Protecting Third Parties in Human Subjects Research

by David B. Resnik and Richard R. Sharp

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Consider the following hypothetical study submitted to an Institutional Review Board (IRB). An investigator proposes to compare the effectiveness of two commercially available kits that test for the presence of cockroach allergens in the home. Exposure to cockroach allergens can exacerbate asthma and cause other respiratory problems. The study will recruit 50 heads of households through newspaper and radio advertisements to participate in the study. Volunteers will be asked to use each of the two test kits according to instructions and to complete a questionnaire on their experience afterward. As part of the study, a professional exterminator will examine each home following the use of the test kits to ascertain whether cockroaches are present. If appropriate, the exterminator will apply a commercially available pesticide in areas of the home to exterminate cockroaches and place pesticide traps in strategic spots to reduce the likelihood of future cockroach presence. Two months after use of the test kits, heads of households will be asked to use each of the kits a second time and to complete the questionnaire. The study will not collect any information from or about other persons living in the home; nor will any other persons living in the home be asked to perform any study-related interventions. The investigators maintain that the risks of the study are minimal since the risks associated with use of the test kits and cockroach extermination are equivalent to the types of risks people ordinarily encounter in daily life. They also assert that potential benefits exist for subjects participating in the study, including education about the health risks of cockroach allergens, evaluation of the presence of cockroach allergens in the home, and administration of pesticides to reduce the number of cockroaches present. In their application to the IRB, they argue that these benefits outweigh any potential risks to subjects.

We suspect many IRBs would regard this study as posing minimal risks to volunteers, but since the study is being done in the homes of research subjects, it may create additional risks to third parties that should be of concern.

Young children and others living in study homes, for example, might accidentally be exposed to toxic pesticides used to kill cockroaches. Unfortunately, federal regulations provide little guidance on how, or whether, IRBs should consider potential harms to affected individuals who are not research subjects.

Since the regulations are silent
Box 1: Examples of Research that May Pose Risks to Third Parties

- Vaccine research in which subjects are exposed to a biological agent that may pose a health hazard to others who come in contact with research subjects
- Studies that involve research interventions in settings occupied by multiple individuals, such as a home, a school, or a community center
- Research in settings in which third-party occupants may assume privacy, such as a home
- Research on mental illnesses associated with violent behavior, in which changes to ongoing treatment programs may present risks to persons living nearby
- Research on a localized environmental hazard that may impact all community residents
- Studies in which lactating women receive experimental medication that may be transmissible through nursing

on these issues, investigators and IRBs are left to determine for themselves the extent to which they may have ethical or legal duties to minimize potential risks to affected third parties. In this article, we examine ethical and regulatory aspects of research-related risks to third parties. We argue that researchers and IRBs have ethical obligations to minimize potential risk to third parties and to take reasonable measures to protect third parties from harm.

Third Parties in Research

What (or who) are third parties in research? If we consider the principal parties engaged in research to be the researchers, research staff, and human subjects, then a third party is an individual (or organization or institution) who is not a researcher or a subject, but who is affected by the relationship between those persons. In our hypothetical case, children living in study homes might be regarded as third parties because they are not research subjects (or researchers), but the interventions taking place in their homes may expose them to potential harms associated with pesticide administration.

Since there may be an indefinite number of third parties potentially affected by a research study, it is important to distinguish between directly affected third parties and other third parties. Directly affected third parties are identifiable individuals or organizations whose rights or welfare may be adversely affected by research procedures. Other third parties are individuals or organizations that may be adversely affected by the research, but cannot be identified beforehand. For example, if a research subject has an automobile accident as a result of losing consciousness while taking an experimental drug, people injured by the accident would be indirectly affected third parties. In this article, we will limit our discussion to directly affected third parties, since it would be impractical (and in many cases impossible) for a researcher or IRB to address risks to other third parties.

The federal research regulations define a human subject as: "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." In our hypothetical example, if researchers were planning to gather data on other people living in the home or would have access to identifiable private information about those people, then those individuals would be considered research subjects. Since the researchers are only gathering data from heads of households using the test kits and completing the survey, however, others in the home would not be considered research subjects.

In some types of survey and pedigree research, relatives of research participants can become research subjects if the investigator collects identifiable private information about those relatives. If an investigator asks questions about the health of other family members, for example, then those relatives could become research subjects if the investigator also obtains information that can uniquely identify those family members. The research subject interacting with investigators and answering questions would be regarded as the primary research subject, and those relatives about whom identifiable private information is collected would be regarded as secondary research subjects. The fact that those relatives may be unaware of the research or fail to provide their informed consent does not affect their status as research subjects. In fact, an IRB may often decide to waive the informed consent requirement if the potential harm to the secondary research subjects is minimal or very unlikely (also if waiving the requirement of informed consent from identifiable relatives does not adversely affect the rights and welfare of those secondary subjects, and the research could not practically be conducted without a waiver). Third parties may become secondary research subjects if investigators inadvertently obtain identifiable data about those persons through study interventions.

Many types of research can place
third parties at risk (see Box 1). As in the hypothetical case above, risks may include harms resulting from incidental or unexpected exposure to toxic compounds or biological pathogens. Third parties also may be harmed as a result of a loss of privacy. In our hypothetical example, researchers may observe embarrassing behaviors or inadvertently discover sensitive information about third parties during visits to study homes. Some of these risks may be legal in nature, such as observations of unsafe conditions or unlawful behaviors that may need to be reported to law enforcement agencies. Other risks may involve the disruption of social relationships—for example, risks involving the revelation of misattributed paternity or discovery of neglect or abuse. Although IRBs often consider analogous risks to research subjects in evaluating proposed research, it is unclear to what extent risks to third parties usually factor into IRB deliberations.

**Federal Guidance**

Although commentators on research ethics have examined how best to protect the rights and welfare of secondary research subjects, with the exception of a recent report by the Institute of Medicine and a recent article in this journal, very little attention has been given to protecting third parties in research. There are several possible explanations for this oversight. First, the federal research regulations do not explicitly require IRBs to address risks to third parties during the review of research, and many IRBs tend to limit their deliberations to issues and concerns related to the regulations. To the best of our knowledge, the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) have not issued any formal guidance on evaluating risks to third parties in research. Second, IRBs may not have sufficient time or appropriate expertise to assess risks to third parties in research, especially given the many demands and pressures of IRB work. To the extent that time and IRB resources may be limited, it is reasonable that immediate risks to subjects should take priority over risks to third parties. Lastly, there may be some confusion among IRB members concerning the difference between a third party and a secondary research subject.

Prior to approving a study, an IRB must assess the extent to which risks have been minimized. However, this requirement applies only to risks to subjects and does not mention potential harms to other individuals. Federal regulations also require IRBs to evaluate whether risks to subjects are reasonable in relation to potential benefits to the subjects and society. This requirement does mention an obligation to examine risks to others.

The informed consent process is another area where the regulations focus on subjects, not third parties. According to the requirements for informed consent, the consent process should include “a description of any reasonably foreseeable risks or discomforts to the subject” and “a description of any benefits to the subject or to others which may reasonably be expected from the research.” The regulations do not require investigators to discuss risks to third parties with subjects, although they require investigators to discuss possible benefits to third parties.

Although most of the regulations focus on risks to subjects, it is worth noting that some passages address risks to third parties. The federal regulations require institutions to have written procedures for reporting “any unanticipated problems involving risks to subjects or others.” While this passage does not state that IRBs have a duty to minimize risks to third parties, it acknowledges the potential for harm to third parties. Additionally, the regulations do protect one type of third party: the fetus. A pregnant woman may not participate in research that involves more than minimal risk if there is no prospect of direct benefit to herself or her fetus. The federal regulations also require that researchers ensure that preclinical and clinical studies are conducted prior to enrolling pregnant women in research to assess the potential for harm to the pregnant woman and fetus.

**The Principle of Beneficence**

The *Belmont Report* is another important source of guidance regarding the conduct of research involving human subjects. The *Report* describes several guiding ethical principles that shaped the development of federal regulations and often is appealed to in interpreting ambiguous sections. Although the *Report* does not offer guidance specific to the protection of third parties in research, the principle of beneficence articulated in the *Report* provides some insight into the weighing of potential benefits and risks in research involving human subjects: “[I]nvestigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. ... Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society).” In contrast to the federal regulations, this passage suggests that investigators have an obligation to consider not only risks and benefits to individual research subjects, but risks and benefits to others such as the families of subjects and society more generally.

The *Report* does not address the rationale for considering risks and benefits to people who are not research subjects. One possible rea-
son for this is that the authors viewed the principle of beneficence as a general guide to ethical conduct whose moral significance does not depend on the unique relationship established between researchers and subjects. From this perspective, the moral obligations of researchers and IRB members are substantively much the same as those of any other moral agent. For example, these duties might be understood to include general obligations to avoid causing harm to others and to act in a manner likely to advance the interests of others. The potential harm to any individual, whether that person is a research subject or not, is relevant if one adopts such an interpretation of the principle of beneficence.

Alternatively, the specific obligations stemming from the principle of beneficence might be interpreted more narrowly. Beginning instead with the assumption that research often creates a fiduciary relationship between investigators and subjects, the principle of beneficence might be understood as implying only that researchers have a special, role-specific obligation to act in a manner that promotes the interests of their subjects. From this perspective, the principle of beneficence supports claims to special duties owed to subjects but does not support duties to persons outside the researcher-subject relationship, such as persons who are not subjects and who have no fiduciary relationship with researchers.

We argue against this narrow interpretation of the principle of beneficence on the grounds that moral duties to third parties stem from the social responsibilities of researchers. Researchers have social responsibilities because they occupy a privileged position in society. Public funds frequently support research activities; public scrutiny and oversight is limited; there is a presumption that the research enterprise will yield basic truths about the world we live in; and so forth. One might understand this privilege as creating a type of social contract wherein researchers are allowed to regulate themselves and conduct their work in a relatively independent manner in exchange for promoting the common good. From this perspective, researchers and members of IRBs (as participants in the larger enterprise of research) have moral obligations to take into account both the impact of their actions on research subjects as well as other people affected by the research, including third parties.

These foregoing considerations suggest that researchers and IRB members have moral duties toward third parties. We examine the scope of these moral duties in the following sections.

The Harm Principle

The harm principle also can shed some light on protecting third parties in research. First formulated by John Stuart Mill in his 1869 essay On Liberty, the harm principle has become one of the most firmly entrenched rules of Anglo-American ethics and social policy. Mill argued that the only legitimate reason for using the power of the state to restrict liberty of action is to prevent harm to others.¹⁸

Other philosophers, most notably Joel Feinberg, have expanded on Mill's basic idea. Feinberg distinguishes between two different harm principles: the private harm principle, which holds that liberty can be restricted to prevent harm to specific individuals or groups, and the public harm principle, which holds that liberty can be restricted to prevent harm to society.¹⁹ While the private harm principle is widely accepted and plays an influential role in most legal systems, the public harm principle is far more controversial, because reasonable people may disagree about what constitutes social harm. Public policy debates about gay marriage, immigration, legalization of drugs, pornography, urban development, school prayer, and desegregation, for example, reflect very different conceptions of what should be considered a social harm.

Feinberg argues that harms must reach a minimal threshold before they should be prevented. There is no justification in using the coercive power of the state to stop people from engaging in rude or disrespectful behavior, for example, unless that behavior rises to the level of assault or intentional infliction of emotional distress. The state should not use its authority to restrict liberty to prevent minor or trivial harms. This does not imply, however, that people have no moral duty to avoid inflicting trivial harms on others. People may still have moral obligations to refrain from rude and disrespectful behavior, even when the state does not enforce those obligations.

For nontrivial harms, Feinberg proposes a balancing test for deciding when to restrict liberty. This test involves balancing the gravity and probability of the potential harm against the value of the conduct that might be restricted and the strength of the rights and corresponding liberty interests at stake. Rights may be restricted when the product of the probability and gravity of the harm (i.e., the magnitude of risk) outweighs the value of the restricted conduct (to the actor and others) and the strength of the liberty interest.²⁰ For example, driving an automobile can present a large risk to others, but society allows people to drive because the activity has a very high value and the protected right—e.g., the right to freedom of movement—is strong. Society is justified in outlawing or controlling some types of activities with automobiles, such as driving while under the influence of alcohol or driving in a reckless manner, because the magnitude of the risk outweighs the value of the activity and the rights at stake.

How might Feinberg’s insights about harm apply to protecting third parties in research? First, the private
harm principle implies that the government should develop laws, regulations, or policies requiring researchers and IRBs to protect individuals and identifiable groups from harm. Second, the government should not develop rules requiring IRBs and researchers to prevent trivial harms to third parties. Researchers and IRBs may still have moral obligations to avoid needlessly inflicting trivial harms on third parties, but the government should not enforce these obligations. Third, Feinberg’s analysis suggests that a balancing test should be used to decide when and how to restrict rights in the context of research. IRBs and researchers should consider the gravity of the potential harm, its probability, the value of the research activity, and the relevant rights at stake.

With respect to this last point, let’s assume that research involving human subjects is usually a beneficial activity for researchers, subjects, and society that involves significant liberty interests on the part of the researchers and the subjects. Under these assumptions, research with human subjects may be restricted to prevent harm to directly affected third parties (individuals or groups) when the product of the probability and gravity of the harm (or risk) outweighs the value of the activity and the rights at stake. In some cases, the balance of these different factors will favor avoiding or eliminating risks to third parties. For example, research that includes pregnant or lactating women could potentially impose such high risks on third parties (i.e., fetuses or infants) that the most reasonable course of action would be to forbid these subjects from taking part in the research.

If research does not pose a risk of serious harm to third parties—i.e., disability, permanent injury, or death—but it poses more than minimal risk, the balance of the different factors will often favor allowing the research to go forward but taking reasonable measures to prevent harm to third parties. For example, in the cockroach allergen study described earlier, researchers can minimize harm to third parties by providing the subjects with appropriate instructions concerning pesticide safety, describing common symptoms of accidental exposure to pesticides, and providing phone numbers to call in case of an adverse reaction. Research subjects can also help minimize risks to third parties by informing affected individuals about potential risks associated with their participation in a research study.

In some cases, the balance of different factors might favor requiring that investigators obtain permission from third parties before conducting research. The most common situation where investigators should obtain permission from a third party before initiating research is when a research study takes place at a particular institution or organization. Suppose researchers are studying the influence of the media on children’s eating habits, for example, and plan to distribute a survey in elementary schools. Nearly all IRBs would require the researchers to obtain letters of support (or permission) from the elementary schools participating in this study. The schools (and many of their employees) would be affected third parties, not research subjects or researchers. One reason researchers should obtain letters of support in this context is that the research could cause harm to children in the schools (e.g., stigma) and may place those schools at risk of legal liability, controversy, or public embarrassment.

Obtaining a letter of support from a school for a study involving its students typically does not raise problems. First, if the school decides not to lend its support to the study, subjects will usually not be negatively impacted. Second, researchers can obtain a letter of permission from the school without compromising the privacy of research subjects since the school can give its permission without knowing who may participate in the study. Third, requiring researchers to obtain a letter of support from the school is not unduly burdensome.

In some situations, however, requiring researchers to obtain permission from affected third parties may introduce practical and moral challenges. First, identifying, locating, and notifying all directly affected third parties may be difficult. In other cases, attempts to inform third parties could bias results if a significant proportion of potential subjects decide not to participate in order to avoid notification of third parties.

Second, requiring third-party authorizations could have an adverse impact on the welfare of research subjects. Suppose, for example, that a woman is gravely ill with brain cancer and wants to try an experimental treatment. The treatment could give her an additional two years of life or it could kill her. If she dies, this will cause economic and psychological harm to her husband. Should her husband have the authority to override her decision so that he can avoid the harms that may occur? We think not. In a situation like this, one must balance the potential harm to the third party against the potential benefit to the subject, including her right to act in a manner that best reflects her autonomous preferences. Unless the potential harm to the third party is serious, and the benefits to the subject are small in comparison, the third party should not be extended a right to veto the subject’s participation in research due to the importance attached to research subjects’ decisional rights and corresponding liberty interests.

Third, requiring third-party authorization may compromise the privacy of research subjects. Suppose the woman with brain cancer in the example above does not want to tell her husband that she plans to participate in a research study. Should
Box 2: Duties Owed to Third Parties in Research

<table>
<thead>
<tr>
<th>Degree of risk to third party</th>
<th>Duty</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk</td>
<td>No duty</td>
</tr>
<tr>
<td>Minimal</td>
<td>Inform subjects about risks to third parties</td>
</tr>
<tr>
<td>More than minimal</td>
<td>Take reasonable measures to protect third parties, such as informing third parties about risks and obtaining permission if necessary</td>
</tr>
<tr>
<td>Serious</td>
<td>Do not conduct the research or redesign the research to minimize risks to third parties</td>
</tr>
</tbody>
</table>

Researchers violate her privacy in order to inform the husband about potential risks to him from her participation? Again, we think not. The research subject's privacy should be protected unless she loses decision-making capacity and her husband needs to make decisions relating to her medical care (and thus needs to know that she is in a research study), or her participation in a study poses a direct and significant threat to her husband's welfare.

Tort Law

The tort system offers researchers and IRBs another source of guidance concerning the protection of third parties from harm. Tort is a legal term for harm or wrongdoing. Tort law includes many different types of lawsuits such as negligence, fraud, battery, conversion, wrongful death, and products liability. There has been a tremendous rise in the number of human research lawsuits in the United States since the death of Jesse Gelsinger during a gene transfer experiment at the University of Pennsylvania in 1999. While we do not recommend that researchers or IRBs focus exclusively on legal liability as a guide to research with human subjects, it is prudent to at least consider legal issues.

Could a third party harmed as a result of research mount a successful tort lawsuit against a researcher or IRB? To answer this question, we will not examine all the possible lawsuits that a plaintiff could file. Instead, we will focus on one of the most important and common torts, negligence. While we know of no successful lawsuit by a third party against a researcher or IRB, we can speculate about how one might arise. Negligence is a cause of action in Anglo-American law with six legal elements (or necessary conditions). To prove that a defendant was negligent, a plaintiff must show that a) the defendant had a legal duty to the plaintiff; b) there is an appropriate standard of care pertaining to that duty; c) the defendant breached the standard of care; d) the defendant caused harm to the plaintiff as a result of the breach; e) the defendant is legally responsible for the harm; and f) the plaintiff has a measurable harm such as pain, psychological damage, or economic loss.

A key element in establishing a negligence claim is defining the standard of care owed to the plaintiff. The most basic way of stating this standard is that we all have a duty to act as a reasonable person would act under the same or similar circumstances. The reasonable person is not the average or normal person, but a legal construct representing the community's norms for the degree of care we owe each other. Judge Learned Hand posited a rough formula for measuring this: the degree of care, D, is a function of the probability that the harm will occur to the person, P, multiplied by the magnitude of the harm, M, divided by the burden of the sacrifice one must make to avoid the harm, B. This conception of the duty of care owed to others is very similar to the balancing approach defended by Feinberg. If the defendant and plaintiff have a professional relationship such as physician-patient or lawyer-client, then a professional standard of care would apply to the defendant's conduct. For physician-researchers, the standard of care would be what the reasonably prudent and competent physician-researcher would do in the same or similar circumstances.

Would a professional standard of care ever apply to the relationship between a researcher and the third party? If the subject is a lactating woman, the researcher is a general practitioner, and the third party is the subject's child, it is possible that the researcher would have a professional relationship with the subject. The researcher also might have a professional relationship with the third party when the third party is a pregnant subject's child. In these rare situations, the researcher would have a stronger duty to the third party than if she did not have a professional relationship with the third party. The researcher would have an obligation to protect the third party from harm and promote the third party's health, which might involve careful monitoring or removing the third party from the research.

What would the applicable standard of care be when third parties are involved in research? If the third party does not have a professional relationship with the researcher, then the duty of care owed to the third party would depend on the probability and magnitude of the harm to the
third party and the burden on the researcher (or IRB) of protecting the third party from harm. If the burden of performing a particular activity to protect the third party is low, the researcher (or IRB) would have a duty to perform that activity, unless the product of the probability and magnitude of harm is lower than the burden of the activity. For example, since the burden of informing the research subject about potential risks to third parties will usually be very low, in most cases researchers should consider informing subjects about risks, and IRBs should consider requiring researchers to inform subjects. Subjects also can help protect third parties by taking appropriate steps to prevent harm, such as warning them about risks. In some cases, researchers would have a duty to warn directly affected third parties if the risks are more than minimal but not serious. (Box 2 summarizes duties to third parties in research.)

Conclusion

Researchers have ethical (and in some cases legal) obligations to protect directly affected third parties from harms caused by research activities. For all research studies, researchers and IRBs should determine whether there are any identifiable third parties who may be directly affected by the research. If a research study poses no risk to third parties, then there is no need to take any additional measures to protect them. If a study poses minimal risks to third parties, then researchers should inform the subjects about these risks so that subjects can take appropriate steps to minimize these risks. If a study poses more than a minimal risk to directly affected third parties, researchers and IRBs should develop a strategy for protecting them from harm. This strategy should balance four different factors: the probability of the harm to the third party, the magnitude of the harm, the benefits of the research (to the subject and society), and the rights at stake. Some reasonable steps to protect third parties might include safety measures to protect exposing third parties to toxic chemicals or agents, warning third parties about potential harm, obtaining letters of support from institutions or businesses directly affected by the research, and, in rare cases, obtaining permission from individuals. If a research project has the potential to cause serious harm to third parties, then the research should not be conducted. The researchers may need to develop a new research design that does not impose such high risks on third parties.

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Disclaimer

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References

2. The federal research regulations define minimal risk as: “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” 45 CFR 46.102(f)
4. 45 CFR 46.102(f).
10. We arrived at this conclusion after searching the OHRP and FDA Web sites and talking with officials at these agencies.
11. 45 CFR 46.111(a)(1). 21 CFR 56.113(a)(1) has identical language (Food and Drug Administration regulations).
12. 45 CFR 46.111(a)(2). 21 CFR 56.113(a)(2) has identical language.
13. 45 CFR 46.116(a). 20 CFR 50.35(a) has identical language.
14. 45 CFR 46.103(b)(1). 21 CFR 56.128(b) has identical language.
15. 45 CFR 46.204.
General Clinical Research Center Staff Nurse Perceptions and Behaviors Regarding Informed Consent: Results of a National Survey

Informed consent is a critical component for ethically conducted human subjects research. Empirical research has suggested that often subjects have a poor understanding of a research study's intended purpose and of their rights as participants. However, the extent to which problems with informed consent are identified by study personnel are unclear, as is how these personnel act to rectify these problems. Although several stakeholders are involved in clinical research—including investigators, research nurses, study coordinators, and research assistants—little research has been performed to determine how any of these stakeholders view the effectiveness of the informed consent process.

To further explore these issues, we conducted a national survey of General Clinical Research Center (GCRC) staff nurses to determine their attitudes, perceptions, and behaviors regarding the informed consent process. GCRCs are specialized facilities that promote clinical research by conducting both inpatient and outpatient studies. GCRC staff nurses monitor research participants at the bedside and help operationalize research protocols. Because GCRC staff nurses have frequent contact with numerous participants involved in study protocols of various types, they represent a unique and well-qualified group to survey regarding the informed consent process.

Study Design and Methods

The study sample included part-time and full-time GCRC registered nurses who routinely assisted in the conduct of clinical research protocols. Since no centralized, single database of GCRC staff nurses is available, all funded and satellite GCRCs were identified from the Web site of the National Center for Research Resources (NCRR). After identifying 97 GCRCs, the nurse manager listed at each site was directly contacted via electronic mail followed by telephone calls for initial nonresponders. Three nurse managers who did not respond after three electronic mails and three telephone calls were considered nonresponders. An additional four GCRC nurse managers declined to provide us with staff nurse contact information or to forward the survey materials to their staff nurses.

Nine hundred and two individuals were identified at 90 different GCRCs and satellite GCRCs. The initial study protocol intended to collect the names and direct mailing information for each GCRC's staff nurse. However, most (82%) GCRC nurse managers contacted requested that we send a packet of surveys for distribution due to concerns about confidentiality and privacy of staff. We used two mailing mechanisms: delivery of a prespecified number of packets (equaling the number of identified nurses on staff) to each nurse manager, or delivery of surveys directly to nursing staff. At GCRCs where the nurse manager received a survey packet, an instructional letter was included requesting that s/he notify all the staff nurses about the study. However, we were unable to determine how many staff nurses the nurse manager actually approached. Thus, to determine our response rate, we included all surveys sent to a specific center within our denominator, assuming that all of the staff nurses had been contacted.

Mailings for the entire sample occurred at three separate intervals from September 2003 to May 2004 with each individual participant or nurse manager receiving a single mailing. Participants were not compensated for their participation. Two reminder electronic mails were sent to nurse managers after the packets were mailed. Surveys were mailed with a cover letter explaining the reasons for the survey, and with a self-addressed, metered return envelope to allow staff nurses to directly return the completed questionnaire to the investigators. Thus, although in some centers nurse managers assisted

in the distribution of the survey, they had no role in the collection and return of complete surveys. The study was approved by the Vanderbilt University Institutional Review Board (IRB), which determined that the study was exempt from informed consent requirements due to the anonymity of the survey respondents.

The survey instrument was initially developed using content suggested from a multidisciplinary team, including clinical researchers, biomedical ethicists, nurses, and patient safety advocates. The questionnaire was pilot-tested for comprehension and appropriateness in two focus groups whose members included 22 non-GCRC research nurses. We subsequently removed, added, or clarified questions. The final survey included 77 items, 14 of which elicited clinical and research experience and typical workload. The nurses were asked whether their center involved pediatric subjects and whether their setting was inpatient, outpatient, or both.

The survey instrument covered a wide array of topics including issues about informed consent, protocol deviations, adverse events, and research processes. Nurses were asked 29 yes/no questions about possible problems during the preceding six months involving subject recruitment (five questions), informed consent (15 questions), adverse events (three questions), or study processes (six questions). The nurses rated the frequency of 12 occurrences over the previous six months using a five-point Likert scale (“never,” “rarely,” “sometimes,” “often,” “very often”). This article focuses specifically on the questions regarding informed consent. We address responses to the other questions in a separate article.4

Frequency questions were categorized into either often (combining the “often” and “very often” response), sometimes, or not often (combining the “never” and “rarely” responses). Categorical data were compared using the X² test. All statistical calculations were performed on SAS v8 statistical software.

Results

Survey response rates are presented in Figure 1 (at http://www.thehastingscenter.org/pdf/irb_2006_jul_aug_figure1.pdf). Ninety-seven GCRCs were eligible for participation. We were unable to contact three centers, and four centers refused to participate. Of the remaining 90 GCRCs, at least one response was returned from 80 (89%). Four hundred and thirty-three surveys were returned from a total of 902 GCRC nurses, for an overall response rate of 48%. Response rates by method of distribution were 57% (78/137) for staff nurses who were directly mailed a survey and 46% (355/765) for staff nurses indirectly contacted through the nurse manager. We found no statistically significant differences in question responses between these two groups (data not shown).

Nurses were predominately female (93%) and over 40 years of age (75%). Fifty-eight percent of GCRC nurses had greater than four years of clinical research experience (Table 1, at http://www.thehastingscenter.org/pdf/irb_2006_jul_aug_table1.pdf). Fifty-one percent reported directly interacting with 12 or more research participants per week, and 47% assisted in nine or more protocols in a typical week. Forty nurses (8%) were exclusively or predominately involved in pediatric research.

Most nurses reported familiarity with the Belmont Report (83%). When asked about routine responsibilities, 17% of nurses reported being regularly present during the informed consent process, yet 78% routinely assessed volunteers’ understanding of the study to which they had consented.

Forty-one percent of GCRC nurses reported they had assisted on a protocol where the participant did not understand the consent document but was nevertheless enrolled in the study (Table 2, at http://www.thehastingscenter.org/pdf/irb_2006_jul_aug_table2.pdf). Twenty-seven percent of nurses assisted on a protocol in which they perceived that a research participant did not understand that the study intervention was for research purposes rather than medical treatment. Eleven percent of nurses had assisted on a protocol in which they believed a subject had been coerced into participating, and 9% had assisted with a protocol in which a participant underwent a study procedure despite having asked unanswered study-related questions.

When asked about their actions related to the informed consent process, 28% of staff nurses said they had contacted a study investigator over the past six months concerning a problem with the consent process, and 13% said they had refused to administer a study intervention to a research participant due to concerns regarding a research volunteer’s understanding of the study. Four survey questions asked staff nurses to rate how often specific occurrences related to the informed consent process had occurred over the preceding six months. Sixty-seven percent of nurses stated that they often or very often contact investigators when they suspect a problem with the informed consent process.
(Figure 2, at http://www.thehastingscenter.org/pdf/irb_2006_jul_aug_figure2.pdf).

Nurses who reported that they were routinely present during the consent process (n = 73) were less likely to report assisting on a protocol where the participant did not understand the consent document (29.7% versus 42.8%, p-value = 0.04) or the potential side effects of the study treatment (13.7% versus 32.2%, p-value = 0.002). GCRC nurses who were routinely present during the consent process also reported being less likely to have assisted on a protocol where the risks of the study were not adequately conveyed (8.1% versus 22.5%, p-value = 0.005).

Discussion

While research has accumulated detailing the deficiencies of the informed consent process as well as the potential methods to improve human subject comprehension, much less data exist regarding research nurses’ perceptions or behaviors regarding the informed consent process. The nurses in our survey believed that almost 40% of research participants did not fully understand the information presented to them in the consent document, yet agreed to participate in the study. This finding is consistent with previous studies showing that 20% to 40% of participants fail to understand one or more aspects of research participation.

Encouragingly, almost 80% of nurses said they routinely assessed a subject’s comprehension of the study. However, this finding must be viewed with caution, as we did not specifically ask how this assessment of subject comprehension was made. Indeed, the breadth and rigor with which each individual nurse assessed subject comprehension may have varied considerably. Twenty-eight percent said they had contacted an investigator regarding their concerns about a subject’s understanding of a protocol, and almost one in seven had refused to administer an investigational agent because of perceived problems with a subject’s understanding of the study. Of interest, although only a minority of GCRC staff nurses was routinely present during the consent process, those that were present tended to report fewer problems with the consent process.

Although prior research has demonstrated that participants are generally satisfied with the informed consent process, when directly questioned, a participant’s level of understanding of the trial in which they are enrolled can be poor. Participants often cannot recall trial specifics such as study duration or medication side effects. In a study of participants enrolled in an oncology clinical trial, most respondents indicated that they felt well informed about the study. Almost three-fourths of participants, however, did not recognize the research intervention as a nonstandard therapy. Other studies have also suggested that participants are often unable to make the distinction between investigational therapies versus standard medical care. In our study, 27% of the respondents recalled interactions with a research participant who was unaware that an intervention was for research purposes only.

Many of the views expressed by our respondents coincide with conclusions from prior studies regarding the deficiencies of the informed consent process and demonstrate that, at least in the case of the GCRC, many staff nurses will take steps to rectify these deficiencies, in some cases even stopping the progress of a study. One finding that merits further investigation is that almost 10% of nurses noted that they never or rarely contact a study investigator if they perceive a problem with the informed consent process. Our study did not address why this communication may not take place. Possible reasons include systems barriers, which might discourage contacting investigators; concerns about investigators’ reactions; pressures to increase the number of research subjects; or nurses’ lack of understanding of the importance of informed consent for clinical research.

Of note, 11% of respondents indicated that they believed a participant might have been coerced into participating. Strictly speaking, “coercion” in research occurs only if the investigator uses a “credible and severe threat of harm” to control the participant’s behavior. It is among the gravest violations of research ethics. However, because we did not provide this strict definition in our survey, nurses may have been referring to incidents in which an investigator overly encouraged or pressured an individual to participate, but did not actually coerce that individual to enroll in a trial.

Nonetheless, some nurses perceived that subjects had enrolled under mild or moderate influence from either a study investigator or perhaps another source, such as a family member. The extent to which their perceptions represent problematic realities is unknown, but the finding raises questions about research ethics, especially at a time when investigators and their research teams are under enormous pressure to “produce.”

One unexpected finding of our study was that nurses who were routinely present during the consent process tended to report less problems with the process. A possi-
ble explanation for this finding might be that these nurses were more aware of the information exchanged between investigators and prospective subjects and thus felt more confident that the subjects had been adequately informed of important study risks and benefits. Alternatively, nurses who are routinely present during the informed consent process may be more likely to identify specific content that the research subject may not fully understand and thus may spend more time explaining this information during the consent process. Additional research is warranted to determine if having nurses routinely present during the consent process improves subject comprehension.

This study has several notable limitations, most important of which is the low response rate. Due to the manner of survey distribution, it is unclear whether some centers did not return a single survey because of survey transmission problems, a unilateral decision of the unit’s nurse manager not to participate, or a decision of the individual staff nurses not to participate. Nurse managers were not included as participants and were approached as a means to identify subjects and distribute the survey packets. We do not know how many respondents a nurse manager may have approached or how they chose to distribute the survey. Even if all non-responders had returned surveys and reflected the “desirable” responses, the proportion of nurses whose answers raise concerns is still greater than ideal.

A second limitation is that the survey collected subjective observations from GCRC nurses. Nurses may have witnessed only a part of the consent process and therefore may have been unaware that participants’ questions might have been addressed when they were not present. Yet most of our respondents noted that they routinely assess the comprehension of subjects and had many years of clinical research experience. Thus, it is likely that, even without being present during the initial informed consent process, they could ascertain when a subject lacked a clear understanding of the study processes. A third limitation is that we did not specifically query when or how the research nurse assessed participants’ comprehension. If they routinely did this several days into a protocol, our results could be confounded by other factors, such as problems with recall.

GCRC staff nurses’ perceptions of informed consent deficiencies are consistent with data from direct patient surveys and indicate that many research participants do not fully understand the purposes of the study in which they are enrolled. The majority of GCRC staff nurses will contact an investigator if they perceive a problem related to subject comprehension, and almost one in seven respondents had refused to conduct a study due to concerns regarding the subjects’ understanding.

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NEWS & NOTES

"The Ethics of Using QI Methods to Improve Health Care Quality and Safety," a new, free report from The Hastings Center, explores the relationship between QI activities and IRBs. It proposes a cooperative effort by public and private entities to develop clearer guidance on the appropriate relationship between ethical oversight of QI and human subjects research regulations, and makes other practical and policy recommendations.

The report is the product of a project funded by the Agency for Healthcare Research and Quality, in the Department of Health and Human Services. It can be downloaded at www.thehastingscenter.org.
The Problem with Optimism in Clinical Trials

BY LYNN A. JANSEN

Much has been written about the so-called therapeutic misconception. Participants in clinical research, as well as investigators, are thought to misunderstand the nature of the trials in which they participate. Recently, in an attempt to further clarify the problem, some writers have distinguished the therapeutic misconception from a “therapeutic misestimation.” Whereas the therapeutic misconception occurs when one confuses the context of experimental clinical research with the context of therapeutic medicine, the therapeutic misestimation occurs when research subjects underestimate the risks of their participation in a clinical trial, overestimate the benefits, or both. Because the therapeutic misconception and the therapeutic misestimation, where they exist, have the potential to compromise informed consent, it is important for the research community to address these problems. But even if these misunderstandings are dispelled, research participants might still be subject to various other types of cognitive and affective mistakes. These, too, have the potential to compromise informed consent.

In this article, I discuss one type of mistake that has received relatively little attention by medical ethicists and researchers. This concerns a phenomenon that social psychologists refer to as “unrealistic optimism.” This phenomenon has been extensively studied by social psychologists in a wide range of contexts. However, its implications for the ethics of clinical research have not been fully appreciated, and the phenomenon may be more difficult to address than either the therapeutic misconception or the therapeutic misestimation.

The Therapeutic Error and Its Causes

It is widely thought that the therapeutic misconception poses an ethical problem for clinical research. To appreciate the significance of unrealistic optimism for clinical research, we need to come to a better understanding of this problem. One framework for thinking about the problem distinguishes a kind of error in clinical research that is ethically problematic—the “therapeutic error”—from the range of different causes that can give rise to it.

The therapeutic error occurs when a research participant falsely believes that participation in a clinical trial is in her best medical interests, and this false belief leads her either to enroll in the trial or continue to participate in the trial after she has enrolled. Note that the therapeutic error is not present when a person participates in a trial that is not in her best medical interests, provided that her motivation for doing so is not based on the just-mentioned false belief. For example, an altruistic person might decide to participate in a clinical trial that is not in her best medical interests because she shares the goals of the research. The possibility of altruistic motivation suggests a potential response to unrealistic optimism in clinical research that will be addressed later in the article.

The therapeutic error presents an ethical problem for obvious reasons. Researchers and investigators should not take advantage of the false beliefs of potential research participants to advance their own research agenda. Doing so amounts to exploiting them to advance the goals of the research. The therapeutic error is also inconsistent with the ideal of informed consent. It can lead people to participate in clinical trials that expose them to risks and harms that they should be exposed to, if at all, only if they accurately understand and freely accept the risks and benefits of participation.

There are different possible causes of the therapeutic error. One important cause is simple misinformation. Researchers all too often present experimental interventions as if they were therapy. This can lead potential research participants to confuse the research context with the therapeutic context. This results in the therapeutic misconception. According to the framework presented here, the therapeutic misconception is ethically problematic primarily because it leads research participants to the therapeutic error. To see why, consider a person who is under the therapeutic misconception and agrees to participate in a trial that is either in her best medical interests, or at least not contrary to them. In this case, the person does not expose himself to unnecessary harms by participating in the trial.
The point of the example is that if the therapeutic misconception never led to the therapeutic error, it would be much less ethically problematic than it is. That is why the therapeutic error is primary, and the therapeutic misconception is best understood as one important cause of it. There are, however, other causes of it as well. The therapeutic misestimation, for example, might be the result of a calculation mistake. It is sometimes suggested, for example, that research participants have difficulty understanding probability judgments. Even when presented with accurate information about the prospective risks and benefits of participation in a trial, they "misestimate" the costs and benefits of their own participation in the trial. Once again, under the framework presented here, this kind of misestimation is ethically problematic to the extent that it contributes to the therapeutic error. If therapeutic misestimations did not lead people to participate in clinical trials that were contrary to their best medical interests, then we would have much less reason to worry about them.

A third general possible cause of the therapeutic error is optimism, and in particular unrealistic optimism. As mentioned above, unrealistic optimism, unlike the therapeutic misconception and the therapeutic misestimation, has not received much attention. Interestingly, to the extent that writers have discussed optimism at all in the context of clinical research, they have tended to depict it as either valuable or at least not ethically troubling. Viewing optimism as a state of mind, they have asked: what could be wrong with having a rosy outlook on the prospects of success for one's participation in a clinical trial?

The framework presented here, however, suggests that optimism may be more than simply a state of mind. It is possible that it, too, can contribute to the therapeutic error. If so, then like the therapeutic misconception and the therapeutic misestimation, unrealistic optimism poses an ethical problem for clinical research. This is the issue that will be explored in the remainder of this article.

Explaining Unrealistic Optimism

To my knowledge, no empirical studies on optimistic bias in the context of clinical research have been undertaken. However, numerous studies document its prevalence with respect to health-related decisions. While it is important to be wary of extrapolating from one context to another, these studies offer insight into how optimistic bias could affect the decision to participate in a clinical trial.

The first thing to say is that unrealistic optimism likely has multiple determinants. It does not result from a simple failure to be adequately informed about the risks and benefits of a decision. Nor is it accurately described as an instance of misunderstanding with respect to either context or probability. Rather, unrealistic optimism is a kind of bias that leads a person to believe that she is more likely to experience positive outcomes and less likely to experience negative outcomes than others who are similarly situated to her. Unrealistic optimism, in other words, affects how persons process information. The problem with the bias is not that it prevents a person from understanding the benefits and risks generally associated with a course of action, but rather that it causes a person to misapply this information to herself. For purposes of this discussion, the errors associated with unrealistic optimism are understood as resulting from either cognitive or motivational distortions that interfere with decision-making.

It is helpful to compare unrealistic optimism with other types of bias, such as the so-called above average effect. Studies show that when people are asked to judge their own abilities relative to those of their peers, a substantial majority respond by claiming that they are above average. Because it is not logically possible for a substantial majority of members of a group to be above average with respect to that group, these studies demonstrate that many people engage in self-serving appraisals of their own abilities.

The tendency to engage in self-serving appraisals has been amply demonstrated in the health care context, and it may help to explain the phenomenon of unrealistic optimism. For example, studies on perceived susceptibility to illness indicate that people tend to underestimate the likelihood that they will develop an illness. One explanation for this is egocentrism. People tend to focus on themselves and ignore information about others. Thus, a smoker might believe that he is much less likely to get cancer than other smokers because he has a good diet, but in forming this judgment he might ignore information about the risk-reducing behavior of other smokers. Likewise, in the context of clinical research, a prospective participant might believe that some negative outcome is much less likely to happen to her than to others because of certain facts about herself or her behavior, and she might ignore risk-reducing facts about others that are equally relevant. In this way, egocentric tendencies would explain unrealistic optimism.

Unrealistic optimism also could result from what social psychologists refer to as the "anchoring and adjustment" heuristic. This is a process in which "people make estimates by starting from an initial value that is adjusted to yield a final answer [and] . . . adjustments are typically insufficient." Applied to the decision to participate in clinical research, participants might set a low initial probability value for a
negative outcome, then adjust this value insufficiently when confronted with evidence that the trial imposes substantial risks on participants.

Interestingly, the anchoring and adjustment heuristic could work in tandem with the therapeutic misconception. If prospective participants in a clinical trial fail to appreciate the difference between research and therapy, they may judge the likelihood to be very low that a physician would enroll them in a study that is not in their best medical interests. This judgment then might serve as an anchor. When they were presented with evidence about the risks of participating in the trial, they might adjust this judgment, but adjust insufficiently. The result would be unrealistic optimism about their participation in the trial.

The self-serving tendency, egocentrism, and the anchoring and adjustment heuristic are all instances of cognitive distortions that can give rise to unrealistic optimism. But unrealistic optimism may also arise from motivational determinants. Some have suggested, for example, that unrealistic optimism results from the need to avoid anxiety, protect self-esteem, or to project a positive image. In this respect, unrealistic optimism resembles wishful thinking. A person who engages in wishful thinking represents the world as she would like it to be rather than as it is. In some contexts, doing this will lead persons to make decisions that set back their interests, but in other contexts it may not. The philosopher Robert Nozick gives the following example. A “mother is presented with courtroom evidence that her son has committed a grave crime, evidence that convinces everyone else but, were she to believe this, would make her life miserable.” Nozick wonders whether it is rational for the mother to believe the positive outcome (her son really is not guilty) despite the lack of evidence for this belief. He suggests that it can be if we understand rational belief as serving the goal of promoting one’s interests rather than as serving the goal of acquiring true beliefs.

Psychological research has tended to confirm that, just as people can get benefits from wishful thinking, they sometimes can benefit from holding unrealistically optimistic beliefs. It is generally thought, for example, that unrealistic optimism can provide the motivational edge necessary for people to complete difficult projects or to continue with difficult health-related interventions when no other options exist. It is probably true, however, that a person cannot deliberately and self-consciously acquire an unrealistically optimistic belief in order to secure these benefits. In all likelihood, the motivational determinants of unrealistic optimism, like those of wishful thinking, must operate at a nonconscious level. This complicates the task of identifying the cause of unrealistic optimism in any particular case. Indeed, while the emphasis here has been on distinguishing motivational from cognitive determinants of unrealistic optimism, in reality, it will often be difficult to determine whether cognitive or motivational factors (or both) are at work.

At this point it should be evident that unrealistic optimism is not simply a hopeful state of mind. Hopeful people need not believe that they are more likely to experience positive outcomes than others who are similarly situated. Nor need they have the bias of believing that they are more likely to experience positive outcomes than the available evidence suggests. Hopeful people merely are disposed to accentuate the positive. For example, a hopeful person may know that she has only a one out of 10 chance of recovering from her illness, but she can—without bias or irrationality—hope for the best. In fact, it is possible for a person to be both unrealistically pessimistic and hopeful at the same time. We might call such a person “a hopeful pessimist.”

The failure to distinguish unrealistic optimism from hopefulness helps to explain why some have claimed that “optimism alone should never be ethically problematic.” It is asserted that, while Institutional Review Boards (IRBs) should make efforts to minimize the kinds of misunderstandings associated with the therapeutic misunderstanding and therapeutic misestimation, they should “encourage and support personal optimism in the research setting.” It should now be easy to see why this recommendation is too quick. To be sure, not all optimism is detrimental. But in some contexts unrealistic optimism can lead people to make decisions that set back their interests.

Is clinical research such a context? Participation in some clinical trials is not contrary to the medical best interests of any of the participants. Some trials offer therapy that is known to be either comparable or superior to all standard available treatments. But other trials do pose substantial risks of harm to at least some of the research participants. These trials have been referred to as “bad deal trials.” Consider, for example, a three-arm, randomized, placebo-controlled trial that compares a standard available therapy with an experimental therapy. Even if the experimental therapy is thought to be as good as the standard therapy, the research trial will not be in the best medical interests of all participants, since some will receive only placebo.

The existence of bad deal trials explains why it is reasonable to think that clinical research is a context in which unrealistic optimism could lead participants to make decisions that set back their interests. Significant empirical evidence demonstrates that when people make health-related decisions, they tend to underestimate the costs of their own risky behavior.
no reason to think that this tendency is not present when people make health-related decisions in clinical trials. In fact, it may be the case that many instances of unrealistic optimism have been misdescribed in the current research ethics literature as instances of the therapeutic misconception or the therapeutic misestimation.

Still, some may think that this cause of the therapeutic error is not as serious as I have been suggesting. People routinely make financial and personal decisions that are influenced by cognitive and affective bias. Many of these decisions also have the potential to set back a person’s interests. Yet we do not judge these decisions to be ethically problematic. However, I have been assuming uncontroversially that clinical researchers have duties with respect to those whom they enroll in their trials. These duties include, at the minimum, the duty to secure the informed consent of research participants. They also include the duty not to exploit the vulnerabilities of research participants for the advancement of their research goals. In other contexts, such as financial and personal, there may be no party with these same duties. That is why unrealistic optimism with respect to research-related decision-making raises ethical concern, while it may not in other contexts.

**Autonomy, Consent, and Harm**

The therapeutic error can compromise the informed consent of research participants. However, it is important to describe correctly the cause of the therapeutic error in order to appreciate how it does so. I argue here that unrealistic optimism compromises informed consent in a way that is different from that of the therapeutic misconception and the therapeutic misestimation. Thus, an effective response to unrealistic optimism in clinical research may require different interventions than those proposed for these other causes of the therapeutic error.

The traditional model of informed consent identifies four components that must be satisfied: 1) competence; 2) provision of information; 3) understanding; and 4) voluntariness. The therapeutic misconception, as well as the therapeutic misestimation, has been widely thought to compromise the understanding component. But unrealistic optimism is not a form of misunderstanding. It is possible for a research participant to be competent, have access to all relevant information, have an adequate understanding of the information, and yet be subject to the bias of unrealistic optimism. This suggests that if unrealistic optimism compromises informed consent on the traditional model, then it must do so because it interferes with voluntariness.

Regrettably, the requirement of voluntariness is not well understood. Nor is it well accounted for in the traditional model of informed consent. To better understand the requirement of voluntariness, it will be helpful to distinguish a strong from a weak conception. The traditional model of informed consent relies on a weak conception of voluntariness—one that puts the focus on external factors such as the absence of coercion or manipulation. It also identifies certain internal factors that compromise voluntariness, such as psychiatric disorder and addiction. The weak conception, however, does not inquire into the causal origins of belief and desire.

The strong conception of voluntariness demands more. It requires that, in addition to the requirements of the weak conception, a person be free from various cognitive and affective distortions that interfere with autonomous decision-making. These distortions compromise autonomous agency since they typically operate behind the back of those who are subject to them. To illustrate, consider the phenomenon of adaptive preference formation. A person who has adaptive preferences has adjusted his desires to the options that are available to him. He cannot get what he wants, and so he comes to want what he can get. This compromises his autonomy since the process of adjustment is not a deliberate strategy for reducing frustration, but rather is the result of a nonconscious causal process.

Adaptive preferences are just one example of a distortion that compromises autonomy. Other examples abound. In addition to adaptive preferences, Jon Elster lists the following: wishful thinking, conformity, and an obsession with novelty. These distortions compromise autonomy in the same general way. They are more like hidden drives than consciously adopted strategies for planning one’s life. The same can be said of unrealistic optimism. Typically, the unrealistically optimistic research participant does not realize that she is unrealistically optimistic. The bias operates behind her back.

Now it is true that many—perhaps all—human decisions are subject to some nonconscious determinants. This means that we should not postulate an excessively ideal model of autonomous preference for clinical research, one that demands perfect information and perfect conscious control. Instead, following Elster, we can define autonomous preferences residually. We can say that an autonomous preference is one that has not been shaped by any one of a fairly well-defined set of nonconscious mechanisms. We then can say that the strong requirement of voluntariness requires that persons have autonomous preferences understood in this way. Doing so sheds light on the ethical significance of unrealistic optimism in clinical research. The phenomenon of unrealistic optimism may not
compromise informed consent as it has been traditionally understood in
the clinical context, but it does compromise informed consent when
informed consent is taken to include the strong conception of voluntari-
ness.

But why should we modify the traditional model of informed consent to include the strong conception of voluntariness? The traditional
model of informed consent was developed for the clinical context. In
this context, the weak conception of voluntariness may be appropriate.
In the clinical context it is reasonable to assume that physicians aim at the
good of their patients. However, in
the research context, the researcher and subject do not necessarily share
the same ends. The primary concern of researchers is to develop general-
izable scientific knowledge. Their primary loyalty is to future patients,
not to the particular research subject before them. This provides a reason
for holding the standards of
informed consent for clinical
research to be more stringent than
those for therapeutic medical care.\textsuperscript{40}

Indeed, this is precisely the reason
why more rigorous standards of disclo-
sure of risks and benefits have already been adopted for clinical research
than for therapeutic medicine.\textsuperscript{41}

These same considerations justify adopting a stronger conception of voluntariness for participation in clinical trials that impose a nonneg-
ligible risk of significant harm.
Perhaps for trials that are not “bad
deal trials,” the weak conception of voluntariness is sufficient. Recall
that the therapeutic error can involve more than a failure to understand the risks and benefits associated with research. It also
involves distortions in the way that people process and apply this infor-
mation to themselves. With respect to some clinical trials, decisions
based on these distortions are as troubling as those based on insufficient disclosure of risks and benefits.\textsuperscript{42}

Cognitive and motivational biases can lead people to believe falsely
that they are not susceptible to the risks present in a bad deal trial.
These biases can also lead participants to imprudently disregard new
information about risks that might lead them to stop participating in a
trial to which they have already consented. A serious commitment to
informed consent in research should therefore include the requirement
that potential research subjects be free from the kinds of distortions and biases associated with unrealistic optimism, at least for bad deal
trials.

But is this too demanding? If we insist on strong voluntariness for participation in bad deal trials, then we may end up excluding some per-
sons who desire to participate in
them. Thus, in the name of safe-
guarding autonomy, we run the risk of eroding it. The assumption
behind this worry is that persons
have an autonomy-based claim to
participate in clinical research.
When they are excluded from par-
ticipation, they are owed a nonpa-
ternalistic justification for the exclusion.

The assumption behind the worry
should be rejected, however. The
purpose of conducting a clinical trial
is not to provide persons with new
therapeutic options, but to con-
tribute to generalizable scientific
knowledge. Exclusion from a cli-
nical trial, whether for ethical or sci-
entific reasons, does not set back the autonomy of anyone, since there is
no general right to have the option
to participate in clinical research.
Furthermore, the proposal recom-
ended here would affect only
those potential research participants whose desire to participate in
research is affected by distortions and biases that have the potential to
subvert autonomous decision-

Responding to Unrealistic
Optimism

Assuming that the argument of
the previous section is correct, it is
important to ask: how might con-
scientious researchers and IRBs
effectively respond to the problem
posed by unrealistic optimism?
Unfortunately, there may be no
complete response to the problem.
Here I shall mention some possible
responses and note their limitations.

Efforts to alleviate the therapeutic
error have focused on improving the
understanding of potential research
participants. Educational interven-
tions—such as improving the lan-
guage in consent forms to make it
clearer that the trial is research
rather than therapy—may be effective
at overcoming the misunderstandings associated with the therapeu-
tic misconception and/or the
therapeutic misestimation. However,
if the cause of the therapeutic error is unrealistic optimism, then efforts
should be directed at improving the voluntariness, rather than the under-
standing, of the decision to partici-
pare in clinical research.

This is not to deny that some
efforts to improve understanding
might also be effective in reducing
unrealistic optimism. This might be
the case, for example, when unrealis-
tic optimism results from a
research participant’s reliance on the
anchoring and adjustment heuristic
discussed earlier. It has been suggested
that researchers should wear red
coats instead of the white coats
associated with medical care and
that investigators should meet with
prospective participants outside of
hospital settings.\textsuperscript{43} It is possible that
such measures would counteract not
only the misunderstandings associat-
ed with the therapeutic misconception, but also impairments to volun-
tariness that result from optimistic bias produced by anchoring and
adjustment.

Still, we should expect that com-
bating unrealistic optimism in gener-
al will require more than correcting misunderstandings. With respect to health-related decisions, unrealistic optimism has been shown to be very resistant to educational interventions. Even after people are made vividly aware of risk factors they tend to persist in optimistic bias. Most people, for example, tend to underestimate the likelihood that they will have a heart attack. This bias persists even after they have been informed, and asked to consider, relevant risk factors. In some cases, the optimistic bias actually increases as a result of becoming better informed about the risks.

Efforts aimed at correcting the way people process information also have proven to be relatively ineffective. Weinstein and Klein, for example, conducted a study designed to encourage participants to give more attention to their own risk-increasing attributes. The idea behind the study was that unrealistic optimism might result from a tendency to overestimate risk-decreasing attributes as compared to risk-increasing attributes. The study showed that, even when people are made aware of and are encouraged to focus on their own risk-increasing attributes, no significant reduction in optimistic bias occurred.

New approaches to “debiasing” may prove to be more effective, but currently we do not have good strategies for correcting unrealistic optimism. Rather than attempting to counteract unrealistic optimism in research participants, a more promising approach would involve identifying and excluding those who exhibit the bias from participation in clinical trials in the first place. Social scientists have developed good instruments for identifying and measuring optimistic bias. In principle, then, the screening process for inclusion in bad deal trials could include an assessment for unrealistic optimism.

This approach would likely reduce the number of persons with optimistic bias in the eligible research subject pool. However, it cannot provide a complete response to the problem for the following reason. Several studies have shown that “optimistic biases are attenuated when people are choosing between goals or selecting possible courses of action to attain these goals, but exaggerated once a particular goal is selected.”

Susceptibility to optimistic bias, then, may be greater after the decision is made to enroll in a trial. Once a participant has enrolled in a trial, he may be reluctant to reconsider his decision to participate. Doing so may cause anxiety or frustrate his sense that he is in control of his situation. This is what would be expected if the cause of unrealistic optimism is the motivational need to reduce anxiety.

Unrealistic optimism in this post-decisional context may lead research subjects to downplay new information regarding potential risks of continued participation in the trial. Like the initial decision to participate, the decision to continue participation can be prompted by unrealistically high expectations of benefit and/or unrealistically low expectations of harm. Should researchers, then, strive to screen for unrealistically optimistic participants in the post-decisional, as well as the pre-decisional, context? Perhaps the answer is yes, but doing so would substantially increase the burdens of conducting research. Alternatively, researchers could seek to recruit only altruistically-minded participants. Since altruistically-minded participants are not motivated by a concern for their own good, they presumably would not be subject to the type of optimistic bias that we have been reviewing.

In the end, the most realistic response to unrealistic optimism in clinical research may involve strengthening the non-consent-based protections in clinical trials. We have seen that unrealistic optimism can compromise the voluntariness of informed consent, thereby undercutting the justificatory force of consent to participate in research. But it is widely recognized that adequate protection for research subjects requires more than simply securing their informed consent to participate. Traditionally, in research ethics, the standard of clinical equipoise has been thought to be an important, non-consent-based ethical standard for conducting experimental trials. The standard of clinical equipoise in effect excludes what was earlier referred to as a bad deal trial; and, recall, these are the kinds of trials in which unrealistic optimism would be most ethically troubling. Alternatively, some have proposed replacing the standard of clinical equipoise with an antieploitation principle. An adequately formulated antieploitation principle would need to address the problem of unrealistic optimism. Researchers who enroll research subjects known to be prone to unrealistic optimism plausibly exploit them by taking advantage of a weakness or vulnerability. Exploitation can occur even when the researcher has no intention to engage in exploitation.

This is not the place for a careful discussion of which standard—equipoise or antieploitation—is better. The point rather is that, to the extent that we have reason to doubt the justificatory force of informed consent, we have reason to strengthen other ethical safeguards for protecting research subjects. Potential research participants commit the therapeutic error only when they enroll in a trial that is not in their best medical interests. Reducing opportunities for participation in such trials would mitigate the problem of unrealistic optimism in clinical research.

**Conclusion**

I have been assuming, of course, that unrealistic optimism does
Indeed pose a problem. The possibility that it does has been largely ignored by those concerned with ethical clinical research. To the extent that optimism has been discussed in this context at all, it has been presented as benign or even beneficial. I have given some reasons for thinking that it may be a cause of the therapeutic error and that dismissing it as benign or unimportant may be a mistake. I have also called attention to the lack of empirical research on the prevalence of unrealistic optimism in human subject trials. Numerous studies in social psychology have found that unrealistic optimism plays an important role in health-related decisions. It would be extraordinary if it were found that it was not a factor in the decisions of subjects to participate in research.

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References
2. See ref. 1, Horng and Grady 2003.
4. The discussion of “cognitive and affective mistakes” in this paper is intended to connect with the nonbehaviorist literature on heuristics and biases, not Skinnerian behaviorism. See, for example, Gilovich T, Griffin D, Kahneman D, eds. Heuristics and Biases: The Psychology of Intuitive Judgment. Cambridge, U.K.: Cambridge University Press, 2002.
7. See ref. 1, Appelbaum et al. 1987.
8. See ref. 1, Dresser 2002.
10. See ref. 1, Horng and Grady 2003.
11. See ref. 1, Horng and Grady 2003.
12. See ref. 1, Horng and Grady 2003.
17. See ref. 1, Gold and Acute 2003.
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