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A Taxonomy of Value in Clinical Research

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A Taxonomy of Value in Clinical Research

Abstract

Medical research that involves human subjects presents what appears to be an intractable ethical problem: patients are exposed to risks in order to create valuable knowledge. A central goal of research is to produce knowledge that is "important," "fruitful," or that will have "value." Indeed, federal regulations require that research risks be reasonable in proportion to potential benefits, and in proportion to the importance of the knowledge to be gained (45 CFR 46.111(a)(z)). Moreover, one reason that subjects participate in research is to produce knowledge that will benefit others.

Comments

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ETHICS & HUMAN RESEARCH

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BY DAVID J. CASARETT, JASON H.T. KARLAWISH, AND
JONATHAN D. MORENO

**A Taxonomy of Value in
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Medical research that involves human subjects presents what appears to be an intractable ethical problem: patients are exposed to risks in order to create valuable knowledge. A central goal of research is to produce knowledge that is "important,"¹ "fruitful,"² or that will have "value."³ Indeed, federal regulations require that research risks be reasonable in proportion to potential benefits, and in proportion to the importance of the knowledge to be gained (45 CFR 46.111(a)(2)). Moreover, one reason that subjects participate in research is to produce knowledge that will benefit others.⁴

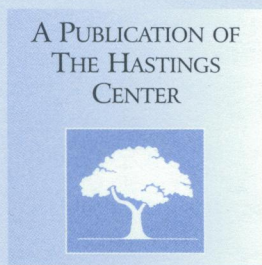
Unfortunately, the concept of value in research has received little attention, particularly as it relates to the ethics of research. While value has been described convincingly as central to ethical research,⁵ it is less than clear how value should be measured. Nor has there been substantive discussion about how assessment of value should contribute to the ethical review of research.

This lack of discussion is puzzling because other ethical requirements of research have received considerable attention and have been extensively specified. For instance, the U. S. Common Rule explicitly mandates consideration of a study's risks relative to its potential benefits, further describ-

ing risks as being minimal, a minor increase over minimal risk, or greater than minimal risk (45 CFR 46). Moreover, these regulations are clear about the need for informed consent (45 CFR 46.116) and for written documentation of such consent (45 CFR 46.117), and subjects are said to be capable of consent, assent, or neither. Although these categories may not be universally endorsed, they nonetheless have provided a useful structure for protecting human subjects.

There has recently been heated debate about how to think about "acceptable" risk in studies that offer little (if any) prospect of benefit.⁶⁻⁸ As a result, IRBs are increasingly pressured to assess the value of a study—that is, the importance of the knowledge to be gained from it—as part of their ethical review. In its final report, the National Bioethics Advisory Commission urged that IRBs assess, for each component of a proposed study, the balance between the risks it poses to subjects and the knowledge it is likely to yield.⁹ This "risk-knowledge" standard offers IRBs guidance in implementing the Common Rule requirement that research risks be reasonable with respect to potential benefits and value.

If investigators and IRBs are to consider value as rigorously as they do risks and potential benefits, they require additional conceptual tools. Specifically, they need a taxonomy of value whose categories



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promote an open and informed discussion like the deliberations now undertaken about risks and potential benefits. In this paper, we suggest such a taxonomy.

We propose that IRBs should balance a study's risks, potential benefits (if any), and value by considering two kinds of value: immediate health value and future health value. We propose further that IRBs should decide whether a study offers either of these kinds of value to future patients, to the population from which the subjects are selected, and/or to the subjects themselves. We contend that the resulting categories provide a common framework for assessing value in clinical research. In some cases, when risk and value must be balanced, these categories can help IRBs and investigators to do so. We conclude by describing ways in which these categories can help IRBs and investigators to address some of the most pressing problems raised by human subjects research.

Assessing Value

All studies must use techniques of design and data analysis that peer reviewers can agree are appropriate and adequate to produce knowledge that is generalizable. Indeed, generalizability is the cornerstone of the Common Rule definition of research: "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (45 CFR 46.102(d)). These requirements collectively describe a study's validity.¹⁰ Validity is a threshold requirement for all research, because it is unethical to expose human subjects to risks in studies that cannot adequately answer the research question.¹¹ At a minimum, thus, investigators and IRBs must consider a study's validity.

Above this threshold of validity, studies also offer value. But IRBs may find it difficult to assess value for several reasons. First, there are

numerous dimensions on which they might base their assessment. For example, IRBs might assess value based on characteristics of the disease or problem under study, such as its prevalence, or the loss of life or decrease in function that it causes. Or they might assess a study's value based on public perceptions of the importance of the disease or problem, or according to whether the study's results are likely to enhance quality of life, decrease morbidity, or decrease mortality. All of these offer plausible guides for assessing value, and the choice among them is not clear.

Second, IRBs face the challenge of measuring a study's value. Even if IRBs could agree on a single dimension of value, the examples above suggest that value is a continuous variable. It will be difficult for IRBs to balance a study's risks against its value without categories of value that are analogous to categories of risks.

Third, value may not be distributed uniformly—that is, a study may offer value to some groups but not to others, raising concerns of justice and appropriate selection of subjects. As the *Belmont Report* notes, research should not focus on "persons from groups unlikely to be among the beneficiaries of subsequent applications of the research."¹² This requirement is also codified in the federal regulations governing research that involves children (45 CFR 46.306(a)) and prisoners (45 CFR 46.406(c)).

These challenges suggest that any taxonomy of research value should have three properties, it should: clearly identify and define a single dimension of value; divide that dimension into clear categories of value, analogous to the categories of research risks and benefits; and be sensitive to fairness of distribution among potential beneficiaries.

Defining Value

Following Emanuel and colleagues we define value as a study's potential to improve health and

well-being.¹³ This definition enjoys wide support and is codified in the Nuremberg code as the necessity of producing "fruitful results for the good of society."¹⁴ Similarly, the Declaration of Helsinki proposes that a fundamental goal of all biomedical research is "to help suffering humanity."¹⁵

Given the range of research that involves human subjects, any definition of value must necessarily be as broad as possible, while at the same time retaining enough specificity to be meaningful. Therefore we understand value to mean the potential of a study to improve health, broadly construed as biological, psychological, or social well-being.¹⁶ Studies that promise to improve individuals' biopsychosocial well-being have "health value."

Health value can be categorized along two dimensions: immediate versus future health value, and the population that receives this value.

Immediate vs. Future Health Value

A study has immediate health value if experts believe that its results can be immediately applied to improve health and well-being. Other studies may produce knowledge that advances understanding of health or illness but will not immediately improve health. These studies have future health value.

Examples of studies that offer immediate value span the spectrum of clinical and nonclinical research. Some of the most obvious are phase III trials of new medications. If a phase III trial finds that the investigational drug under study is effective, it has the potential to improve the health of patients as soon as the drug receives regulatory approval. But other nonclinical studies offer immediate value as well. For instance, a study of needle-sharing practices among intravenous drug users might produce results that could be translated immediately into more effective educational interventions to promote safer behavior.

Similarly, epidemiologic studies that define the prevalence of child abuse in a population could be used to promote legislation or social service interventions.

Examples of studies that offer future health value are numerous as well. One of the most widely discussed and debated is the phase I trial, which is a preliminary test of a potential therapy's safety. Even if a potential therapy is demonstrated to be safe in a phase I trial, its effectiveness has not yet been demonstrated. The results of a phase I trial cannot be applied immediately to improve health and well-being. Other research that offers future value includes studies of normal psychological function, ethnographic studies of social interaction, or studies of normal physiological function. In general, the results of these sorts of studies may advance understanding and they may lead to future studies that improve health and well-being. However, they are unlikely to produce results that could directly improve health and well-being. Their value lies in their contribution to future research.

The distinction between immediate and future value is ethically important because, in general, a study that offers immediate value offers far greater certainty of an effect on health and well-being. If value is an ethical requirement of research, then the threshold of immediate (vs. future) value seems logical. For instance, further testing that is necessary after a phase I trial (e.g. phase II and phase III trials) introduces uncertainty as to whether an intervention that is tested in a phase I trial will ever be applied in a clinical setting to improve health. Similarly, the scientific threads that connect studies of normal physiology with future studies that offer health value are usually difficult to discern. Of course, even with a phase III trial that promises immediate health value, there is uncertainty whether the intervention will be effective, and whether the agent will be approved and clinically available.

Nevertheless, there is far greater certainty that a phase III study will produce an improvement in health or well-being than there is for virtually all phase I studies.

This distinction between immediate and future value is based on a judgment about whether a study's results will improve health or well-being. It does not include a judgment about the magnitude of those improvements, the number of patients who might benefit from them, or the amount of time that it will take to complete the study. Thus a study that takes several years to complete has immediate value if its results will produce even a minor improvement in the health of a few patients. But if another study's results cannot immediately improve health, it would have only future value, even if its results will pave the way for future improvements for large numbers of persons.

Two caveats are essential here. First, it is important to note that these determinations of value should be made a priori, during a study's design and IRB review. For instance, an IRB could conclude that a phase III study of a new medication has immediate value. This assessment is still valid even if, at the study's conclusion, the newer medication is found to be less effective than standard care. Indeed, when a study is designed to test the equivalency of two or more therapies that are currently in clinical use, a negative result might offer considerable immediate value, if one of the therapies offers substantial advantages in terms of its side effect profile, convenience, or cost.

Second, these assessments are probabilistic. That is, they are made under conditions of uncertainty and must rely on the best information available. For a study to have immediate value, experts need to agree that there is a reasonable possibility of producing results that would improve health and well-being.

Health Value for Groups of Individuals

To see how health value can be assessed in a way that is sensitive to concerns about justice, it is necessary to consider how a study may offer value to different groups of patients. There are three groups for whom IRBs should assess health value: future patients, the population from which the research subjects are selected, and the subjects themselves. (Table.)

Health Value for Future Patients. The broadest group for whom value can be assessed is that of unidentified future patients, to whom we implicitly refer when we use the common phrase "benefits to society." If a study is to offer value to future patients, its results must be generalizable. This means that the sample of subjects in the study must be representative. And the study must be designed to answer a question about which there is genuine uncertainty.

A randomized controlled trial to determine whether an intervention is effective in treating a condition might offer immediate value to future patients, as might a study to evaluate a new diagnostic test. Studies to define the prevalence of a public health threat or a threat to quality of life, such as job-related stress, would meet this criterion as well if their results could be translated into programs or policies to promote timely detection and intervention.

Studies that offer future value to future patients are those that may lead to subsequent studies whose knowledge will improve the health of others. A wide variety of studies offer this category of value. For instance, studies to define mechanisms of cell physiology do not produce results that will immediately improve health, but may lead to other research that would. The same is true of studies of normal cardiovascular physiology, descriptive studies to identify potential biomarkers of a disease, and phase I trials of new medications.

Health Value for the Subject Population. An IRB could also determine whether the study is likely to produce either immediate or future health value for a second group: the population from which the study participants are selected. The answer to this question is important because it is sensitive to concerns about justice in research design and recruitment. Specifically, this question assesses the concordance between those who are likely to be recruited into a study and those who stand to benefit from a study's results.

If a study is to offer immediate health value for the target population, several conditions need to be met. First, members of that population must have access to any improvements in health or health care that the study produces.^{17,18} This requires that a health care delivery system exist to provide patients affordable access to a treatment or test. Moreover, the providers in that health care system must be able to learn of the research results and must be able and willing to apply them in clinical care. For nonclinical research, such as a study to assess the prevalence of elder abuse among emergency room visits, this requires a plan to translate results into case-finding procedures, policy, or services.

A study that cannot meet these requirements would provide only future health value to the study population. One example might be a clinical trial of an HIV therapy in underdeveloped countries where that therapy is not currently available. Another would be a study that is conducted in a population whose members would not have access to a new medication that proves to be effective because of cost or a restrictive formulary system.

Some studies offer neither immediate nor future health value to the population from which subjects are drawn. In general, these are studies that ask a question that is not relevant to that population, although it may be relevant to future patients

not in the population. One example is a study that involves terminally ill cancer patients to test a new medication, like an HIV vaccine, that is not related to end-of-life care. Another example is a phase I trial that involves healthy subjects who do not have the disease that the study agent is targeted to treat. These studies offer neither immediate nor potential future clinical value for the population of subjects who are involved.

Health Value for Research Subjects. Finally, a study's value can also be assessed for the subjects themselves. Like assessments of value to the study population, this measure, is sensitive to concerns about justice. If subjects take risks and assume burdens of research in order to produce knowledge about a disease, test, or treatment, those subjects have a stronger claim than other patients on any future improvements to health and well-being that may result. Benefits from the results of a study are distinct from other potential benefits, such as improved health or decreased symptoms, which may accrue to subjects over the course of a study. Subjects may benefit from a study's results but not from their participation in the study, or vice versa. Benefit from the results of a study is also distinct from other indirect or "collateral," benefits of participating in research.¹⁹ For instance, subjects in a study may benefit if tests reveal an undiagnosed medical condition. However, these subjects will not necessarily benefit from the aggregate results of the study, which define a study's value.

Three conditions must be met if a study is to offer immediate health value for its subjects. First, the disease or condition under study must be chronic or relapsing. This makes it possible that the knowledge generated by the study will be relevant to the subject's care when the study is completed. For example, the knowledge generated by a study of hypertension or sleep apnea is likely to benefit the subjects themselves

because knowledge related to their disorder will be relevant to their ongoing care. On the other hand, the knowledge generated by a study of resuscitation for trauma patients would benefit the subjects only in the unlikely event that they suffer similar trauma again—even if such a study offered subjects potential direct medical benefits due to the research intervention, it would not offer immediate health value, because they would be unlikely to benefit from the knowledge to be gained.

Second, the subjects enrolled must live long enough to benefit from the knowledge produced. Subjects in a trial comparing two anti-hypertensive agents are likely to benefit from the study's results, whereas cancer patients who enroll in phase I trials of chemotherapy agents are unlikely to benefit from knowledge about the efficacy of those agents. They are unlikely to survive long enough to participate in future studies, or to receive the agent as part of clinical care. However, other phase I trials may offer future health value to participants—for example, a phase I trial of gene therapy for genetic disorders that may produce effective therapies in the future. If such a study were to enroll subjects with a mild form of the disorder, who have a favorable prognosis, they themselves might benefit from future therapies that resulted.

Third, if a study is to offer immediate or future value for subjects, there must be mechanisms in place to translate clinically relevant knowledge into improved care. This means that the results of a study must be shared with the subjects or their healthcare providers. This might involve a letter or telephone contact to the subjects, or to each subject's physician, outlining the study's results for clinical practice. Clinical research centers devoted to diseases such as cancer, asthma, or Alzheimer's disease have an infrastructure that is ideally suited to achieve this requirement by provid-

ing rapid feedback to clinicians, and active education programs for patients and families.

Subjects must also have access to therapies that prove to be beneficial. If a medication has been approved for clinical use, subjects must have access to it through their pharmacies and health plans, which further means they must have the health insurance or resources necessary to obtain it. A study of a medication that has not been approved for clinical use

would have immediate clinical value only if subjects have access to the medication through an open label phase. That is, if a medication has not yet been approved, the only way in which research subjects stand to benefit from the study's results immediately is if the medication is made available through an open label continuation trial.

Balancing Risks, Potential Benefits & Value

This analysis is useful only if it helps IRBs to determine whether a study's risks are balanced by its benefits and by the importance of the knowledge to be gained as federal regulations require (45 CFR 46.111 (a)(2)). Specifically, an IRB must consider whether a study's risks are reasonable in relation to its benefits, and whether any risks without corresponding benefits are reasonable in proportion to the knowledge to be gained (45 CFR 46.111 (a)(2)). It is in the second analysis that IRBs might use the categories described above. This analysis requires the IRB to focus on the components of the study that are designed solely to answer a research question.

It is important to note, though, that IRBs need not use these categories for guidance in reviewing all studies. For instance, considerations

Table
Features that Enhance a Study's Value

Value for Future Patients	Value for the Study Population	Value for Research Subjects
<ul style="list-style-type: none"> • Results are generalizable • Study has clinically realistic inclusion criteria • Research question(s) are relevant to health and well-being 	<ul style="list-style-type: none"> • Current or planned mechanisms exist to translate results into improvements in care/policy • An intervention that proves to be effective will be available to the population • Research question(s) are relevant to the population 	<ul style="list-style-type: none"> • Study focuses on chronic/relapsing condition • Subjects have adequate life expectancy to benefit • Investigators have described mechanisms of follow-up and continued contact with subjects

of value are not necessary when all of a study's risks are outweighed by its potential benefits to subjects themselves. If no additional risks or burdens are imposed in order to gather generalizable data, an IRB need not consider the study's risk-value balance. Similarly, when a study offers no potential benefits, but also poses only minimal risks (e.g., an anonymous survey, or most ethnographic research) value need not be considered; a requirement of validity is sufficient.

There are three categories of studies, however, for which value should be assessed. First, IRBs should assess a study's value for the subject population if it recruits from a vulnerable or captive population, i.e., those who are "relatively (or absolutely) incapable of protecting their own interests."²⁰ These populations might include adults with cognitive impairment, residents in chronic care facilities, patients in intensive care units, and underserved populations both in this country and abroad. These populations are particularly susceptible to opportunistic recruiting that takes advantage of limited knowledge or a paucity of alternatives to research participation. To offset this risk, and to discourage opportunistic recruiting, IRBs should consider the value that a study promises to the population from which subjects are select-

ed. This requirement is an extension of the Common Rule's regulations governing research that involves prisoners, which requires that research involving these vulnerable subjects be designed to advance knowledge about conditions that are relevant to that population (45 CFR 46.306).

If a study recruits vulnerable patients, and offers immediate health value to future patients, it should also offer immediate health value to the population from which the study subjects are selected. This requirement should be applied to most clinical trials. For instance, a study of two anti-hypertensive medications that offers immediate health value for future patients, and recruits subjects from a disadvantaged inner-city population, should offer the same value to the study population. This means that the study's results must be applicable to the population. More importantly, there should be adequate systems of health care delivery and adequate access to care to ensure that the results of that research reach that population. Similarly, if pharmaceutical trials that offer immediate value in the developed world are conducted in underdeveloped countries, they should offer immediate value to patients in those countries as well.

The second class of studies for which this taxonomy is useful are

those in which the study's risks are significant, there are no potential benefits to subjects, and the subjects themselves are unable to give informed consent, such as a wash-out study that involves patients with active schizophrenia. This study may pose substantial risks to the subjects but offers little or no direct medical benefit if subjects would be responsive to standard therapy.²¹ The substantial ethical concern posed because the subjects themselves do not stand to benefit directly from research participation in such cases are magnified by challenges of informed consent.

These concerns may be ameliorated if a study's results will have immediate health value for the subjects themselves. Direct benefits from the knowledge to be gained are distinct from benefits derived during the study as we have seen, but can nevertheless offset some of the risks of study participation. IRBs should thus determine whether such high risk studies are likely to offer immediate health value for the subjects themselves. For instance, if a wash-out study could determine whether a medication is effective, investigators should be prepared not only to describe how the results of the trial will be relayed to the subjects or their clinicians, they should also be able to outline plans for ensuring access to this new therapy.

A third class of studies for which this taxonomy of value is useful are studies that present greater than minimal risks but offer no prospect of direct benefit, such as phase I trials. For these studies, at least for patient-subjects, altruism should arguably be the most important reason that subjects enroll. IRBs and investigators have an important opportunity to take this altruism seriously by incorporating a description of value into the informed consent process and the informed consent document itself. Ideally, the informed consent process for these trials should include a description of the value that the study will offer using the categories outlined above,

in language that is easily understandable. This disclosure can help a potential subject to determine whether the research risks are reasonable in proportion to his or her desire to help others.

Moving Debate Forward

We describe a taxonomy of value that should be useful to investigators and particularly to IRBs in assessing the ethics of proposed research. This taxonomy relies on the concepts of immediate and future health value and considers the persons who are likely to benefit from the knowledge to be gained. Together, these concepts provide necessary structure to the assessment of the importance of the knowledge to be gained from the research.

It should be noted, however, that this taxonomy should be open to discussion. Like categories of risk, benefit, and informed consent, categories of value must be further refined through deliberation among investigators, IRBs and the public. For instance, to refine categories of value, it will be important to understand the way that subjects and their families understand value. In addition, discussion is needed to determine how investigators and IRBs can efficiently and fairly apply a taxonomy of value.

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