Review

Bench-to-bedside review: Human subjects research – are more standards needed?

David T Huang[1] and Mehrnaz Hadian[2]

[1]CRISMA Laboratory, Department of Critical Care Medicine, Department of Emergency Medicine, University of Pittsburgh, 641 Scaife Hall, Pittsburgh, PA 15261, USA
[2]Department of Critical Care Medicine, University of Pittsburgh, 641 Scaife Hall, Pittsburgh, PA 15261, USA

Corresponding author: David T Huang, huangdt@ccm.upmc.edu

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Abstract

There are many controversial issues surrounding ethics in study design and conduct of human subjects research. In this review we briefly touch on the origin of ethics in clinical research and how the current regulations and standards came into practice. We then discuss current controversies regarding informed consent, conflicts of interest, institutional review boards, and other relevant issues such as innovative procedures and quality improvement projects. The question of whether we need more standards is a very important yet challenging one to which there is no simple answer. We address this question by reviewing and commenting on relevant literature. We conclude that what is needed are not more standards *per se*, but rather refinement and uniformity of current standards, and their interpretation and application both to protect human subjects and to advance medicine.

Introduction

Ethics and standards in human subjects research have long been controversial, even after decades of debate, experience, and regulation. Most recently, in February 2006, the US National Institutes of Health (NIH) announced several programs to address these issues [1]. Shortly after, in March 2006, a British drug trial resulted in the hospitalization of six participants, bringing new attention to the issue of standards in human subjects research [2]. Multiple questions were raised by the lay press, academia, and regulatory bodies. Were more standards in human subjects research needed, or were current standards not followed? Alternatively, was this incident an unavoidable consequence of medical research?

In this review, we discuss the origin of ethics in clinical research and the historical tragedies that led to current regulations and standards. We then review some of the many current controversies and conclude with a discussion on whether we need more standards. Our review is restricted primarily to a US perspective.

Ethics in clinical research: origin and regulatory bodies

Modern ethics in human research mainly emerged after World War II, when Nazi physicians used prisoners for inhumane 'experiments'. This resulted in the creation of the Nuremberg Code in 1947, which clearly stated voluntary consent as an absolute requirement for human subjects research [3]. As a result, it became almost impossible to conduct any clinical research in mentally impaired and other vulnerable groups. However, this created another ethical dilemma [4]. Was it ethical to exclude all mentally ill, pediatric, and critically ill patients from the potential benefits of research, simply because they could not consent to it [5-7]?

In 1964, the Declaration of Helsinki - proposed by the World Medical Association - changed some of the absolute rules of the Nuremberg code; for example, it allowed the use of surrogate consent in the case of individuals with impaired decision making [8]. In 1979, in response to the infamous Tuskegee scandal, the US Department of Health Education and Welfare released the landmark Belmont Report, and required all clinical researchers to comply with the key principles of respect for the individual, beneficence, and justice, and to assess the risks and benefits to each research subject [9]. In 1989, the US NIH mandated that all trainees it supported receive instruction in medical ethics and responsible research conduct [10-12]. In 1991, the US Office of Human Research Protection was established to oversee ethical aspects of clinical research, which in turn resulted in the establishment of institutional review boards (IRBs). In 1999 the death of a young research participant,

COI = conflict of interests; FDA = US Food and Drug Administration; IRB = institutional review board; NIH = US National Institutes of Health; QI = quality improvement.

Jessie Gelsinger, in a gene therapy trial brought to the forefront multiple issues, including adequacy of informed consent, failure of researchers to report adverse events to regulatory bodies, and inadequate federal oversight of clinical trials [13-15]. This case was also notable in that the university and one of the scientists held equity in a company expected to benefit from the gene therapy research. This led to increased scrutiny of potential researcher and institutional conflicts of interest (COIs) and clinical research in general by US regulatory bodies [16].

Informed consent

Perhaps the most basic yet complex principle of research ethics is informed consent. An ethically valid informed consent has four key components [17]: disclosure, understanding, voluntariness, and competence. This creates challenges for researchers in pediatrics, psychiatry, emergency, and critical care medicine [18-21]. Can surrogate consent be a fair and ethical solution, or can we ask for waived consent and, if so, under what circumstances? In a study of people at risk for Alzheimer's disease, more than 90% thought that surrogate consent was acceptable for minimal risk studies as well as randomized trials of new medications. However, this percentage, although remaining a majority, significantly decreased for more invasive studies and when deciding for a loved one (for example, only 61% felt a surrogate-based lumbar puncture study was definitely or probably acceptable for a loved one) [22]. Another study examined the accuracy of surrogate decision makers for intensive care research. Coppolino and Ackerson [23] recorded the responses of 100 elective cardiac surgery patients to two hypothetical research trials, and compared the responses with the patients' surrogate decision makers' predictions. The investigators found that the overall surrogate positive predictive value for a low-risk study was 84.0% and for a high-risk study it was 79.7%. These percentages, although high, also represent a false-positive rate of 16-20.3%, leading the authors to recommend further assessment and evaluation of surrogate consent for intensive care research.

However, it is important to recognize that if surrogate consent were eliminated, then it would virtually eliminate almost all critical care research because many critically ill patients are incompetent or unable to make a sound decision [7]. Family members are frequently unavailable, may not know the patient's wishes, or may not be specifically legally authorized to give consent for the patient's involvement in research. Therefore, some have questioned whether the concept of informed consent is even applicable to research involving the critically ill [24].

In the USA only certain emergency and resuscitation research can be done without prospective informed consent. This is based on the 1996 US Food and Drug Administration (FDA) 'Final Rule' and the US Department of Health and Human Services' parallel 'Waiver of Informed Consent' regulations. These require community consultation, public notification, and independent data and safety monitoring to allow exemption from informed consent [25-28].

These regulations further stipulate that they can only be applied to emergency research for which human subjects can not give informed consent because of their life-threatening conditions (for example, unconsciousness); the condition requires immediate intervention; available treatments are unproven or unsatisfactory; clinical equipoise exists; the research might directly benefit the subject; the research intervention must be administered before informed consent from the subjects' legally authorized representative is feasible; and the responsible IRB concurs and documents that these conditions had been met. Other methods such as deferred consent, implied consent, or delayed consent are no longer deemed acceptable, despite previous use in early resuscitation research [29]. However, in the 10 years since the release of the Final Rule, investigators in the USA have reported variability in IRB interpretation, and have called for standardization and refinement of the rule. To address these concerns, as well as concerns from ethicists and other stakeholders, the FDA recently announced a public hearing on emergency research to be held on 11 October 2006. An updated FDA guidance document is expected following this hearing that is intended to assist IRBs, investigators, and sponsors in the development and conduct of emergency research using exception from informed consent.

Conflicts of interest

COIs can exist on many levels [30]. Almost half of faculty IRB members and 25% of all investigators have some industry affiliation [31,32]. IRBs can also have indirect financial COIs when reviewing research protocols for which their institution receives compensation [33]. An example of a potential COI involving medical school IRBs was identified in a study in which consent form provisions for compensation for research-related injuries differed when the sponsor was industry compared with nonindustry. Coverage for all medical bills related to research-related injuries was offered in 61% of industry-sponsored protocols. In contrast, only 22% of protocols without industry sponsorship offered coverage (mostly limited to emergency bills), and 60% of consent forms specified that no financial support was available for medical bills from research-related injuries [34]. The authors of this study noted that legal representatives for medical schools must be concerned about financial liability. They suggested that to avoid the potential concern of dual loyalties and COIs, to decrease costs and delays, and to provide compensation for injured individuals, a no-fault compensation system be created for individuals injured by research, as previously called for by the Institute of Medicine and other groups.

COI concerns also exist within the FDA and NIH; many internal and external experts at these organizations also work as consultants or are salaried employees for various

industries, many of which have a stake in the very area that the two institutions are concerned with [30]. Balanced against this is the legitimate need for effective collaboration between government, academia and medicine, in order to advance medicine. Recent new regulations have been implemented by the NIH to minimize their employees' industry consulting to avoid COIs [35]. The effectiveness and acceptability of these new regulations in maintaining an appropriate balance between industry and the NIH remains to be determined.

A less apparent but important COI is that of the lay press. High profile stories may lead to higher pay and promotion for journalists [30]. There have been widely covered stories of alleged research misconduct that were later proved to be false but only after much negative publicity [36-40].

IRB effectiveness and inconsistency

One of the main criticisms of IRBs is apparent inconsistency among the different IRBs (for example, repeated modification to the same research protocol) [41-44]. Some have even posited that having different standards at different institutions may be inherently unethical [6]. The duplication of approvals and renewals also costs a great deal of time and resources, for both investigators and IRBs. The end result can be detrimental to both study subjects and research community, due to IRB inconsistencies resulting in significant delay [44-48]. Centralization of IRB function, as has been done with the National Cancer Institute's Central IRB Initiative, offer a potential solution, by coordinating and centralizing IRBs for large, multicenter studies. Such coordination could not only reduce the administrative burdens of local IRBs and investigators, but also improve patient access to clinical trials and enhance protection of human subjects by providing consistent, national, expert review before dissemination at the local level. An analogous body for critical care research might provide similar benefits, but the logistical barriers to creating such a body are not trivial.

Innovative procedures and quality improvement projects

Another important issue is that clinical research and quality improvement (QI) studies may have equal risks for patients, but only the former requires informed consent and adherence to human subject research regulations. The important question is how to define clinical care, clinical research and QI, when in many complex interventional QI projects the potential for overlap is large [49]. Like QI projects, significant innovations are also not subject to research regulations. In many cases a new surgical procedure enters clinical practice without extensive evaluations of risks or benefits [50]. When this occurs, the only way to find possible adverse effects is by retrospectively examining a series of completed cases [50]. However, if a surgeon decided to conduct a systematic, prospective comparison of traditional and innovative methods, then this would be deemed clinical research and would require IRB review. Some have questioned this seeming paradox in which innovative procedures, many quite invasive, require less formal oversight than that of simple observational research [50,51] For these reasons some maternal fetal surgeons and palliative care physicians have stayed out of formal research and started practicing new treatments as 'significant innovations'. Current IRB standards impose significant barriers to research in pregnant women or terminally ill patients [52-56].

Similarly, an intensivist who believed in the potential benefit of a novel method of ventilator support (for example, high-frequency oscillation) might find it easier to simply start using this therapy on his or her own patients and later publish a case series or retrospective review. However, such an approach, although avoiding potentially burdensome regulation, would provide less useful and less convincing data than a formal, prospective, randomized trial.

Intellectual properties versus patients' ownership of their tissues

In 1980 a landmark case occurred between John Moore, a patient with hairy cell leukemia, and University of California researchers. The researchers worked on Mr Moore's blood and spleen tissues, and patented and commercially marketed a permanent cell line to produce a number of proteins. Mr Moore sued the university and researchers for using his tissues without his permission, on the basis of ownership of his body. The California Supreme Court ruled against him, ruling that he lost ownership rights to his tissues once they had been removed from him [57].

Based on this ruling, one can conclude that patients can question what is going to be done to their tissues, and enter into partnership agreements with researchers and institutions, but only before such tissues are removed from their bodies. This was exactly the case for Ted Slavin, a hepatitis B patient who sold his serum for $10/cc to pharmaceutical companies who wanted his antibodies to develop hepatitis B vaccines [58]. In March 2006, a court ruled in favor of Washington University in another case of patient ownership of their tissues. In this case, a Washington University clinician researcher moved to another institution. When Washington University did not agree to give him the tissue repository he had compiled from his many patients, he sent a letter to his patients asking them to demand that Washington University release their tissues to him, on the basis of patient ownership of their tissues. The judge ruled that the court recognized the research participants' right to discontinue participation in a study, but that this did not extend to 'a right to control the disposition and use of excised biological material'. In other words, no donor has the right to redirect tissue samples to other institutions or researchers once the donation has been made [59].

Defining usual care

A particularly difficult study design challenge is how to define 'usual care' in clinical trials, when a comparator control arm

that reflects current medical practice is desired. For many aspects of critical care, uncertainty exists regarding what is 'best' care, and as a result significant variability in clinical practice exists. This variability makes defining usual care difficult, because usual care by one clinician, hospital, or region might be viewed as substandard by an external reviewer. Even if clinical guidelines exist, disagreement among clinicians regarding the strength of the underlying data, and other factors, contributes to incomplete guideline compliance. Further complicating matters is the question of how tightly to control a 'usual care' arm.

To address this issue, in November 2005, in response to a request from the Office of Human Research Protections, the NIH convened a 2-day conference (entitled 'Considering Usual Medical Care in Clinical Trial Design: Scientific and Ethical Issues'). Multiple questions were discussed and examined: how can one determine whether a flexible usual care arm is appropriate?; when a usual care arm is included in a trial, what particular ethical issues may arise?; and how can the results of trials with heterogeneous usual care groups be interpreted? No simple, universal approach emerged. Rather, discussants concurred that the issue was extremely complex and that each study would have to be separately considered. A 'points to consider' document designed to provide a conceptual framework and guidance for investigators will be generated from this conference's proceedings.

Do we need more standards?

In response to this question, in an editorial discussing pediatric research, Dr John Lantos believes that we do not [6]. He stated that adding more regulations will slow or prevent research projects, while probably not actually improving protection of human subjects. Furthermore, he argued that additional regulatory burdens, as discussed above, will drive investigators to clinical innovation outside formal research protocols, paradoxically increasing risk to patients while decreasing the quality of new data arising from such innovation. He argues that clinical research in many cases is far safer than routine clinical care, because of the additional safeguards and monitoring that research requires and, as noted above, because clinical innovations and QI projects are being performed outside formal research protocols [6,50,51]. We largely agree, and find particularly compelling his position that increased, well meaning regulation would probably not improve protection of research subjects, but potentially might bring about the opposite. In an accompanying article, Wendler and Foster [60] argue for additional, uniform legal standards for pediatric research in particular and human subjects research in general. Notably, their argument is based on the premise that existing federal regulations do not adequately protect investigators, rather than the children themselves. In our opinion, this illustrates the extent to which legal, rather than purely ethical, concerns have become a significant part of any discussion on human subjects research.

Regarding informed consent, Truog and coworkers [61,62] suggest that informed consent in critically ill patients should be waived if five criteria are satisfied: all treatments offered in a trial are available and practiced outside of the trial; the trial does not add more than minimal risk; clinical equipoise exists; no reasonable patient would prefer one treatment over the other; and the patient and surrogates are informed of the institution's policy regarding the criteria for waiver of informed consent. These criteria are reasonable and relevant to critical care research. Clinical studies in critical care are often designed to compare two or more accepted treatment alternatives and not necessarily evaluation of a novel therapy. These studies also often involve nontherapeutic procedures such as additional blood draws or clinical data abstraction, which pose minimal or no risk to patients [24,63].

So, do we need new standards? Perhaps we do, but in the direction of refining existing standards, not adding more. We need an equally high or better standard for protection of human subjects, but with less legalistic and repetitive processes [45]. Decreasing the number of IRB approvals required for multicenter and international collaborative research projects would be one positive step. Some have proposed a centralized system for reviewing multisite clinical trials, similar to systems used in the UK or by the National Cancer Institute [33,64-67]. A challenge to adopting UK systems is that in the USA many laws differ across states. Researchers can be held liable in state courts if relevant federal law does not exist, is vague, or conflicts with state laws [60,68,69].

In the landmark 1966 article that sparked the creation of modern informed consent standards and IRB oversight, entitled 'Ethics and Clinical Research' [70], Dr Henry Beecher wrote that besides informed consent, the most important, and most reliable, safeguard is the presence of an 'intelligent, informed, conscientious, compassionate, and responsible investigator'. To that end, the NIH and many US universities require that its trainees and investigators receive mandatory training in research ethics. Although no one would advocate solely relying on investigator beneficence, at the same time more rules and regulations will not enhance what Dr Beecher considered most important, and also do not necessarily result in enhanced human subject safety. Perhaps the clearest example of this is that for many studies, current regulations have been so strictly interpreted that the required

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informed consent documents are often excessively lengthy and legalistic. Such documents, although satisfying legal and regulatory standards, do not necessarily well serve the prospective human subject.

Conclusion

In conclusion, we believe that what is needed are not more standards but rather refinement and uniformity of current standards, and their interpretation both to protect human subjects and to advance medicine through research.

Competing interests

The authors declare that they have no competing interests.

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