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 Tuskeegee Experiment was a watershed event 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 assuring compliance with federal regulations.

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Section 4 Chapter 31

Research and publication

Research with vulnerable persons such as children and prisoners

Samia Hurst and Bernice Elger

The Case

Complex regional pain syndromes (CRPS) are increasingly recognized in children, and treatment is unsatisfactory in many cases. An anesthesiologist designs a clinical research project to study the efficacy of lumbar sympathetic blockade (LSB) with lidocaine compared to intravenous (IV) lidocaine in pediatric patients with CRPS who have not responded to traditional therapy. The study is a double-blind placebo-controlled study, involving 40 children between the ages of 7 and 12. All will receive general anesthesia and placement of a lumbar sympathetic catheter. Patients will then be randomized to receive either IV lidocaine plus saline via lumbar sympathetic catheter, or LSB with lidocaine plus IV saline. In obtaining informed consent, the researcher explains to parents and children (to the degree that the children can understand) the risks of general anesthesia and lumbar sympathetic catheter placement.

In answer to the expressed desires and expectations from patients and parents of pain relief, the researcher informs them that the "real" drug may be effective (in fact, he thinks it will be), but that it is equally important that researchers determine if LSB lidocaine is ineffective in relieving the pain. Several parents express concerns that their children may be subjected to the risks of general anesthesia and of lumbar catheter placement, but not receive the benefit of pain relief. They want assurances that their children will receive lidocaine and not placebo.

What are the ethical considerations in human subjects research when the patients who are being studied belong to vulnerable groups, such as children? Should human subjects research be conducted in vulnerable populations?

Vulnerable persons enrolled as research participants require special protection. This is recognized in a number of international and national regulations, including the US federal regulations on research with human subjects (see Table 31.1). When designing and conducting a research study, it is important to know which potential participants are vulnerable, which studies do or do not justify their inclusion, and what protections are necessary when they do participate in research.

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 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.

Clinical Ethics in Anesthesiology: A Case-Based Textbook, ed. Gail A. Van Norman, Stephen Jackson, Stanley H. Rosenbaum and Susan K. Palmer. Published by Cambridge University Press.

Table 31.1. Vulnerability in research according to international guidelines

Belmont report	• Racial minorities • The economically disadvantaged • The very sick • The institutionalized
U.S. – Department of Health and Human Services (DHHS) 45 CFR 46	• Children • Prisoners • Pregnant women and foetuses
Declaration of Helsinki	• Incompetent persons • Persons susceptible to coercion • Persons who will not derive direct benefits from participation • Persons for whom research is mixed with clinical care
CIOMS	• Those with limited capacity or freedom to consent or to decline to consent... [including] children, and persons who because of mental or behavioural disorders are incapable of giving informed consent, • Junior or subordinate members of a hierarchical group... [such as] medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police, • Elderly persons, • Residents of nursing homes, • People receiving welfare benefits or social assistance and other poor people, • The unemployed, • Patients in emergency rooms, • Some ethnic and racial minority groups, • Homeless persons, • Nomads, • Refugees or displaced persons • Prisoners • Patients with incurable disease • Individuals who are politically powerless • Members of communities unfamiliar with modern medical concepts
ICH tripartite guidelines	• Members of a group with a hierarchical structure such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees in the pharmaceutical industry, members of the armed forces, and persons kept in detention • Patients with incurable diseases • Persons in nursing homes • Unemployed or impoverished persons • Patients in emergency situations, • Ethnic minority groups, • Homeless persons • Nomads, • Refugees, • Minors, • Those incapable of giving consent

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?
(2) Are some potential subjects identifiably more likely than other persons to incur this wrong, or likely to incur it to a greater degree?
(3) Am I/are we among those who share in the duty to minimize, or avoid, this wrong?
(4) 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 parents or legal representative has been obtained,"[13] 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 in 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 on this point, including reluctance on the part of the parents of capable children to involve them.[15] Children sometimes wish their parents to decide for them, and this, of course, should be respected.

Protections provided by parental permission and children's assent are further complemented by requirements that explicit refusal by children be respected.[8] EU directive 2001/20/EC further specifies that "parental consent must represent the minor's presumed will,"[13] and that no financial incentive may be offered. Children who are unable to assent to research may become able to do so, especially in long-term studies. In such cases, their assent (or consent as the case may be), must be sought at that time.

With such protections in place, a (small) net risk in research involving children is acceptable. Allowing such studies is not only necessary to allow the conduct of research needed by children themselves, it is also compatible with motivations of altruism for research participation, a reason accepted by many parents as well as children.

Research involving prisoners

Why are prisoners[a] vulnerable?

Prisoners are not a homogenous group. Statistically, they include a higher percentage of members from other vulnerable groups, such as the poor, illiterate, mentally ill, and – in many countries – foreigners who do not understand or speak the local language sufficiently to understand explanations regarding research.

As a group, prisoners are vulnerable due to their particular situation: being detained and therefore being deprived of the freedom to move freely, which implies that they are, possibly, under the influence of different kinds of pressures. Several prison-related factors are relevant for ethical considerations about research 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 co-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 might force others to participate or, 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 ethics 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.

Treating 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.[16,17] 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.[16,17]

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 could be indicated to ensure that they have understood the information. It could also mean to provide prisoners with more time than nonprisoners to consider their decisions. Most regulations prohibit incentives in the form of money or better living conditions or influence on prison terms. Other means to ensure that prisoners' choices are in line with their best medical interest is to grant them access to an independent and qualified doctor who is not part of the research team who could advise prisoner patients impartially.

A third strategy is to increase oversight mechanisms by research ethics committees (RECs) or ERCs.[b] In the US, for example, ERCs that approve research with prisoners need to have a particular composition including a prisoner representative who has experience with prison healthcare. RECs should receive clear indications how to evaluate specific ethical issues concerning research with prisoners such as the principle of subsidiarity and issues of distributive justice: prisoners should not bear a disproportionate burden of 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.

Table 31.2. Vulnerability as a greater likelihood of being wronged

Requirements*	Examples of vulnerability
Social or scientific value	• Lack of access to either benefit or knowledge derived from research
Scientific validity	• Rare disease, leading to difficulties in reaching statistical power to demonstrate therapeutic effectiveness
Fair subjects selection	• All persons likely to be victims of discrimination
Favorable risk-benefit ratio	• Potentially higher risks: unstable patients, emergency research, foetuses, pregnant women • Potentially lower benefits: subjects in phase I studies, terminally ill patients • Subjects whose risk-benefit ratio might sometimes be the object of lesser concern to those responsible for protection: terminally ill patients, disenfranchised persons, poor subjects in developing countries, subjects without access to health care outside of research.
Independent review	• All persons likely to be victims of discrimination, if those responsible for review share discriminatory views.
Informed consent	• Difficulties in receiving or understanding the relevant information: not knowing the language used, or how to read • Lack of decision-making capacity: some children, some patients with mental disorders, comatose patients. • Lack of freedom to make a voluntary choice • Through limited freedom: prisoners • Through social weakness: minorities, refugees, sometimes women • Through hierarchical weakness: lab employees, students
Respect for potential and enrolled subjects	• Health care providers, researchers and students close to the study team who are at increased risk of faulty confidentiality • Groups and communities at risk of stigmatisation in the interpretation of study results

*With permission from Emanuel, E. J., Wendler, D. and Grady, C. (2000). What makes clinical research ethical? *JAMA*, **283**(20), 2701–11.

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 the design of a protocol. Under US regulations, ERCs may approve research involving children under three sets of circumstances: "minimal risk," "prospect of direct benefit," and "minor increase over minimal risk." A prospect of direct benefit is defined as a research situation where risks are justified by the anticipated benefit to the subjects and where the relation of the anticipated benefit to the risk is at least as favourable as that of alternatives available to potential subjects.

Linking the acceptable risk threshold to the prospect of direct benefit in this manner has come under criticism for conflating risks acceptable in therapy and in research, and allowing healthy children to undergo greater research-related risk than those accepted in the case of sick children. An alternative proposed by Wendler is based on the "net risks test."[7] 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

Table 31.3. Protection of vulnerable subjects by Ethics Review Committees*

Are potential research subjects at risk of being wronged by this research project?	Example 1: breach of confidentiality	• Health care providers are at greater risk. • IRBs share in the duty of protection • Minimization: could require specific anonymisation of data to limit colleagues' access to their personal information
Are some potential subject identifiably more likely than other persons to incur this wrong, or likely to incur it to a greater degree?	Example 2: unfavourable risk/benefit ratio	• If they stand to benefit less, terminally ill patients may be at greater risk. • IRBs share in the duty of protection. • Their risk/benefit ratio should be specifically examined by researchers and IRBs rather than assumed to be the same as for other potential subjects.
Is our IRB among those who share in the duty to minimize, or avoid, this wrong?	Example 3: being enrolled without valid consent	• Subjects of emergency research lack time to think through the options. • IRBs share in the duty of protection. • This can be minimized if consent is asked at that time only for those parts of the protocol that are truly urgent. • The remaining problems with consent at that time can be compensated by including a requirement that an independent clinician confirm that enrolment is not contrary to the potential subject's interest.
If yes, what should we do to avoid this wrong, or minimize this increased likelihood or degree, or ensure it is compensated in ethically justifiable ways?	Example 4: being denied the benefit of research	• Patients in developing countries who lack access to care are excluded from an important part of the social benefits of research. • Although IRBs are not alone in bearing some responsibility for this, it is among the points they should examine in general, and thus also for the purposes of protecting the vulnerable • Minimization: reasonable availability (World Medical Association 2008) aims to minimize this problem • Compensation: fair benefits (Participants in the 2001 Conference 2002) aim to compensate it.

*With permission from Hurst 2008.

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"[8] or "those ordinarily encountered in daily life."[9] 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),"[10] or the level "normally encountered in the daily lives of people in a stable society"[11,12] 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 risk; (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

Notes

[a] In this text, the term "prisoner" is meant to include any kind of detained person, in any kind of detention facility. The term prison is used in its British meaning all kinds of detention facilities, such as jails, federal prisons or other places of detention.

[b] Institutional review boards (terminology used in the US). In this chapter we do not make any difference between the terminology: both REC and IRB refers to the competent body of research oversight in a given country.

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Section 4 Chapter **32**

Research and publication

The ethics of research on pain and other symptoms for which effective treatments already exist

Monica Escher and Samia Hurst

The Case

Dr. Smith is an anesthesia 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 oral 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 recombinant human hyaluronidase to improve the absorption of SQ 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 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 national and international regulatory documents aim to protect participants in research while also taking into account the interests of future patients by allowing research to be conducted[1] 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

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