or otherwise morally problematic study procedures.

Acknowledgments

This work was supported in part by a grant from the National Institute for Allergy and Infectious Diseases, National Institutes of Health: Ro1 AI/T135AI07660. We are extremely grateful to the investigators who gave us permission to speak with participants in their research studies.

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7. See ref. 4, Benatar 2002.
13. Investigators who allowed us to conduct interviews at their sites were promised confidentiality with regard to study title, institutional affiliation, funder, and country.


27. See ref. 19, Taub et al. 1981.


Vulnerable Subjects and Canadian Research Governance

Bravo et al. have recently suggested in this journal that the Québec civil law should be changed to eliminate the need for proxy consent by a court appointed legal representative in order to conduct research involving cognitively impaired individuals. They prefer more informal models that would defer to family members. In contrast, Tomossy and colleagues have argued for the adoption of statutory protections for vulnerable subjects across Canada, noting that Québec is the only Canadian province having such a framework.

In the absence of legislative supports, Tomossy and colleagues questioned the legal validity of research involving persons unable to provide consent. Such divergent approaches invite reflection on the Canadian research and regulatory climate.

The recommendation by Bravo et al. to revise the Québec law is nourished in part by their survey of Québec Research Ethics Boards (REBs) and researchers. Thirty-seven REBs associated with universities and hospitals that were surveyed are designated by the Québec government to inform researchers of the law. The educational role assigned to Québec REBs is in keeping with their formal status as independent watchdogs that guard research subjects' rights and welfare. It also complements the educational role outlined for REBs in the Tri-Council Policy Statement (TCPS), the ethical framework for federally sponsored research in Canada. Québec and federal clinical trials regulations, in addition to the TCPS, require REBs to have a member knowledgeable in the law regarding biomedical research. In spite of these requirements, Bravo et al. found that a high proportion of researchers in Québec admitted soliciting the consent of a traditional proxy, half without first determining whether the potential subject has a legal representative.

They also observed that a high percentage of both researchers and members of REBs were not well informed about the relevant law in Québec. Furthermore, they assert that while the Québec law is often violated by researchers and REBs, this does not imply that older adults are being put at risk, arguing further that there is no empirical evidence that legal guardians afford better protection to cognitively impaired adults than caring family members without legal authority. While this may indeed be the case, one might equally assert an absence of empirical evidence to support their claim as well.

In contrast, a statute-based regulatory framework across the country, as advocated by Tomossy and colleagues, would aim to provide a mechanism beyond self-regulation to protect the rights, dignity, and welfare of research subjects, including an expanding aging vulnerable population that is increasingly targeted for research. This approach is partly framed by a governance lens that focuses on the pressures of a highly competitive and commercial research climate on a mainly self-regulating national research terrain. It is also informed by the McDonald report, which assessed the integrity and effectiveness of national governance arrangements in Canada.

The McDonald report examined REBs in leading research centers in Canadian provinces including Québec and concluded that serious reform was in order. The report raised the concern that the research community has been too passive to the interests and rights of research subjects. It noted that Canadian REBs tend to pay little attention to benefits and harms for research subjects; researchers consider ethics to be a matter of navigating through the REB; and institutions see ethics review as little more than an administrative step in the processing of research proposals. It also highlighted complex relations between interest groups within the research community that can have an impact on the rights and welfare of research subjects. For example, some Québec REB members raised concerns about being pressured by private research sponsors to approve protocols that clashed with Québec’s civil code. REBs also routinely report to the office that seeks research funding, which it was noted in the report reflects an institutional

Conflict of interest. It has been observed that these relations occur in a research milieu where competition to recruit research subjects is fierce and can involve lucrative financial incentives. In addition, it has been noted that researchers, hospitals, and universities not only rely more on corporate funding but are also developing, testing, and taking out patents on their own medical devices and drugs.

Accountability issues raised by the McDonald report and concerns about conflict of interest not only remain active and unresolved, but have been heightened by revelations of the practices of REBs and researchers. Weijer recently noted that 19 out of 20 Canadian REBs in a multicentered trial—some at leading universities and teaching hospitals—approved protocols that clashed with the Helsinki Declaration and the TCPS. Another insider reported that while his REB rejected an unethical study involving an angiotensin-converting enzyme (ACE) inhibitor versus an angiotensin-II blocker versus placebo in diabetics with proteinuria, seven Canadian universities teaching hospital boards approved it and the study ran for two years. The U.S. Office for Human Research Protections (OHRP) recently reproached an REB at a leading Canadian university that is involved in a U.S. National Institutes of Health (NIH) sponsored clinical trial. OHRP determined that the REB failed to inform vulnerable research subjects and their proxies that the experimental treatments being measured involved serious risks, including possible death, and that trial subjects would be withdrawn from best current therapeutic treatment and randomly assigned to an experimental treatment that might increase their risk of dying. The U.S. Food and Drug Administration (FDA) also recently reproached a Canadian investigator in light of the death of a young research subject who died from being mistakenly administered 22 times more chemotherapy than outlined in the protocol. While the protocol was reviewed and approved by the local REB, the principal investigator had not submitted it to Health Canada for review which is required under Canadian regulations.

A Vice President of Research at the Canadian Institute of Health Research noted at a recent national conference that while a leading research center that was in the public spotlight has strengthened its ethics oversight to counter the perception that researchers do their own ethics review, the concern about widespread problems at other institutions across Canada remains.

Against a national backdrop of violations of research subjects’ rights and welfare and where the specter of conflict of interest haunts a competitive and commercial research terrain in various forms, the recommendation by Bravo et al. to dismantle Québec’s statutory-based protections should not be followed. Too many accountability concerns surround local REBs and researchers to abandon a law that is intended to protect vulnerable persons who can be easily exploited, as the violations noted above indicate. Health Canada has acknowledged the need to reform the local REB system of protection given serious informed consent violations and conflicts of interest that may exist between researchers, research sponsors, and research institutions. A statute-based regulatory framework along the lines suggested by Tomossy and others should be part of a national dialogue for regulatory reform. It does not follow that, as Bravo et al. suggest, since the Civil Code provisions requiring proxy consent are not being followed by the research community, they should be eliminated. Rather, what needs to be explored with greater vigor is how the law can be implemented (such as through education) and enforced, and how the public can become better informed of its rights. Herein lies the challenge on the regulatory horizon for governments that lay claim to represent the public good.

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The subcommittee will meet on November 15, 2005 to discuss the proposed pediatric protocol “Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty” and recommend whether the NIH supported study should proceed. The subcommittee will review the protocol in accordance with HHS regulations 45 CFR 46.407 and FDA regulations 21 CFR 50.54. The protocol and other documents are available at http://www.hhs.gov/ohrp/children/gnrh.html.


OHRP is soliciting public comment on a letter OHRP sent to the NCI and on an NCI position paper. The letter and position paper reflect conflicting views about the circumstances under which a member of the PedCIRB who is also an investigator with the Children’s Oncology Group would have a conflicting interest for a research protocol under review at the PedCIRB. The letter and position paper are available at http://www.hhs.gov/ohrp/news/recentnews.html#20051007. OHRP will accept public comments through December 15, 2005 (email: ohrp@osophs.dhhs.gov).

Office for Human Research Protections. “Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others.”

OHRP draft guidance for IRBs, investigators and HHS includes proposed recommendations for defining, reporting, and handling adverse events and unanticipated problems that affect research subjects or others. The draft guidance is available at http://www.hhs.gov/ohrp/requests/com101105.html. OHRP will accept public comments through January 13, 2005 (email: ohrp@osophs.dhhs.gov).

Accreditation of Human Research Protection Programs.

In October 2005 the Partnership for Human Research Protection, Inc. (PHRP) announced that it would discontinue its accreditation program effective November 15, 2005. This leaves the Association for the Accreditation of Human Research Protection Programs (AAHRPP) as the sole organization that offers accreditation for an institution's human research protection program.
Part I: What Is the Requirement for Data Sharing?

Openness has long been a norm of science, but until about 1990 the practice of sharing research data varied widely and was rarely subject to specific rules and procedures. However, recent changes in federal regulations have dramatically altered this picture. Now there are specific requirements, rules, and procedures for data sharing.

As of October 1, 2003, the National Institutes of Health (NIH) requires all investigator-initiated proposals for grants with direct costs greater than $500,000 in any single year to specify plans for sharing research data or explain why data sharing is not possible. This policy has important implications for Institutional Review Boards (IRBs), which oversee the way in which informed consent and confidentiality are handled in relation to data sharing, and for researchers who must prevent disclosure of identities and spend more time and effort in preparing data.

In addition, in accordance with provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the Department of Health and Human Services issued the Privacy Rule which permits research use of individually identifiable health information without the individual's authorization when an IRB approves a waiver of authorization. Criteria for waiving authorization include the treatment of identifiable data and restrictions on their reuse and disclosure to others.

Many investigators who conduct research with humans are not acquainted with these matters. In this three-part series, we provide information to IRBs to help them guide investigators in complying with data sharing requirements and to educate their research administrators about their responsibilities involving data sharing agreements with research funders and secondary data users. In the first article, we review current data sharing practices and requirements involving selected funding agencies and then discuss why researchers share data.

We begin the second article by describing how data are prepared for sharing; we then discuss the data sharing provisions of the HIPAA Privacy Rule and address ways that consent statements might be adapted to permit data sharing. The second article also addresses why the removal of names and addresses alone may be insufficient to deidentify data and would, therefore, preclude data sharing under the HIPAA and NIH confidentiality provisions. In addition, we provide an example of a reidentification technique and describe methods for evaluating the risk of reidentification and disclosure. The third article provides an overview of the technical and administrative procedures for assuring confidentiality in data files. It concludes with a summary of the issues that IRBs and research administrators need to consider in order to satisfy the requirements for responsible and legal data sharing.

Current Data Sharing Practices

Data sharing has been a well-established practice in some physical sciences (e.g., astronomy, oceanography) for many decades, and in meteorology for well over a century. Some agencies that fund human subjects research also have long required or encouraged data sharing. For example, the National Science Foundation (NSF) incorporates as a default element of its research grants a general requirement that its grantees arrange to make their data available to other scientists. In addition, the National Institute of Justice (NIJ) incorporates in its research contracts, grants, and cooperative agreements the stipulation that investigators return resulting data to the agency, which then prepares and archives that data in the National Archive of Criminal Justice Data at the Inter-university Consortium for Political and Social Research (ICPSR). In some of the biosciences, the sharing of reagents, cell lines, probes, clones, descriptions, quantitative data, and other items of data has been the basis for rapid scientific development. However, many bioscience researchers have experienced a tension between the ideal of data sharing and institutional, pro-
Table 1.
Glossary of Key Terms

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<th>Term</th>
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<td>Anonymous</td>
<td>Strictly speaking, the removal of identifiers only, but used here synonymously with deidentification. At issue in data sharing is what to regard as an identifier that should be removed to prevent reidentification. Hence, in this context, the term “anonymous” is used to mean deidentified.</td>
</tr>
<tr>
<td>Deidentification</td>
<td>The removal of direct identifiers together with the removal or modification of other information about study participants in order to minimize the risk of reidentification.</td>
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<tr>
<td>Identifier (also referred to as</td>
<td>Information that is uniquely or very closely associated with only one person, e.g., name, address, telephone number(s), Social Security number.</td>
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<tr>
<td>direct or explicit identifier)</td>
<td></td>
</tr>
<tr>
<td>Microdata files (also referred to</td>
<td>Computerized files that consist of individual records, each containing values of variables for a single person, household, business establishment, or other unit.</td>
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<tr>
<td>as “line listed” or “person”</td>
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<tr>
<td>records)</td>
<td></td>
</tr>
<tr>
<td>Public-use data products</td>
<td>Data products that are released to anyone without restrictions on use or other conditions, except for the payment of fees to purchase publications or data files in electronic format.* Typically, public-use data products are released either as tables or files.</td>
</tr>
<tr>
<td>Reidentification</td>
<td>(a) The association of information about a study participant in a released file with the name of that participant; or (b) the identification of a study participant from information contained in a released file.</td>
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</table>


Fessional, and other pressure to retain dominance in their field, protect their investment, or comply with university licensing requirements. Most of this bioscience research has not involved human subjects. Where it does, confidentiality adds further to the tension of sharing. The tension between the confidentiality promised to elicit cooperation from the research participant and the public sharing of data is resolved by the deidentification of data using disclosure avoidance methodologies. We will describe these methods in our third article.

Some major surveys (e.g., labor, voting behavior, social attitudes, economics)—whose data have been rendered anonymous (“deidentified”)—have long been subject to sharing requirements, and their data reside in archives readily available to scientists and the public. A major national archive, ICPSR, permits its subscribers to access its data sets via the Internet. Students as well as scientists have routinely used these data for teaching and research purposes since 1962.

Federal statistical agencies have also released deidentified data from a wide variety of surveys as “public-use” microdata files. In addition, several of these agencies have developed special facilities known as Research Data Centers, where approved researchers can analyze data that have not been deidentified under carefully controlled conditions. A brief description of such centers is given in our third article.

While these large-scale data sharing arrangements have been very successful, the sharing of smaller human subjects data sets from biomedical studies and social-behavioral research has had a contentious history. Questions and concerns have been raised about what constitutes data and sharing; who pays the cost of data preparation, archiving, and sharing; who owns data gathered under federal funding; who is required to share; what the informed consent requirements are; and how confidentiality of human subjects data can be protected. In 1989, an article appeared in this journal that informed IRBs of challenges they would face as investigators began to share more kinds of human subjects data. That article outlined the reasons for data sharing, its ethical foundations, barriers to sharing, rights of the original researcher, how IRBs may be involved, and how to solve problems surrounding data sharing. The article had a tentative tone. At that time, data sharing was still new to most small-scale biomedical and social-behavioral research. While NSF and NIH by then were fostering data sharing, the role of IRBs in this matter was still ambiguous. This is no longer the case.

With respect to sharing social-behavioral research and biomedical data, two things have changed. First, federal funding agencies are requiring, rather than urging, data sharing when it can reasonably occur. In such cases, grant proposals must contain evidence of a well-planned sharing arrangement that provides data in a useful form to other researchers without breaching promises of confidentiality. Second, there is a clear role for IRBs in reviewing protocols when research funding is contingent on an agreement to share data. These changes raise pressing questions for IRBs and investigators that we...
explore in the three-part series:

- What constitutes data? Do data subject to sharing requirements include the initial data, as well as cleaned and transformed data used to produce the analyses? Do they include the financial data (grant administration data) for the project? (Part I)
- If researchers do not share data in identifiable form, how does the primary researcher reduce the risk of identifiability to acceptable levels? By what criteria are “acceptable” levels of risk to be judged? (Part II)
- What are acceptable ways of sharing data without breaching confidentiality? (Part III)
- Must researchers share data with anyone who asks? May the principal investigator (PI) charge a fee for sharing? If so, how much? Who is responsible for sharing? Does the IRB have any role in these decisions? (Parts II and III)
- How final a plan for data sharing can or must be developed before any data are gathered? What do funders expect? What should an IRB expect? (Part III)
- What institutional resources may be needed to comply with sharing agreements? (Part III)
- Do the informed consent provisions permit data sharing? If so, how does the PI obtain assurances of confidentiality and security from secondary users? (Part III)

Data Sharing Requirements of Selected Agencies

Not all public funders require data sharing. The most specific requirement is the most recent. NIH mandated, effective October 1, 2003, that all research grant proposals over $500,000 include a detailed description of how data will be prepared for public use or restricted use by others without breach of confidentiality—or explain why this cannot be done. Simple stripping of direct or implicit identifiers may not be sufficient to fulfill this requirement. Given the many private and Internet-based data sets available today, data matching software can enable snoops to determine with a high degree of accuracy the identity of some research participants whose data are technically “anonymous” because they were stripped of names, addresses, and other direct identifiers.

The NIH has pioneered methods of assuring confidentiality, since data collected under its sponsorship typically have been highly sensitive. The agency’s long-standing and specific data sharing requirement—that those receiving grants, research contracts, or cooperative agreements deliver data to NIH at the completion of the project—leaves it with the responsibility to archive deidentified data with ICPSR, and to keep identifiable data within its own secure archives where they may be used on a restricted basis. (We will discuss such archives in Part III.)

Other agencies, such as the NSF, have less specific requirements. Over the past 25 years, the NSF has strongly encouraged data sharing and sought to better understand how to maximize the usefulness of shared data. The agency has funded projects developing various technologies of data sharing (e.g., via the Internet). Although the NSF’s requirements are not as specific as the NIH’s new rules, NSF proposals that spell out specifically how data will be shared and what methods of nondisclosure will be employed have a distinct advantage over those that do not.

In 1999, the Office of Management and Budget revised the federal requirements for grants and agreements with nonprofit organizations. Agencies are required to share “research data relating to published research findings under an award that were used by the federal government in developing an agency action that has the force and effect of law.” This means that if published results of funded research become the rationale for a government agency to take some action, the data must be made available to those who want to re-examine the analysis of the data on which the alleged results were based.

Why Share Data?

Apart from funder requirements, there are many other reasons to share data. Most investigators embrace the norm of openness, and peer pressure is used to promote this norm with reluctant colleagues. Scientific societies urge data sharing, and many journal editors require it as a condition of publication. Shared data give some assurance of the validity of the research and provide a common ground upon which to work out controversy over the analysis of research findings.

Data sharing provides an efficient and feasible way to make comparisons across populations; build upon one’s own data with additional related data; reanalyze data with different designs, methods, or hypotheses; promote interdisciplinary analyses; validate original results; conduct methodological and policy research; and create curricula in research methodology or statistics using real participant-level data. Researchers who do secondary analysis of data, and those whose research draws on
Kinds of Sharing

Certain kinds of data sharing within institutions are normal and expected, as when an investigator shares data with a graduate student, collaborator, or close colleague. In these instances, the investigator also shares the trust the participants have placed in him or her, and respects that trust by sharing only with persons of integrity. Integrity is the basis of confidentiality in such sharing arrangements.

Other kinds of informal sharing have also occurred over the years. Given the norm of openness in science, most researchers have, at some time in their career, received a request from another scientist for data, materials, samples, tools, or some other items that would permit that other scientist to replicate or extend the work. When research findings are questioned, colleagues and boards of inquiry may ask for information bearing on every aspect of the research from its beginning to the final data analyses. Arguments over statistical interpretation have sometimes required not just the initial data, but additional research and analysis. With that background in mind, consider some of the kinds of sharing arrangements that exist. In the first two kinds of sharing described below, the initial researcher affirms to the colleague how confidentiality will be assured and how a general standard of scientific integrity will be upheld. In many cases, this affirmation is implicit, and a formal contract would be offensive.

Collaborative reanalysis: Researcher A produces results that Researcher B questions. They decide to work together on a reanalysis using techniques that B suggests. A understands the data and teaches B, while B teaches A new kinds of analysis. The data and materials may never have to leave A's laboratory. The new analysis may end up being published under joint authorship.

Reciprocal exchange of data: A and B use comparable techniques to study different populations, or are doing research with some other common topic; the reciprocal exchange of data enables them to make useful comparisons.

Unilateral sharing: A's data are made available to B. If the data are sensitive, identified, or include irreplaceable samples or artifacts, B must make a good case for needing the data (e.g., a proposal is presented). B might do the work in A's lab under supervision, or might receive the data to be used elsewhere. Conditions may be imposed that assure confidentiality (using techniques to be described in Part III) of identified data (e.g., video tapes) or to assure that reidentification does not occur.

Projects organized for sharing: An anthropologist organizes a research program to benefit as many stakeholders as possible. He trains indigenous people to gather and analyze data on members of their community and gives the data, software, computers, and other necessary items to the legitimate local government so this body may continue to gather and analyze data for its own policy purposes. The PI trains research personnel in appropriate confidentiality practices. Alternatively, an anthropological project involving various investigators may be organized for reciprocal sharing.

Public data archives: A's data are documented and altered to prevent reidentification of any of the research participants (using techniques to be described in Part III). The data are stored in an archive, such as ICPSR, which then handles requests for the data and may assist borrowers in understanding the data. Secondary users of A's data do not need IRB approval to use these data, as the data are deidentified, hence are not human subjects data in the regulatory sense (as defined under 45 CFR 46.102(e)).

Restricted access archives and research data centers: Alternatively, the archive may store identified or identifiable data and employ mechanisms (described in Part III) to limit the possibility of a breach of confidentiality by controlling access and uses by secondary users. For example, the Murray Research Archive at Radcliffe College holds data from longitudinal studies of human development. Some of the data include videotapes. Some users conduct their research under supervision at the Murray Archive. Others are permitted to remove such data under highly restrictive conditions. Similarly, several federal agencies, e.g., the National Center for Health Statistics (NCHS), the U.S. Census Bureau, and the Agency for Healthcare Research and Quality, maintain facilities where researchers can analyze data not released to the general public. In these data centers, researchers work under controlled conditions and their research output is subject to disclosure analysis to insure that what is taken away cannot lead to the reidentification of research participants. NCHS also permits remote analysis of (but not actual access to) confidential data.
Disclaimer

The order of the authorship is alphabetical. The views expressed are those of the authors and not necessarily those of the United States Census Bureau or the National Center for Health Statistics.

Acknowledgments

The authors want to thank all individuals who reviewed drafts of their paper, including Janet Chiancone, May Chu, Patrick Clark, Donna Eden, Peter Joffis, Michael Nolte, and Deborah Tress.

Virginia A. de Wolf, PhD, is a United States Federal Statistician (retired); Joan E. Sieber, PhD, is Professor of Psychology, Emerita, at California State University East Bay, Hayward, CA; Philip M. Steel, MS, is Director Avoidance Staff Member at the United States Census Bureau, Washington, DC; and Alvan O. Zarate, PhD, is Confidentiality Officer at the National Center for Health Statistics, Hyattsville, MD.

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2. Documents pertaining to NIH's data sharing policy can be found at http://grants2.nih.gov/grants/policy/data_sharing.


5. http://www.icpsr.umich.edu/NACJD.


7. For an extensive list of social science archives worldwide see http://www.sossresearch.com/4c.html.


11. Other important issues exist, such as ownership of data when commercial entities sponsor biomedical research; however, these are topics for another paper.


15. Latanya Sweeney has written articles on the reidentification of individuals from supposedly anonymous data. One example describes how she reidentified the medical records of William Weld, the Governor of Massachusetts at the time, by linking data from a state employee health insurance file with information from the Cambridge, MA voter list. Sweeney L. k-Anonymity: A model for protecting privacy, International Journal on Uncertainty, Fuzziness and Knowledge-Based Systems 2002;10(5):557-570, http://privacy.cs.cmu.edu/people/sweeney/k-anonymity.html.

16. See ref. 5.

17. See ref. 4.

18. Joan Sieber served as NSF's Acting Program Director of Societal Dimensions of Engineering, Science, and Technology during 2001-2002 and was actively involved with aspects of NSF's data sharing program.


20. See ref. 21, Section C.13(d)(1) of Circular A-110.


23. For the websites of the NCHS Research Data Center and the Census Bureau's Research Data Center Program see ref. 10. For the Agency for Health Care Research and Quality's CPACT Data Center see http://www.meps.ahrq.gov/datacenter.htm.

24. A description of remote access, as well as other types of restricted access used by federal statistical agencies, is available in the Confidentiality and Data Access Committee's publication entitled "Restricted Access Procedures," http://www.fasm.gov/committees/cdac/cdacfaq.pdf.
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