Commentary

The ethical analysis of risk in intensive care unit research

Charles Weijer

Associate Professor of Bioethics and Surgery, Adjunct Professor of Philosophy, Dalhousie University, Halifax, Canada. At the time of writing, Visiting Scholar, Department of History and Philosophy of Science, University of Cambridge, and Visiting Fellow, Clare Hall, Cambridge, UK

Correspondence: Charles Weijer, charles.weijer@dal.ca

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Abstract

Research in the intensive care unit (ICU) is commonly thought to pose 'serious risk' to study participants. This perception may be at the root of a variety of impediments to the conduct of clinical trials in the ICU setting. Component analysis offers a promising approach to the ethical analysis of ICU research. Because clinical trials commonly involve a mixture of study interventions, therapeutic and nontherapeutic procedures must be analyzed separately. Therapeutic procedures must meet the requirement of clinical equipoise. Risks associated with nontherapeutic procedures must be minimized consistent with sound scientific design, and be deemed reasonable in relation to the knowledge to be gained. When research involves a vulnerable population, such as adults incapable of providing informed consent, nontherapeutic risks are limited to a minor increase over minimal risk. Understood in this way, the incremental risk posed by participation in ICU research may be minimal. This realization has important implications for review by institutional review boards of such research and for the informed consent process.

Keywords clinical trials, ethics, informed consent, intensive care, research regulation, risk

Clinical research in the intensive care unit (ICU) setting is essential to ensuring that patients are treated with interventions that are both effective and safe. Unfortunately, lack of clarity as to when research risks are acceptable in relation to anticipated benefits has impeded important clinical trials. Federal regulation governing 'Exception from informed consent requirements for emergency research' considers research risk on the aggregate, and as a result it imposes considerable restrictions on the conduct of research without consent [1]. Recently, the US Office for Human Research Protections investigated three ARDSNET clinical trials for purportedly exposing trial participants to undue risk [2]. During the protracted review, enrollment in the Fluid and Catheters Treatment Trial was suspended.

If burdensome regulation and unnecessary trial suspension are to be avoided, then clear thinking about research risk is required. A comprehensive and systematic approach to the ethical analysis of research benefits and harms by institutional review boards (IRBs), called component analysis, was recently proposed [3]. It was endorsed by the US National Bioethics Advisory Commission in its final report and by a number of commentators [4–6]. The present commentary provides the reader with a brief introduction to component analysis and highlights its application to ICU research.

The central insight of component analysis is that clinical research often contains a mixture of study interventions. Therapeutic procedures, such as a particular ventilation strategy, insertion of a pulmonary artery catheter, or administration of a drug, are given with therapeutic warrant. That is, they are administered on the basis of evidence supporting the expectation that the intervention may benefit the study participant. Nontherapeutic procedures, such as downloading data from monitors, drawing extra blood for pharmacokinetic drug levels, or abstracting information from the patient's chart, are administered without therapeutic warrant and are performed solely to answer the study question. Because therapeutic procedures hold out the prospect of benefit to trial participants and nontherapeutic procedures do not, a separate moral calculus is required for each type of intervention.

ICU = intensive care unit; IRB = institutional review board.

Therapeutic procedures must meet the standard of clinical equipoise [7]. Clinical equipoise requires in essence that therapeutic procedures in a clinical trial be consistent with competent clinical care. More formally, it requires that at the start of the trial there exist a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment. The IRB ensures that this standard is met by reviewing the justification in the study protocol, the relevant literature and, if necessary, the opinions of impartial experts. Therapeutic procedures are acceptable if the IRB certifies that there is sufficient evidence supporting each of the procedures such that, were it widely known, expert practitioners would disagree as to the preferred treatment.

Nontherapeutic procedures do not offer the prospect of benefit to trial participants and hence a harm–benefit calculus is inappropriate. Rather, two standards must be met. Risks of nontherapeutic procedures must be minimized consistent with sound scientific design and, furthermore, they must be deemed reasonable in relation to the knowledge to be gained. The IRB ensures the first standard is met by asking whether all nontherapeutic procedures are necessary to answer the study question and, if possible, by identifying procedures that might equally well piggyback on routine clinical interventions. The second standard requires that the IRB judge the scientific and social value of the study to be sufficient to merit the nontherapeutic risks posed to participants. This requires input from both scientific and community members of the IRB.

When clinical research involves members of a vulnerable population, such as pregnant women, prisoners, children, or adults incapable of providing informed consent, additional restrictions may apply. A threshold may limit the amount of nontherapeutic risk to which vulnerable research participants may be exposed legitimately. In the case of children, nontherapeutic risks are limited to a minor increase over minimal risk [8], that is, a minor increase over the 'risks of daily life' [9]. It has been cogently argued that a similar degree of protection ought to be afforded to adults incapable of providing informed consent – a vulnerable group comprising a large proportion of participants in ICU research [10]. To determine whether risks associated with nontherapeutic procedures meet this standard, the IRB reasons by analogy. It asks whether risks posed by nontherapeutic procedures are the same as those ordinarily encountered in daily life or are sufficiently similar to those risks. The IRB may deem a study acceptable only if the moral calculi for both therapeutic and nontherapeutic procedures are satisfied.

ICU research is commonly thought to pose 'serious risk' to participants. Component analysis allows us to disambiguate this claim, and focus attention on the incremental risk posed to ICU patients who enter a clinical study. ICU patients are by definition seriously ill. Clinical equipoise ensures a rough parity in terms of benefit, harm, and uncertainty between the procedures that patients would receive as a part of clinical practice and therapeutic procedures in a clinical trial. Thus, whatever incremental risks are posed to participants stem from nontherapeutic procedures. In ICU research, these procedures are commonly limited to downloading data from monitors, abstracting chart information, and a few extra blood tests. In these cases, studies are properly understood as posing only minimal risk – a finding with implications for both IRB review and the informed consent process.

We argued elsewhere that acute care research in which it is not possible to obtain the consent either of the patient or of their proxy decision maker might proceed under a simplified version of the waiver of consent [11]. We argue that this approach offers a superior alternative to the unduly restrictive 'Exception from informed consent requirements for emergency research' [1]. Provocatively perhaps, component analysis also suggests a novel approach to informed consent. In this approach, the focus is shifted away from the life-threatening complications of the patient's illness, which are present regardless of whether the patient participates in research, to the incremental risks posed by study participation. The consent negotiation is thereby allowed to concentrate on the question, 'What difference will it make to me to participate in this study, as opposed to being treated in accordance with routine clinical care?'

Competing interests

None declared.

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