

# The Ethical Analysis of Risk

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The institutional review board (IRB) is the social-oversight mechanism charged with protecting research subjects. Performing this task competently requires that the IRB scrutinize informed-consent procedures, the balance of risks and potential benefits, and subject-selection procedures in research protocols. Unfortunately, it may be said that IRBs are spending too much time editing informed-consent forms and too little time analyzing the risks and potential benefits posed by research.<sup>1</sup> This time mismanagement is clearly reflected in the research ethics literature. A review of articles published between 1979 and 1990 in *IRB: A Review of Human Subjects Research*, for example, reveals a large number of articles on informed consent and confidentiality (142 articles) and considerably fewer on the assessment of risks and potential harms (40), study design (20), and subject-selection procedures (5).<sup>2</sup>

The obligation to ensure that study participation presents a favorable balance of potential benefits and risks to subjects is central to upholding the ethical principle of beneficence and fulfilling the IRB's protective function.<sup>3</sup> Some believe it to be the single most important determination made by the IRB. It ensures that potential research subjects — be they sick or well, young or old, capable or not — are presented with the option of entering a research study only when agreeing to do so would be a *reasonable choice*. Accordingly, the Common Rule requires that the IRB ensure that:

- (1) Risks to subjects are minimized:
  - (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

- (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.<sup>4</sup>

The moral analysis of risk is neither obvious nor intuitive. Rules, including those of the Common Rule, are not self-interpreting. They must be situated within a conceptual framework that facilitates their interpretation by the IRB. The articulation of a conceptual framework for the ethical analysis of risk might therefore be a project assisting IRBs in fulfilling their mandate — the protection of research subjects.

Regarding the analysis of risk in research, the authors of *The Belmont Report* observed that “[i]t is commonly said that benefits and risks must be ‘balanced’ and shown to be ‘in a favorable ratio.’ The metaphorical character of these terms draws attention to the difficulty of making precise judgments.”<sup>5</sup> Unpacking these metaphors for the sake of

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*Journal of Law, Medicine & Ethics*, 28 (2000): 344–361.

enabling more precise judgments will occupy the bulk of this paper. What are the risks and potential benefits of research? How was the ethical analysis of risk understood by the members of the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (hereafter the "National Commission")? What can be learned about the conceptual foundations of current regulation? What conceptual framework should guide the ethical analysis of risk? What changes to U.S. regulations would the implementation of such a framework require?

My work on this paper was commissioned by the U.S. National Bioethics Advisory Commission (NBAC) as a part of its project "Ethical and Policy Issues in the Oversight of Human Research in the United States." It is fitting, therefore, that the work of an earlier commission, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, receives special consideration in this paper. No other ethics body has had as much influence on the development of research ethics and regulation. As we shall see, pivotal conceptual advances in the moral analysis of risks and potential benefits can be traced back to the National Commission.

There have been considerable refinements in our understanding of the ethical analysis of risk in the last twenty-five years. Nonetheless, this paper relies heavily of the solid intellectual work that precedes this period. All of the work of the National Commission is a source for learning and much of it ought to be preserved in our current understanding and regulation. Two papers of Robert J. Levine, a staff member and consultant to the National Commission, remain foundational in research ethics: "The Boundaries Between Biomedical or Behavioral Research and the Accepted and Routine Practice of Medicine" and "The Role of Assessment of Risk Benefit Criteria in the Determination of the Appropriateness of Research Involving Human Subjects." This paper will assume familiarity with them.<sup>6</sup>

#### RISKS AND POTENTIAL BENEFITS IN RESEARCH

Risk is a multidimensional concept involving both the *probability* and *magnitude* of harms to research participants.<sup>7</sup> All too often, risk is equated with the magnitude of the outcome (e.g., death or serious disability). The proper ethical analysis of risk requires that both the magnitude of the harm and its probability of occurring be considered. A one-in-a-million risk of death is properly treated differently from a one-in-ten risk of death. Benefit, on the other hand, is the magnitude of a positive outcome without reference to its probability. In the comparison of harms to benefits, reference is often made to the need to consider the "risk-benefit ratio" presented by study participation. But this is not a parallel construction and, hence, it is strictly speaking incorrect. One speaks accurately of "harms and benefits" or "risks and potential benefits."

Research subjects may be exposed to a broad array of risks and potential benefits as a result of study participation. Risk is not a concept exclusive to biomedical research; social science studies also present risks to participants. Indeed, there is a surprising degree of overlap between the kinds of risks presented in biomedical and social science research. As study methodologies continue to cross conventional disciplinary boundaries, we can expect increasing convergence in the risks and potential benefits involved in biomedical and social science studies. We will thus need to consider whether the moral calculi involved in risk assessment suffice for the assessment of risks in research in a variety of disciplines. Consider the risks to participants in the following four case studies.

#### Study A: Placebo-controlled trial of a drug for people with acutely symptomatic schizophrenia

The study involves schizophrenic patients who are newly hospitalized with acute symptoms of their disease.<sup>8</sup> Despite the existence of an effective treatment for such symptoms, patients are randomly assigned to take a new antipsychotic drug, a standard drug, or a placebo. Patients are treated in a hospital for four weeks, where they are assessed with a variety of psychometric scales. Risks to subjects include the possibility that the new medication may have serious adverse effects, some of which may be irreversible; patients assigned to the placebo will be deprived of needed treatment for a month; patients may suffer from continuing hallucinations or paranoia; they may be at increased risk of suicide; and, finally, they may pose a risk to others. The ethics of placebo-controlled trials in schizophrenia is discussed in detail elsewhere.<sup>9</sup>

#### Study B: Hypnotic induction of partial deafness to see whether paranoid symptoms result

Several hypnotically suggestible, but otherwise healthy college students are randomly selected to receive one of three hypnotic suggestions: partial deafness without awareness of the cause; partial deafness with awareness of the cause; and no deafness but an ear itch.<sup>10</sup>

The hypothesis is that persons in the first group, as compared with those in the other two groups, will demonstrate more symptoms of paranoia. Subjects are assessed with a variety of measures, including psychometric scales and a scoring of observed behavior. After being evaluated, the subjects are hypnotized again, debriefed at the end of the study, and reassessed after one month. The study poses a variety of risks to participants, including the distress associated with paranoia and hearing loss, risk of suicide, the possibility of harm to others, and uncertain sequelae from hypnosis. Some of the ethical issues raised by this study are discussed elsewhere.<sup>11</sup>

### Study C: Questionnaire examining high school students about their sexual practices

The study involves the administration of a pencil-and-paper questionnaire to 400 Minneapolis high school students during regularly scheduled health classes.<sup>12</sup> The survey seeks to document attitudes and behaviors related to HIV prevention. Accordingly, the adolescent participants are asked whether they are sexually active, what types of sexual activity they have experienced (e.g., oral, vaginal, or anal intercourse), and the sex(es) of their partners. Various risks are presented by this study to participants: teachers or parents may become aware of undisclosed sexual activity; others may become aware of same-sex relationships; and participants might become aware that they are at risk of developing HIV. The ethical issues raised by this study are thoroughly reviewed elsewhere.<sup>13</sup>

### Study D: Genetic epidemiology of BRCA1 and BRCA2 mutations in Ashkenazi Jews

The BRCA1 and BRCA2 mutations are known to be associated with an increased risk of breast and ovarian cancer. The study seeks to determine what proportion of Ashkenazi Jews (i.e., Jews of middle, northern, or eastern Europe or those of such ancestry) carry the mutations in question and what risk is conferred by them in a non-high-risk population.<sup>14</sup> Participants who respond to advertisements will be asked to give a blood sample and fill out an epidemiological survey, including questions on health, family history of cancer, and family members who might also be willing to participate. Personal identifiers will be destroyed before genetic tests are conducted and test results will not be disclosed to participants. The risks to participants are the risks of venipuncture, anxiety provoked by answering questions related to family history of cancer, and the risks of genetic testing, including unwanted disclosure of risk, discrimination, and stigmatization. A review of the ethical issues in genetic epidemiology studies may be found elsewhere.<sup>15</sup>

### Four categories of risk

As illustrated by these four examples, research participation may expose the study participant to a wide spectrum of risks. Levine divides risks into four categories: physical, psychological, social, and economic.<sup>16</sup> Let us consider each briefly:

- *Physical risks:* The research subject may suffer bodily harm — minor or serious, temporary or permanent, immediate or delayed — as a result of his or her participation in the study.
- *Psychological risks:* Study participation may af-

fect the research subject's perception of self, cause emotional suffering (e.g., anxiety or shame), or may induce aberrations in thought or behavior.

- *Social risks:* Research findings, or even study participation itself, may expose subjects to the possibility of insurance or employment discrimination, or other forms of social stigmatization.
- *Economic risks:* Research subjects may directly or indirectly bear financial costs related to research participation.

So defined, risk is an inherently inclusive concept. As demonstrated by the above examples, a given study may present a variety of types of risk. For example, Study C (the sexual practices questionnaire) poses both psychological and social risks. Furthermore, no category of risk is exclusive to medical or social science studies: Study B (deafness and paranoia) — a social science study — presents physical risks, and Study A (schizophrenia trial) and Study D (breast cancer genes) — medical studies — generate psychological risks. Despite the diverse research settings and issues involved, all four of the study examples pose non-trivial risk to research subjects.

Levine provides a comprehensive description of particular potential benefits and risks presented to research subjects and society by biomedical and social science research and the listing will not be repeated here.<sup>17</sup>

### ANALYSIS BY THE NATIONAL COMMISSION

How was the ethical analysis of risk understood by the members of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research? What can be gleaned from their reports about the conceptual foundation of current regulations?

The National Commission sat from 1975 to 1978 and issued ten reports on human subjects research. The National Commission's work represents the first sustained, in-depth exploration of the moral analysis of risk in research. As such, it has had a lasting influence on research ethics scholarship and federal regulation. Little recognized is that the National Commission's views on risk analysis evolved over its four-year term. Three distinct views on the ethical analysis of risks and potential benefits in research can be found in the National Commission's opus: analysis of entire protocols; analysis of protocols with particular components; and analysis of components. In turn, each underlies an aspect of current federal regulations on human subjects research.

Six reports of the National Commission were selected for analysis based on their impact on public policy and the perception of the National Commission staff on the par-

particular report's overall success.<sup>18</sup> These reports are *Research on the Fetus* (1975); *Research Involving Prisoners* (1976); *Research Involving Children* (1977); *Research Involving Those Institutionalized as Mentally Infirm* (1977); *Institutional Review Boards* (1977); and *The Belmont Report* (1978).<sup>19</sup> What follows is a critical review of the ethical analysis found in each report.

### Ethical analysis according to entire protocols

*Research on the Fetus* was the first of the National Commission's reports. It was produced under several constraints.<sup>20</sup> Congress required that the report be completed in only four months and it imposed a moratorium on fetal research pending the completion of the report. Thus, Levine observes:

As a consequence of these time constraints, the Commission completed its report, *Research on the Fetus*, before it had the opportunity to address the general conceptual issues in its mandate. If the conceptual clarifications ... had preceded the report, it is likely that the Commission would have developed substantially different recommendations.

In the report, the National Commission defines research as "the systematic collection of data or observations in accordance with a designed protocol."<sup>21</sup> The schema for risk analysis presented in *Research on the Fetus* relies on separating whole research proposals into two types, therapeutic research and non-therapeutic research. Therapeutic research is that which is "designed to improve the health condition of the research subject by prophylactic, diagnostic, or treatment methods that depart from standard medical practice but hold out a reasonable expectation of success."<sup>22</sup> Non-therapeutic research, on the other hand, is "not designed to improve the health condition of the research subject by prophylactic, diagnostic, or treatment methods."<sup>23</sup>

Separate recommendations are presented for each type of study. Recommendation (1) addresses therapeutic research directed toward the fetus. Under this provision,

*Therapeutic research directed toward the fetus* may be conducted or supported, and should be encouraged, by the Secretary, DHEW [Department of Health, Education, and Welfare], provided such research (a) conforms to appropriate medical standards, (b) has received the informed consent of the mother, the father not dissenting, and (c) has been approved by existing review procedures with adequate provision for the monitoring of the consent process.<sup>24</sup>

Recommendation (4) outlines ethical criteria for the assessment of non-therapeutic research. It states:

*Nontherapeutic research directed towards the fetus in utero* (other than research in anticipation of, or during, abortion) may be conducted or supported by the Secretary, DHEW, provided (a) the purpose of such research is the development of important biomedical knowledge that cannot be obtained by alternative means, (b) investigation on pertinent animal models and non-pregnant humans has preceded such research, (c) minimal or no risk to the well-being of the fetus will be imposed by the research, (d) the research has been approved by existing review procedures with adequate provision for the monitoring of the consent process, (e) the informed consent of the mother has been obtained, and (f) the father has not objected to the research.<sup>25</sup>

While there is intuitive appeal in categorizing studies as a whole, the validity of this approach has been criticized. Levine points out that this categorization invariably leads to deep conceptual problems. This is illustrated by inserting the National Commission's definition of research into its definition of therapeutic research. Levine argues:

There is, of course, no such thing as a "systematic collection of data or observations ... designed to improve the health condition of a research subject ... that departs from standard medical practice." Thus, the Commission developed recommendations for the conduct of a nonexistent set of activities ....<sup>26</sup>

A further problem exists with this approach. The inclusion of one or more therapeutic procedures in a study leads to it being identified as therapeutic research. Once this categorization has taken place, there is no limit to the number of procedures without therapeutic intent that might be presented to research subjects as therapeutic. Thus, this approach not only leads to confusion, it leaves research subjects without adequate protection.

Despite its shortcomings, this approach is found in the current U.S. Department of Health and Human Services (DHHS) regulations on the protection of fetuses in research. The regulations divide research on the fetus into two categories: research "to meet the health needs of the particular fetus," i.e., therapeutic research; and research for "the development of important biomedical knowledge," i.e., non-therapeutic research.<sup>27</sup> As this approach to the ethical analysis of risk is not found elsewhere in the federal Common Rule or DHHS regulations, it may be a historical artifact of *Research on the Fetus* in the current regulations.

### Ethical analysis according to whole protocols with particular components

Recognizing the problems arising from the distinction of therapeutic versus non-therapeutic, the National Commission largely abandoned the use of these terms in subsequent reports. In the preface to *Research Involving Prisoners*, it states: "The Commission recognizes problems with employing the terms 'therapeutic' and 'nontherapeutic' research, notwithstanding their common usage, because they convey a misleading impression."<sup>28</sup>

In *Research Involving Prisoners*, the category of therapeutic research is replaced with "research on practices which have the intent and reasonable probability of improving the health and well-being of the subject."<sup>29</sup> While cumbersome, this manner of speaking at least avoids the conceptual confusion pointed to by Levine *supra*. In creating this new means of analyzing risk, the National Commission recognized that:

additional interventions over and above those necessary for therapy may need to be done, e.g., randomization, blood drawing, catheterization; these interventions may not be "therapeutic" for the individual. Some of these interventions may themselves present risk to the individual — risk unrelated to the therapy of the subject.<sup>30</sup>

Despite this recognition, the report fails to advise the acceptable level of non-therapeutic risks. Indeed, in this regard, Recommendation (4) merely states:

All research involving prisoners should be reviewed by at least one human subjects review committee or Institutional Review Board ... [T]he committee or board [IRB] should consider at least the following: the risks involved ...<sup>31</sup>

Clearly, IRBs require more detailed guidance on the ethical analysis of risks and potential benefits in research than is provided in *Research Involving Prisoners*.

The report does contain early ruminations about the notion of "minimal risk." Minimal risk is referred to nominally in *Research on the Fetus*, but only in *Research Involving Prisoners* do we see recognizable beginnings of what would become a central concept in the moral analysis of risk. First, a standard similar to that of minimal risk is articulated for research without therapeutic procedures:

Research designed to determine the effects on general health of institutional diets and restricted activity, and similar studies that do not manipulate bodily conditions (except innocuously, e.g., obtaining blood samples) but merely monitor or analyze such conditions, also present little physi-

cal risk and are necessary to gain some knowledge of the effects of imprisonment.<sup>32</sup>

Second, there is an explicit recognition that in determining which risks ought to be acceptable, a comparison should be made between the risks of research and those of daily life — in this case, the daily lives of persons who are not incarcerated:

The risks involved in research involving prisoners should be commensurate with risks that would be accepted by non-prisoner volunteers. If it is questionable whether a particular project is offered to prisoners because of the risk involved, the review committee might require that non-prisoners be included in the same project.<sup>33</sup>

Both of these standards find expression in current Department of Health and Human Services regulations.<sup>34</sup>

The concept of minimal risk is first fully expressed in the National Commission's report *Research Involving Children*.<sup>35</sup> It is natural that the most detailed recommendations regarding the analysis of risks and potential benefits are found in this report. Levine explains that:

because infants and very young children have no autonomy, there is no obligation to respond to it through the usual devices of informed consent. Rather, respect for infants and very small children requires that we protect them from harm. No discernable risk seemed to the commission to be virtually impossible; therefore, they stipulated a definition of "minimal risk" as the amount that would be acceptable without unusual standards for justification.<sup>36</sup>

The National Commission defines minimal risk as "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children."<sup>37</sup> This definition differs from the one found in the DHHS regulations in its stipulation of *healthy* children; DHHS does not so limit minimal risk.<sup>38</sup> The National Commission provides a number of *prima facie* examples of procedures that pose no more than minimal risk, including "routine immunization, modest changes in diet or schedule, physical examination, obtaining blood and urine specimens, and developmental assessments" (emphasis added).<sup>39</sup> Again, this differs from the DHHS regulations in its inclusion of a procedure — routine immunization — administered with therapeutic intent.

The concept of minimal risk is central to the schema for risk analysis presented in *Research Involving Children*. Recommendation (2) requires that the IRB ensure that

"[r]isks are minimized by using the safest procedures consistent with sound research design and by using procedures performed for diagnostic or treatment purposes whenever feasible."<sup>40</sup> Thus, if a blood sample is needed from a child, one ought, whenever possible, to use blood left over from a venipuncture done for therapeutic purposes. If the research does not involve therapeutic or non-therapeutic procedures that present more than minimal risk, it may be approved provided the above condition is fulfilled. Recommendation (3) states:

Research that does not involve greater than minimal risk to children may be conducted or supported provided that an Institutional Review Board has determined that: (A) the conditions of Recommendation (2) are met; and (B) adequate provisions are made for assent of the children and permission of their parents or guardians, as set forth in Recommendations (7) and (8).<sup>41</sup>

Separate recommendations, as follows, apply to research involving therapeutic or non-therapeutic interventions that exceed the minimal risk threshold.

If research involving a therapeutic intervention poses more than minimal risk, the IRB must ensure that the balance of potential benefits and risks is at least as favorable as alternatives. Recommendation (4) states:

Research in which more than minimal risk to children is presented by an intervention that holds out the prospect of direct benefit for the individual subjects, or by a monitoring procedure required for the well-being of the subjects, may be conducted or supported provided that an Institutional Review Board has determined that:

- (A) such risk is justified by the anticipated benefit to the subjects;
- (B) the relation of anticipated benefit to such risk is at least as favorable to the subjects as that presented by available alternative approaches;
- (C) the conditions of Recommendation (2) are met; and
- (D) adequate provisions are made for assent of the children and permission of their parents or guardians, as set forth in Recommendations (7) and (8).<sup>42</sup>

In short, the IRB should evaluate such interventions in the same way they are evaluated in clinical practice:

[The IRB] should compare the risk and anticipated benefit of the intervention under investigation (including the monitoring procedures nec-

essary for the care of the child) with those of available alternative methods for achieving the same goal, and should also consider the risk and possible benefit of attempting no intervention whatsoever.<sup>43</sup>

If, on the other hand, the research involves a non-therapeutic intervention that poses more than minimal risk, the provisions of Recommendation (5) apply:

Research in which more than minimal risk to children is presented by an intervention that does not hold out the prospect of direct benefit for the individual subjects, or by a monitoring procedure not required for the well-being of the subjects, may be conducted or supported provided an Institutional Review Board has determined that:

- (A) such risk represents a minor increase over minimal risk;
- (B) such intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, psychological or social situations, and is likely to yield generalizable knowledge about the subject's disorder or condition;
- (C) the anticipated knowledge is of vital importance for understanding or amelioration of the subject's disorder or condition;
- (D) the conditions of Recommendation (2) are met; and
- (E) adequate provisions are made for assent of the children and permission of their parents or guardians, as set forth in Recommendations (7) and (8).<sup>44</sup>

Risks presented by non-therapeutic procedures are justified, therefore, in part by the importance of the knowledge to be gained from the research study as a whole. However important the knowledge, risks associated with the non-therapeutic interventions are effectively limited to "a minor increase over minimal risk." Risks exceeding this threshold require the approval of a national ethics advisory board and the secretary of the responsible federal agency (Recommendation (6)). The majority of the members of the National Commission defend this threshold for permissible risk as posing no significant threat to the child's health. The added requirement that such risks be commensurate to the child's experience ensures that such risks will be familiar. "Such activities, then, would be considered normal for these children."<sup>45</sup> Importantly, if the research

Table 1. Applying the Recommendations from *Research Involving Children* in a Mixed Clinical Study.

NON-THERAPEUTIC PROCEDURE	THERAPEUTIC PROCEDURE	
	No more than minimal risk	More than minimal risk
No more than minimal risk	Recommendation (3) only	Recommendations (3) and (4)
More than minimal risk	Recommendations (3) and (5)	Recommendations (4) and (5)

involves both a therapeutic intervention and a non-therapeutic intervention that exceed minimal risk, then *both* Recommendations (4) and (5) are to be applied by the IRB.

This provision (Recommendation (5)) was the subject of the most enduring disagreement among members of the National Commission. Commission member Robert Turtle dissented from the provision, arguing that it should be impermissible to expose children to non-therapeutic procedures that pose more than minimal risk. He objected strenuously to the suggestion that sick children might be exposed to greater non-therapeutic research risk than healthy children would be:

Children, who through no fault or choice of their own, are subjected to greater risks incident to their condition or treatment, cannot ethically be assumed to qualify for additional increments of risk. To do so, is to add to the potential burdens that result, directly or indirectly, from the child's illness.<sup>46</sup>

It scarcely needs to be observed that these provisions for the moral analysis of risk are complex. The recognition that a study may involve therapeutic procedures, non-therapeutic procedures, or *both* is a substantial leap forward over the schema for risk analysis found in *Research on the Fetus*. In *Research Involving Children*, the members of the National Commission solved both of the shortcomings associated with attempting to classify research as therapeutic or non-therapeutic (i.e., confusion and leaving research subjects without adequate protection) discussed *supra*.<sup>47</sup> The solution nonetheless created problems of its own.

First, the concept of minimal risk is applied to both therapeutic and non-therapeutic procedures in the examples provided in Recommendation (3). It is unclear in what meaningful way minimal risk can apply to therapeutic procedures. According to Recommendation (4), therapeutic procedures that involve more than minimal risk are justified, just as they are in clinical practice. In other words, there is no limit to the risk that may be posed by such procedures as long as they are reasonable in relation to potential benefits. Only non-therapeutic procedures should be subject to a threshold for permissible risk, such as "a minor increase over minimal risk."

Second, the National Commission's use of minimal risk

in the recommendations seems at odds with its definition of "minimal risk." Recall that the National Commission defined "minimal risk" as risk commensurate with the risks of daily life of *healthy* children. Fixing the standard to the daily lives of healthy children seems designed to protect sick children from being exposed to more non-therapeutic research risks than healthy children. This presumed intention is contradicted by Recommendation (5), which allows non-therapeutic risks that are a "minor increase over minimal risk" as long as "such intervention of procedure presents experiences to subjects that are reasonably commensurate" with their experience.<sup>48</sup> Thus, a spinal tap done purely for research purposes may be permissible in a child with a neurological disorder for which such procedures are common, but not in a healthy child. The definition of "minimal risk" would be consistent with its use in Recommendation (5) if there were no reference to healthy children, as is the case in the current DHHS regulations.<sup>49</sup>

Third, little guidance is provided for the analysis of risks and potential benefits for procedures that pose no more than minimal risk (Recommendation (3)). Recommendation (2) requires that risks be "minimized by using the safest procedures consistent with sound research design."<sup>50</sup> This cannot, however, sensibly apply to risks posed by therapeutic procedures, since considerations of research design are largely irrelevant to them. One might reasonably ask: What ethical test ought the IRB apply to research involving a therapeutic procedure posing no more than minimal risk? From this report, no answer is forthcoming.

Fourth, research may involve both therapeutic and non-therapeutic procedures. Indeed, it is fair to say that this is often the case in clinical research. If a study involves a therapeutic intervention and a non-therapeutic intervention, then multiple recommendations may apply. The various possibilities are summarized in Table 1. If both procedures present only minimal risk, then only Recommendation (3) applies. If the therapeutic procedure presents more than minimal risk, but the non-therapeutic procedure presents minimal risk, then Recommendations (3) and (4) apply. If the reverse is the case, then Recommendations (3) and (5) apply. If both procedures present more than minimal risk, then Recommendations (4) and (5) apply. Since each of the recommendations refers to whether the research study as a whole involves a particular type of intervention, it is unclear how multiple recommendations are to be applied to a

particular study. Without doubt, it is a cumbersome approach and it may easily lead to confusion or conflict.

Despite these difficulties, the model for risk assessment found in *Research Involving Children* is clearly reflected in the current DHHS regulations for the protection of children in research. Indeed, there is a one-to-one correspondence between certain regulations and Recommendations made by the National Commission. More specifically, 45 C.F.R. § 46.404, "Research not involving greater than minimal risk," corresponds to Recommendation (3); § 46.405, "Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects," corresponds to Recommendation (4); § 46.406, "Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition," corresponds to Recommendation (5); and § 46.407, "Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children," corresponds to Recommendation (6). Note that the conceptual model for risk analysis underlying 45 C.F.R. §§ 46.404-407 differs from that underlying protections for the fetus noted *supra*.

The schema for the analysis of risks and potential benefits of research found in *Research Involving Those Institutionalized as Mentally Infirm* is essentially identical to that found within *Research Involving Children*.<sup>51</sup> Accordingly, I will add only a few comments at this point. The report refers primarily to persons who are both incapable of providing informed consent and institutionalized. It addresses the problems of including such persons in research by incorporating elements of *Research Involving Prisoners* and *Research Involving Children*. The definition of "minimal risk" refers to the "risk ... normally encountered in the daily lives ... of normal persons."<sup>52</sup> Thus, the risks associated with institutionalization may not be used to justify exposing subjects to greater research risks. Recommendations (1) through (5) track with Recommendations (2) through (6) from *Research Involving Children* and they will not be further elaborated here.

### Ethical analysis according to a study's components

The final reports by the National Commission support an ethical analysis of the risks and potential benefits of a study according to its components, be they therapeutic interventions or non-therapeutic interventions.

The previous reports of the National Commission focused on risk analysis for particular vulnerable populations. In *Institutional Review Boards*, members of the National Commission articulated for the first time ethical standards to apply to the review of all human subjects research. The report explicitly acknowledges that a protocol may contain

therapeutic procedures, non-therapeutic procedures, or both:

A research project is described in a protocol that sets forth explicit objectives and formal procedures designed to reach those objectives. The protocol may include therapeutic and other activities intended to benefit the subjects, as well as procedures to evaluate such activities.<sup>53</sup>

According to *Institutional Review Boards*, risks must be analyzed systematically and should involve a procedure-by-procedure review of risks, benefits, and alternatives. In the words of the National Commission, "[t]his evaluation should include an array of alternatives to the procedures under review and the possible harms and benefits associated with each alternative."<sup>54</sup> The risks associated with particular procedures are acceptable only if "risks to subjects are minimized by using the safest procedures consistent with sound research design and, wherever appropriate, by using procedures being performed for diagnostic or treatment purposes; [and] risks to subjects are reasonable in relation to anticipated benefits to subjects and importance of knowledge to be gained ...."<sup>55</sup>

*The Belmont Report* provides little additional detail with regard to this model of ethical analysis. It famously articulates three ethical principles to guide the conduct of clinical research: respect for persons, beneficence, and justice. Beneficence demands that one do no harm *and* maximize possible benefits while minimizing risks.<sup>56</sup> Translating this principle into practice requires that the IRB ensure that research participation presents subjects with a favorable balance of possible benefits and risks. *The Belmont Report* once again emphasizes that this is to be done in a systematic and rigorous manner:

... The idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments.<sup>58</sup>

Levine renders the thinking of the National Commission somewhat clearer in two papers contained in the appendix of *The Belmont Report*. In the first, "The Boundaries Between Biomedical or Behavioral Research and the Accepted and Routine Practice of Medicine," Levine rec-

ognizes the existence of “complex activities.”<sup>59</sup> Such activities involve procedures administered with different intents. Some interventions may be administered for therapeutic purposes, while others solely to answer a scientific question. It is this difference in intent that drives the ensuing moral analysis according to the components of a research study.

The recognition of “complex activities” is further elucidated by Levine in *Ethics and Regulation of Clinical Research*, the seminal text in research ethics. He states:

... 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. For example, if the risk is minimal, the research may be conducted as described in Recommendations (3) and (7) [of *Research Involving Children*], no matter what the risks are of the therapeutic components. 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.<sup>60</sup>

Levine’s description is clearly at variance with the actual text of *Research Involving Children*. The passage is significant as an account of Levine’s own views on the ethical analysis of risk, developed for the National Commission. It may also be an accurate description of the view of the National Commission itself, as reflected in *Institutional Review Boards* and *The Belmont Report*.

It is this last model of risk assessment, “component analysis,” that serves as the conceptual framework for the analysis of risk found in the Common Rule. Risks associated with non-therapeutic procedures must be minimized and “reasonable in relation to ... the importance of the knowledge that may reasonably be expected to result.”<sup>61</sup> Risks associated with therapeutic procedures must be “reasonable in relation to anticipated benefits ... to subjects.”<sup>62</sup>

Our historical analysis of the National Commission reports reveals that differing aspects of the current DHHS regulations are, in fact, supported by differing, and mutually incompatible, conceptual frameworks for the moral analysis of risk. The following is a summary of these differing frameworks.

- Regulations for the protection of fetuses in research reflect a “whole protocol” approach to risk analysis, which requires that protocols be

classified as either “therapeutic” or “non-therapeutic” research.<sup>63</sup>

- Regulations for the protection of children in research reflect a “protocols with particular components” approach. This approach defines separate standards for protocols with either therapeutic or non-therapeutic components. Recognizing that a given study may contain both a therapeutic and non-therapeutic procedure, it allows for both standards to apply simultaneously to a given study.<sup>64</sup>
- The Common Rule, outlining general protections for research subjects, relies on the “component” approach to risk analysis. Procedures administered with therapeutic intent are justified when the benefits to subjects outweigh the risks. Procedures administered without such a warrant — so-called non-therapeutic procedures — are justified only if they are minimized and if the risks are reasonable in relation to the knowledge to be gained.<sup>65</sup>

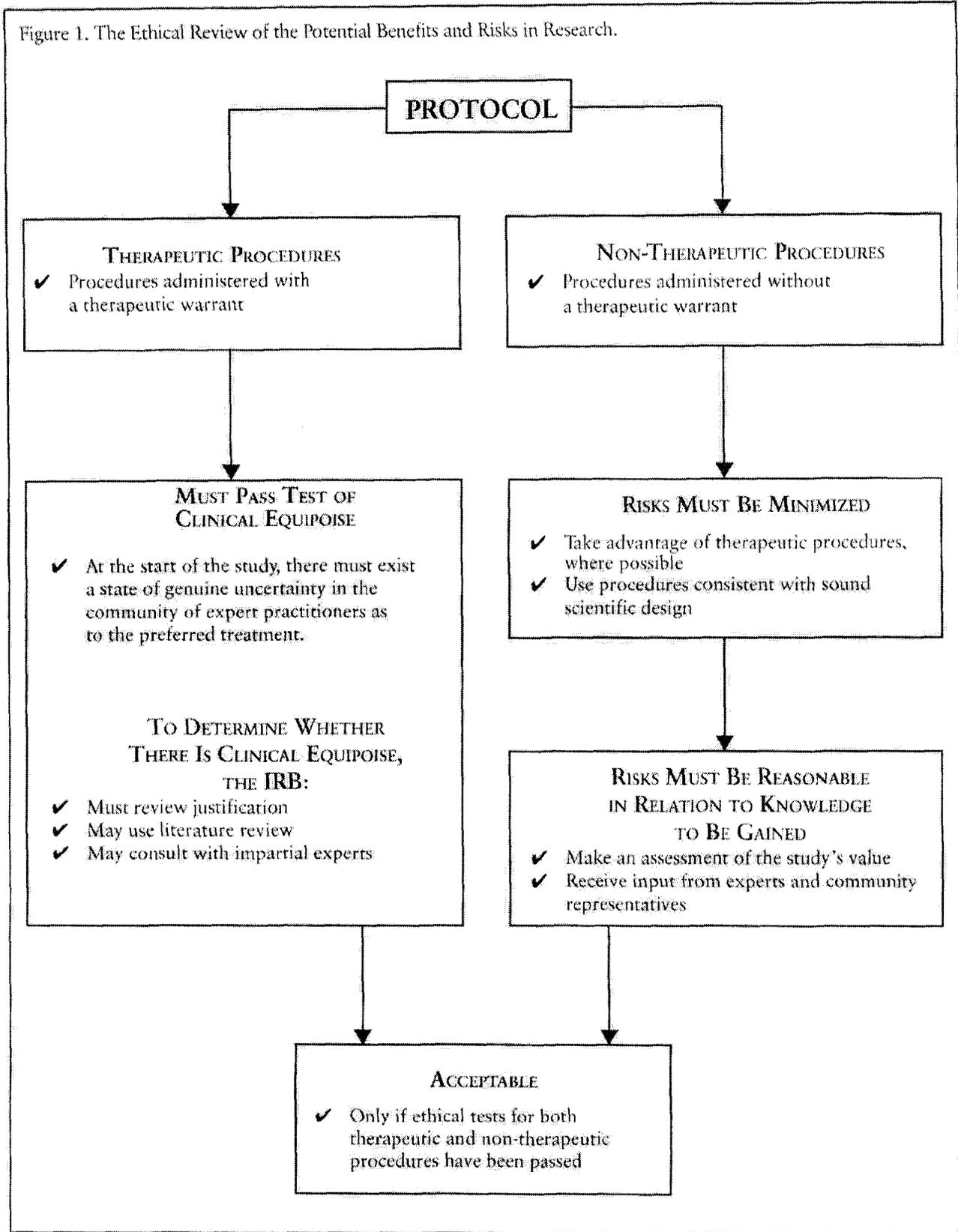
The existence of incompatible frameworks underlying the current regulations is obviously problematic. It has surely led to ambiguity in enforcement and confusion among IRBs attempting to implement the regulations in a consistent manner. One conceptual framework ought to guide the moral analysis of risks and potential benefits in research.

#### TOWARDS A COMPREHENSIVE APPROACH

The ethical analysis of the various “components” in a research study presents a number of advantages:

- It acknowledges that clinical research often contains a mixture of procedures, some administered with therapeutic intent and others that answer the research question.
- Therapeutic procedures and non-therapeutic procedures are, by definition, administered with differing intents. This difference is morally relevant.
- Therapeutic procedures are justified by their potential to benefit the subject, while non-therapeutic procedures are justified by their potential to generate knowledge. These two benefits are largely incommensurable.
- A rigorous separation of the moral calculi for therapeutic and non-therapeutic procedures protects research subjects better than any other approach. This separation prevents the justification of risky non-therapeutic procedures by the benefits that may flow from therapeutic procedures.

Figure 1. The Ethical Review of the Potential Benefits and Risks in Research.



- It is a more parsimonious model for analysis than other alternatives, and it therefore avoids confusion and conflict.

Freedman and colleagues were the first to formalize a “component” approach to the ethical analysis of research risk.<sup>66</sup> This approach is summarized in Figure 1. Three main topics will be discussed here: the moral analysis of potential benefits and risks presented by therapeutic procedures; the moral analysis of potential benefits and risks presented by non-therapeutic procedures; and the role of the concept of minimal risk in the protection of vulnerable research subjects.

### Therapeutic procedures

Therapeutic procedures are those interventions in research — drugs, surgical procedures, devices, or psychological procedures — administered with therapeutic intent (Figure 1). This category also encompasses monitoring procedures that would reflect ideal practice, even if these procedures are not routinely used in clinical practice. Consider what procedures might be considered therapeutic in the four case studies presented at the beginning of the paper.

- In Study A, a novel antipsychotic drug is compared with placebo. Both of these procedures are therapeutic interventions. The use of psychometric scales may be therapeutic if they are used routinely in clinical practice to guide treatment or if their use would reflect ideal practice. We do not have enough information to make this judgment, so we will assume that they are non-therapeutic.
- In Study B, hypnosis is used to implant one of three suggestions related to deafness. Hypnosis is used therapeutically in certain circumstances, but in this case, the use is non-therapeutic. The study population is not in need of any treatment. They are healthy college students and are participating solely for the purpose of testing a hypothesis.
- In Study C, a questionnaire related to sexual activity is administered to high school students. This is not a therapeutic intervention.
- In Study D, an epidemiological survey is administered and genetic tests for mutations associated with breast cancer are done on blood samples. The study is directed at all adult members of a community, not merely those who may require a detailed work-up for a genetic predisposition to breast cancer. Furthermore, results will not be given to participants. These interventions are, therefore, non-therapeutic.

Having determined which procedures are administered with a therapeutic warrant, how do we determine whether they are morally acceptable? Therapeutic procedures must pass the test of clinical equipoise (see Figure 1).<sup>67</sup> A major competing notion — the uncertainty principle — has recently been shown to be inferior to clinical equipoise.<sup>68</sup> Clinical equipoise is a norm developed in response to the question: When may the ethical physician offer trial participation to his or her patient? Competent medical practice requires that the physician exercise a standard of care — that is, practice accepted by at least a respectable minority of expert practitioners. The innovation of clinical equipoise is the recognition that study treatments — whether they be the experimental or control treatments — must be consistent with this standard of care. Thus, a physician, in keeping with his or her duty of care to the patient, may offer trial enrollment when “[t]here exists ... an honest, professional disagreement among expert clinicians about the preferred treatment.”<sup>69</sup>

A state of clinical equipoise may arise in a number of ways. Evidence may emerge from early clinical studies that a new treatment offers advantages over standard treatment. Alternatively, there may be a split within the clinical community, with some physicians preferring one treatment and other physicians preferring another. This scenario is well documented in the literature and calls for a randomized controlled trial (RCT) to settle which is the better treatment.<sup>70</sup> Clinical equipoise permits these important randomized controlled trials. It would have physicians respect the fact that “their less favored treatment is preferred by colleagues whom they consider to be responsible and competent.”<sup>71</sup>

When evaluating a study containing one or more therapeutic procedure, the IRB must take reasonable steps to assure itself that a state of clinical equipoise exists. This will involve a critical evaluation of the study’s justification. In selected cases, it may also require a search of the medical literature or consultation with relevant experts who have no connection with the study or its sponsor. A variety of treatment-related factors are also likely to contribute to this determination: the efficacy of the treatment; side effects, both reversible and irreversible; ease of administration; patient compliance; and perhaps even cost. It is important to recognize that clinical equipoise does not require a numeric equality of treatment risks (or benefits, for that matter). It is more accurate to say that equipoise requires approximate equality in treatments’ therapeutic index — a compendious measure of potential benefits, risks, and uncertainty. Thus, a novel treatment may pose considerably more risk to subjects as long as it also offers the prospect of considerably greater benefit. With novel interventions, the uncertainty associated with the intervention’s side effects will almost always be greater than the uncertainty associated with the treatments currently used in clinical practice.

Study A is the only one of our four case studies that involves the use of therapeutic procedures. The IRB must ask itself whether a state of clinical equipoise exists among the new antipsychotic drug, the placebo, and the alternatives available in clinical practice? It follows from clinical equipoise that placebo controls will generally only be permissible for first-generation treatments — that is, when no standard treatment is available. Once effective treatment exists, new interventions must be tested against the best available standard treatment.<sup>72</sup> This standard is consistent with that found in the most recent revision of the *Declaration of Helsinki*.<sup>73</sup>

Because effective treatment exists for the treatment of schizophrenia, the use of a placebo in this case is impermissible.<sup>74</sup> The IRB must not approve the study unless either the placebo control is replaced with an active control or the patient population is restricted to those who have had no response to standard therapy, including any routinely used second-line or third-line agents. A detailed rebuttal of scientific arguments made in favor of the routine use of placebo controls can be found elsewhere.<sup>75</sup>

### Non-therapeutic procedures

The remaining procedures administered in a clinical study are, by definition, not administered with a therapeutic warrant and are properly referred to as “non-therapeutic procedures” (see Figure 1). Such procedures are administered solely for scientific purposes — to answer the research question at hand. As all research is a “systematic investigation ... designed to develop or contribute to generalizable knowledge,” it is difficult to imagine a study that does not include a non-therapeutic procedure.<sup>76</sup> A non-therapeutic procedure may be as simple — and innocuous — as randomization, chart review, filling out a questionnaire, an interview, or recording data in some other manner; it may, however, be invasive or otherwise fraught with risk, as with generic testing, organ biopsy, or collection of information related to illegal practices. All four of our case studies include non-therapeutic procedures.

- Study A (trial of new medication in schizophrenia) proposes to test subjects regularly with psychometric scales. Filling out such forms is time consuming and potentially upsetting, and may expose subjects to the risk of discrimination.
- Study B (hypnosis and deafness) involves a number of non-therapeutic procedures. Subjects will be hypnotized and given a hypnotic suggestion solely for research purposes. Subjects will be observed, fill out psychometric scales, and be hypnotized again to remove the hypnotic suggestion. Distress and paranoia may result from the hypnosis; the effect of the hypnotic sugges-

tions is uncertain; and there are risks associated with the administration of psychometric tests.

- Study C (adolescent sexual practices) also involves only non-therapeutic procedures. The questionnaire addresses a number of sensitive areas of inquiry, including sexuality and practices that predispose the subject to the transmission of HIV. Subjects may find the questions anxiety-provoking and authority figures in the subjects’ lives may learn of what the subjects’ said, leading to stigmatization.
- Study D (breast cancer genes) also involves only non-therapeutic procedures. The epidemiological survey and genetic tests may generate information that is anxiety-provoking or indeed may lead to workplace or insurance discrimination. Beyond risks to the individual study participants, the Jewish community as a whole may be wrongly labeled as “cancer-prone” and subjected to discrimination and stigmatization.

By definition, risks associated with non-therapeutic procedures cannot be justified by the prospect of benefits to individual research subjects. Hence, a risk-benefit calculus is inappropriate to assessing the acceptability of these risks. The IRB must first ensure that the risks associated with non-therapeutic procedures are minimized “by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes” (see Figure 1).<sup>77</sup> Second, the IRB must ascertain that the risks of such procedures are reasonable in relation to the knowledge to be gained (see Figure 1).<sup>78</sup> Thus, the ethical analysis of risks associated with non-therapeutic procedures involves a risk-knowledge calculus. The knowledge that may result from a study is essentially its scientific value. Freedman has argued that the proper assessment of the scientific value of a study requires not only the opinion of experts from relevant disciplines, but also the opinion of representatives from the community at large.<sup>79</sup>

In Study A, the IRB should ensure that all of the tests being administered are required and consider whether psychometric tests that are routinely administered might provide equivalent information. In Study B, hypnosis and hypnotic suggestion present worrisome risks. Can the information be gained in another way — for example, by studying those who are already deaf? Can the risks associated with hypnosis be minimized? Study C also presents non-trivial risk, in part because the questionnaire is administered in a high-school setting. Paying careful attention to maintaining anonymity, allowing students to unobtrusively opt out of the questionnaire or certain questions, and seating stu-

dents so they cannot see each other's answers will minimize risk. In Study D, destroying subject identifiers and not informing participants of the results of the genetic testing considerably alleviate some of the risks to subjects. In all of the case studies, the risks of these procedures must be reasonable in relation to the knowledge to be gained.

Study D poses one category of risk that is not dealt with by this model — risks of discrimination and stigmatization to the Jewish community. The protection of communities in research is a novel area of inquiry in research ethics. Another paper commissioned by the NBAC argues for a new ethical principle of respect for communities.<sup>80</sup> Subsequent work has detailed possible protections for communities in research.<sup>81</sup> Most recently, a rational schema for mapping appropriate protections onto specific communities, such as Ashkenazi Jews, has been reported.<sup>82</sup> More work is required to determine how the ethical analysis of risk for communities in research ought to proceed.

### Minimal risk

Minimal risk is a widely used concept in the regulation of research internationally. It can be found in the present-day laws or guidelines of Australia, Canada, the Council for International Organizations of Medical Sciences, the Council of Europe, the United Kingdom, and the United States.<sup>83</sup> That a research study poses minimal risk means that “the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”<sup>84</sup>

Minimal risk has been the subject of considerable debate and confusion in the literature. As we have seen, the concept of minimal risk was applied to both research with a therapeutic procedure and research with a non-therapeutic procedure in *Research Involving Children*. In the context of our schema for the ethical analysis of risk, this makes little sense. If a state of clinical equipoise exists, it follows that the therapeutic indices of the various study treatments (and the alternatives available in clinical practice) are roughly equivalent. Thus, when considering the limit of risk to which research subjects may be exposed, we must focus on non-therapeutic risks. The risks of non-therapeutic procedures are the incremental risks associated with participation in a study.

Freedman and colleagues have argued that the definition of “minimal risk” in the Common Rule is best understood as a core definition with examples.<sup>85</sup> Minimal risk refers to risks “ordinarily encountered in daily life” — or, shorter, risks of daily life.<sup>86</sup> The second part of the definition provides two examples of minimal risk, both of them being procedures encountered “during the performance of routine physical or psychological examinations or tests.”<sup>87</sup>

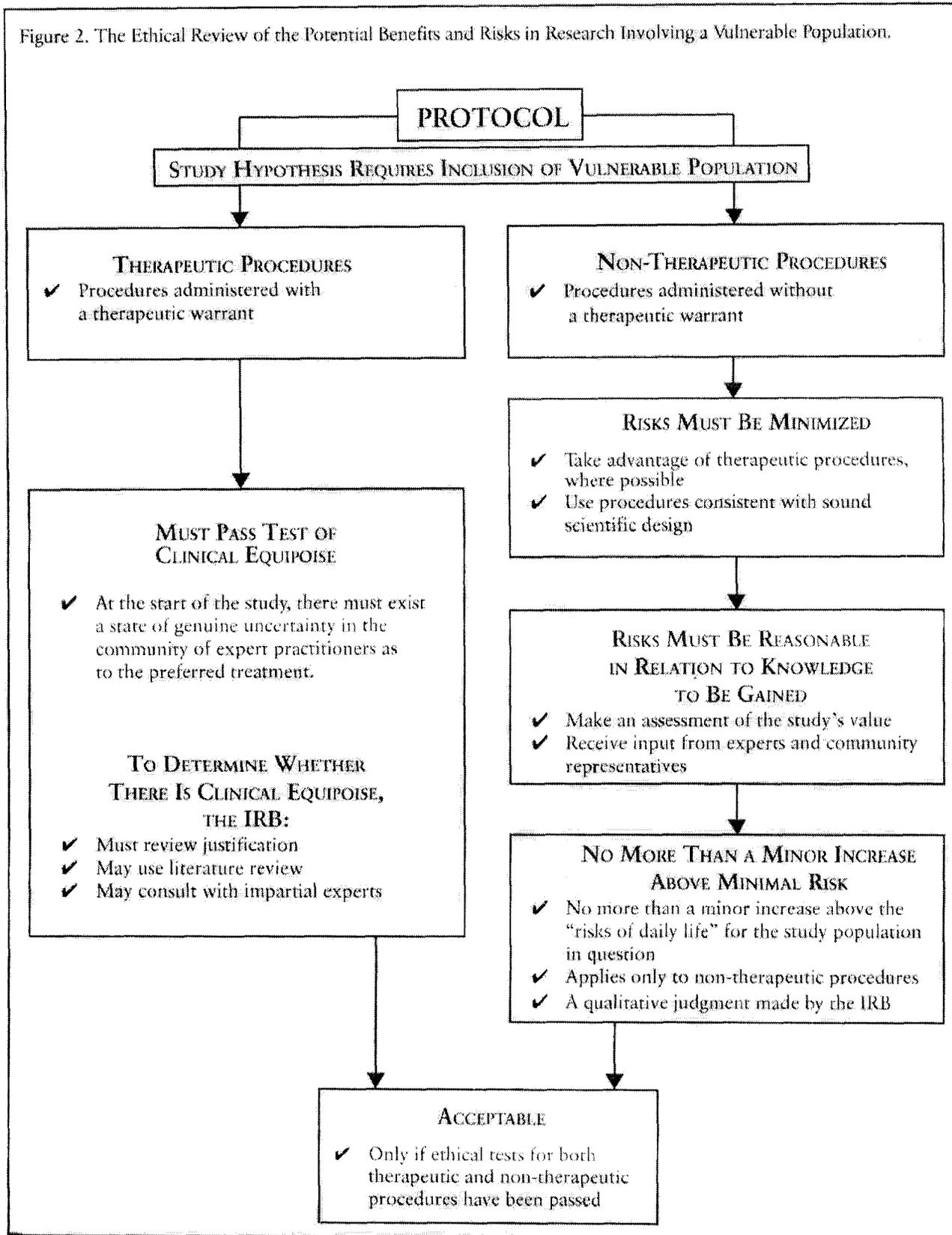
This definition has been criticized on the grounds that it is difficult to know what counts as risks of daily life and that the quantification of such risks is elusive.<sup>88</sup>

Freedman and colleagues concluded that the first claim is untrue and the second irrelevant.<sup>89</sup> Minimal risk does not refer to *any risk* encountered by *any person*, as some individuals engage in hazardous professions and pastimes and others never leave their house. Rather, it refers to the risks that are common to us all — driving to work, crossing the street, exchanging information over the Internet, or getting a blood test at the doctor's office. While it may be difficult to quantify the precise probability of given outcomes associated with each of these activities, we can nonetheless easily identify them as risks of daily life. As Freedman and colleagues observe: “We are, by definition, ... acquainted with them; and, almost by definition, if we are unsure whether they belong within the set of common tasks then they don't.”<sup>90</sup> The assessment of whether a procedure presents a minimal risk is not primarily a quantitative determination; rather, it is a qualitative or categorical judgment made by the IRB. Research interventions may be determined to be of minimal risk because either the procedure is in fact encountered in daily life or it is sufficiently similar to those routinely encountered.

The threshold of “a minor increase over minimal risk” corresponds to the custodial duty that parents have for their children. Responsible parents make decisions regarding new activities for their child based on the child's daily life (“minimal risk”) and make allowances for the importance of new experiences (“a minor increase over”). Thus, the threshold of a “minor increase above minimal risk” corresponds to the decisions made by responsible parents. This does not speak to the motivation of parents in enrolling their child in research; rather, it demonstrates that enrollment may be consistent with the norms of the parents' custodial duty to their child. While the majority of researchers and parents are scrupulous, some are not. The IRB acts *in loco parentis* by evaluating non-therapeutic risks as a responsible parent would, thereby ensuring that parents, scrupulous or not, will only have an opportunity to enroll a child in a study that passes such a test.

The concept of minimal risk serves two basic functions in regulation. First, it may be used as a “sorting mechanism,” directing the attention of the IRB to studies posing greater risk. Second, it serves as a threshold, limiting the amount of non-therapeutic risk to which vulnerable research subjects may be exposed. The provision in the Common Rule allowing for expedited review is an example of the use of minimal risk as a sorting mechanism. If a study is found to pose only minimal risk, it may, with certain other caveats, receive approval by the IRB chair (or an IRB member chosen by the chair) without a full IRB review. The regulations state:

Figure 2. The Ethical Review of the Potential Benefits and Risks in Research Involving a Vulnerable Population.



An IRB may use the expedited review procedure to review either or both of the following:

- (1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,
- (2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in § 46.108(b).<sup>91</sup>

Several problems are apparent with this provision. First, the requirement that non-therapeutic risks be both minimal risk and included in the list of "Research activities which may be reviewed through expedited review procedures" is curious. The list is obviously designed to include procedures that pose minimal risk to healthy adult subjects. For example, "moderate exercise by healthy volunteers" and "collection of blood samples by venipuncture ... from subjects 18 years of age or older" are permitted procedures. This eliminates from expedited review any study involving venipuncture in children or exercise by adults who are ill. This seems inconsistent with minimal risk, as defined, which does not limit the standard to healthy persons or adults.<sup>92</sup>

Second, the provision for expedited review offers an incomplete set of criteria. A given study might pose only minimal risk to subjects and yet raise serious ethical concerns that ought to make it ineligible for expedited review. One such case is a study that involves a vulnerable population. Studies involving vulnerable populations require special scrutiny by the IRB and should not be eligible for expedited review. Another such case is a study that has serious methodological flaws. Freedman observes that the ethical requirement that a study have a sound research design (validity) is absolute.<sup>93</sup> Thus, a study ought to be eligible for expedited review only if three conditions are fulfilled:

1. the study poses no more than minimal risk to participants;
2. it does not involve a vulnerable population; and
3. there are no serious methodological flaws.

Most important is the role of minimal risk as a threshold for allowable non-therapeutic risk in research involving vulnerable populations. Vulnerable populations in the

Common Rule include children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.<sup>94</sup> Given the heterogeneity of these populations, vulnerability itself must be a complex notion. Indeed, it encompasses groups who have one or more of the following characteristics: undue susceptibility to harm (e.g., pregnant women); incapability providing informed consent to study participation (e.g., children); or being so situated so as to render the voluntariness of consent suspect (e.g., prisoners).<sup>95</sup> In light of these characteristics, those qualifying as vulnerable are entitled to special protections in research (see Figure 2). Three protections are often invoked. First, a vulnerable group may only be included in research when their participation is essential to the hypothesis being tested. Second, if persons are incapable of providing informed consent, the consent of a proxy decision-maker is required. Third, the amount of non-therapeutic risk to which the vulnerable group may be exposed is limited to minimal or a minor increase over minimal.

The importance of the last protection can scarcely be overemphasized. Clinical equipoise ensures that therapeutic procedures in a study are comparable with each other and with alternatives in clinical practice in terms of their therapeutic indices. Thus, the incremental risk posed by study participation is that posed by non-therapeutic procedures. If vulnerable populations, such as children or incapable adults, are to be protected in any meaningful way, the risks of non-therapeutic procedures must be limited to a minor increase above minimal risk. This standard has the advantage of mirroring the custodial duty of parents to children and caretakers to incapable adults.

The NBAC proposes to eliminate this important protection. In its report *Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity*, no limit is placed on the non-therapeutic risk to which an incapable adult may be exposed, provided certain consent provisions are obtained (Recommendation (12)).<sup>96</sup> This is shortsighted. When the limit of a minor increase above minimal risk is eliminated as a threshold for permissible non-therapeutic risk, no amount of risk is ruled out for research involving incapable persons. As long as the research question is important enough and informed-consent provisions are fulfilled, any amount of non-therapeutic risk is permissible. This change, if translated into regulation, will effectively undermine protections for incapable persons in research. Incapable persons will then be exposed to exploitation legitimated by the very regulations that were supposed to protect them.

#### IMPLICATIONS FOR U.S. REGULATIONS

It is clear that the Common Rule and the DHHS regulations were profoundly influenced by the works of the National Commission, as the different models of risk analysis

§ 46.102(i) Minimal risk means that the probability and magnitude of harm is no greater than that encountered in the daily lives of all (or the great majority) of persons in the population from which research subjects are to be recruited. It refers only to the risks associated with non-therapeutic procedures.

The role of the concept of minimal risk in expedited review needs to be clarified. The use of a list of procedures drawn up only for healthy adults is inconsistent with the concept's definition and use. Furthermore, minimal risk is not a sufficient condition for a research protocol to receive expedited review. Generally speaking, the study protocol must also be methodologically sound and not involve a vulnerable population. To this end, I would recommend that § 46.110(a) be deleted and that § 46.110(b) be changed as follows:

§ 46.110(b) An IRB may use the expedited review procedure to review either an entire protocol or a protocol amendment provided the review(s) determine:

- (1) the study methods are valid;
- (2) it does not involve a vulnerable population; and
- (3) it poses no more than minimal risk.

The ethical analysis of risk for research involving children can be simplified greatly with this conceptual approach. Simplifying these regulations will avoid confusion and help IRBs protect children who are research subjects. I would recommend deleting §§ 46.405, 46.406, and 46.407 and changing § 46.404 as follows:

§ 46.404 In order to approve research involving children covered by this policy, the IRB shall determine that all of the following requirements are satisfied:

- (a) the conditions of §§ 46.111(a)(1), 46.111(a)(2), and 46.111(a)(3) are satisfied;
- (b) answering the study's scientific hypothesis requires the inclusion of children as research subjects; and
- (c) risks associated with non-therapeutic procedures are no more than a minor increase over minimal risk.

A new section must be added to the DHHS regulations detailing protections for adults who are incapable of giving informed consent. The protections for incapable adults will, for the most part, be similar to those for children. I recommend the following:

that have been used by the National Commission are all reflected in the regulations. This incompatibility of ethical frameworks must be corrected if IRBs are to use the regulations to fulfill their mandate to adequately protect research subjects. What follows is a summary of the changes that I would recommend to the Common Rule and the DHHS regulations pertaining to risk analysis in order to achieve a single conceptual framework — namely, the “component analysis” approach. Specific recommendations for changes to Subparts B (pregnant women) and C (prisoners) of the DHHS regulations are not included.

To begin with, the concepts of therapeutic and non-therapeutic procedures ought to be specifically named and defined, as they are central to this approach to risk analysis. They should be defined as follows:

§ 46.102(k) *Therapeutic procedures* are study interventions administered with the intent of providing direct benefit to the research subject.

§ 46.102(l) *Non-therapeutic procedures* are study interventions that are not administered with therapeutic intent and are only intended to answer the scientific question of the study.

The general obligations of IRBs regarding the ethical analysis of the potential benefits and risks of research should be stated more clearly. I recommend the following:

§ 46.111(a) In order to approve research covered by this policy the IRB shall determine that both of the following requirements are satisfied:

- (1) Therapeutic procedures fulfill the requirements of clinical equipoise. That is, at the start of the study there must exist a state of genuine uncertainty in the community of expert practitioners as to the preferred treatment.
- (2) The risks associated with non-therapeutic procedures must be minimized (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. Risks of non-therapeutic procedures must be reasonable in relation to the knowledge to be gained.

The definition of “minimal risk” has been a source of considerable controversy and confusion. The definition ought to be simplified and clarified as follows:

§ 46.500 In order to approve research involving incapable adults covered by this policy, the IRB shall determine that all of the following requirements are satisfied:

- (a) the conditions of §§ 46.111(a)(1), 46.111(a)(2), and 46.111(a)(3) are satisfied;
- (b) answering the study's scientific hypothesis requires the inclusion of incapable adults as research subjects; and,
- (c) risks associated with non-therapeutic procedures are no more than a minor increase over minimal risk.

#### ACKNOWLEDGMENTS

This article is dedicated to my three teachers, Benjamin Freedman z"l, Abraham Fuks, and Robert J. Levine. I am grateful for the helpful comments on earlier drafts of this paper by Drs. Chris MacDonald, Eric Meslin, Paul Miller, and Marjorie Speers. This work was commissioned by the U.S. National Bioethics Advisory Commission and funded by a Canadian Institutes of Health Research New Investigator Award and Operating Grant as well as a Dalhousie University Clinical Research Scholar Award.

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