

1-1-1983

Institutional Review of Medical Research: Cost-Benefit Analysis, Risk-Benefit Analysis, and the Possible Effects of Research on Public Policy

Robert L. Schwartz
University of New Mexico - School of Law

Follow this and additional works at: https://digitalrepository.unm.edu/law_facultyscholarship



Part of the [Health Law and Policy Commons](#)

Recommended Citation

Robert L. Schwartz, *Institutional Review of Medical Research: Cost-Benefit Analysis, Risk-Benefit Analysis, and the Possible Effects of Research on Public Policy*, 4 *The Journal of Legal Medicine* 143 (1983).
Available at: https://digitalrepository.unm.edu/law_facultyscholarship/626

This Article is brought to you for free and open access by the UNM School of Law at UNM Digital Repository. It has been accepted for inclusion in Faculty Scholarship by an authorized administrator of UNM Digital Repository. For more information, please contact amywinter@unm.edu, lsoane@salud.unm.edu, sarahrk@unm.edu.

INSTITUTIONAL REVIEW OF MEDICAL RESEARCH

COST-BENEFIT ANALYSIS, RISK-BENEFIT ANALYSIS, AND "THE POSSIBLE EFFECTS OF RESEARCH ON PUBLIC POLICY"

Robert L. Schwartz, J.D.*

INTRODUCTION

Although the propriety of outside review of medical research involving human subjects has been recognized since the beginning of the nineteenth century,¹ there was no formal federal policy requiring such review until the Surgeon General imposed it upon those applying for Public Health Service research grants in 1966.² The 1966 policy, which required prior consideration of "the risks and potential medical benefits of the investigation" before a protocol even could be submitted to the Public Health Service for funding

* Professor of Law, University of New Mexico School of Law. Address reprint requests to Professor Schwartz at University of New Mexico School of Law, 1117 Stanford, N.E., Albuquerque, New Mexico, 87131. The author is greatly indebted to Jack Brant, an Albuquerque attorney, and Nancy Scanlan Neary, a law student at the University of New Mexico, for their invaluable assistance in the preparation of this article. The author is also indebted to Robert Levine for his vigorous efforts in obtaining a wide range of commentary on earlier drafts of this article.

¹ Robert Levine suggests that Thomas Percival's 1803 statement that "no [medical experimentation] should be instituted, without a previous consultation of the physicians or surgeons, according to the nature of the case" is generally thought to be "the first authoritative statement that, before proceeding with a therapeutic innovation, a physician ought to consult with peers." R. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH* 208 (1981).

² CURRAN, *GOVERNMENTAL REGULATION OF THE USE OF HUMAN SUBJECTS IN MEDICAL RESEARCH; THE APPROACH OF TWO FEDERAL AGENCIES, IN EXPERIMENTATION WITH HUMAN SUBJECTS* 402 (P. Freund ed. 1970).

consideration, constituted the first articulated administrative requirement that research be permitted only if some risk-benefit criteria were satisfied.³

The Surgeon General's policy was the seed of the most significant development of decentralized administrative decision making in the past twenty years. In 1974, Congress enacted the National Research Act⁴ which established the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission), and empowered the Commission to "conduct a comprehensive investigation and study to identify basic ethical principles"⁵ which should underlie the conduct of human subjects research. The commission was also empowered to develop guidelines and procedures to assure that research would be carried out in a manner consonant with such ethical principles⁶ and to recommend to the Secretary of the Department of Health, Education, and Welfare (DHEW) actions appropriate to apply the guidelines to human subjects research supported by the Department.⁷

The act required the establishment of Institutional Review Boards (IRBs) at many institutions under contract to DHEW. The IRBs thus established were required to review biomedical and behavioral research employing human subjects at their institutions "in order to protect the rights of the human subjects of such research."⁸ The language of the act and its mandate to the National Commission made clear that the primary goal of IRB activity was to be the protection of human subjects of research. Further, this protection was to be based on an articulated perception that government-sponsored research on human subjects should be conducted in an ethically sound fashion.

³ R. LEVINE, *supra* note 1, at 209. The policy statement specifies that no research involving human subjects shall be funded by the Public Health Service without provision for review by the grantee institution of "the judgment of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation. A description of the committee of the associates who will provide the review should be included in the application." CURRAN, *supra* note 2, at 436-37. This policy statement is illustrative of continuing federal concern regarding the functions of IRBs: informed consent; risk-benefit analysis; and, the types and categories of individuals who serve on IRBs. Of course, all of these factors relate to the overriding function of the IRB—protection of the rights and welfare of human subjects.

⁴ Pub. L. No. 93-348 (1974).

⁵ *Id.* at § 202(a)(1)(A) (i).

⁶ *Id.* at § 202(a)(1)(A) (ii), (iii).

⁷ *Id.* at § 202(2)(1)(A) (iv).

⁸ *Id.* at § 212(A).

By 1975, when DHEW promulgated as regulations its Policy for the Protection of Human Research Subjects,⁹ virtually every university, medical school, and research hospital had established an IRB which operated within the requirements of both the federal regulations and locally imposed rules.¹⁰ The regulations were substantially revised in 1981,¹¹ and this year federally mandated review of research involving human subjects will be undertaken by hundreds of IRBs, which will review thousands of research protocols.

In keeping with the purpose of the National Research Act that research will be conducted in accord with basic ethical principles which require the protection of human subjects of research, IRBs are enjoined to determine if "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."¹² This injunction was the subject of a specific recommendation of the National Commission¹³ and it has been included in both the

⁹ 45 C.F.R. pt. 46 (1975).

¹⁰ The schizophrenia that is a consequence of the IRB's status as both a federal administrative agency and a local board is discussed in R. LEVINE, *supra* note 1, at 226-40.

¹¹ See Department of Health and Human Services, Office of the Secretary, Final Regulations Amending Basic HHS Policy for the Protection of Human Research Subjects. 46 Fed. Reg. 366 (1981), now codified in 45 C.F.R. pt. 46 (1981).

The Department of Health and Human Services amended its policy for protection of human research subjects in response to a variety of sources of commentary and pressure. The 1981 amendments substantially reduced the scope of the existing HHS regulatory coverage by exempting broad categories of research which ordinarily present little or no risk of harm to subjects. Specifically, the regulations exempted from coverage research using only survey or interview procedures, observation of public behavior, or study of data, documents, records, and specimens. The regulations also set forth expedited review procedures for categories of proposed research involving only minimal risks to subjects or minor changes in research already approved by an IRB. Further, the regulations required full review procedures for categories of human subjects research not qualifying for exemption or expedited review. Finally, the regulations provided for informal consent procedures, established IRB membership requirements, and ensured, to the extent possible, congruence with revised FDA regulations on IRBs. The overriding purpose behind the regulatory revision appears to have been a narrowing of the scope of IRB consideration in those areas where protection of subjects of research is less necessary because subjects are less threatened. The revisions also reflect awareness of the need for broad-based IRB membership in order to provide sensitivity to characteristics of and risks to the total spectrum of possible subject populations, including those populations less able to give truly informed, uncoerced consent.

¹² 45 C.F.R. § 46.111(a)(2) (1981). The same provision is included in the Food and Drug Administration's regulations governing IRBs, 21 C.F.R. § 56.111(a)(2) (1981).

¹³ NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, DHEW PUB. NO. (OS) 78-0008, REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS (1978). As part of its mandate under Pub. L. No. 93-348, the National Commission issued this report as an evaluation of the performance of IRBs and their review mechanisms. The Commission also provided a series of recommendations designed to improve the ethical review process.

1975 and 1981 federal regulations governing research involving human subjects.¹⁴

Although the risk-benefit analysis expected of IRBs is similar to cost-benefit analysis employed by public policy makers, risk-benefit analysis is not merely cost-benefit analysis in a human subjects context. The 1981 revision specifies that IRBs may not consider "the possible effects of the research on public policy"¹⁵ in defining *risk* (but not benefit) for purposes of applying their risk-benefit calculus. In other words, it appears that IRBs must weigh potential benefits to the subjects and society against risks to the subjects alone, and not against any potential risks to society at large. In weighing risks to research subjects against benefits to both subjects and society, IRBs must, in effect, load the scale in favor of the benefits and, thus, in favor of permitting research. Therefore, the administratively mandated IRB analysis can amount to only an incomplete and misleading version of traditional cost-benefit analysis, which the President now requires of every federal agency in the development of every significant policy.¹⁶ Simply put, the revised regulations require IRBs to consider a substantially larger class of benefits than risks. Since the weighing of risks and benefits is the only

¹⁴ The previous regulations, promulgated March 13, 1975, and effective until July 27, 1981, provided that IRB review was to determine if "[t]he risks to the subjects are so outweighed by the sum of the benefits to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks." 45 C.F.R. § 46.2(b)(1) (now superseded) published at 40 Fed. Reg. 11,854 (1975).

¹⁵ 21 C.F.R. §56.111(a)(2) (1981); 45 C.F.R. § 46.111(a)(2) (1981).

¹⁶ Exec. Order No. 12,291, 46 Fed. Reg. 13,193 (1981):

[I]n order to reduce the burdens of existing and future regulations, increase agency accountability for regulatory actions, provide for presidential oversight of the regulatory process, minimize duplication and conflict of regulations, and insure well-reasoned regulations, it is hereby ordered as follows:

...
 Sec. 2. General Requirements. In promulgating new regulations, reviewing existing regulations, and developing legislative proposals concerning regulations, all agencies, to the extent permitted by law, shall adhere to the following requirements:

- (a) Administrative decisions shall be based on adequate information concerning the need for and consequences of proposed government action;
- (b) Regulatory action shall not be undertaken unless the potential benefits to society for the regulation outweigh the potential costs to society;
- (c) Regulatory objectives shall be chosen to maximize the net benefits to society;
- (d) Among alternative approaches to any given regulatory objective, the alternative involving the least net cost to society shall be chosen; and
- (e) Agencies shall set regulatory priorities with the aim of maximizing the aggregate net benefits to society, taking into account the condition of the

substantive discretionary authority allowed to IRBs,¹⁷ and because they are particularly suited for it,¹⁸ it is especially unfortunate that the regulations forbid them to do an adequate analysis.

Apart from regulations governing risk-benefit analysis of proposed research projects, most of the federal regulations governing IRB conduct are procedural. The regulations dictate with precision the formal aspects of the IRB's operation and the investigator's relation to the IRB¹⁹ and to the subjects employed in research;²⁰ they enumerate who must be represented on an IRB,²¹ exactly what kinds of research are subject to review by the IRB,²² what types of written documentation must be submitted by researchers,²³ and

particular industries affected by regulations, the condition of the national economy, and other regulatory actions contemplated for the future.
Section. 3. Regulatory Impact Analysis and Review.

(d) To permit each proposed major rule to be analyzed in light of the requirements stated in Section 2 of this Order, each preliminary and final Regulatory Impact Analysis shall contain the following information:

- (1) A description of the potential benefits of the rule, including any beneficial effects that cannot be quantified in monetary terms, and the identification of those likely to receive the benefits;
- (2) A description of the potential costs of the rule, including any adverse effects that cannot be quantified in monetary terms, and the identification of those likely to bear the costs;
- (3) A determination of the potential net benefits of the rule, including an evaluation of effects that cannot be quantified in monetary terms;
- (4) A description of alternative approaches that could substantially achieve the same regulatory goal at lower cost, together with an analysis of this potential benefit and costs and a brief explanation of the legal reasons why such alternatives, if proposed, could not be adopted....

The order also required that essentially every pending "major" rule not effective before February 17, 1981, be postponed until it is subjected to cost-benefit analysis. A "major" rule is one that has an annual effect on the economy of \$100 million, or meets other criteria. Because the Department of Health and Human Services determined that IRB review costs about \$200 for each protocol, it determined that the new HHS regulations do not constitute a "major" rule. The Office of Management and Budget did not object to this characterization.

¹⁷ See Part I in text.

¹⁸ See Parts IV and Conclusion in text. As decentralized community-based decision-makers, IRBs reflect the ethical priorities of the local institutions and communities that they represent. In the aggregate, they perform a pivotal, if unacknowledged, function in the formulation of public health care policy within the framework of federal regulations.

¹⁹ *E.g.*, 21 C.F.R. §§ 56.108, .109, .111 (1981); 45 C.F.R. §§ 46.103(b)(4), 46.108-.111 (1981).

²⁰ 45 C.F.R. §§ 46.116-.117 (1981).

²¹ 21 C.F.R. § 56.107 (1981); 45 C.F.R. § 46.107 (1981).

²² 21 C.F.R. §§ 56.102-.105 (1981); 45 C.F.R. §§ 46.102, .103 (1981).

²³ 21 C.F.R. §§ 56.109(b), .109(c), .111, .115, (1981); 45 C.F.R. §§ 46.108, .109, .111, .115-.117 (1981).

what "assurances" must be provided to the federal government regarding the continued fulfillment of IRB obligations.²⁴ The requirements that the IRB monitor the informed consent process²⁵ and act to protect the privacy of human subjects²⁶ do no more than codify existing common law and recognize the preexisting statutory requirements.²⁷ The IRB's duty to assure that "risks to subjects are minimized" requires determination of whether the scientifically equivalent result could arise from a different, less risky, research design. This is an essentially technical requirement which is of interest primarily to research statisticians. Although IRBs have recently been entrusted with the substantive authority to require that the selection of subjects be equitable,²⁸ this authority has not yet had any apparent effect upon IRB action. At most, it has resulted in the formal requirement that potential research subjects not be provided any undue inducement to volunteer—a confusing requirement not easily applied.²⁹

The only real discretion permitted the IRB, and the only basis for denying approval to a research protocol which meets all of the formal legal requirements, is the IRB's required evaluation of the risks and benefits of the protocol.³⁰ Although that evaluation has legal and medical parameters, it is

²⁴ 21 C.F.R. §§ 56.108, .115 (1981); 45 C.F.R. § 46.103 (1981).

²⁵ 21 C.F.R. §§ 56.109(b), .109(c), .111(a)(4) (1981); 45 C.F.R. §§ 46.109(b), .111(a)(4), .116(c), .116(d), .117 (1981).

²⁶ 21 C.F.R. § 56.111(a)(7) (1981); 45 C.F.R. § 46.111(a)(7) (1981).

²⁷ See, e.g., J. LUDLUM, INFORMED CONSENT 19-41 (1978); see also 44 Fed. Reg. 47,713-18 (1979), which contains a detailed discussion of the history of United States government treatment of informed consent in the context of research involving human subjects. This discussion was published as a preamble to the proposed F.D.A. regulations on informed consent which are now codified at 21 C.F.R. pt. 50 (1981).

²⁸ 21 C.F.R. § 56.111(a)(3) (1981); 45 C.F.R. § 46.111(a)(3) (1981). The requirement that the selection of subjects be equitable as a condition for IRB approval of a proposed research protocol did not exist in the previous regulations governing IRB actions. See also NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, DHEW PUB. NO. (OS) 78-0012, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH 18-19 (1978). The report states that the ethical principle of justice, one of the three general principles applied to the ethics of research upon human subjects, requires that there be fair procedures and outcomes at the individual and social levels of selection of research subjects. Justice requires fairness in the selection of individual subjects for participation in relatively risky or beneficial studies. Social justice requires equitable distribution of the risks and benefits of research among specific populations, some of whom require greater degrees of protection.

²⁹ For an excellent evaluation of this confusing requirement, and one that recognizes the difficulty of applying it, see R. Macklin, "Due" and "Undue" Inducements: On Paying Money to Research Subjects, I.R.B., May, 1981, at 1.

³⁰ 21 C.F.R. §56.111(a)(2) (1981); 45 C.F.R. §46.111(a)(2) (1981).

not one that is likely to be left to the institution's legal counsel or a subcommittee of physicians. While undeveloped designs or faulty consent forms may lead to postponement of a protocol's approval, those ultimately not approved are commonly the victims of the committee's risk-benefit analysis. The mere fact that ultimate disapproval is rare does not suggest that the risk-benefit analysis is taken lightly. There is good reason for the perception that the risk-benefit analysis ought to be the primary obligation of the IRB, and it is not surprising that many IRB members consider that to be their most important function.³¹

I. COST-BENEFIT ANALYSIS AND RISK-BENEFIT ANALYSIS

IRBs are required to evaluate risks to subjects in relation to anticipated benefits, if any, to subjects and "the importance of the knowledge that may reasonably be expected to result."³² In requiring IRBs to evaluate the importance of knowledge that may be gained by proposed research, as well as risks and benefits to subjects, the regulations clearly intend that IRBs act as something more than procedural watchdogs of human subjects research. IRBs have been established as policy making boards, not merely ministerial agencies which apply inflexible federally mandated criteria. The fact that the federal regulations do provide criteria,³³ and that the IRBs operate on a case-by-case basis, does not alter their policy making obligations.

The function of determining whether risks are "reasonable"³⁴ and whether the selection of subjects is "equitable,"³⁵ where neither of those terms is defined, is inconsistent with mere clerical responsibility. In addition, IRBs must be composed of persons having varied backgrounds³⁶ to ensure racial and cultural diversity and "sensitivity to such issues as community

³¹ The only statistical study done in this area revealed that 97% of the biomedical scientists on IRBs give heavy emphasis to their duty to balance the risks and benefits of research. No other duty of the IRB is given heavy emphasis by nearly that many biomedical scientists, who make up the majority of IRB members. That same study indicated that 87% of all others on IRBs gave heavy emphasis to the balance of risks and benefits. R. COOKE & A. TANNENBAUM, A SURVEY OF INSTITUTIONAL REVIEW BOARDS AND RESEARCH INVOLVING HUMAN SUBJECTS Table VI.18, 170 (Dept. of Commerce, Nat'l Technical Information Service PB-273 360, 1977). See also R. LEVINE, *supra* note 1, at 211 ("[M]ost of the I.R.B.'s time is devoted to considerations of risks and hoped-for benefits and to informed consent. . . .").

³² 21 C.F.R. §56.111 (1981); 45 C.F.R. §46.111 (1981).

³³ 21 C.F.R. §56.111 (1981); *E.g.*, 45 C.F.R. §§46.111, .116 (1981).

³⁴ 21 C.F.R. §56.111(a)(2) (1981); 45 C.F.R. §46.111(a)(2) (1981).

³⁵ 21 C.F.R. §46.111(a)(3) (1981); 45 C.F.R. §46.111(a)(3) (1981).

³⁶ 21 C.F.R. §56.107(a) (1981); 45 C.F.R. §46.107(a) (1981).

attitudes.”³⁷ This requirement demonstrates that IRBs were not intended to fulfill only narrow ministerial functions but that they were intended to reflect upon and create a community research policy. Thus, it is reasonable to expect IRBs to develop and apply policy as other public policy agencies do. In fact, the risk-benefit analysis now required of IRBs appears to be analogous to the cost-benefit analysis adopted by public policy analysts. But, as we shall see, the new risk-benefit criterion is far less comprehensive and valid than the traditional cost-benefit model.

A. Cost-Benefit Analysis

Although the decision to require cost-benefit analysis of *all* government policy making has cast new attention on the issue,³⁸ this method of policy evaluation has been discussed for many years, and it has become one of the most respected forms of rigorous policy analysis.³⁹ Cost-benefit analysis requires that a decision maker weigh both the costs and the benefits of any proposed policy and that the policy be instituted if, and only if, the benefits outweigh the costs.⁴⁰ The costs include each of the harms that might befall those concerned with the policy, weighted by the chance that the harm will come about. Similarly, the benefits include all of the good that might accrue to those concerned, weighted by the chance that it will, in fact, occur.⁴¹ In applying this calculus, any person who might suffer any harm or realize any good as a consequence of the adoption of the policy must be counted among “those concerned.”⁴² One proponent of the application of cost-benefit analysis puts it this way:

The basic notion is very simple. If we have to decide whether to do “A” or not, the rule is: do “A” if the benefits exceed those of the next best alternative course of action, and not otherwise. If we apply this rule to all possible choices, we shall generate the largest possible benefit, given the constraints within which we live. And no one could complain at that.

Going on a step, it seems quite natural to refer to the “benefits of the next best alternative to A” as the “costs of ‘A.’” For if “A” is done, those alternative benefits are lost. So the rule becomes: Do “A” if its benefits exceed its costs, and not otherwise

³⁷ *Id.*

³⁸ Exec. Order No. 12,291, *supra* note 16. The interest is not limited to the executive branch. *See also* Industrial Union Dept., AFL-CIO v. American Petroleum Inst., 448 U.S. 607, 667-71 (1980) (Powell, J.); *Donovan v. Castle & Cooke Foods*, 51 U.S.L.W. 2331 (9th Cir. Nov. 19, 1982).

³⁹ *See generally* L. ANDERSON & R. SETTLE, *BENEFIT-COST ANALYSIS: A PRACTICAL GUIDE* (1977).

⁴⁰ *See generally*, E.J. MISHAN, *COST-BENEFIT ANALYSIS* (1976).

⁴¹ *See* L. ANDERSON & R. SETTLE, *supra* note 39.

⁴² *Id.*

The only basic principle is that we should be willing to assign numerical values to costs and benefits, and arrive at decisions by adding them up and accepting those projects whose benefits exceed their costs.⁴³

There is hardly any kind of decision for which this analysis has not been recommended, from the most personal to those of international import.⁴⁴ Although it is most often applied to administrative decisions which must be made by agencies of the state, it has also been proffered as a model to be employed by physicians in a wide range of medical decision making⁴⁵ and it has been used to evaluate general public health policies.⁴⁶ Although the "cost" term suggests an economic analysis, the cost-benefit model is routinely applied outside of the economic sphere.⁴⁷

There are, of course, problems in applying this form of analysis, and some of these problems are particularly severe when the model is applied to medical decision making. The device assumes a utilitarian foundation⁴⁸ and does not permit the recognition of any absolute values.⁴⁹ It requires the

⁴³ R. LAYARD, *COST-BENEFIT ANALYSIS* 9-10 (1972).

⁴⁴ See, e.g., *BENEFIT-COST ANALYSIS OF SOCIAL REGULATION* (J. Miller III & B. Yandle eds. 1979) (case studies by economists for the Council on Wage and Price Stability, illustrating the usefulness of economic analysis in appraising the performance of federal regulatory agencies). Calabresi, *The Decision for Accidents: An Approach to Non-Fault Allocation of Costs*, 78 HARV. L. REV. 713 (1965) (discusses society's decision to bear the risk of accidents as based on an evaluation that some activities are sufficiently valuable to society to justify their inherent risks; suggests requiring greater benefit from activities posing a greater risk). See also R.H. Crandall, *Cost-Benefit Analysis in a University Setting: The Housing of Students* (1968) (Ph.D. Thesis, University of California); R.F.J. DEWHURST, *BUSINESS COST-BENEFIT ANALYSIS* (1972); UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION, U.N. PUB. SALES NO. E. 78.II.B. 3, *GUIDE TO PRACTICAL PROJECT APPRAISAL: SOCIAL BENEFIT-COST ANALYSIS IN DEVELOPING COUNTRIES* (1978).

⁴⁵ Pauker & Kassirer, *Therapeutic Decision Making: A Cost-Benefit Analysis*, 293 NEW ENG. J. MED. 229 (1975); see also Rosenshein, Farewell, Price, Larson & Dale, *The Cost Effectiveness of Therapeutic and Prophylactic Leukocyte Transfusion*, 302 NEW ENG. J. MED. 1058 (1980).

⁴⁶ *Cost-Benefit Analysis of Newborn Screening for Metabolic Disorders*, 291 NEW ENG. J. MED. 1414 (1974).

⁴⁷ See text accompanying notes 43-46.

⁴⁸ There must be some standard measuring unit through which all costs and benefits can be measured in order for them to be compared. For John Stuart Mill, of course, that unit was pleasure. J.S. MILL, *UTILITARIANISM* (1863). Cost-benefit analysis assumes that the greater the amount by which the benefits of an alternative exceed its costs, measured in some uniform terms, the better the alternative. That is the heart of any utilitarian scheme. Needless to say, most of those who subscribe to cost-benefit analysis do not compute a formally articulated and precisely quantified number of utility points for each cost and benefit of an alternative. This system may provide a very useful analytical framework even if it does not provide one with the mathematical precision to which it aspires. As Mill explained, "[t]hough the application of the standard may be difficult, it is better than none at all." *Id.* at 33.

⁴⁹ Since every alternative is measured in terms of some standard unit, every value is finite (and necessarily not absolute). When interests are recognized as fundamental or highly significant, though, they will possess values that cannot be overcome as a practical matter.

valuation of that which some believe cannot be valued, requires the measurement of that which some believe cannot be measured, and mandates the comparison of those quantities and qualities that some believe cannot be compared.⁵⁰ How, for example, can life or health be valued? What does it mean to weigh the pain and suffering that is associated with chemotherapy with the hope that life can be extended? Of course, society does place a value on life and health when it is necessary to do so,⁵¹ and while the application of cost-benefit analysis sometimes appears to require comparing apples and oranges, many people feel comfortable making just that comparison when they reach into the fruit basket. Thus, despite significant problems of cost-benefit analysis, it is not surprising that its compelling simplicity and wide acceptance has given rise to the formal requirement that something like it—risk-benefit analysis—be a part of the formal duty of an IRB evaluating a research protocol.

B. Risk-Benefit Analysis

Like cost-benefit analysis, risk-benefit analysis requires consideration of concepts that are not parallel. Risk suggests prediction that a potential injury will occur, often expressed in terms of probability of occurrence. Benefit, on the other hand, connotes actuality rather than probability.⁵² Unlike cost-benefit analysis, however, risk-benefit analysis performed by IRBs must determine both the balance of risks and benefits and the extent to which risks are minimized by the proposed research protocol. Thus, risk-benefit analysis is more complex than cost-benefit analysis required of other federal policy making bodies.

Furthermore, commentators on the federal regulations suggest that IRBs should evaluate a taxonomy of risks and benefits beyond those of a physical dimension. Risks are classified and should be evaluated as physical,

⁵⁰ For example, it may require that an IRB compare the substantial side effects likely to be felt by several terminally-ill patients in a Phase I drug study with the slight chance that many future sufferers with the same disease will be cured. It would be ludicrous to assume that any IRB could employ a ledger sheet divided into two columns and simply add up the risks and benefits of the research—but, inevitably, those risks and benefits must be (and *are*) considered and weighed.

⁵¹ Juries are called upon to do this whenever they decide for the plaintiff in wrongful death actions. See G. MOONEY, *THE VALUATION OF HUMAN LIFE* (1977). Mooney reviews several ways in which the market (or a government agency) has placed a monetary value on human life. He also reviews particular cases in which prevailing British public policy necessarily, if implicitly, assumed a human life to have a value ranging from less than £50 (decision on screening of material oestriol excretion in pregnant women to prevent still births) to more than £20,000,000 (change in building regulations).

⁵² R. LEVINE, *supra* note 1, at 23.

psychological, social, and economic.⁵³ Obviously, this taxonomy of risks could be applied to both the individual subject and to society, and originally it was intended to be applied to both.⁵⁴ Benefits are classified as physical, psychosocial, and derivative (or kinship), and are likewise considered relative to both the immediate subject and society as a whole.⁵⁵ IRBs consider probability and magnitude of risks and benefits as part of their analysis.⁵⁶ They must likewise determine that benefits of the proposed research are maximized and risks are justified by the probability of direct benefit to the individual subject.⁵⁷

However, there are some costs and some benefits that good policy analysts would surely consider relevant but which the new regulations forbid the IRB to consider. The regulations provide:

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.⁵⁸

Thus, in evaluating risks and benefits of research, an IRB may not consider the probability of injury or benefit to subjects of a proposed research protocol relative to their probability from hypothetical but unsubmitted research. The wide range of choices available to policy makers is not before the IRB. The IRB cannot decide which experiment, of the universe of possibilities, ought to be conducted. The IRB cannot compare the research protocol with "the next best alternative course of action," but, rather, must compare it with the absence of the proposed research. The IRB has no authority to deny approval to a drug study because it believes the resources would be better spent on basic research, and it cannot turn down a proposal for muscular dystrophy research because heart disease poses a more threatening and wide-ranging problem. This deviation from a pure cost-

⁵³ Levine, *The Role of Assessment of Risk Benefit Criteria in the Determination of the Appropriateness of Research Involving Human Subjects*, in 1 APPENDIX TO THE BELMONT REPORT, DHEW PUB. No. (OS) 78-0013, 2-1—2-59 (1978).

⁵⁴ *Id.*

⁵⁵ *Id.* at 2-6—2-30.

⁵⁶ *Id.* at 2-50—2-54.

⁵⁷ *Id.*

⁵⁸ 45 C.F.R. §46.111(a) (1981).

benefit analysis is predicated, quite reasonably, upon the nature of the IRB's task: the review of only such proposals as are submitted to it. To the extent that comparison of risks and benefits of proposed research with those of alternative protocols is impossible, the IRB is precluded from performing a comprehensive risk-benefit analysis.

Furthermore, the IRB is empowered to consider only the risks and benefits to the subject, not those that might affect their relatives, the medical center, the careers of the investigating physicians, the drug companies, or other patients or potential patients, except to the extent that they may benefit from the "knowledge that may reasonably be expected to result."⁵⁹ In other words, the definition of "those concerned" is considerably narrower than the definition that would be applied by traditional cost-benefit analysts.⁶⁰

Finally, there is no realistic hope that an IRB will be able to assign numerical values to all of the risks and the benefits of a research protocol, or to the importance of the knowledge that may reasonably be expected to result from the research, and then calculate the risk-benefit ratio with precision. The National Commission, which recommended that IRBs use the risk-benefit analysis, recognized the "metaphorical character"⁶¹ of the requirement, and admitted that "only on rare occasions will quantitative techniques be available for the scrutiny of research protocols."⁶² The real function of the risk-benefit criterion is to require strict ethical scrutiny of proposed protocols. The careful, rational, and analytic evaluation of those factors considered in the risk-benefit analysis is grounded in the ethical principle of beneficence, the obligation to research subjects first, to do no harm and second, to maximize possible benefits and minimize possible harms.⁶³ Thus, risk-benefit analysis should require the articulation of all of the risks and benefits associated with research, thereby causing the evaluation to be more comprehensive. Of course, the fact that the analysis cannot be an exact one with a numerically certain conclusion does not mean that the evaluation cannot be a rigorous one. As the National Commission pointed out, "the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated in so far as possible."⁶⁴

Risk-benefit analysis, then, differs from cost-benefit analysis for the following reasons: it does not compare proposed research with hypothetical

⁵⁹ 21 C.F.R. §56.111 (1981); 45 C.F.R. §46.111 (1981).

⁶⁰ See L. ANDERSON & R. SETTLE, *supra* note 39.

⁶¹ THE BELMONT REPORT, *supra* note 28, at 16.

⁶² *Id.*

⁶³ See R. LEVINE, *supra* note 1, at 10.

⁶⁴ THE BELMONT REPORT, *supra* note 28, at 16.

alternative protocols to properly analyze the costs of not doing the proposed research; it narrowly defines the parties to be affected by the proposed research; and it weighs factors in an essentially non-quantifiable equation. Some of the ways in which risk-benefit analysis varies from cost-benefit analysis, however, are less significant than they first appear. After all, no policy maker can choose among all possible formal policies; and the development of almost any public policy requires the analysis of costs and benefits that are difficult to measure. In the end, the risks and benefits that fall upon the research subject, along with the knowledge obtained from the experiment, might seem to include almost all of the costs and benefits likely to accrue to anyone concerned.

The regulation specifically admonishes IRBs *not* to consider two kinds of risks and benefits that otherwise might go into the calculus. The first exception, that IRBs may not evaluate the "risks and benefits of therapies subjects would receive even if not participating in the research,"⁶⁵ does not weaken the risk-benefit analysis. The risks and benefits thus excluded are *not* risks and benefits of the *research* which the IRB is to review. The regulatory admonition to consider only the consequences of the research, not the therapeutic adjunct of the research, simply defines the proposed conduct which is the subject of the risk-benefit analysis. This exception to risk-benefit analysis is not truly an exception at all; if a subject is to undergo a particular risk or acquire a particular benefit regardless of whether the proposed research is performed, then that risk or benefit is obviously irrelevant to the propriety of the research.

II. RISK-BENEFIT ANALYSIS AND THE PUBLIC POLICY EXCEPTION

The second specific exception to the risks and benefits an IRB may consider is far more significant. The IRB may not consider "possible long-range effects of applying knowledge gained in 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."⁶⁶ But the knowledge that may reasonably be expected to result from the experiment derives its importance entirely from the potential long-range effects of applying that knowledge. Why are IRBs not permitted to consider the "long-range effects" of applying that knowledge as among the weighted risks? How are these

⁶⁵ 21 C.F.R. §56.111(a)(2) (1981); 45 C.F.R. §46.111(a)(2) (1981).

⁶⁶ *Id.*

long-range effects to be distinguished from short-range effects, which must be considered? If the IRBs are not to consider the long-range effects, then is some other agency required to do so, or are those effects irrelevant?

In promulgating the “long-range effects” exception to the risk-benefit analysis regulation, the Department of Health and Human Services could not have intended to prohibit IRBs from considering the medical advances that are the primary purpose of entirely justifiable research. Medical advancement is often the only reason for doing research, and we cannot always expect short-term solutions to medical problems that have plagued humanity for centuries; often the long-range conquest of disease is all that can be contemplated. The eventual development of medical knowledge may be the primary justification for imposing the risks of a particular study on its human subjects. Protection of these subjects requires that their risks be justified. If no immediate physical benefits to subjects are probable, then the long-term medical benefits to society that are anticipated from knowledge to be gained in research must be sufficiently predictable and significant to justify the risks imposed upon subjects.

It may be for this reason that the “long-range effects” exception applies only to consideration of the *risks* of the research; the long-range effect of biomedical knowledge upon public policy was probably assumed to be among the *benefits* of the research. Given this assumption, direct medical benefits to afflicted individuals, advances in scientific knowledge, and potential effects of this knowledge on public policy may all be considered as benefits of a research protocol. But could the regulations really require that a “long-range effect” on the social fabric be considered by the IRB if it were viewed as a “benefit,” yet *not* be considered if it were viewed as a “risk”? Under such an irrational scheme different members of the same IRB considering the same protocol would have to consider different factors in applying the same risk-benefit criterion. For example, consider the hypothetical review by an IRB of a proposed study to evaluate the viability of second trimester fetuses. Whether one potential social consequence—the availability of effective late abortions—could even be considered by an IRB member would depend on whether that member characterized the social consequence as a “risk” or a “benefit.” The regulations could not have anticipated this absurd interpretation; rather, it must have been intended that only direct medical consequences of research would be considered by the IRB. Thus, the “long-range effects” exception must apply to *non-medical* consequences of the research. The primary purpose of the exception must be to limit consideration of “the possible effects of the research on public policy,” the example given in the very terms of the exception.

The intent of the exception may be gleaned from evaluating the National Commission's first proposal.⁶⁷ Their original recommendation included none of the caveats which eventually appeared in the final draft of the regulations;⁶⁸ recommendation 4(D) of the National Commission required only that IRBs determine that "risks to subjects are reasonable in relation to anticipated benefits to subjects and the importance of the knowledge to be gained."⁶⁹ However, the National Commission's *commentary*, which was published along with the recommendations, made it clear that "the possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy affecting a segment of the population) should not be considered as among those research risks falling within the purview of the IRB."⁷⁰ When the Department of Health and Human Services subsequently drafted the formal regulations, it included this part of the commentary, with the significant exception of the term "affecting a segment of the population," in the effective text.⁷¹ What had been offered merely to explain the rule became part of the rule itself.

While the reasoning behind the National Commission's recommendation remained unclear to many commentators,⁷² the contemporary controversy over research involving race and IQ,⁷³ and the commission's example of "public policy affecting a segment of the population" may indicate only that the National Commission intended to exclude hotly-debated political issues from the consideration of the IRB. The National Commission, in its quest to develop the IRB as a stable institution, may have recognized that highly politicized and possibly partisan IRBs would not be well respected at medical centers, and would be unlikely to develop into strong institutions. Thus, the IRBs were to be permitted, at most, to "advise institutional authorities" of long-range effects which may implicate "the desirability of

⁶⁷ IRB REPORT, *supra* note 13, at 19-20.

⁶⁸ 21 C.F.R. §56.111 (1981); 45 C.F.R. §46.111 (1981).

⁶⁹ IRB REPORT, *supra* note 13.

⁷⁰ *Id.* at 24.

⁷¹ Compare 45 C.F.R. §46.111(a)(2) (1981) with IRB REPORT, *supra* note 13, at 24.

⁷² Robert Veatch announced that, "I frankly cannot understand what they are attempting to exclude." Veatch, *The National Commission on I.R.B.s: An Evolutionary Approach*, 11 HASTINGS CENTER REP. 26 (1981).

⁷³ See, e.g., N.Y. Times, Mar. 9, 1975, at 32, col. 1; Apr. 18, 1975, at 66, col. 7; Nov. 28, 1976, at 26, col. 4. The controversy focused on contemporary versions of the theories of British psychologist Dr. Cyril Burt, whose research supported belief in the hereditary nature of intelligence. Burt's theories were adopted by Dr. William B. Shockley, a physicist and engineering professor who espoused the belief that the disadvantaged position of blacks in society is largely due to racially inherited inferior intelligence.

approving the research at that institution.”⁷⁴ The decision to omit “affecting a segment of the population” from the final regulation may simply constitute a broader statement of the public policy exception. This omission may also indicate a reluctance on the part of the Department even to make reference to the particularly sensitive IQ debate.

In fact, the original DHEW regulations, promulgated in 1975, also would seem to have forbidden IRB consideration of the public policy consequences of proposed research protocols.⁷⁵ Those regulations only permitted consideration of the risks to the subject, the benefit to the subject, and the “importance of the knowledge to be gained.”⁷⁶ Apparently, some IRBs interpreted “risks to the subject” to include the risk of living in a society which might adopt an unfortunate social policy as a consequence of the research. Stretching this criterion beyond its obvious intent permitted those IRBs to engage in proper and comprehensive cost-benefit analysis. The new regulations provide explicitly that such an evaluation would be improper.

This regulatory model of risk-benefit analysis, which excludes *as risks* (but not benefits) the potential effects of research on public policy may improperly and irrationally weight the balance in favor of benefits, thereby resulting in less protection for research subjects. Furthermore, requiring IRBs to perform risk-benefit evaluations in such a narrow sense severely limits the power of the IRB to protect society, which is generally affected by the conduct of biomedical research. The real risks to society imposed by the IRB’s inability to consider long-range effects of research on public policy may be illustrated by reviewing three contemporary issues in biomedical research.

III. SOME PROBLEMS CREATED BY THE PUBLIC POLICY EXCEPTION

A. Drugs and the Elderly

If the regulations really do remove public policy considerations from IRB analysis, then they ignore extremely important factors which will not be evaluated at any other stage of the approval process. For example, there is

⁷⁴ IRB REPORT, *supra* note 13, at 24.

⁷⁵ See 45 C.F.R. §46.2 (1975), published at 40 Fed. Reg. 11,854 (1975). “The risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks.”

⁷⁶ *Id.*

much doubt about the propriety of developing drugs to treat common cognitive and emotional problems of the elderly.⁷⁷ The market for such drugs is a rapidly developing one, and it is financially well supported by a fairly secure medicare program. In addition, the failure to develop nonpharmacological therapy to deal with senile dementia has excited interest in otherwise relatively unpromising drugs that treat the unhappy, unstable, agitated, unkind, or irrational elderly.⁷⁸ Some physicians believe that the formal FDA approval of such drugs may lead to overmedication of the elderly; the elderly could be drugged into submission for the benefit of nursing home staff or other beleaguered caretakers.⁷⁹ Despite this unexplored negative potential, a technical evaluation of the formal risks of any proposed drug upon a research subject, leavened by an analysis of the importance of the knowledge that is likely to come from the research, may render a favorable risk-benefit ratio. Such research may impose almost no risk on any particular subject, and thus the "risk-benefit" ratio will be acceptable even if little benefit is anticipated.

If IRBs must naively approve such research projects, which meet all of the requirements of the federal regulations, then our policy of health care for the elderly may be significantly altered. This would occur without any formal and rational analysis of the propriety of developing such medication except for the economic analysis done by proposing drug companies. Of course, it may be that, after full consideration of all of the social policy consequences, IRBs would still approve such research. The problem with the current regulations is that they forbid IRBs from making a proper analysis. They prohibit just that which the National Commission thought the risk-benefit ratio would initiate—the systematic and comprehensive analysis of all of the risks and benefits of engaging in formal research. If IRBs were permitted to consider, as a risk, the potential misuse of any successful development of drug therapy for the cognitively and emotionally impaired elderly, then the risks and benefits of the proposed studies of those therapies could be weighed more carefully and thoughtfully, and the balance might be

⁷⁷ Schwartz, *Research and the Elderly Subject: Some Ethical Legal Considerations*, 17 *PSYCHOPHARMACOLOGY BULL.* 64 (1981) (discussing the tension between beneficial effects of research on pharmacological treatments of senile dementia and the interest in protecting the elderly subjects of such research in view of the effects of the disease itself, nursing home residency, and advanced age on the consent process). See also Lawton, *Do Elderly Research Subjects Need Special Protection? Psychological Vulnerability*, *I.R.B.*, Oct. 1980, at 5.

⁷⁸ Ratzan, *Being Old Makes You Different: The Ethics of Research with Elderly Subjects*, 10 *HASTINGS CENTER REP.* 32 (1980).

⁷⁹ *Id.*

one that was more sensitive to the actual subjects of the research, as well as to elderly members of society at large.

B. Sleeping Pill Development

The process of review of research protocols that allow drug companies to enter or control small corners of the sleeping pill market provides another example of the importance of having IRBs consider long-range and policy effects of proposed research. There are many who believe that the availability of a wide variety of sleeping pills has done more harm than good.⁸⁰ The general availability of those medications, the ease with which they are prescribed, and the almost universal insurance reimbursement for their prescription has altered our national health care policy, which now favors the study and use of sleeping pills over nonpharmacological methods of treating insomnia.⁸¹

The regulations, as they are written, do not allow comprehensive evaluation of studies proposed by companies with new sleep medications. IRBs are not permitted to consider how many patients will be treated with drugs rather than with some alternative therapy if a new drug is finally approved by the FDA. They may not consider how many people will be injured in highway accidents by those who have taken the newly-approved drug.⁸² Neither the insomniac patients nor the innocent drivers can be considered in IRB risk-benefit analysis, although in a typical policy cost-benefit analysis they would be considered "parties affected" by a policy in favor of wide sleeping pill availability. The clinical studies proposed to test drugs do not (and usually cannot) measure the number of industrial accidents that might be caused by those who medicate themselves, nor the number who will be injured by imbibing alcohol, against their physician's orders, while under the influence of the sleeping pill.⁸³ In 1979, when the Institute of Medicine of the National Academy of Sciences published its report on the development of sleeping pills, it revealed that:

Approximately 150 studies of hypnotic drug efficacy were reviewed in the course of preparing this report; all but a handful were sponsored by pharmaceutical companies. The results of most of these are extremely difficult to

⁸⁰ INSTITUTE OF MEDICINE, NATIONAL ACADEMY OF SCIENCES, REPORT OF A STUDY: SLEEPING PILLS, INSOMNIA, AND MEDICAL PRACTICE (1979).

⁸¹ *Id.*

⁸² 45 C.F.R. §46.111(a)(2) (1981) limits IRB review to risks to "subjects" in relation to benefits to "subjects." 45 C.F.R. §46.102(a) defines a "subject" for purposes of the regulations as one with whom the investigator deals directly, by intervention or interaction.

⁸³ N.A.S. STUDY, *supra* note 80.

interpret. There has been a failure to set high standards of interpretability, replicability, and general validity in the published studies. In the design of the original experiments as well as in the report of the outcomes, the manufacturer has a strong influence on which aspects are to be emphasized. . . . It is noteworthy that nearly all the investigations of residual adverse effects of hypnotics on daytime psychomotor performance tests have taken place overseas where support was provided by the respective foreign governments.⁸⁴

The National Academy of Sciences study included a formal appendix on "Assessing Hazards and Benefits of Hypnotic Drugs." It suggested many important considerations which IRBs are forbidden to include in their risk-benefit determinations.⁸⁵ If IRBs were permitted to consider all of the policy consequences of approval and general availability of a type of therapy, then study design and health care policy would surely be influenced. As it now stands, health care policy is determined largely by those who stand to profit financially by the outcome, not by those institutions that are impressed into the drug companies' service.

C. Testing Unorthodox Cures

Another consequence of excluding "possible effects of research on public policy" from IRB consideration is that it divests IRBs of authority to approve research which might show the inefficacy or danger of politically popular but unproven therapies.⁸⁶ Perhaps the best example is the public policy controversy surrounding laetrile. The medical establishment's refusal to research this unpromising drug contributed to such interest in laetrile that thousands were driven to it, and nearly half of the states passed legislation aimed at making it available.⁸⁷ Many physicians simply could not believe that there could be public policy consequences of the failure to do research. Debate over the ethical propriety of formally studying laetrile in human subjects even though it showed no promise in animal studies pervaded the

⁸⁴ *Id.* at 151.

⁸⁵ *Id.* at 155-98.

⁸⁶ Of course, there is always a risk in not doing research. See Macklin, *On the Ethics of Not Doing Scientific Research*, 7 HASTINGS CENTER REP. 11 (1977). In the stereotypical case the risk of not doing research is that a potentially effective therapy will not be discovered. Sometimes, however, the risk is that a naively accepted and available treatment will not be proved ineffective.

⁸⁷ Indeed, one of the primary arguments advanced by laetrile supporters was that the drug was never proven ineffective. The pro-laetrile lobby hinted that the medical establishment was afraid of giving laetrile a fair clinical trial. See, e.g., Statement of the Honorable Lawrence P. McDonald, A Representative from Georgia, to the Food and Drug Administration In Relation to Laetrile, Docket No. 77N-00481 (1977). See also Schwartz, *Laetrile: The Battle Moves into the Courtroom*, 65 A.B.A. J. 224 (1979).

literature,⁸⁸ and it was only when the popularity of laetrile became unquestioned that the National Cancer Institute began such a study. How any IRB could approve that study remains unclear, however. The anticipated benefits for the subjects were nonexistent. Furthermore, there was no hope of developing any knowledge except that which could be employed to alter the public policy of state legislatures that approved laetrile use. In fact, opponents of laetrile argued that there was substantial risk to any subject ingesting laetrile.⁸⁹ At least four IRBs did approve the study,⁹⁰ however, and it seems to have served its public policy purpose.⁹¹

Research has not been permitted in other areas of alleged quackery despite political interest in developing unorthodox therapies. Surely IRBs ought to consider the legal availability of acupuncture, for example, in determining whether acupuncture research is appropriate.⁹² Similarly, an IRB considering proposed research on the therapeutic efficacy of sexual relations between patient and therapist ought to be able to consider the current prevalence of this practice as a policy issue that will undoubtedly be affected by the outcome of the research.⁹³ The fact that the conduct of the research, and proof of the inefficacy of the therapy, may save hundreds of patients from demeaning and harmful treatment is worthy of consideration by an IRB. Otherwise, an IRB may have to determine that the risks to the subject (which might be substantial) outweigh the potential benefits (which might be insignificant), and thus disapprove a study all agree is important. The only impact of the knowledge to be gained in such cases arises out of the

⁸⁸ See, e.g., Lipsett & Fletcher, *Ethics of Laetrile Clinical Trials*, 297 NEW ENG. J. MED. 1183 (1977).

⁸⁹ N.Y. Times, Feb. 24, 1981, §III, at 2, col. 1.

⁹⁰ The NCI clinical trial was conducted at The Mayo Clinic, Memorial-Sloan Kettering Cancer Center, U.C.L.A., and the University of Arizona. Presumably, the study was approved by an IRB at each institution.

⁹¹ The study revealed laetrile to be essentially nontoxic (at appropriate doses) but ineffective. See Moertel, Ames, Kovach, Moher, Rubin, & Tinker, *A Pharmacologic and Toxicological Study of Amygdalin*, 1981 J.A.M.A. 591 (toxicity study); *Study Says Laetrile Is Not Effective as a Cure*, New York Times, May 1, 1981, p. A26, reporting Dr. Moertel's conclusion, presented to the American Society of Clinical Oncology, that laetrile is "not effective." There has been no substantial political activity supporting the legalization of laetrile since the NCI study report was issued.

⁹² This is, quite obviously, becoming a serious political issue, and it bears many of the social, political, and scientific attributes of the laetrile controversy. See *Andrews v. Ballard*, 498 F. Supp. 1038 (S.D. Tex. 1980).

⁹³ A good debate on the ethical propriety of such research is found in Riskin, *Sexual Relations between Psychotherapists and Their Patients: Towards Research and Restraint*, 67 CALIF. L. REV. 1000 (1979), and Culver, *Should We Research Doctor-Patient Sex*, I.R.B., May, 1981, at 7.

application of that knowledge—the proven harm or inefficacy of the treatment—to public policy.

As these examples illustrate, IRBs are not permitted to do an analysis that accurately evaluates all of the risks and benefits of proposed research. While IRBs may protect research subjects in a narrow sense, their evaluations may not justify the sometimes significant risks requested of their immediate subjects. In addition, those subjects, and the community at large, are not protected by any independent evaluation of risks that may accrue from knowledge gained through proposed research on public policy. The current regulation frustrates the broader ethical commitment of human subjects research to the society whose health and well-being the medical profession strives to foster. IRBs should be allowed to consider the full range of research risks and benefits currently foreclosed to them by the regulations. Without neglecting the primary task of protecting the immediate subjects of research, they should be permitted to protect society as a whole by considering the public policy risks of proposed research.

IV. IRB AND SOCIAL POLICY

Of course, there are practical problems with the role of the IRB that is here envisioned. Institutions have provided only limited resources to their IRBs, and they may not have the energy, finances, or expertise to undertake an evaluation of the long-term social consequences of every research protocol that comes before them. Similarly, membership on the IRB could become a matter of political concern at some institutions if IRBs were to be perceived as legislatures responsible for weaving our social fabric through control of research. This politicization of the IRB, in turn, might present challenges to the academic freedom of researchers. The first problem might be overcome if IRBs generally were entrusted with a discussion of the serious social consequences of the research they review; the second may not be a problem at all. Any outside limitation of research can give rise to a claim that academic freedom has been breached, and the principle that allows IRBs to exist now is one that assumes that the protection of human subjects can override the absolute freedom to engage in any kind of experimentation.

A more significant objection to the serious acceptance of comprehensive cost-benefit analysis by the hundreds of IRBs throughout the country is that different ones may act inconsistently. What some would approve, others would deny. Rather than constituting a weakness of the system, though, this aspect of decentralized decision making is its greatest strength. If an

insufficient number of institutions found sleeping pill research to be acceptable, for example, then that research would stop—without a formal centralized decision from any single political authority. The ethics of Washington, or Wilmington, would not be imposed on Portland, and the evaluation made in Mobile would not be imposed on researchers in Los Angeles. Of course, a decision to approve a study is not a decision to put a product on the market. The decision by a few isolated IRBs to forbid research on hypnotics may only bring that issue to the public attention and preserve those institutions' own integrity. Widespread decisions by many IRBs to forbid such research may result in less of that kind of research, and, if such decisions are widespread enough, then the proposed product will not be able to be tested and placed on the market. While IRBs are not the only barrier to commercial medical development, the fact that Congress and the FDA may also intervene (to limit the availability of sleeping pills, for example) does not mean that individual IRBs—or individual physicians, for that matter—should ignore the social consequences of their use.

The real problem with the public policy exception to risk-benefit analysis is that it refuses to recognize that long-term policy is going to be made in the legislatures, doctors' offices, and the marketplace regardless of whether the research is done. If a formal research study can provide information which will help that policy be enlightened, then ought not that be considered a potential benefit of the research? Similarly, if such research is likely to yield misleading information or information which can be easily abused to justify otherwise unacceptable social policy, then ought not that be considered a potential risk of the research? As long as such consideration is prohibited, some public policy will have to be made in the dark, or some formal research—such as the NCI trial of laetrile—will have to be approved even though it is inconsistent with the formal IRB mandate. As Ruth Macklin explains in her evaluation of the costs of not doing scientific research generally, “the ultimate practical decision would seem to depend on what sort of society we want to live in.”⁹⁴ The regulations, as they are now written, reflect a society highly suspicious of research—especially research that may influence formal policy making. The consequences of the policy exception to risk-benefit analysis demonstrate a schizophrenia in the community's approach to regulation of research. Society appears willing to permit research likely to be a scientific success, even if it may lead to medical abuse, and even when society can foresee the abuse. On the other hand, society is so

⁹⁴ Macklin, *supra* note 86, at 13.

research risk-averse when formal experimentation is unlikely to be a scientific success that it would rather suffer quack cures than test a drug which is likely to be ineffective.

CONCLUSION

While the obligation to engage in something analogous to cost-benefit analysis has been imposed upon IRBs reviewing formal research protocols, the regulations do not permit IRBs to do comprehensive cost-benefit analysis. Instead, IRBs are required to test protocols by considering only risks and benefits imposed upon the subjects and the importance of the knowledge expected to emerge from the research. Although this does not substantially weaken the analysis, the specific regulatory prohibition on IRB consideration of any long-range effects of applying the knowledge gained by the research renders their risk-benefit analysis hollow and misleading. Even if this exception were applied only to IRB consideration of public policy effects, and not to potential medical applications, it would result in a narrow and incomplete evaluation of research protocols.

In the name of protecting human subjects, the regulation has truncated the substantive discretionary power of the IRBs to perform complete risk-benefit analyses of proposed research. In attempting to focus the attention of IRBs on protection of the immediate subjects of research, the regulation ignores the fact that the whole community is at once the subject and the beneficiary of biomedical research through the inevitable effects of that research on public policy. The regulations governing risk-benefit analysis preclude the complete evaluation of risks to research subjects in the broad, as well as the immediate, sense and tip the scales of the evaluation in favor of benefits, and thus in favor of permitting the research. The regulations place IRBs in the uncomfortable position of fulfilling their narrow legal mandate only by failing to fulfill their ethical mandate to respect the greater community which this risk-benefit analysis should also protect from research that may ultimately lead to inappropriate or dangerous social policy.

The problem with removing policy analysis from the risk-benefit equation is that if the policy evaluation is not done by the IRB, then it will not be done at all. There is no provision for federal review of the long-range policy consequences of most research, and a serious evaluation of issues with political implications would be very difficult at a centralized and politically sensitive agency. The investigators themselves have such an interest in performing the research that their evaluation of the long-range public policy

effects of their own research cannot be considered adequate. Although some potential subjects may consider the effects of the research on public policy when they decide whether to consent to participate, they are not likely to be able to analyze those effects adequately. In many cases, those potential subjects will be discouraged from analyzing the policy consequences of the research because many consent forms include the statement that an IRB has already reviewed the experiment and found the risk-benefit ratio to be acceptable. Finally, the National Commission's suggestion that such decisions should be left to local "institutional authorities"⁹⁵ has proved unsatisfactory. While a few such institutions have become intensely interested in these issues, at a great many institutions, those interested in such questions are found on the IRB, and other institutional agencies tend to defer all non technical research questions to the IRB.

Formal IRB discussion of long-range policy consequences of research will permit fair and comprehensive evaluation of research protocols. In addition, logic dictates that it would lead to better and more socially acceptable long-range public policy. Finally, a formal, open, multi-disciplinary discussion of public policy consequences of formal research may foster better understanding of the scientific and ethical problems among the many constituencies represented on IRBs. Risk-benefit analyses that consider policy questions will lead to better IRB decisions, and better medical and public understanding of the goals and limitations of research. The regulations should be reformed to permit, if not require, IRB consideration of the public policy consequences of proposed research.

⁹⁵ IRB REPORT, *supra* note 13, at 24.