RESEARCH ETHICS

Refuting the net risks test: a response to Wendler and Miller's ''Assessing research risks systematically''

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Earlier in the pages of this journal (p 481), Wendler and Miller offered the ''net risks test'' as an alternative approach to the ethical analysis of benefits and harms in research. They have been vocal critics of the dominant view of benefit–harm analysis in research ethics, which encompasses core concepts of duty of care, clinical equipoise and component analysis. They had been challenged to come up with a viable alternative to component analysis which meets five criteria. The alternative must (1) protect research subjects; (2) allow clinical research to proceed; (3) explain how physicians may offer trial enrolment to their patients; (4) address the challenges posed by research containing a mixture of interventions and (5) define ethical standards according to which the risks and potential benefits of research may be consistently evaluated. This response argues that the net risks test meets none of these criteria and concludes that it is not a viable alternative to component analysis.

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The debate over clinical equipoise and the duty of care is perhaps the most pressing in research ethics today. The relationship between physician–researcher and patient–subject has long been considered fiduciary, entailing a variety of duties governing the conduct of research by the physician–researcher.[1] Prime among these is the duty of care, requiring the physician–researcher to protect and promote the interests of the patient–subject. Freedman introduced as specification of the duty of care the notion of clinical equipoise, which requires that the administration of therapeutic procedures in clinical studies be consistent with competent medical care.[2] In work commissioned by the US National Bioethics Advisory Commission, clinical equipoise was set into a comprehensive and systematic approach to the evaluation of research benefits and harms called ''component analysis.''[3]

In a number of recent articles, FG Miller and colleagues have challenged this view. One of their central claims is that norms governing the physician–patient relationship, including a duty of care, do not govern the relationship between the physician–researcher and the patient–subject. They assert that ''the basic goal and nature of the activity determines the ethical standards that ought to apply.''[4] Since the purpose of clinical practice is promotion of the health of the patient and the purpose of clinical research is the generation of generalisable knowledge, norms governing these distinct activities must not overlap. Hence, according to Miller and colleagues, those who recognise the duty of care and endorse clinical equipoise suffer ''therapeutic misconception'' about norms appropriate to clinical research.

Focusing on their negative ambition to undermine clinical equipoise and duty of care, Miller and colleagues have failed to articulate a coherent, positive view of the nature of the relationship between physician–researcher and patient–subject, the norms that govern it, and the specification of these norms.[5] Simply put, they have, so far, failed to develop a viable constructive position. We noted this in an article in *Nature Medicine* in 2004,[6] where we challenged them to come up with a constructive alternative to component analysis that fulfils five criteria:

> To be tenable, an alternative approach to the ethical analysis of risks and potential benefits must (1) protect research subjects; (2) allow clinical research to proceed; (3) explain how physicians may offer trial enrolment to their patients; (4) address the challenges posed by research containing a mixture of interventions; and (5) define ethical standards according to which the risks and potential benefits of research may be consistently evaluated.

Miller and Wendler's article ''Assessing research risks systematically: the net risks test'' is the much anticipated response.[7] Given that those authors have not challenged the criteria we proposed, we assess whether their response satisfies these criteria.

THE NET RISKS TEST

Setting aside component analysis, Miller and Wendler offer in its stead the so-called net risks test. It provides research ethics committees (RECs) with a ''method to ensure that research interventions do not pose excessive risks.''[7] It involves three steps.

First, for each study procedure, the REC should

> assess the risk–benefit profile of each intervention by comparing its risks with the potential clinical benefits for participants. The REC should then assess the risk–benefit profile of the available alternatives to each intervention, which, in some cases, may be no intervention at all, and then compare the risk–benefit profile for participants of each research intervention with that of the available alternatives.[7]

If the study intervention has a risk–benefit profile comparable with those of alternatives, it does pose a net risk; if, on the other hand, the profile is less favourable, it does. In the first case, the intervention is acceptable; in the second case, it must be subjected to further scrutiny.

Second, the REC must "ensure that the risks of each intervention that poses net risks are not excessive and are justified by the social value of the knowledge to be gained by its use in the study."[7]

Third and finally, the REC should "calculate the cumulative net risks of all the interventions in the study under review, and ensure that, taken together, the cumulative net risks are not excessive."[7]

IS THE NET RISKS TEST A VIABLE ALTERNATIVE TO COMPONENT ANALYSIS?

We now consider whether the net risks test satisfies the five criteria mentioned above. In our view, each criterion must be satisfied if the net risks test is to be considered a viable alternative to component analysis. As we presently explain, it fails demonstrably to meet any of them.

Does it protect research subjects?

The state has an obligation to protect citizens who give of themselves to further medical knowledge. It meets that obligation by enacting and enforcing clear and effective regulatory norms that protect the interests of research subjects. The REC is best understood as an arm of the state that ensures that regulations are upheld and, thereby, that the state's obligations to research subjects are fulfilled. Specification of clear and effective standards for acceptable benefits and risks in research lies at the core of this enterprise, for it is only through such standards that the welfare interests of research subjects may be meaningfully protected.

With this in mind, it is difficult to see how the net risks test offers meaningful protection for the welfare of research subjects. First, by the authors' own description, it is a "method to ensure that research interventions do not pose excessive net risks."[7] The second and third stages of the test require that the REC ensure that both individual interventions and interventions taken cumulatively do not pose excessive risks to subjects. But the test offers only illusory protection, as the authors never define excessive risk. Miller and Wendler do not even provide an example of an intervention or set of interventions whose risks ought to be deemed excessive. With this key element in their normative apparatus left undefined, they effectively leave the determination of whether research risks are excessive to the unfettered discretion of RECs. Accordingly, Miller and Wendler provide no reason for confidence that their approach promises effective protection for research subjects.

Second, the net risks test requires that the net risks of an intervention be found "not excessive and … justified by the social value of the knowledge to be gained by its use in the study."[7] Because the first element in this conjoined standard is imprecise, we are left with a standard claiming that net risks of interventions may be determined acceptable merely by comparison with the value of the knowledge to be gained from them. In this frankly utilitarian calculus, risks to subjects are justified by prospective benefit to others without meaningful constraint on the process of justification. This means that given a sufficiently important scientific question, any net risk to subjects may be justified. This is particularly noisome, as net risks may be posed by procedures administered solely for research purposes and by substandard medical treatments in research. A standard that so transparently cedes the interests of patient-subjects to the pursuit of scientific ends provides no protection at all. The net risks test straightforwardly violates the Declaration of Helsinki in that it fails to ensure that "considerations related to the well-being of the human subject … take precedence over the interests of science and society."[8]

Does it allow clinical research to proceed?

One might think that with standards as lax as those set by the net risks test, even if it fails to protect research subjects it must surely at least facilitate clinical research. There are grounds to believe otherwise. Clinical research depends critically on the voluntarism of patients and healthy subjects. Without sufficient numbers of volunteer participants, important studies could not be completed in a timely manner. Volunteering with good will, research subjects reasonably trust the state to offer due regulatory protection for their interests. Regulations that provide unclear and ineffective protection should be expected only to undermine the trust of study volunteers. Regulations that effectively subordinate the interests of subjects to the interests of science risk potentially devastating consequences for trust in science. The net risks test, were it to be enacted into regulation, would threaten to undermine the trust that lies at the very foundation of clinical research.

Does it explain how physicians may offer trial enrolment to their patients?

Much of the debate about research ethics in the 1970s and 1980s focused on the question, How may a physican, consistent with her legal and moral duties to her patient, offer the patient enrolment in a randomised, controlled trial (RCT)? Some believed that the physican's offer of trial participation is wholly inconsistent with her duty of care to the patient. They therefore concluded that RCTs must be abandoned.[9] Clinical equipoise offers a research-friendly solution to this problem. It deems the administration of therapeutic procedures in research consistent with the physican's duty of care where at the start of the trial a state of honest professional disagreement exists as to the preferred treatment.[10] This solution is broadly accepted as removing the normative impediment to the conduct of RCTs.

Wendler and Miller recreate the historical problem, and yet, it seems to us, they fail to solve it. As explained above, Miller and colleagues' central objection to the dominant view is premised on their assertion that the norms governing clinical practice must not overlap with those governing clinical research. Since clinical practice is governed by the duty of care, they reject the duty of care and its specification, clinical equipoise, as norms applicable to clinical research. On their view, however, even if the physican-researcher does not owe a duty of care to the patient-subjects, a physican considering referring her patient to a clinical trial does. This means that the physican must act and advise in the best medical interests of her patient. But can the physican responsibly refer a patient to research approved in accordance with the net risks test? The test explicitly permits patient-subjects to be exposed to substandard medical treatments. When a study involves substandard treatment, advising a patient to participate in it is clearly contrary to his medical interests and thus contravenes the physican's duty of care. In these cases, Wendler and Miller are left in the uncomfortable position of affirming as ethical clinical research which it would be impermissible for any competent clinician to refer her patient to participate in.

Does it address the challenges posed by research containing a mixture of interventions?

Clinical research often contains a mixture of procedures. Some procedures offer the patient-subject the prospect of direct benefit, whereas others, done purely for research purposes, offer no such prospect. Given that risks associated with the former procedures may be justified by appeal to the prospect of direct benefit for subjects, whereas risks associated with the latter procedures may not, different moral tests are required for

the two kinds of procedure. Just what these moral tests should be is a problem that occupied much of the time of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978).[3] The ultimate view of the National Commission has been described by RJ Levine as follows:

> … the Commission calls for an analysis of the various components of the research protocol. Procedures that are designed solely to benefit society or the class of children of which the particular child-subject is representative are to be considered as the research component. Judgments about the justification of the risks imposed by such procedures are to be made in accord with other recommendations … The components of the protocol ''that hold out the prospect of direct benefit for the individual subjects'' are to be considered precisely as they are in the practice of medicine.[10]

This view of the National Commission finds mature expression in component analysis as described authoritatively by us elsewhere.[6]

Component analysis is best understood as a specification of norms entailed by the obligation of the state to protect the welfare interests of research subjects. Since it is recognised that both patients and healthy persons participate in clinical research, fulfilment of the state's obligation requires recognition of two distinct norms. First, patients who are research subjects enjoy a right to competent care. Second, all research subjects (patients and healthy subjects) enjoy a right to protection from exposure to undue harm solely in the interests of others. The first norm is specified by the requirement that therapeutic procedures satisfy clinical equipoise. The second norm is satisfied by the requirements that risks of non-therapeutic procedures are (1) minimised consistent with sound scientific design, (2) reasonable in relation to knowledge to be gained and (3) no more than a minor increase above minimal risk, when the study involves a vulnerable population. This reasoning, straightforward as it is, is misinterpreted by the authors. They state:

> [Component analysis] allows RECs to approve non-therapeutic interventions that are not in the medical interests of the participants, provided the risks are sufficiently low and the knowledge to be gained justifies the risks. In contrast, [component analysis] prohibits RECs from approving therapeutic interventions that are not in the medical interests of the participants, even when the risks are just as low or even lower, and the knowledge to be gained justifies the risks … This difference in judgement seems ethically arbitrary.''[7]

We think it plain that the distinction between moral tests for therapeutic and non-therapeutic procedures is far from arbitrary. The requirement that therapeutic procedures fulfil clinical equipoise ensures that the patient qua research subject has her right to competent medical care protected. Non-therapeutic procedures have no bearing on the provision of competent care; they do, however, have a bearing on the right of patients and healthy persons qua research subjects not to be exposed to undue harm solely in the interests of others. Accordingly, non-therapeutic procedures are governed by different requirements, detailed above. The charge of arbitrariness has no foundation.

What is troubling is that the net risks test does not make a distinction between the moral standards that govern therapeutic and non-therapeutic procedures in clinical research. Too quickly convinced that the distinction is arbitrary, Wendler and Miller abandon it and suggest that one moral test—the net risks test—applies to all study procedures. Regardless of deficiencies in the standards in the test, the immediate effect of dispensing with demarcation is to undermine patients' entitlement to competent care. The interests subject to that entitlement are simply lumped together with the interests all subjects have in protection from harm. This seems a difficult move to defend.

Two strategies are open to the authors. The first is to deny that the welfare interests of patients differ from the welfare interests of healthy persons. Put plainly, they must claim that the welfare interests of a 20-year-old man with Hodgkin's disease are just the same as those of his healthy counterpart. Of course, both individuals have a broad interest in health, but the life-threatening illness of the first individual makes immediate his interest in receiving competent medical care; this interest is not shared by his counterpart. A second strategy would be to acknowledge that patients and healthy persons have different interests but to argue that the distinct interests of patients should not be protected—at least not in clinical research. In short, they must claim that the interests of the 20-year-old in receiving competent care for his Hodgkin's disease do not matter. But refusal to recognise these interests seems inconsistent with the state's obligation to provide due protection for all research subjects, including patients who volunteer for clinical research. Neither move seems a promising line of argument.

Does it define ethical standards according to which the risks and potential benefits of research may be consistently evaluated?

Consistent evaluation of risks and benefits in research requires the articulation of well-justified ethical standards that provide clear guidance to RECs. We have already seen that the net risks test fails to provide clear guidance to RECs simply because the key threshold concept—''excessive risk''—is left undefined. This alone undermines the possibility of consistent evaluation of benefits and harms under the test. However, even worse, the net risks test is completely opaque. Consider the first step in the test. The REC is instructed to

> assess the risk–benefit profile of the available alternatives to each intervention … and then compare the risk–benefit profile for participants of each research intervention with that of the available alternatives. When the risk–benefit profile of the research intervention is at least as favourable for the participants as that of the available alternatives … it poses no net risks. Conversely, research interventions that offer participants a less favourable risk–benefit ratio than one or more of the available alternatives … pose net risks.[7]

Consistent implementation requires answers to the following questions:

- What is a risk–benefit profile and how does one construct one?
- How does one compare the risk–benefit profile of one intervention with that of another?
- What are the available alternatives and how does one determine what they are?
- What is a favourable or less favourable risk–benefit ratio and how does one determine this?

Without clear definitions of core normative concepts, and clear guidance as to how to implement them, the prospects of

the net risks test generating consistent evaluation of benefits and harms seem poor.

RESPONDING TO CRITICISMS OF COMPONENT ANALYSIS

Wendler and Miller have failed to articulate a viable alternative to component analysis. Indeed, their proposed alternative fails to satisfy any of the five criteria of plausibility that we have put forward and which they have left unchallenged. In the final section of this paper, we will briefly address Wendler and Miller's criticisms of component analysis. We identify two significant misrepresentations of component analysis, address a purported lack of definitional clarity, and justify classifying placebo as a therapeutic procedure.

First, Wendler and Miller rename component analysis as ''dual-track analysis''. This renamed concept is then attributed both to us, the authors of component analysis, and to others who have adopted or otherwise endorsed the concept. Purported flaws found in these other writings are then attributed to component analysis. This strategy is inimical to the clarity requisite to fair and focused debate.

Furthermore, component analysis is misrepresented in their fig 1. The assessment is not of single interventions, but of therapeutic or non-therapeutic interventions in aggregate. Reference to the requirement of a risk threshold for research involving vulnerable populations has been wholly deleted. For a correct diagrammatic representation of component analysis, see our article in *Nature Medicine*.[6]

Furthermore, contrary to Wendler and Miller's implication, the terms ''therapeutic procedure'' and ''non-therapeutic procedure'' are clearly defined in our work. Recognising some years ago the problems posed with definitional reliance on intent, definitions now consistently appeal to ''warrant''. In our authoritative discussion of component analysis we define our terms as follows. Therapeutic procedures are ''[d]rug, surgical and behavioral interventional interventions … 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.''[6] Non-therapeutic procedures are ''[o]ther interventions, such as venipuncture for pharmacokinetic drug levels, additional imaging procedures or questionnaires not used in clinical practice, are given without therapeutic warrant. They are administered solely for the purpose of answering the scientific question.''[6] Two brief comments are to be made about the definitions. First, the definitions are complementary, that is, a procedure that does not fulfil the definition of ''therapeutic'' is deemed non-therapeutic. Thus, the distinction between therapeutic and non-therapeutic procedures is analytic, or completely sharp. Second, the possibility of unanticipated benefit resulting from the administration of a non-therapeutic procedure neither makes the procedure therapeutic nor blurs the distinction. Mere possibility of unanticipated benefit does not amount to ''evidence sufficient to justify the belief that [it] may benefit research subjects''.[7]

Finally, placebo controls are correctly understood as therapeutic procedures. As discussed above, the state has an obligation to protect research subjects. For patients, this entails recognition of their right to competent treatment. This norm is specified in the requirement that therapeutic procedures satisfy clinical equipoise. Patients in clinical research can be assured of their right to competent treatment only if each of the treatment arms is consistent with competent care. Each of the treatment arms, be it the experimental or control arm, must be subjected to this requirement if the patient's right to competent care is to be meaningfully protected. In some cases, non-treatment will be deemed consistent with competent care (eg, mild depression, alopecia); in other cases, it will not (Hodgkin's disease, acute psychosis). To suggest that placebo is a non-therapeutic procedure is simply to beg the question as to its permissibility.

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