

be a rational, indeed moral, course of action for many: an expression of hope, and of struggle, and of concern for the improvement of care for others. I do not therefore believe these additions will fatally harm prospects for the conduct of Phase I trials; but time will tell.

The Research and Ethics Committee of JGH was spared at this time some of the most difficult issues associated with Phase I studies, notably, those implicated in the use of totally novel agents. The relevant Talmudic warning against unnecessary complications is, *Dai l'tzara b'sha'ata*—sufficient unto the day is the evil thereof. In the cohort-specific consent process, it has taken a first step that makes us more comfortable in joining the many other centers engaged in Phase I studies. We hope others will join us in refining this process.

ACKNOWLEDGMENTS

The discussions on which this paper is in part based occurred at the Research and Ethics Committee, Sir Mortimer B. Davis-Jewish General Hospital of Montreal. I am grateful to all of my colleagues on that committee, and in particular to our chair, James Robbins, PhD. R.J. Levine, MD, as always provided important suggestions and critique. A discussion with Gary Shapiro, MD, was my first occasion to confront the specific complexities of Phase I cancer trials. Dr. Shapiro afforded both clarity and an entree to some of the professional literature. The basic notion of requiring cohort-specific information is one he and I arrived at independently; his approach to the form in which this should be done may differ from mine. None of the above are responsible for any errors of fact or judgment in this manuscript.

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Protecting Human Subjects From Harm Through Improved Risk Judgments

by Eric M. Meslin

Public and scientific concern for the way biomedical research is designed and conducted is evidenced in the codes of ethics and international guidelines that emphasize the protection of the rights and welfare of research subjects.¹ Common to most current codes and guidelines is a requirement for institutional review of protocols. In 1987 delegates to the Fourth International Summit Conference on Bioethics, in Ottawa, Canada recommended that:

In order to safeguard the rights and well-being of patients and research subjects, research ethics committees should be established in all countries. All research projects involving human subjects must be submitted for approval to a research ethics committee.²

Standards for research ethics committees (RECs) have been developed throughout the world, although the present discussion concerns committees in North America. In the United States, for example, research ethics committees, known as Institutional Review Boards (IRBs), have been federally mandated since 1966. These committees are required to make judgments about the ethical appropriateness of proposed research by ensuring that, among other things, protocols explain how and to what extent the informed consent of research subjects will be obtained, and that the risks of harm are reasonable in relation to the hoped-for benefits.³ In Canada, the Medical Research Council first released guidelines in 1978, and recently published its *Guidelines on Research Involving Subjects*, which discuss issues of informed consent and risk-benefit analysis in detail.⁴

The issue of informed consent has preoccupied RECs while relatively little emphasis has been given to the task of comparing risks and benefits. That

imbalance is unfortunate, because unlike the requirements for informed consent, for which there is a sophisticated literature,⁵ and about which there is a comprehensive discussion in guidelines and regulations,⁶ RECs cannot appeal to such sources when preparing to make risk-benefit judgments. The U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was aware of this problem when it wrote in its 1978 *Belmont Report* that:

It 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. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible.⁷

In the decade since *Belmont*, little progress has been made toward the goal of "making precise judgments." Some commentators have suggested that the committee structure itself is to blame.^{8,9} These arguments focus on the REC's ability (or inability) to conduct the "risk-benefit analysis" as a whole. I believe that there are other reasons unique to the initial assessment of risk, separate from any analysis of risk in connection with benefit that account for this. The first reason (or problem) is conceptual, namely, that we still lack agreement on fundamental terms, such as harm and risk. Although this problem can probably be resolved quickly, a second, practical problem remains, namely, whether RECs can or should conduct risk assessment.

The Conceptual Problem: Agreement on Fundamental Terms

The principal reason RECs are encouraged to conduct a risk-benefit analysis is to ensure that subjects are protected from harm, or at least that the harms will be minimized. RECs may be reluctant to make risk judgments because some fundamental terms, such

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as harm and risk, are left undefined in codes and guidelines. While there is no evidence to suggest this has caused great confusion, clarity in the use of fundamental terms may eliminate the potential for confusion. This may prove difficult since there is ambiguity in the meaning of these terms.

Harm. Typically, we think of harm as physical damage such as a broken bone or a sprained ankle. This definition covers many of the adverse consequences of research about which RECs must be aware including everything from a bruise following a venipuncture to an adverse reaction to an investigational drug. Unfortunately, this definition does not work well for other types of harm subjects may suffer including psychological, social, and economic harms.¹⁰

Appeal to a legal conception of harm as "injury" might be attractive, especially as countries begin to discuss mechanisms for compensating subjects who are *injured* in research.¹¹ Unfortunately there is still confusion in the law regarding the relationship between harm and injury; sometimes injury is identified with harm and sometimes it is contrasted with it.¹² For example, injury can be defined as a harm or disability (such as physical damage), but it can also be defined as a *wrong* or injustice (from the latin *injuria*).¹³

Joel Feinberg has offered a useful definition of harm: someone is harmed when his or her interests have been thwarted, defeated, invaded, or set back.¹⁴ Tom Beauchamp and James Childress have recently employed this definition for discussions about bioethics.¹⁵ The real attraction of identifying "harm" with a setback to interests is that it accounts for a diversity of conditions for which harm as physical injury makes a poor analogy.¹⁶ RECs should give some thought to employing Feinberg's definition of harm in their deliberations. This brief analysis illustrates the difficulty in stipulating a definition of harm for medical research. Similar problems confront the concept of risk.

Risk. Risk is related to but not identical with harm. Robert Levine has explained the distinction by showing how risk and harm are not parallel constructions, as appears to be the case whenever we use the short-hand expression "risk-benefit analysis."¹⁷ Moreover, risk does not refer only to the chance or probability that a harm will occur but also to the severity or magnitude of the future harm. In this way risk is analytically related to harm. Risk refers to the probability and magnitude of a future unwanted harm. These two concepts are themselves worthy of further analysis. For example,

since probability is an expression of uncertainty, two broad categories have been described:

The first, and simpler [type of uncertainty], can be described and its problems dealt with, largely in what we call an *objective probability* framework....The second kind of uncertainty, broadly speaking, deals with potential hazards and exploring the unknown. There may still be a probabilistic element, but it is often subjective rather than objective.¹⁸

Similarly, the severity or magnitude of harm refers not only to the amount of damage, but its duration, the permanency of its consequences, as well as subjective considerations such as the extent to which it alters or affects lifestyle.¹⁹

Clearly there is much conceptual work to be done, and resolution of these conceptual problems may be achieved quickly (if we want them to be), especially as RECs begin to include philosophers and bioethicists who can provide such expertise. Therefore, let us assume that agreement on fundamental terms can be reached. The *practical* problem that remains is that RECs do not comfortably engage in risk judgment, limiting their ability to protect subjects from harm. I propose that risk judgments in medical research will be improved by creating a framework in which RECs engage in a limited form of risk assessment.

The Practical Problem: Risk Assessment by RECs

Risk assessment is a technique used to determine the nature, likelihood, and acceptability of the risks of harm,²⁰ issues that RECs are expected to consider in the conduct of protocol review. It is usually comprised of three elements: risk identification, risk estimation, and risk evaluation.²¹ Defined in this way, no doubt many RECs already engage in some form of risk assessment, even if this consists only of requiring investigators to disclose the risks of harm on consent forms.

It is worth remembering the technical merits of risk assessment discussed by the National Commission:

[Risk] assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about the proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are

justified. For subjects, the assessment will assist the determination of whether or not to participate.²²

In addition to the technical merits, there is a symbolic reason for encouraging RECs to conduct risk assessment. A commitment to quantify objectively the risks of harm in research demonstrates a level of ethical accountability that the Nuremberg and Helsinki codes and the *Belmont Report* had hoped would occur. As Bernard Barber wrote of risk assessment, "The process is in itself, 'consciousness-raising'; it leads to higher ethical awareness."²³

It is, however, a matter of both scientific and philosophic debate as to whether risk assessment should involve objective or subjective factors (or both). The "objectivist" school argues that quantitative risk assessment should be a value-free determination limited only by the technical ability to derive probability estimates.²⁴ The "subjectivist" school counters by arguing that the values of those who conduct the assessment, those who interpret the results, and those who bear the risks should play a central role in the overall assessment.²⁵ Neither school is entirely correct. Raanan Gillon graphically illustrates the limitations of an exclusive reliance on objective measurements of harm:

...the quantity of breast tissue to be lost in a mastectomy cannot provide an adequate measure of the harm to be anticipated from the loss of that breast or part of breast—the area of baldness to be expected from radiotherapy or chemotherapy cannot provide an adequate assessment of the harm such baldness may produce.²⁶

Both objective and subjective considerations ought to influence REC decisionmaking, the former because risk judgments should be empirically based insofar as possible, and the latter because there are some risks that cannot be quantified. We also know that the way information is framed when disclosed has an important bearing on the interpretation, perception, and acceptability of risk.²⁷ So much for the problem. How do we solve it?

Two considerations might help RECs to determine how they will use risk assessment: (1) the availability of empirical data and (2) the role of experts and nonexperts in this process. The first consideration is that the influence of empirical data on the assessment of risk is not often explicitly acknowledged. Empirical data are the principal currency of exchange in the scientific community and those who produce the best quality are the richer. It has been shown that the more relevant the

available data to decisionmakers, the more confident the probability estimate about the likelihood the risk will be realized as a harm.²⁸ However, the current paucity of data on research injury ensures that it will always be difficult to derive risk estimates.²⁹ Therefore efforts should be made to gather data systematically on the frequency of research harm.

A second consideration is whether "experts" alone should conduct risk assessments or whether nonexperts should also be involved. Currently, subject involvement is limited to deciding whether to participate in research on the basis of information disclosed through the consent process. But obviously, the REC has already made a judgment about risk. Since RECs and subjects possess different types of unique expertise, consideration should be given to involving both in the risk assessment process. We should expect RECs to fulfill their obligation to assess risk objectively, but recognize that due to the availability of data and their perception of risk as experts, there will be occasions when subjective bias will influence the quality of the assessment. We should also expect subjects (as nonexperts) to participate in risk assessment, possibly by soliciting their expressed preferences regarding the acceptability of risk. Thus, the present task is not to determine *whether* these considerations should be implemented for risk judgments, but *how*.

A Proposed Model for Risk Judgments

A four-cell matrix was developed that permits RECs and subjects to identify types of harm and estimate and evaluate their probability and magnitude.³⁰ The matrix was developed as a visual representation of the central conceptual issues involved in making risk judgments (See Figure 1). This is one attempt to develop a structure for decisionmaking that can be adopted by RECs. In brief, it requires that RECs attempt to make explicit those factors necessary for judgments about the probability and magnitude of harm, including the objective and subjective aspects discussed above.

In order to complete the first cell—the objective probability of harm—empirical data on the frequency of harms is required. There is a paucity of data on the numbers of subjects harmed in research. But as the U.S. President's Commission concluded several years ago, "The absence of data on injuries is not, needless to say, the same as data on the absence of injuries."³¹ One can hope that an REC would encourage its

institution to develop a mechanism for recording research harms.

Completion of the second cell—the subjective probability of harm—allows RECs to be explicit about the paucity of data on the frequency of harm from experimental procedures and to acknowledge this limitation. RECs and subjects can devise subjective probability estimates. Completion of these two cells would give RECs a better sense of the probability of harm to subjects. It would be a more comprehensive assessment owing to its inclusion of both objective and subjective considerations.

Completion of the third cell—the objective magnitude of harm—may be an especially difficult task. Indeed, one of the fundamental problems with applying risk assessment techniques in medical research review is not so much that there is little agreement on *what* the risks of harm are, but rather that their severity will be perceived differently by investigators, RECs, and subjects.³² To account for this difficulty, I propose that a scale of objective magnitude be created by institutions, in cooperation with investigators. The objective magnitude of harm could be ranked according to such factors as the harm's immediate duration, its latency period, the permanency of the consequences, and the extent to which the harm affects or alters lifestyle, considerations described elsewhere.³³

As with the determination of probability, a determination of magnitude would not be complete without acknowledgment of the subjective factors. Therefore, completion of the fourth cell—the subjective magnitude of harm—is accomplished using an ordinal scale, where harms are ranked according to whether they are worse than or better than other harms. This ensures that discrepancies in the perception of the severity of harm between REC members will not be overlooked.

As the scientific community moves toward an international ethic of medical research, a great premium will be placed on guidelines and procedures. Agreement on definitions and the use of terminology is just one problem to be solved. If RECs are unable to analyze meaningfully the risks of harm in research protocols it may be because they may lack the philosophical expertise to agree on definitions of fundamental terms. But it also may be because they lack a method for making risk judgments. I have argued that consideration should be given to expressing risk in a systematic way that accounts for the objective and subjective factors which attend such judgments, including the availability of data and the involvement of subjects.

RECs should, therefore, engage in a limited form of risk assessment, for which the four-cell matrix is only a

Figure 1

PROPOSED MATRIX FOR RISK JUDGMENTS IN MEDICAL RESEARCH

		General Considerations	
		Objective	Subjective
Expression of Risk	Probability of Harm	1	2
	Magnitude of Harm	3	4

Source: Eric M. Meslin, "Protecting Human Subjects from Harm in Medical Research: A Proposal for Improving Risk Judgments By Institutional Review Boards," (Ph.D. dissertation, Georgetown University, Washington, DC, 1989).

general guide. Completing the matrix like the one I have proposed encourages decisionmakers to make explicit the objective and subjective aspects of risk judgments and about the values that RECs bring to such judgments.

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CALENDAR

APRIL 5-6: The College of Physicians, The Hastings Center, and the Delaware Valley Ethics Committee Network will sponsor a national conference on **Keeping Ethics in Ethics Committees** to be held at Hershey Hotel, Philadelphia, PA. Registration deadline is March 1. For information contact Philip Boyle, Associate for Medical Ethics, The Hastings Center, 255 Elm Road, Briarcliff Manor, NY 10510; (914) 762-8500.

APRIL 19-21: The 1990 Spring National Meeting of the Society for Health and Human Values will be held in Hershey, PA, and devoted to the topic **The Dynamics of Scientific Change in Medicine**. The meeting will examine the processes of theoretical change in biomedical science, the development of new medical technologies, and the diffusion of clinical innovation into practice from the perspectives of the history, philosophy, and sociology of science and medicine, biomedical ethics, and health policy studies, religious studies, literature, cultural anthropology, and the human subjects research aspects of these processes. For a more detailed description of the conference, contact Eric T. Juengst, Ph.D., or Susan Lederer, Ph.D., Department of Humanities, The Pennsylvania State University College of Medicine, Hershey, PA 17033.

REQUEST FOR ASSISTANCE: The McGill Centre for Medicine, Ethics and Law (Montreal, Quebec, Canada) on Sunday, January 7, 1990 was the victim of a fire that destroyed its premises, Lady Meredith House, and virtually all of its contents, including files, manuscripts, speeches, texts in preparation and the personal libraries and archives of Centre staff. Any persons in possession of manuscript material coming from the McGill Centre are asked if they could arrange to have photocopies sent to the persons concerned. In order to rebuild our collection of professional materials, we also appeal to anyone with spare copies of important works on bioethics, medicine and law, and philosophy of law — in particular, those works no longer in print — to contact Gloria Morgan, Administrative Assistant, McGill Centre for Medicine, Ethics and Law, 1110 Pine Ave. W., Montreal, Quebec H3A 1A3, Canada. Telephone: (514) 398-7400; FAX: (514) 398-4668.