Balancing Access to Participation in Research and Protection from Risks: Applying the Principle of Justice

Sarah H. Kiskaddon

Institutional Review Board, Connecticut Children’s Medical Center, University of Connecticut, Hartford, CT 06106

ABSTRACT The problem for Institutional Review Boards (IRBs) of balancing access to participation in research with protection of research subjects has always been a difficult one. IRBs, charged with applying the “Common Rule,” as well as the Belmont Principles, in their review of clinical research, are given little guidance on approaching this problem. This article argues that the third Belmont Principle, the Justice Principle, may provide a useful framework for considering this balance. The changing research environment is discussed in an historical context, and the Justice Principle is considered both in the context of individual rights, as well as the potential benefit to classes of people. The author further suggests that application of the Justice Principle be driven by findings derived from an analysis of the first 2 principles. This feedback model will enable a more formal application of the Justice Principle and less ambiguous, more transparent, decisions regarding the equitable selection of subjects. The author calls for more systematic attention to the Justice Principle by IRBs, and proposes a model that includes incorporating the deliberation of the other Belmont Principles into the Justice Principle. J. Nutr. 135: 929–932, 2005.

KEY WORDS: • IRB • human subjects • Belmont Principles

There has always been a natural tension, for those charged with reviewing clinical research, between ensuring access to the benefits of research and protecting the subject from research risks. Researchers and Institutional Review Boards (IRBs) have not always struck the same balance. I would argue here that it would be helpful to both investigators and those who review their projects to have some ethical framework for analyzing this problem. I will discuss the continued relevance of the Belmont Principles, both as codified in the Common Rule (1) and as guiding philosophical principles for IRBs in the review process. The Belmont Principles, particularly the Justice Principle, will be discussed in the context of a changing research environment. I will also propose new ways of thinking about these principles, specifically encouraging IRBs to rigorously apply well-defined principles in an interactive, nonstatic model.

The problem

Current regulations, as well as the Belmont Report on which they are based, offer little practical guidance to IRBs in assessing the proper balance between protection on the one hand and access to potentially beneficial research on the other. This is understandable, given the difficulty of fully anticipating the variety of research situations that might arise. This indeed is why the requirements of review by a diverse and independent board is the cornerstone of human subject protection.

However, the consequence of this neglect, certain communities or classes of

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2 To whom correspondence should be addressed. E-mail: skiskad@ccmckids.org.
people have historically been left out of clinical research, denying them both the burdens and the benefits of clinical research. This eventually resulted in requirements by the NIH and FDA for their inclusion (2). Today, these requirements are often implemented with a rigid, strictly numerical approach, without regard to the underlying ethical principle involved.

The changing research environment

This balancing of access to, and protection from, research risks is taking place in the context of a rapidly changing research environment. Although the NIH and FDA have encouraged, and even regulated, the inclusion of all classes of people in clinical research, several trends in the research environment point to the need to reconsider this approach in favor of a more balanced approach. Trends such as high-profile injuries of research subjects, with the attendant lawsuits on their behalf; increases in funding from private industry, as opposed to public funding; and, finally, studies questioning the benefits of so-called therapeutic research, require a more considered approach when ensuring “access” to clinical research.

First, lawsuits on behalf of research subjects, against investigators, IRBs, and academic institutions are becoming increasingly common (3). Historically, personal injury lawsuits by research subjects were rare; however, both the frequency and the stakes of these lawsuits are on the rise, and the lawsuits are now beginning to implicate IRBs. In addition, and perhaps not unrelated, is the fact that this is occurring in the context of changes in the sponsorship of clinical research. Increasingly, research funding is from private sources, as opposed to the federal government. As a result, conflicts of interest have become the focus of much litigation, as well as a focus of much policy reform (4,5).

Finally, there has also been recent literature highlighting the nonbeneficial (to the individual participant) nature of most clinical research. Generally, HIV and oncology trials were considered to be exceptions to this rule; however, recent reports have suggested that even most cancer research provides little or no direct benefit to participants. A new report in the Lancet (6), by researchers at the Dana-Farber Cancer Institute in Boston, has found no evidence to support the belief that adults who enroll in clinical trials of investigational cancer treatments fare better than patients who do not.

The study analyzed two dozen published studies that compared outcomes among cancer patients and found that there was no evidence that clinical trial patients had better outcomes. (The exception was some studies in children and adults with blood cancers.) Cancer experts not connected with the Dana-Farber study found it convincing: “I’m, in general, accepting of the conclusion that there is no good evidence that being in a trial improves patients’ outcomes” [Harmon Eyre, Chief Medical Officer, American Cancer Society (7)]. Most oncologists expressed surprise at the finding reported in a recent issue of the Lancet (8). It appears that investigators themselves have been vulnerable to the “therapeutic misconception” that most clinical trials offer direct benefit (9).

Researchers and IRB members must have a good understanding of the benefits and the burdens of participation in clinical research before calling for increased access to participation from all segments of society. Under these circumstances, the goal of protecting “access” to research participation may only be justified when two criteria are met: 1) the class of people as a whole, will benefit from the knowledge resulting from the research; and 2) the individual participant understands and agrees to participate, knowing the improbability of direct benefit to themselves.

The Belmont Principles

The Belmont Principles of respect for persons, beneficence, and justice are well known to most researchers and IRB members. Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects (10).

However, whereas the first two principles have been codified into the regulatory structure, the Justice Principle has largely remained elusive to hard and fast rules. Yet, its value remains in its requirement that a difficult and necessary balance be found between access to beneficial research on the one hand and protection from undue burdens on the other.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness; thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only “undesirable” persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized, may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience or because they are easy to manipulate as a result of their illness or socioeconomic condition (8).

Thus, the Justice Principle, as described in the Belmont Report, requires that the selection of subjects be equitable. This analysis requires IRBs to not only consider the individual’s access to research participation but also to consider the impact on the class of individuals as a whole. For example, for many years “women of child-bearing potential” were excluded from enrollment in clinical trials, and as a result, many FDA-approved treatments were largely untested in this population. A similar situation developed in the pediatric population, where up to 80% of prescriptions for children are prescribed off-label (due to the lack of testing in children) (11).

The principle of justice (both social and individual justice) within the context of a particular research protocol requires an understanding of whether the research context provides direct benefit or not, as well as a finding, on the vulnerability of the research participants, a risk/benefit analysis, and even some context for understanding the long-term indirect benefits as well. Some of these inquiries are built into the regulations, for example, those that apply to children (12) require the establishment of a risk/benefit conclusion before moving to the next stage of approval. A model for applying the Justice Principle, in practice, would greatly aid in the analysis.

Historical perspective

With respect to the Justice Principle, much has been written about the historical shift in perspective from an environment of protection, particularly toward the urban poor, as well as other vulnerable groups, toward a focus on access by these same groups. The former approach was based on historical tragedies such as the Tuskegee Study and others that seemed...
to target vulnerable populations (2). However, the 1980s and 1990s saw a gradual "paradigm shift" toward a focus on access to clinical trials, which was based largely upon the perceived benefits of enrolling in HIV treatment trials and other potentially life-saving clinical research (2).

The pendulum may indeed have swung from protection of research subjects to ensuring access to research by all populations. This is reflected in the current NIH and FDA requirements for inclusion of minorities, women, and children as participants in clinical research. However, given the changes in the research context cited above, a more balanced and complete analysis of both the social and individual aspects of Justice Principle, may now be needed.

I argue here that the pendulum needs to swing back to the middle with respect to the Justice Principle, given what we now know about the lack of direct benefit for research subjects. It is also unclear what the indirect societal benefits will be, given the privatization of funding for clinical research.

**Applying the Belmont Principles**

Typically, IRBs have relied on the informed consent process as the primary mechanism for ensuring respect for persons, which in practice has tended to focus heavily on the wording of the consent form. This does not go far enough. In the words of bioethicist Rebecca Dresser, "You want people to understand that the primary aim is to produce knowledge to benefit people in the future" (7). More needs to be done to convey this purpose and thus to overcome the "therapeutic misconception" (held by both investigators and participants).

The role of the IRB, in interpreting and in implementing the research regulations is incomplete without an examination of each of the Belmont Principles with respect to each research project. Further, the analysis of these principles affect how we apply each of the other principles. The basic idea is that IRBs must begin to recognize that the Belmont Principles of respect for persons, beneficence, and justice, should be viewed, not independently, but informed by the outcome of the analysis of each principle.

While "balancing" protection and access may sound laudable, it is not necessary to view them as conflicting or to regard them as necessary "trade-offs." This old model only encourages arbitrary choices about which principle will be prioritized. More may be gained by integrating the ethical principles in a way that allows empirical conclusions to be drawn regarding the application of each of the 3 Belmont Principles to the research at hand. For example, "respect for persons" may be achieved through many different mechanisms, considering not only the informed consent process but also whether there is the prospect of direct individual benefit and whether the class of persons will eventually benefit from the research.

For example, whether there is direct benefit for the individual subject should influence the analysis of the Justice Principle. Justice may require attention to the barriers to individual access when there is direct benefit, but may also involve a discussion of collective justice (i.e., to classes of women, children, etc.) to ensure that the resulting information that is developed is not restricted in its application and that all segments of society may ultimately reap the benefit of clinical research. Likewise, the best mechanism for respecting the person may vary depending upon the conclusion reached regarding the application of the principles of beneficence and justice.

Because IRBs are necessarily the body with the responsibility for applying these ethical principles, the Justice Principle may be useful as the final step in a principled analysis of research protocols. A nonstatic model of analysis of each principle and informed feedback between the principles is likely to affect a more appropriate response.

**The Justice Principle and access to research**

IRBs may have a tendency to overlook that access to participation in clinical research is not only important when the participant receives direct benefit but also when the class as a whole may benefit from the results of the research. The principle of justice, as well as the principle of respect for persons, require promoting high-priority research for communities of people, regardless of the prospect of direct, individual benefit. Being "left out" of the progress toward the development of safe and effective treatments does not respect that class of persons, nor does it serve the principle of justice. In practice, this can be challenging for investigators and IRBs, particularly when the population is vulnerable.

As an example, one of the most difficult analysis may involve the inclusion of children or other participants with limited decision-making capacity. When research situations arise in which reliance on the individual subjects informed consent provides only limited value, the analysis of each of the principles requires adjustment based on the findings or outcome of the analysis of each Belmont Principle.

Many clinical studies did not test or develop age-appropriate formulations for use in children, perhaps as result of the additional protections provided by the regulations for the vulnerable populations. Consequently, Congress has provided funding and directives to NIH and other agencies to support research on a variety of child health problems.

This has resulted in increasing enrollment of children in clinical trials and to changes in a number of recommendations or warnings about the use (or nonuse) of specific medications by children. These changes emphasize the importance of pharmacokinetic studies in children (13). Thus, attempting to apply the Justice Principle to pediatric studies highlights the difficulty inherent in protecting the participants in research, while not depriving the class a whole of the benefits of the data on the treatments and conditions affecting children.

**CONCLUSION**

A coherent conceptual framework is needed that allows for and encourages, IRBs to review the Belmont Principles as interrelated and applicable to studies under review. A model that informs the review process and aids in a meaningful way to the application of the Code of Federal Regulations, would help IRBs strike a "principled" balance between access to the benefits and burdens of research, as well as to provide adequate protection for the participants of research.

It is important for IRBs to include an evaluation of the impact of studies with respect to generating new knowledge, especially for particular classes of people. The Justice Principle requires IRBs to be aware of the state of research findings in a particular area, as well as the potential long-term benefit of the knowledge for the population as a whole. Regulatory guidance definitions cannot provide this context. IRBs will, to some extent, rely on investigators to provide this information.

For example, in applying the first principle of respect for persons, the IRB may make the finding that the population under consideration in a particular research project is vulnerable (i.e., children, adults with dementia), further, that there is no direct benefit (Beneficence Principle), and therefore that
the Justice Principle is meaningful only in its social justice aspect. Thus, in the final analysis, the Justice Principle provides the opportunity for reviewers to balance societal goals and individual protections.

In conclusion, I would suggest that an informed feedback model that applies the Justice Principle as the final step in the review process may allow for a more formal analysis of each of the Belmont Principles, thereby encouraging IRBs to make decisions less on arbitrary factors and more on relevant ethical principles in each specific research context. It may also force IRBs to attend more specifically to the Justice Principle (particularly in a protocol that does not hold out the prospect of direct benefit). It will also remind us not to lose sight of the importance of the equitable selection of subjects and to the importance of furthering social justice.

The need to foster competent ethical review of research involving human subjects is recognized by researchers as well as by IRB members. Developing models and innovative approaches to ensure a more consistent and transparent process will go a long way toward ensuring that the needs and the interests of researchers, as well as their IRBs are met. It is hoped that this model may be further developed and may eventually assist with the ethical review, with the implementation of regulatory standards, as well as aid in identifying the challenges to the application of the Justice Principle in today’s research environment.

LITERATURE CITED