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Protecting Third Parties in Human Subjects Research

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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.¹ 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.

Informed consent will be obtained from all heads of households asked to use the test kits and 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.² 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 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

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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.³

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.”⁴ 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.⁵ 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 practicably be conducted without a waiver).⁶ Third parties may become secondary research subjects if investigators inadvertently obtain identifiable data about those persons through study interventions.⁷

Many types of research can place third parties at risk (see Box 1).⁸ 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.

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

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,⁹ 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.¹⁰ 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.¹¹ 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.¹² 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.”¹³ 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.”¹⁴ 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.¹⁵

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).”¹⁶ 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 reason 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 of 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.¹⁷ 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 argues 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 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.²¹ 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 1999.²² 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 law-suits 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.²³

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.²⁴ 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 s/he 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.)

Box 2

Duties Owed to Third Parties in Research

Degree of risk to third party	Duty
No risk	No duty

Degree of risk to third party	Duty
Minimal	Inform subjects about risks to third parties
More than minimal	Take reasonable measures to protect third parties, such as informing third parties about risks and obtaining permission if necessary
Serious	Do not conduct the research or redesign the research to minimize risks to third parties

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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