

When are research risks reasonable in relation to anticipated benefits?

Charles Weijer & Paul B Miller

The question “When are research risks reasonable in relation to anticipated benefits?” is at the heart of disputes in the ethics of clinical research. Institutional review boards are often criticized for inconsistent decision-making, a problem that is compounded by a number of contemporary controversies, including the ethics of research involving placebo controls, developing countries, incapable adults and emergency rooms. If this pressing ethical question is to be addressed in a principled way, then a systematic approach to the ethics of risk in research is required. Component analysis provides such a systematic approach.

The question “When are research risks reasonable in relation to anticipated benefits?” is at the very heart of pressing disputes in the ethics of clinical research. Institutional review boards (IRBs) are criticized for inconsistent decision-making, a phenomenon that may be traced in part to reliance on the vagaries of intuition to interpret federal regulation on acceptable risks and potential benefits¹. Further, the problem of acceptability of risks and potential benefits in research runs through a number of contemporary controversies, including the ethics of research involving placebo controls², developing countries³, incapable adults⁴ and emergency rooms⁵. If IRBs are to be given clear guidance, and if pressing ethical questions are to be addressed in a principled way, then a systematic approach to the ethics of risk in research is required.

A systematic approach to the ethical analysis of risks and potential benefits in research called “component analysis” has recently been developed⁶. Component analysis is built on the recognition that clinical research often contains a mixture of therapeutic and nontherapeutic procedures and that separate moral standards are required for each. It refines an approach originally

developed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in *Institutional Review Boards* and the *Belmont Report*^{7,8}. As these documents informed the development of the *Common Rule*, component analysis is a needed explication of federal regulation. In its final report on research involving humans, the US National Bioethics Advisory Commission endorsed component analysis, as have a variety of other commentators^{4,9,10}.

In a recent flurry of articles, however, critics of component analysis have suggested that it is a flawed approach. It is argued that one of the core concepts of component analysis, clinical equipoise, conflates the ethics of clinical practice with the ethics of research¹¹. It has also been argued that component analysis is misapplied to the ethical analysis of placebo controls². Without engaging these criticisms directly, we would like to point out that it seems the critics have failed to appreciate how component analysis is supported by reasonable arguments. They have also failed to appreciate that it provides much needed guidance to IRBs on the ethical analysis of research risks and potential benefits, and that it also offers the prospect of principled resolution of a wide variety of contemporary controversies. If component analysis does indeed meet these ends, then, even if flawed, one ought not to dispense with it until a more robust alternative is articulated.

Component analysis provides clear criteria for IRBs

The *Common Rule* instructs IRBs to ensure that “[r]isks to subjects are minimized” and “[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be reasonably expected to result” (45 *CFR* 46.111(a)(1,2)). Unembellished imperatives often provoke more questions than they answer. Which risks to subjects must be minimized? To what extent must they be minimized? Which risks and which potential benefits are to be considered in the reasonableness determinations? By what measure does one determine that risks are reasonable in relation to benefits to subjects? By what measure does one determine that risks are reasonable in relation to the knowledge that may result? In the absence of careful explication of these regulatory requirements, it is difficult to see how IRBs can effectively fulfill their mandate of protecting research subjects¹².

Component analysis builds on the recognition that clinical trials often contain a mixture of interventions administered with differing purposes. Drug, surgical and behavioral interventions are administered with therapeutic warrant; that is, they are administered on the basis of evidence sufficient to justify the belief that they may benefit research subjects. Other interventions, such as venipuncture for pharmacokinetic drug levels, additional imaging procedures or questionnaires not used in clinical practice, are given without therapeutic warrant. They

Charles Weijer and Paul B. Miller are in the Department of Bioethics, Dalhousie University, 5849 University Avenue, Halifax, Nova Scotia B3H 4H7, Canada.
e-mail: charles.weijer@dal.ca

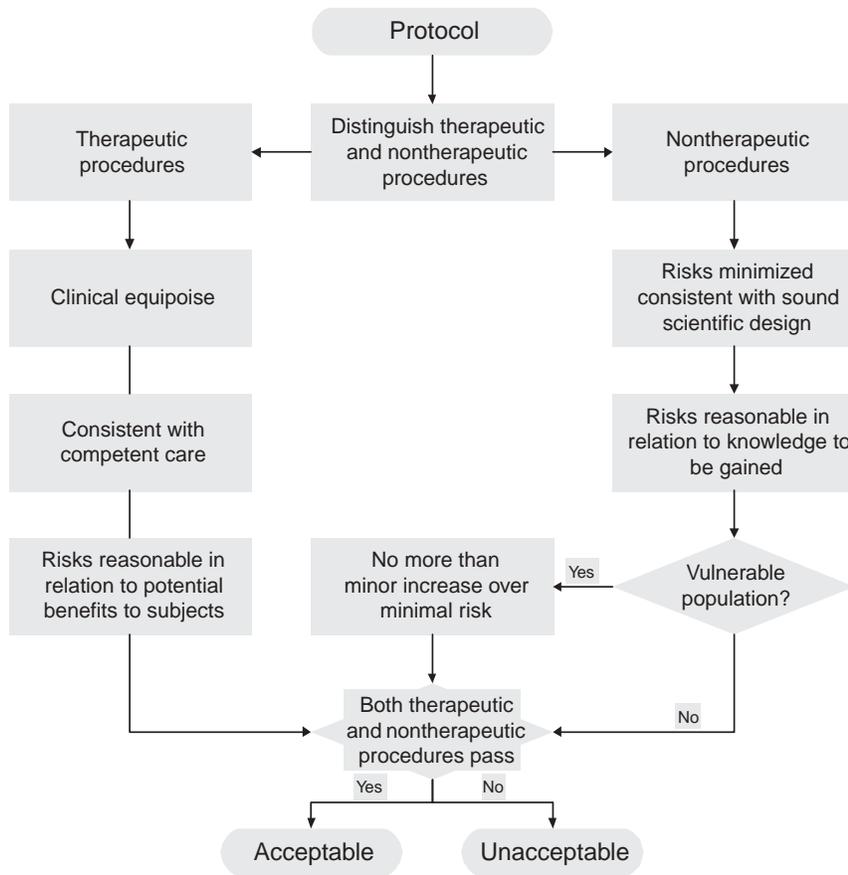


Figure 1 Component analysis of risks and potential benefits in research.

are administered solely for the purpose of answering the scientific question. As this distinction is morally relevant, IRBs must apply separate moral standards to their assessment of therapeutic and nontherapeutic procedures (Fig. 1).

Therapeutic procedures must meet the ethical standard of clinical equipoise (Fig. 1)¹³. Clinical equipoise is a research-friendly response to the question “When may a physician offer enrolment in a clinical trial to her patient?”. It provides that she may do so when the therapeutic procedures in a clinical trial are consistent with competent medical care. More formally, clinical equipoise requires that at the outset of a trial there exists a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment. Procedurally, the IRB does not make this determination by surveying practitioners. Rather, it scrutinizes the study justification, reviews relevant literature and, when required, consults with independent clinical experts. Clinical equipoise is satisfied if the IRB concludes that the evidence supporting the various therapeutic procedures is

sufficient that, were it widely known, expert clinicians would disagree as to the preferred treatment.

Nontherapeutic procedures do not offer the prospect of direct benefit to research subjects. When assessing risks associated with nontherapeutic procedures (“nontherapeutic risks”), the IRB must determine that two separate ethical standards are met. The IRB must determine that nontherapeutic risks are, first, minimized consistent with sound scientific design and, second, reasonable in relation to the knowledge that may be gained from the study (Fig. 1). Procedurally, the IRB ensures that nontherapeutic risks are minimized by, where feasible, requiring the substitution of “procedures already being performed on the subjects for diagnostic and treatment purposes” (45 CFR 46.111(a)(1)(ii)). The IRB’s determination that the risks of nontherapeutic procedures are reasonable in relation to knowledge requires that it judge the study’s scientific value sufficient to justify risks to subjects. Because this judgment involves the appraisal of social priorities, community representatives must be included as fully participating members of the IRB¹⁴.

When research involves a vulnerable population, such as pregnant women, prisoners or children, additional protection may be required. A threshold may be invoked limiting the nontherapeutic risks to which vulnerable subjects may be exposed (Fig. 1). For children, nontherapeutic risks are limited to the standard of a “minor increase over minimal risk,” in other words, a minor increase over the risks “ordinarily encountered in daily life” (45 CFR 46.406(a), 46.102(i)). Procedurally, to determine whether the risks of nontherapeutic procedures fulfill this criterion, the IRB reasons by analogy¹⁵. It asks whether risks posed by nontherapeutic procedures are the same as those ordinarily encountered in daily life or are sufficiently similar to these risks (45 CFR 46.102(i)). Whether the referent for minimal risk ought to be the daily lives of healthy or sick children remains controversial^{16,17}.

Research risks are reasonable in relation to anticipated benefits when the IRB determines that the moral standards for both therapeutic and nontherapeutic procedures are fulfilled.

Component analysis enables principled resolution of controversies

Component analysis provides clear criteria for IRBs to use in judging whether the risks of research are reasonable in terms of what might be gained by the individual or society. But does it enable principled resolution of controversial issues in research that turn on evaluation of harms and benefits? Consider the four controversies cited above.

Placebo controls

When is it acceptable to offer patients enrolment in a placebo-controlled trial in which they assume the risks of forgoing standard treatment? When applying component analysis, one must first determine whether the placebo control is a therapeutic or nontherapeutic procedure. It may be a combination of the two. A placebo control is at least a no-treatment control. A no-treatment control is the null case for therapeutic procedures and it, along with therapeutic procedures in the experimental arm, must pass the test of clinical equipoise. According to clinical equipoise, a no-treatment control is appropriate when there is no effective treatment for the condition of interest, the trial selectively enrolls treatment-resistant patients, the study is a test of an add-on treatment versus placebo in which all subjects receive standard treatment or treatment exists but “no treatment” is nonetheless consistent with competent medical care¹⁸.

Although there may be effective treatments for minor medical conditions, for example allergic rhinitis, mild dermatitis, mild hypertension or baldness, a competent physician may nonetheless recommend no treatment for these conditions. The use of a placebo control for minor medical conditions is, therefore, unproblematic¹⁹.

Placebo controls may involve additional interventions administered for scientific purposes, for example, sugar pills, saline injections or sham surgical interventions. These interventions are administered with the purpose of simulating, as closely as possible, factors in the treatment context not directly related to the therapeutic properties of the experimental intervention. These are non-therapeutic interventions and the risks associated with them must be minimized and deemed reasonable in relation to the knowledge to be gained. In many, perhaps most, placebo-controlled trials the risk of the non-therapeutic intervention, for example the sugar pill, is close to zero. When the placebo control involves interventions posing greater risk, such as saline injections or sham surgery, it is more difficult to justify. The IRB must ask whether the scientific ends of the study can be met with less risky interventions. Are the risks counterbalanced by the importance of the knowledge to be gained? Because the use of a no-surgery control arm presents a less risky alternative and because the risks posed by sham surgery may in some cases be serious, these moral requirements pose substantial obstacles to the ethical use of sham surgical controls²⁰.

International research

For clinical trials in developing countries, is the care to which subjects are entitled determined by local or international standards? Consider the controversy over clinical trials comparing short-course zidovudine to placebo for the prevention of perinatal transmission of HIV in sub-Saharan Africa and Thailand. The ACTG 076 regimen was the gold standard in developed countries²¹, but was not used in these trials. Critics argued that the novel regimen ought to have been compared to ACTG 076 and that the failure to do so set up a double standard for research in developed and developing countries²². Defenders responded that no treatment was available in developing countries and that ACTG 076 was an unaffordable and impractical treatment alternative in this setting²³.

In component analysis, both short-course zidovudine and the no-treatment control are therapeutic interventions that must satisfy clinical equipoise. Does clinical equipoise

allow the control treatment to be determined by local standards? Angell argues that it does not and that the trials are unethical²⁴. Crouch and Arras disagree and their reasoning seems convincing²⁵. They remind us that the fundamental purpose of a clinical trial is the resolution of disagreement as to the preferred treatment. In other words, the aim of a trial is to alter clinical practice. Crouch and Arras state that “Because clinical trials are responsive to and centrally concerned with the realities of clinical practice, it is crucial for the clinical trialists to take the study context into account when designing and conducting such studies”²⁵. Keeping in mind the pragmatic purpose of clinical trials, clinical equipoise seems to permit a trial design that asks “whether the shorter AZT regimen is safe in these populations, and, if so, whether the demonstrated efficacy is large enough, as compared to the placebo group, to make it affordable to the governments in question”²⁵.

Incapable adults

Should incapable adults be included in clinical trials? If so, to how much risk should they be exposed by interventions performed solely for the sake of science? Regulations for the protection of incapable adults in research were first proposed in 1978 but were never implemented²⁶. Repeated calls for additional protections for incapable adults have gone unheeded. The *Common Rule* requires that IRBs be “particularly cognizant of the special problems of research involving vulnerable populations”, including incapable adults, and ensure that “additional safeguards have been included in the study to protect the rights and welfare of these subjects” (45 *CFR* 46.111(a)(3), 46.111(b)). IRBs are given no guidance, however, as to what additional safeguards are required. Thus, the central problem remains “designing appropriate protections for persons with mental disorders who participate in ... research ... while providing the opportunity to obtain the potential for benefit that may arise from ... participation”¹².

It is cogently argued that the failure to address this problem through specific regulations runs the risk of both stymieing needed research and failing to protect incapable adults involved in research⁴. A failure to distinguish between therapeutic and nontherapeutic procedures in the ethical analysis of harms and benefits leads to “a situation that could exploit vulnerable subjects in the pursuit of knowledge” (p. 1391)⁴. Component analysis is identified as essential to the protection of incapable adults. Incapable adults

are vulnerable for the same reason that children are: they are not able to protect their own interests through informed consent. Thus, although specific protections for the complex and diverse population of incapable adults may at points differ from the protections currently afforded children, “regulations governing pediatric research provide a model” for developing protections for incapable adults. This implies that a threshold ought to be invoked limiting the nontherapeutic risks to which incapable adults may be exposed (Fig. 1).

Emergency research

Under what circumstances, if any, may clinical trials in emergency medicine enroll subjects who are incapable of providing informed consent and for whom no proxy decision-maker is available? Debate as to what protections ought to be afforded to subjects in emergency research is premised on the assumption that it poses more than minimal risk. “Deferred consent” was invoked for a number of studies in the 1980s, but rejected by the Office for Protection from Research Risks because one cannot logically consent to a procedure that has already been performed^{27,28}. As a result, emergency research came to a halt until complex regulations permitting the waiver of consent were implemented (21 *CFR* 50.24). These regulations fail to distinguish between therapeutic and nontherapeutic procedures and link the permissibility of risk to severity of illness by requiring that risks in the aggregate be:

... reasonable in relation to what is known about the medical condition of the potential class of participants, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity. (21 CFR 50.24)

In this novel requirement, the level of permissible aggregate risk is linked to the severity of the patient’s condition. This opens the door to exploitation as it allows sicker patients to be exposed to higher levels of risk solely to meet scientific ends.

Component analysis has been applied to the problem²⁹. Component analysis ensures, through the proper application of clinical equipoise, that the sum of risks and potential benefits of therapeutic procedures in a clinical trial are roughly similar to that which a patient would receive in clinical practice. The incremental risk posed by research participation, therefore, stems from nontherapeutic study procedures. Thus, a risk threshold such as minimal risk

can only be sensibly applied to nontherapeutic procedures. The emergency room context generally limits nontherapeutic research interventions to chart review, additional history and physical examinations and recording data collected from monitoring equipment – all procedures that arguably pose no more than minimal risk to subjects. As the absence of a proxy decision-maker renders emergency subjects relatively more vulnerable than children or incapable adults, a more restrictive risk threshold, such as minimal risk *simpliciter* may be appropriate.

Critics must articulate a robust alternative

To our knowledge, component analysis is the only systematic elaboration of the entailments of the ethical principle of beneficence for IRB review of human subject research. It is supported by arguments that are, at first sight, reasonable. As we have seen, component analysis provides IRBs with much needed and clear criteria for the ethical analysis of research benefits and harms. Further, it enables principled resolution of a variety of pressing problems in the ethics of research. Even if component analysis turns out to be a flawed approach, and we by no means grant that it is, it would continue to possess a social imperative in the sense that IRBs and policy makers require a systematic approach to make effective and consistent decisions. These facts seem to impose, therefore, a special burden on the critics of component analysis. If component analysis is to be overthrown, critics must articulate a robust alternative.

To be tenable, an alternative approach to the ethical analysis of risks and potential benefits must protect research subjects; allow clinical research to proceed; explain how physicians may offer trial enrolment to their patients; address the challenges posed by research containing a mixture of interventions; and define ethical standards according to which the risks and potential benefits of research may be consistently evaluated.

Consider, for example, Miller and Brody's recent suggestion that clinical equipoise be abandoned and that "an alternative framework for the ethics of clinical trials is needed"¹¹. They state that their "alternative framework provides accurate ethical guidance concerning clinical research" (p. 26)¹¹. With regard to the ethical analysis of risks and potential benefits in research, their alternative approach, stated in its entirety, is: "Favorable risk-benefit ratio. Risk-benefit assessment of research protocols ultimately comes down to a matter of judgment" (p.27)¹¹. Although we agree that judgment is required, this framework fails to provide the promised guidance. Indeed, it does not meet any of the five tenability requirements mentioned above. Miller and Brody's alternative does not provide clear criteria to IRBs and seems unlikely to enable principled resolution of contemporary controversies.

Conclusion

Optimal protections for research subjects requires that substantive and procedural requirements flowing from fundamental ethical principles be elaborated and adopted. Component analysis represents the only systematic approach to the ethical analysis of risks and potential benefits in research. It is supported by reasonable arguments. Further, it provides clear criteria for IRBs to use in judging whether the risks of research are reasonable in terms of what might be gained by the individual or society. Finally, it allows for the principled resolution of moral issues that turn on the evaluation of harm and benefit in research. If critics are to mount a successful assault upon component analysis, they must acknowledge these accomplishments and articulate a robust alternative.

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Department of History and Philosophy of Science at the University of Cambridge and Visiting Fellow at Clare Hall, Cambridge, UK.

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