New issues facing IRBs

IRB review is a continually evolving process. In recent years, issues of privacy and confidentiality have become major focuses of human subjects protections under the guise of the Health Insurance Portability and Accountability Act of 1996. Initially designed to avoid loss of insurance based on violations of privacy, the rules regarding privacy and confidentiality have proven daunting to review and enforce. Consent documents have expanded greatly to accommodate required language. Investigators have legitimately complained that the requirements are excessive and impair research activities. Balancing these concerns are the very real problems associated with identity loss and the concerns that private health information could be used to discriminate against individuals. IRBs have also become embroiled in the desire to minimize conflicts of interest in research. All of this activity has created an increasing burden for investigators, IRB members and human subjects protection program staff members. Fortunately, there seems to be a movement to simplify and streamline some of these review processes. One can only hope that we will achieve a balance of appropriate review and adequate protections which can be accomplished in an efficient and professional manner.

Key points

- Regulation of human subjects research has evolved in the wake of scandals involving mistreatment of human research subjects.
- Modern human subjects protections had their roots in the war crimes trials of German physicians who experimented on prisoners during World War II.
- Important early declarations regarding the ethical treatment of human research subjects include the Nuremberg Code, and the WMA Declaration of Helsinki.
- The description of the Tuskegee Experiment was a watershed in the history of US human research ethics, leading to the publication of the Belmont report elaborating the ethical principles in treatment of human subjects research.
- US IRBs have largely functioned as regulatory bodies ensuring compliance with federal regulations.

References


Further reading


Section 4. Research and publication

Research with vulnerable persons such as children and prisoners

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This does not mean that vulnerable persons should never be enrolled in research. Historically, scandals have involved abusive studies where vulnerable persons were included because they were less able to resist. Excluding vulnerable persons from research entirely, however, can lead to their exclusion from: (1) research with potential benefit; and (2) the more general benefits of the research endeavor: knowledge about conditions relevant to them, their sometimes specific needs and risks, and the possibility to generalize available data to the situations they present with.

Who is vulnerable?

Attempts to define vulnerability have differed in their scope.1 A European "principle of vulnerability" presents it as a universal expression of the human condition.2 Such broad definitions, encompassing humanity in its entirety,3,4 are unhelpful in protecting human subjects as they cannot provide reasons for special protection. In a more restricted definition, "vulnerability" in research on human subjects is often applied to individuals who are unable to give informed consent or more likely to be exploited.5 National and international regulations are based on this sort of definition: vulnerability is usually linked either to consent or to the risk of harm.

One way to synthesize these different definitions is to consider that vulnerability as a claim to special protection is an identifiably increased likelihood of being wronged.6 It encompasses any wrongs, including those we incur when something to which we have a valid claim is denied us. Defining vulnerability in this way means that we start by identifying the sorts of wrongs likely to occur in the conduct of research, then identify those people more likely to suffer these wrongs. Many individuals are vulnerable in this way; but this definition makes the identification of different kinds of vulnerability, and the development of targeted protections, easier.

Protecting vulnerable persons in research

Necessary protections have two components: fair subject selection, and the specific care required to minimize wrongs to vulnerable persons once they are enrolled in research. Recruitment of research subjects should respect fairness in the distribution of research-related risks and benefits. It is not justifiable to conduct research on an "easily available" population — for example, the rural poor in developing countries — simply because the study will be easier to conduct with them than with persons living in better circumstances. Neither is it defensible to reserve access to potentially beneficial research to the socially privileged. The rationale for the planned recruitment strategy must be based on the balance of potential harms and benefits and the need to obtain generalisable results, and discussed in the protocol.

Specific care requires that the risks and needs of those more likely to suffer wrongs in the conduct of research be identified, and targeted special protections outlined. Protecting vulnerability in clinical research starts with a good grasp of criteria for ethical research, in general. Investigators designing research with vulnerable subjects, and ERCs reviewing such research, should ask themselves the following questions:

1. In which ways are potential research subjects at risk of being wronged in this research? Are some potential subjects identifiable more likely than other persons to incur this wrong, or likely to incur it to a greater degree?

2. Am I/are we among those who share in the duty to minimize, or avoid, this wrong?

3. If yes, what should we do to avoid this wrong or minimize its increased likelihood or degree, or ensure it is compensated in ethically justifiable ways?

Based on the sorts of wrongs that can occur in clinical research, examples of vulnerability are outlined in Table 31.2. Examples of protections tailored to the wrongs involved are outlined in the Table 31.3. In some cases, excluding vulnerable persons from participation in a research project will be an appropriate way to minimize the risk of harm or other wrongs. Sometimes, however, it won’t be. A study designed to address health problems specific to a vulnerable population, such as research on advanced dementia, could benefit the same population of vulnerable persons from which subjects are recruited, and cannot be conducted on nonvulnerable subjects; a condition known as the subsidiarity principle. A study that, although it could be conducted enrolling only non-vulnerable subjects, could be designed in a way to give sufficient extra protection for vulnerable subjects. When such studies offer prospective benefit to research subjects, excluding vulnerable populations rather than providing protections to allow their recruitment can itself be harmful. If a subject in a research protocol with prospective benefit is imprisoned during the study, for example, terminating his participation may not be in his interest. In the rest of this chapter, we focus on two specific populations of individuals often vulnerable in the conduct of research: children and prisoners.

Research involving children

Why are children vulnerable?

Going from the state of being a child to that of being an adult is a continuous process, during which societies identify varying points as the threshold marking the passage from one state to the other. Children are considered vulnerable because, during much of their development, they are incapable of decision-making regarding medical intervention. Even when they are capable of decision-making for clinical care, consent for research requires something more: research-related risks are born for the benefits of others, a fact potential subjects are at risk of misunderstanding even in the best of cases. Although minors who are mature adolescents can often understand the consequences of their choice regarding medical interventions and then provide informed consent for clinical care, this is not considered sufficient in the case of research. Additionally, we are more reluctant to expose children to research-related harms, in part again because the risks undergone in this context cannot be consented to by the child herself, but also because we recognize a general responsibility of protection towards children beyond that which their parents endorse.

What follows from the vulnerability of children for research ethics?

Fair subject selection requires that children be enrolled only when the research question cannot be answered by conducting the study with adults — for example, because the targeted condition is specific to children or because the research question regards the situation of children specifically. When children are recruited in research, protections are required to circumscribe
responsibility for the care and custody of the child." EU directive 2001/20/EC specifies that research can only be conducted on minors if "the informed consent of the parent or legal representative has been obtained," apparently requiring the agreement of both parents.

Regulations also require that older children and adolescents should be informed to the level they can understand, and that they should provide assent - defined as "affirmative agreement" in US regulations and provided in writing - when they are capable of doing so.14 Determining when assent should be sought is delicate as children's ability to understand research participation varies across, but also within, age groups. While it is usually found that children under 7 years of age are not capable of giving assent, and those over 14 years often are, this requires specific assessment, especially in the intermediate age group. Letting families decide when children are old enough to be involved is a decision to enroll in research is one possibility, but it should be applied with caution; data suggest that considerable disagreements can arise within families involving prisoners. First, prisoners are vulnerable because they have limited choices: they cannot freely choose and consult their own physician. Their access to healthcare depends on the available health structures. Prisoners might not have access to alternative healthcare or adequate and independent clinical advice when a research study is carried out in a prison. Second, prisoners are vulnerable because the pressures from prison officers and detainees, as well as pressures resulting from their living conditions, could interfere with free informed consent. Prisoners might accept participation in research because they fear punishment if they do not participate. Hierarchical structures are strong among prison inmates and leaders, on the contrary, could force inmates not to participate. Prisoners are also vulnerable to real or perceived incentives to become a research subject, especially if they think that participation could be advantageous because research subjects obtain better living conditions or shorter prison terms than other prisoners.

Among ethic scholars and researchers, controversy exists as to whether prisoners should be considered competent to give informed consent. At one extreme are those who, based on the principle of beneficence, claim that, since studies are lacking which prove prisoners' capacity to give truly informed consent, one should not let them decide on their own. At the other extreme is the opinion that prisoners should not be treated differently from other potential research subjects, since their mental faculties are not fundamentally changed by detention. A part of this question is empirical: there has been insufficient exploration of whether prisoners have a tendency to make different decisions while in prison from those they would make if they were not detained. A second argument refers to the right to respect autonomy: being deprived of liberty does not include deprivation of the autonomy to decide about one's body and healthcare-related issues.

Treated prisoners, by definition, as incompetent concerning health-related matters is a violation of their human rights.

What follows from the vulnerability of prisoners for research ethics?
The vulnerability of prisoners has triggered various strategies for their protection against research risks and abuse.15,16 Strategies are used either alone or cumulatively by different guidelines and legislations. The first is characterized by different forms of restrictions. The most extreme form is general prohibition of all forms of research with prisoners as is the case in some of the US. Others, such as US federal regulations, allow only certain categories of research to be carried out with prisoners. Categories are allowed either because they imply only minimal risk or because their benefits are particularly important and outweigh the (limited) risks.18 The Council of Europe varies restrictions according to the type of benefit. It restricts only research that does not promise direct benefit to prisoners. If research is expected to produce indirect benefit, i.e., benefit only to prisoners as a group, it is allowed only if three conditions are fulfilled: (i) Research of comparable effectiveness cannot be carried out without the participation of persons deprived of liberty; (ii) The research has the aim of contributing to the ultimate attainment of results capable of conferring benefit to persons deprived of liberty; (iii) The research entails only minimal risk and minimal burden. Research without at least indirect benefit is prohibited.18 A second strategy is to require higher efforts than with nonprisoners to assure informed consent and freedom of choice. This could imply that prisoners should be informed several times and particular tests are required to include them in the research. A third strategy is to increase oversight mechanisms for their protection against research risks, and research should be carried out inside prisons only if results of comparable efficiency and meaning cannot be obtained with nonprisoners. Stricter oversight mechanisms might include the obligation to visit the prison before, during, and after the study to control whether confidentiality, informed consent, and other ethical requirements are respected. A fourth strategy is to require special ethical training for researchers carrying out research with prisoners to assure that they are aware of ethical issues and specific risks related to research with prisoners, and engage themselves in the protection of prisoners from abuse through research.

Such strategies are important to protect prisoners from the risk of abuse, and preferable to their exclusion from research entirely. Empirical studies inside prisons can be beneficial and are necessary to obtain evidence-based answers to some research questions that need to be addressed in order to improve prisoners' healthcare.

Key points

- With children, prisoners, and other vulnerable populations, the challenge is to find the right balance between protection from abuse and the need to grant vulnerable populations access to participation in research.
- Although the exclusion of vulnerable subjects from a specific study will sometimes be an appropriate way to minimize their risk of being wronged in the conduct of research, this will not always be true.
- Studies designed to address health problems specific to a vulnerable population are needed to improve care for this very population, and often cannot be conducted on others.
- Participation in research can hold a prospect of benefit from which it is sometimes wrong to exclude vulnerable persons. In such cases, enrollment with special protections tailored to the sort of wrong to be avoided is ethically preferable to exclusion.
acceptable risks and to compensate the lack of consent by the children.

Limiting risks to children has implications for the timing of a protocol. Interventions relevant to both children and adults should undergo at least initial testing on adults in order to minimize unknown risks at the time when children will be recruited to assess questions more specific to them. Other implications regard sets of circumstances: "minimal risk" and "minor increase over minimal risk;' "prospect of direct benefit for sick children' has a net risk, however, especially if the expected risk is that of sick children. An alternative proposed by Wendler is based on the "net risks test.' As any assessment of risk in research, it should focus on the research-related risk; risks that potential research subjects would not run outside the protocol. Sick children enrolled in research will often undergo standard therapy as well as experimental interventions, and risks inherent to the standard therapy are not research-related. The assessment should further focus on the net risk: risks that are not balanced by the prospect of direct benefit to the child. Paediatric pharmacokinetic studies, for example, hold no prospect of direct benefit: their entire risk is a net risk. A phase III study of a novel therapy proven effective in adults, however, does hold a prospect of direct benefit for sick children. Such a study can still have a net risk, however, especially if the expected benefit is modest. Finally, ERCs should assess this net research-related risk and accept it if it is no greater than "those associated with routine medical and psychological examination" or "those ordinarily encountered in daily life." US regulations combine these two thresholds. Comparison of the net research-related risks posed by a study should be with "the level of risk average children face in daily life (or during routine examinations)," or the level "normally encountered in the daily lives of people in a stable society" in order to avoid placing an excessive burden on children suffering from diseases requiring invasive treatment or living in circumstances such as war-torn countries, whose risks in daily life far exceed what is acceptable in research. Because children are unable to provide consent for their own participation in research, permission must be sought from their parents or other legal guardians.

US regulations specify that the permission of both parents is required unless (1) the investigational procedure involves no more than minimal risks; (2) there is a prospect of direct benefit to the child; or (3) "one parent is deceased, unknown, incompetent, or not reasonably available" or "only one parent has legal responsibility for the child."
In this text, the term "prisoner" is meant to include any kind of detained person, in any kind of detention facility. As used in its British meaning, all kinds of detention facilities, such as jails, federal prisons or other places of detention.

References

Further reading

The Case
Dr. Smith is an anesthesiology resident on the hospital "pain service," who has been asked to consult on a patient who has been admitted for palliative care for terminal colon cancer. The patient has had breakthrough pain on maximal and therapy. He feels nauseous and limits his oral intake. Subcutaneous (SQ) administration of morphine is initiated, and brings partial relief. The patient requests epidural analgesia. The attending on the pain service is conducting a placebo-controlled crossover research study evaluating the efficacy of administration of SQ morhine to improve the absorption of morphine in patients with terminal illness. Each study subject will receive morphine via a different method on each of 3 days: Intravenous morphine, SQ morphine plus placebo, and SQ morphine plus hyaluronidase. As part of her role on the pain service, Dr. Smith is supposed to help recruit clinical research subjects, but she is bothered by the fact that this particular patient is terminally ill, is in considerable pain, and is requesting a specific therapy that is not on the research protocol. Is it ethical for her to try to recruit him for this study?

Research on the management of pain and other symptoms is crucial to provide better care for acute, post-operative, and chronic symptoms, as well as better symptom management at the end of life. However, participation in clinical research places subjects at risk of harm for the benefit of others. This tension is intrinsic to all clinical research, and underlies the need for protection of human subjects. A number of international and national regulatory documents aim to protect participants in research while also taking into account the interests of future patients by allowing research to be conducted. All refer to similar basic principles, which have been synthesized thus: social value, scientific validity, fair subject selection, favorable risk/benefit ratio, independent review, informed consent, and respect for enrolled participants. All of the requirements are equally necessary, and each is relevant to research on the management of pain and other symptoms, which requires the same ethical protections as any other form of research with human subjects. Some aspects, however, do present difficulties more specific to the context of symptom management studies. These include difficulties related to scientific methodology, fair subject selection, obtaining a favorable risk/benefit ratio, and informed consent.

Scientific methodology
Although individual patients may benefit indirectly from research participation, the intention of research is to generate valid data to inform the care of future patients. The research may involve delaying pain relief in participants. The investigator is responsible for minimizing risks and avoiding unnecessary harm for the patients. He/she is also accountable for the scientific validity and clinical relevance of the experimental question. Methodological issues in the design of symptom management trials, the collection of adverse effects, and the reporting of data, have ethical importance. Failure to give proper attention to these issues can make the results of a trial difficult to interpret and prevent comparisons. This limits usefulness in clinical practice, causing research to fall short of its purported goal and fail to fulfill its commitments towards patients and society. Risks to human subjects must be justified in part by the social benefit of research. Therefore any risk, however small, in a study that cannot answer its research question is excessive. Randomized, double-blind trials have become standard in acute as well as in chronic pain trials. The inclusion of patients with moderate to severe pain at baseline may be crucial for sensitivity, i.e., the ability to detect the analgesic effect of the tested drug. Primary outcomes are usually a difference in pain