

Health-Related Activities Along the Boundary Between Research and Practice: When to Take Alternate Approaches to Providing Ethical Oversight

A White Paper by the PRIM&R Project on the Boundary Between Research and Practice

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EXECUTIVE SUMMARY

This report summarizes a three-year effort by Public Responsibility in Medicine and Research (PRIM&R) to develop guidance for persons making decisions regarding the need for ethical review or oversight of health-related activities conducted along the boundary between research and practice. When these activities contain elements that resemble experimentation with human beings, the persons carrying them out have to decide whether they should—or may be told they must—submit them to an institutional review board (IRB) for formal ethics review. Yet the need for review may or may not correlate with whether the activities meet the regulatory definition of “research,” which would make IRB approval mandatory. Thus, practitioners, as well as ethicists and other interested parties lack—and need—clear decision rules to guide them in making such decisions.

The project organizers selected four domains of health practice in which such boundary questions arise: innovative medical and surgical clinical interventions, public health practices, community-engaged health activities, and quality assurance/quality improvement activities. We assembled a working group of ethicists and subject-matter experts for the four domains, each charged with describing the features of the practices in question that resemble research and the circumstances under which the practices might merit formal ethical review (not necessarily by an IRB) and with identifying any mechanisms other than IRBs that could provide the needed ethical review.

The findings and conclusions of these four working groups were then assembled to ascertain commonalities across the four domains. From these, we have produced a working list of alternative strategies for ethics review and a proposed set of considerations to help decisionmakers determine what ethics review, if any, might be required for activities conducted along the boundary between research and practice.

BACKGROUND

In recent years, professionals engaged in such health-related activities as measuring the quality of health care, protecting the public’s health, engaging the community in health improvement, or employing novel means to treat patients have protested when told that their activities constitute “research” and hence require prior approval by an Institutional Review Board (IRB).¹ They object that their activities do not cross the “boundary” of human subjects research as defined by the federal regulations and therefore do not require IRB review.² These practitioners also want

to avoid IRB oversight because it is regarded as unduly burdensome, inflexible and time consuming.³ Even when the people involved admit that the activity presents ethical difficulties, they regard an IRB, whose experience and expertise involve the ethics of research with human subjects, as the wrong body to provide review, a view that some IRB members and staff are also likely to hold, since they are already overburdened, under-resourced and aware of their lack of relevant expertise.⁴ Yet, in the absence of alternative mechanisms for review, the activity may either receive no ethical oversight or be referred to an IRB on the grounds that an activity seems enough like “research” to justify turning to the IRB to address the ethical issues raised by activity.⁵

Recent progress in these practice domains has incited further debate over when they may constitute research as defined in the Common Rule.⁶ The Common Rule’s definition of research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge...”⁷ arguably encompasses a wide range of activities in these domains. Clinicians constantly test new procedures to evaluate their efficacy. Community based projects are often designed to produce generalizable knowledge for the benefit of the community and ones like it. Quality improvement initiatives are increasingly designed as systematic applications of new practices to determine whether they improve the delivery of health care. Expanded availability of public health data enhances the ability of public health practitioners to systematize their investigations. For example:

- The availability of data about clinical innovation (through electronic health records and otherwise) produces findings that support new medical and surgical interventions.⁸
- The beneficiaries of community-based projects have brought their unique insights to the table for project development and management.⁹
- More powerful surveillance and evaluation tools provide rigorous evidence about the effects of public health activities.¹⁰
- The continuous monitoring of outcomes by hospitals and other organizations has produced information that is useful for improving the quality of health care.¹¹

In order to avoid the conclusion that such activities must go through an IRB because they were designed to produce information that may have utility beyond the circumstances in which they are conducted, some people have suggested that the definition of “research” be modified to exclude one domain or another.¹² Yet such attempts—which typically focus on certain characteristics of the activity that is to be excluded—are problematic for at least two reasons: modifications to the definition will likely not eliminate conflicting interpretations of what activities fall inside or outside the definition, and a revised definition will do nothing to illuminate when and why professionals in the four domains ought to submit their planned activities to ethics review, whether by an IRB or some other body.

To see whether a response other than a redefinition of research could resolve this intractable tension, we undertook a project in 2011-12 to provide guidance within four domains to institutions and practitioners—public health, clinical innovation, community engagement, and quality improvement—who wish to determine when certain activities should receive formal ethics review and, if so, whether such review should be provided by an IRB or some other body.¹³ We hope this guidance will be of use to officials responsible for research and practice as they determine when ethical review is appropriate or necessary and when it is not required, and for implementing other means of review for non-research activities. Finally, though this project was not aimed at rewriting the definition of research, our conclusions may be of use to those undertaking the current revision of the rules governing federally supported research with human subjects.

THE ORIGINS OF “THE BOUNDARIES”

The issues addressed here are not new. The National Research Act of 1974 authorized the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission) and charged it with identifying the basic ethical principles for conducting research with human subjects. In doing so, Congress told the commission to take account of “the boundaries between biomedical or behavioral research involving human subjects and the accepted and routine practice of medicine.”¹⁴

Responding to this mandate, in *The Belmont Report*, which elaborated the foundational principles for research with human subjects, the National Commission took the following approach to explaining when an activity was practice rather than research:

For the most part, the term ‘practice’ refers to interventions that are designed solely to enhance the well being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.¹⁵

The *Report* then provided the following example: “When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is ‘experimental,’ in the sense of new, untested or different, does not automatically place it in the category of research.” (A medical practice committee should, however, consider when a major innovation should be incorporated into a formal research project according to the *Report*.)¹⁶ The National Commission did not further explore the ambiguous borderland between innovative practice and research, nor did it extend its considerations of boundaries to other nonmedical practices such as activities in sociology, quality assurance, or public health.

The charge to the National Commission and its response reveal the two central concepts that were then operative in explaining what lay across the boundary from research. First, Congress—and then the National Commission—was focused on medical interventions. The task at hand was to distinguish when medical interventions constitute the practice of medicine,

which should be free from interference by the regulators of research, and when they constitute research. This limited focus means that most of the domains of interest in the current project were not directly anticipated in *The Belmont Report*. Second, and perhaps more important, the assumption on which the idea of a boundary rested was that the norms of medical ethics apply: an ethical physician caring for a patient (conventionally or experimentally) would be dedicated to the patient's best interests, and any needed oversight of the physician could be supplied by bodies focused on practice rather than research.¹⁷ However, for the latter activity, whose aim is the advancement of knowledge and not individual benefit, history had shown that more is needed than self-enforced professional ethics. But the converse was also true, namely, the federal regulations being created to provide special protection of research subjects (including through prospective, independent ethical review) need not be imposed upon the decisions made by physicians providing medical care, who were presumably guided by the profession's ethical obligations.

Both of these original premises for the concept of a boundary between practice and research are directly relevant to the present project. First, while the National Commission was focused on medical practice, in the nearly 35 years since *The Belmont Report*, research institutions and federal officials often seem to have assumed that the same rules are in principle applicable to all health-related activities, such as quality assurance, community engagement, and public health practices. Many institutions and sponsors have become increasingly aware of and concerned about the financial threat posed by litigation that can be brought on by even the appearance of negligence in human subjects protection, particularly as both practice and research become more complicated due to advanced technologies and the imperative for innovation.¹⁸ A "better safe than sorry" mentality has also arisen because of high-profile examples of institutions whose entire federally funded research operation has been halted for failing to adhere strictly to federal human subjects regulations. Fearing legal or regulatory sanctions, institutions may err on the side of caution and subject to IRB review all health-related activities undertaken by their employees that even remotely resemble research, despite the employees' unhappiness at having to deal with what they regard as inapt and burdensome bureaucratic procedures.

Second, three of the practices that were the subject of the current project—quality assurance, community engagement, and public health practices—do not share with medical practice a commitment to the primacy of each patient's individual interests. So if they aren't "practice" in the medical sense (i.e., they are not solely patient-centered), it is not surprising that IRBs and institutional officials regard them as the opposite, namely research, requiring IRB review.

The tension between practitioners in domains such as public health and quality assurance, on the one hand, and their institutions and regulators, on the other, was not reduced by the National Commission when it offered a positive description of research (as compared with the picture provided by characterizing research as being "not practice"): "[T]he term 'research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge." This definition from *The Belmont*

Report continues to provide the core of the present regulatory definition of research as “a systematic investigation...designed to develop or contribute to generalizable knowledge.”¹⁹

Resolving the tension will require more than clarifying the attributes of particular practices that might on balance argue for or against review by an IRB because part of the heritage of the National Commission’s original mandate has been that running parallel to the dichotomy of “research-or-practice” is the dichotomy of “IRB-or-nothing.” What is needed, therefore, is not simply the ability to situate an activity on one side or the other of an imaginary boundary line. Rather, what one has to do, as to each particular health-related activity, is to determine whether the ethical issues it raises are ones that need review by an IRB, by some other objective entity, or solely by those directly engaged in the activity. The aim is to ensure that practices that impact the rights and welfare of people are conducted ethically, just as it is for all types of research.

ISSUES TO CONSIDER WHEN DECIDING WHETHER FORMAL REVIEW IS NEEDED

The central objective of this project was to see whether a set of attributes could be defined to guide institutions and practitioners in the four domains when they are deciding whether to seek formal ethics review by a third party. Four general and preliminary points of consensus emerged.

First, classification of an activity as occurring within one of these domains should not, by itself, insulate it from formal ethics review. Just because an activity is deemed “practice” does not mean that it does not need, or would not benefit from, formal ethics review. In considering whether to seek review, the practitioner should consider the attributes of the effort, and not the domain within which the activity sits, alone. (Seven such attributes are discussed in the next section.)

Conversely, the fact that an effort may involve the gathering and analysis of data or other “research-like” components—or may even have “research” in its title, such as when program evaluation is called “evaluative research”—does not necessarily mean that the project needs to be reviewed as research in the Common Rule sense. Further, certain preliminary activities, such as the community-engagement efforts associated with developing a program of community-based participatory research (CBPR), do not necessarily require such review.

Third, several oft-cited criteria are *not* helpful in making such determinations. Among these are:

- **Seeking to publish findings from the activity**²⁰: It appears that some journal editors, in an attempt to walk the high road, are requiring evidence of IRB review before accepting for publication articles that report the results of a range of activities in the boundary-land domains. Plainly, observations arising from clinical or public health practice and quality improvement and community engagement activities can be highly relevant to promoting learning in these fields, when properly documented (typically based on data-assembly that does not involve intervening with the human beings affected by the activity). Often the decision to submit “lessons learned” for publication is

made after the fact, based on the potential value to the broader learning community. While deciding to seek publication only after-the-fact does not in itself carry any weight, the context within which the “lessons” were discovered needs to be examined: the central question is whether the objective of the activity included knowledge-creation or rested largely on other grounds, such as benefit to the individuals involved or to the health of the public. It also elevates form over substance for editors to insist upon, or practitioners to initiate, retrospective IRB review. Post-facto submission to an IRB, solely for the purpose of being able to claim the project was reviewed, is not merely wasteful of time and effort but more importantly does not achieve a central goal of IRBs, namely prospective evaluation of the design of a research activity and independent evaluation of the minimization of risks and the appropriateness of their balance with benefits *before* people are exposed to the activity.

- **Generalizable knowledge**²¹: The role that the generalizability of knowledge plays in the regulatory definition of research creates problems in an era of increased data accumulation, for example, in electronic medical records and automated systems for gathering health-related data. Further, improved statistical methodologies, which make possible sophisticated meta-analyses of data originally gathered for other purposes, may have made the criterion of generalizability if not obsolete at least not very helpful in identifying where the border lies between research and activities in some of the four domains, particularly in the QI/QA and public health realms. As a learning society, we should always attempt to obtain insights beyond the individual experience, and every instance of doing so is not ipso facto “research.”²²

Fourth, individuals and their rights affected by activities in the four domains can be afforded protection by several mechanisms other than IRBs, several of which are described in the final section below.

ATTRIBUTES THAT ARE USEFUL IN MAKING THE DECISION

Based on shared characteristics of activities occurring in the four domains, seven descriptive statements were developed to guide analysis of the attributes of an activity and determination of whether formal ethics review might or might not be needed. The seven attributes were in turn divided into “decision-drivers” and “decision-informers.” These characteristics are to be considered together. None is definitive for identifying an activity that either warrants ethical review or does not, but each is relevant to determining the impact of the activity on the rights and welfare of those involved.

Decision-Driving Attributes:

1. **An activity DOES/DOES NOT *significantly* depart from standard practices.**²³
“Standard practice” should be determined on the basis of published (peer-reviewed), evidence-based guidelines developed within each of the domains under consideration. We commend those domains that specify the level of quality and the extent of evidence

upon which each point of guidance is based, recognizing that the very efforts to increase this evidence may draw on activities occurring “at the boundary.” An activity that significantly departs from standard practice creates the potential for unexpected adverse events.²⁴ Furthermore:

- Such activities may frequently involve interventions or questions at the level of the individual. Documentation or collection of evidence per se does not define the need for ethics review.
- Such activities may involve the absence or presence of independent expert group endorsement.

2. **An activity DOES/DOES NOT pose more than negligible risk of serious and irreparable harm to anyone involved.** Risk has two components: (1) the extent and severity of potential harm occurs along a two-dimensional continuum, from minimal to grave and from easily corrected to permanent; likewise, (2) the likelihood of harm varies along a separate continuum, from nonexistent to highly probable and from theoretical to well-documented. The point here is not to define when an activity should be undertaken (a decision that requires a comparison of its risks against the known risks of alternative interventions, including inaction, and that will depend upon the authority of the actor to impose such risks), but rather to suggest that the need for ethical review of an activity that is not submitted to an IRB as “research” should turn in part on the nature of the risks involved in the activity. A thorough understanding of these dimensions by those engaged in the activities is therefore essential. The risk-related aspects of activities within the four domains that deserve consideration include:

- Collection of personal, identifiable health-related data under circumstances in which such information may/may not be divulged to those outside the usual clinical care givers, for example, the collection of data by fieldworkers in a community-based activity or for public health purposes. In considering this attribute, the degree of risk may be affected by whether the persons having access to the data operate within a clinical setting (such as a hospital) and can be instructed in and monitored according to the data-protective norms of that setting, even if they are not care-givers themselves.
- Risk of psychological distress, anxiety, and stress beyond what a regular person faces in day-to-day activities, recognizing the inherent distress of conditions of ill-health or community insecurity that can exist independent of the activity being carried out.
- Risk of a breach of confidentiality that could lead to criminal responsibility or financial harm, recognizing, again, that certain behaviors and conditions for which a practice is undertaken or care is sought may by their very nature need to be reported

because of legal or organizational requirements, even if the persons involved do not want to disclose them.

- Significant conflict of interest between the persons affected and the practitioners and sponsors (or any other type of conflict of interest that would harm a person or community), recognizing that the extent to which potential conflicts can be made transparent and otherwise managed may militate for or against external review.
- Collection and storage of blood and tissue samples with the possibility of use for specified or as-yet unspecified future research.

Decision-Informing Attributes:

3. The activity involves observing the results of a planned, consistent protocol rather than of a series of actions that are frequently adjusted in light of experience.
4. The activity involves the systematic application or implementation of innovative or incompletely evidence-supported interventions.
5. The activity involves collection of data not primarily for the benefit of the individuals or community from which they were collected.
6. The activity involves deception or a lack of full disclosure of the intent of the intervention, (e.g. activities with commercial and marketing interests).
7. The activity involves an imbalance of power in the relationship between the actor and those affected such that it is doubtful (or at least uncertain) that consent or assent has been given freely by the persons affected (or their recognized authorized responsible agent, as for example in the case of children).

Application

Case 1

This case is based on activities taking place after the John's Hopkins – Michigan Health and Hospital Association Keystone Project that was considered by the Office for Human Research Protections to be in violation of the federal regulations requiring IRB review of human subjects research. Applying the analysis framework presented above would have lead to the decision that the activity, though meeting the regulatory definition of "research" would not have warranted ethical oversight.

Facts: P, a physician-investigator at an academic medical center (C), has developed a program to encourage intensive care units (ICUs) to adopt practices designed to reduce or prevent catheter-related bloodstream infections. The catheter-related bloodstream infections reduction (CRBIR) program has five components, including the placement of a central line cart and a checklist of five clinical procedures that constitute a well-established means of preventing

infections. In studies at his own academic medical center and then at a state-wide association of hospitals, P has demonstrated that this program can reduce or prevent catheter-related bloodstream infections in patients in hospital ICUs. P now plans to cooperate with hospital associations (A1-12) in twelve additional states who are interested in implementing this CRBIR program at their member hospitals. P wants to understand how hospitals use his program on a wide-scale basis and what factors influence the effectiveness of those efforts.

Relying on technical assistance from P, the participating hospitals (H1-600) will use the CRBIR program to improve patient safety in their hospitals and will monitor both the manner in which their physicians, nurses, and other personnel implement the program and the results for patients in terms of catheter-related infections and other outcomes. The hospitals will also provide these data (e.g., the number of infections and the number of “catheter days” occurring at the hospital over identified periods of time) in aggregate form to P. These data will not include the names of any individual patients or healthcare personnel.

In addition to these data, staff at the participating hospitals will respond to two surveys dealing with their perceptions of (1) the culture of safety and (2) the process of implementing the infection-reduction program in their ICUs. These surveys, which will be identified by institution but not by individual respondent, will permit P to compare staff perceptions with the rates of infection across the different hospitals. Each hospital will also receive its own survey results for the purpose of informing hospital leaders about the internally perceived quality of ICU operations and the process of implementing the infection-reduction program at their hospital.

Question: P is uncertain whether the IRB should review any of these activities. If such review is needed, which institutions—C, Ax, and/or Hx—should provide review of which issues and in what manner?

Ethical Oversight Analysis

Decision-Driving Attributes:

1. Does the new checklist program constitute a significant departure from standard practice?

The case states that the procedures in the checklist “constitute a well established method of reducing infections.” Therefore it would be reasonable to assume that the administration of the five clinical procedures does not create unknown risk to patients. What may be considered a “departure from standard practice” is the use of the five component program, including the checklist, in an effort to ensure that every procedure is fully implemented.

2. Does the use of the checklist pose more than negligible risk of serious and irremediable harm to anyone involved?

There is no information in the case that would suggest that the use of the checklist would create any risk of physical harm to either patients or practitioners beyond that which hospital

patients and employees experience in the regular course of their treatment or jobs respectively. Those risks are covered under other ethical systems.

Other risks to consider are invasion of privacy, breach of confidentiality, and psychological distress. With regard to infection/catheter-day data, and considering each of these non-physical risks in turn, there are no facts provided in this case that suggest a risk to privacy above that which occurs during the ordinary course of any hospital stay. The additional collection and distribution of data, however, may pose some additional risk of confidentiality breach beyond that which patients might otherwise experience. The process of aggregating the data and excluding the names of patients and personnel, however, makes it unlikely that this harm will occur. Moreover, the extent of harm that could result from the inadvertent release of this data within the hospital setting is insignificant.

Similarly, the staff surveys will not pose significant risk of harm given their anonymity and relatively non-sensitive content.

Finally, there are no facts in the case that suggest the existence of conflict of interest on the part of the researcher or other healthcare personnel. Neither is there any plan to collect and store biospecimens that would create a risk of harm based on the future use of these materials.

Decision-Informing Attributes:

3. The activity involves observing the results of a planned, consistent protocol rather than of a series of actions that are frequently adjusted in light of experience.
4. The activity involves the systematic application or implementation of innovative or incompletely evidence-supported interventions.

The case describes two plans to systematically administer a protocol involving an intervention that has not yet been proven effective: the one is the checklist plan and the other is the survey. These attributes, numbers 3 and 4, suggest the possibility of exposure to yet unknown adverse events. However, the five procedures used to prevent infections are considered “well established” for preventing infections, and the survey is anonymous and covers non-sensitive topics. These activities are less likely to expose patients to additional risks than to result in improved care.

5. The activity involves collection of data not primarily for the benefit of the individuals or community from which they were collected.

This attribute points in the direction of research since the data collection from both the checklist plan and the employee survey are intended for assessing the value and effectiveness of the checklist for future patients. The benefits to the immediate patients are not the objective of the project.

6. The activity involves deception or a lack of full disclosure of the intent of the intervention, (e.g. activities with commercial and marketing interests).

There are no facts suggesting the use of deception of any kind in this project.

7. The activity involves an imbalance in power in the relationship between the actor and those affected such that it is doubtful (or at least uncertain) that consent or assent has been given freely by the persons affected (or their recognized authorized responsible agent, as for example in the case of children).

There is always a power imbalance between sick hospital patients and their healthy caretakers. However this imbalance is not enhanced by the use of the checklist and there are no facts to suggest that highly vulnerable patients, such as children, will be involved in either the checklist or survey project.

Is Ethics Review Warranted?

Based on the above analysis, a reasonable conclusion would be that ethics review is not warranted. However, that conclusion does not mean that the activity does not constitute “research” as defined under 45 CFR 46. Indeed, the activities described in this case may constitute research as ones involving “a systematic investigation...designed to develop or contribute to generalizable knowledge...” The conclusion that the activity does not warrant ethics review but does constitute “research” suggests that the activity should be considered research that is exempt from IRB review.

Case 2

Facts: An epidemiological study of HIV transmission was proposed for a Los Angeles prison. The proposed population was the gay and transgender prisoners who were housed in a designated area of the prison that was generally preferred as safer. Prisoners entering that area of the prison were required to be HIV tested. If they did not agree to this they would be placed in solitary confinement or in a less safe area of prison.

Ethical Oversight Analysis

Decision-Driving Attributes:

1. Does the activity significantly depart from standard practice?

The study is intended to assess the prevalence of HIV infection in the prison population. It involves the administration of a diagnostic test that is widely used in standard practice as an effective tool for determining the presence of the HIV virus. No activity is planned that represents a significant departure from standard practice.

2. Does administration of an HIV test and housing placement pose more than negligible risk of serious and irremediable harm to anyone involved?

Administration of an HIV test and retention of the test results pose a range of risks from physical injury resulting from the needle stick of the test itself, to invasion of privacy resulting from the knowledge obtained by healthcare workers of a positive result, to the risk of breach of confidentiality that could occur from the inadvertent disclosure of the highly sensitive information of a positive test. Additional risk to a gay or transgender prisoner who refuses to take the test, and is placed with the general prison population is also significant.

Decision-Informing Attributes:

3. The activity involves observing the results of a planned, consistent protocol rather than of a series of actions that are frequently adjusted in light of experience.
4. The activity involves the systematic application or implementation of innovative or incompletely evidence-supported interventions.

The HIV testing will be administered systematically and consistently, in accordance with an established plan. However, it does not involve any innovative intervention that has not been thoroughly tested.

5. The activity involves collection of data not primarily for the benefit of the individuals or community from which they were collected.

The purpose of collecting this data seems to be for the purpose of determining the prevalence of HIV infection among the prison population who identify as gay or transgender. There is no information to suggest that the tested individuals will benefit from the testing itself. However, their consent to be tested allows them to remain or enter the preferred area of the prison.

6. The activity involves deception or a lack of full disclosure of the intent of the intervention, (e.g. activities with commercial and marketing interests).

No information provided in the case indicates the use of deception or lack of full disclosure.

7. The activity involves an imbalance in power in the relationship between the actor and those affected such that it is doubtful (or at least uncertain) that consent or assent has been given freely by the persons affected (or their recognized authorized responsible agent, as for example in the case of children).

The relationship of the researchers to the prisoners certainly involves an imbalance of power. Prisoners of any kind are considered vulnerable to coercion and abuse. Gay and transgender prisoners may be considered more vulnerable still. Moreover, removal to the general population for a gay or transgender prisoner who refuses to take the HIV test may be considered coercive.

Is Ethics Review Warranted?

Although this initiative may not meet the regulatory definition of research, it certainly raises ethical issues that should be evaluated by an ethics committee or some other entity qualified to advise the researchers on how to conduct the study ethically.

ALTERNATIVE MEANS FOR ETHICAL REVIEW

When a consideration of the factors set forth above leads to the conclusion that it would be desirable or perhaps essential for an activity in one of the four domains to undergo prospective ethical review—and, indeed, when this felt need provides the impetus for labeling the activity “research,” out of a sense that IRBs are the only means that are readily available to provide such review—what alternative modalities of review exist? (The project participants noted that some institutions may, as a matter of convenience, ask their IRB to provide this service. In doing so, an institution must address the potential for confusion—both inside and outside the IRB—that such an assignment can create as to whether the activity receiving ethical scrutiny is “research” and should be judged by the standards and expectations that are relevant in reviewing research proposals.)

The project participants discussed a number of modalities that have been used to provide ethical evaluation of activities along the boundary with research other than formal review by an IRB:

1. Collaborative Peer Review

Collaborative peer review processes can be an effective means for providing prospective scrutiny of activities that need ethical review. For example, surgeons at Boston Children's Hospital who want to try novel procedures on patients outside of a formal research protocol go through a process that involves peer review of the procedure and enhanced informed consent from the patient (or surrogate decisionmaker). This process requires communication among surgeons, the patient safety office, the IRB office, and the hospital ethics committee. After a new surgical procedure has been performed a certain number of times, the surgeon must then seek approval either to adopt the procedure as clinical practice or to structure the further evaluation of the procedure as a formal research project, which would then be subject to the usual review by the IRB. This movement, from ad hoc innovation to formal evaluation under a research protocol, was endorsed in *The Belmont Report* when the National Commission explained the concept of the boundary between medical practice and research.

2. Advisory Committees

Outside of institutions, such as hospitals, where “peer review” is readily available, various advisory bodies may be able to provide comparable evaluation of the ethical aspects of various activities. For example, government agencies and intergovernmental organizations (such as the World Health Organization) have empanelled scientific and technical advisory groups to review practice-based and public health activities, and a practice-based network may have a steering

committee. Likewise, in certain public health activities and community-based participatory research, community advisory boards are used to enhance communication and information sharing among those planning the activities and the community. Within public health, these may actually be legally constituted bodies, such as Boards of Health, or even elected or appointed governing bodies. All these groups may have been created for other purposes—such as providing scientific advice and community input—but, with appropriate guidance and tools, they can be utilized to examine the ethical issues raised by activities that the organization or group proposes to carry out.

3. *Ethics Consultations*

Alongside formal review by the IRB, various sources of ethics consultation are available in many clinical and academic settings. Typically, such advice is sought by investigators when designing a research project that raises an unfamiliar ethical issue or when the IRB has rejected a protocol. The advice may come from someone in a formally designated “research ethics consultation service” separate from the IRB (such as those established at a number of Clinical and Translation Science Awardee institutions), from a colleague with expertise in bioethics, or from an experienced member or staff of the IRB (either ad hoc or during regular “office hours” that are provided to allow informal conversations about questions faced by investigators). Such consultations typically involve much less paperwork or formality than full IRB review; are usually focused on ethical issues not regulatory compliance; and are advisory rather than binding. When done correctly, ethics consultations are user-friendly and low-cost ways to provide sound advice. In order for ethics consultations to be effective, there must be assurance that the one offering advice understands the scope of the practice about which he or she is being consulted, the subtleties of working along the “boundaries” and, of course, the regulations governing research with human beings, should it be necessary to suggest to the actor that the activity amounts to “research” and needs to be submitted to the IRB.

4. *Colleagues and Supervisors*

A central consideration in the boundary-spanning domains is the need for practical, local, accessible solutions. Many, perhaps most, practice innovations in clinical medicine, public health, community engagement, and quality assurance occur outside the perimeters of academic or governmental institutions, so formal ethics review mechanisms or even the resources for ethics consultations are simply not a part of the landscape. In such settings, thoughtful advice from a trusted, respected colleague or supervisor may be the only external safeguard for the ethical protections of individual patients, organizations, and communities. Thus, assuring individual education in ethical practice and continued re-enforcement of personal professional responsibility for all health professionals remain the backbone of ethics protections in practice settings.

5. *Guidance for Self-Evaluation and Referral*

Mechanisms that assist those at the research boundary of innovative practice to triage their efforts and projects, particularly by providing explicit decision criteria rather than comfortable, but not always useful, categories or labels, may be effective ways to determine whether activities require oversight. Understanding the array of organizational options for ethics review in addition to the IRB, combined with the development of decision rules about which oversight body would be the most appropriate, can substantially unburden the IRB and expedite innovation while ensuring necessary protection of the rights and welfare of the people affected. The examination of the ethical aspects of an activity may have to be undertaken by the persons carrying out the activity in many instances because other mechanisms are not available; even when such mechanisms exist, the decision to seek prospective ethical review is likely to be dependent on a recognition by the people proposing the activity that it raises ethical issues that ought to be reviewed before the activity commences. To facilitate both of these, professional organizations, IRBs, and other institutional bodies should provide guidelines, checklists, and other types of guidance documents as resources to make it easier for actors in the four domains and their staff members to know when to approach a reviewing body for advice or to address the ethical issues themselves if they have to. Such resources may be useful for decreasing the amount of unnecessary or duplicative paperwork. The data submitted on such forms may also be used in retrospective audits to evaluate the success of these processes. Progressively, web-based tools have replaced paper for these efforts. Examples of helpful guidelines and checklists include those which:

- Assist researchers in determining whether their activity meets the definition of human subjects research requiring formal IRB review, including by describing “high triggers” that indicate that IRB review is necessary.
- Assist researchers in determining whether their activity/research is exempt from the requirement for IRB review.
- Assist researchers in determining which alternative oversight body should review their protocols.
- Determine whether medical record review requires oversight body approval.
- Outline how to take advantage of the flexibility in the regulations.

Internal training programs that teach staff and students about the definition of research, the criteria for ethics review, and ethical research design may also help to reduce redundancies and streamline research activities.

CONCLUSIONS

The worlds of clinical, organizational, community, and public health practice entail many activities that utilize interventions not grounded on an adequate evidence base. Indeed this “gray zone” may represent the bulk of the activities in these fields. Such is the art of practice.

Expecting or requiring detailed review of all such endeavors by IRBs is neither feasible nor desirable. Rather, IRB review should be reserved for those interventions having one or more of the attributes described here that carries the activity as a whole across the “boundary” from practice to research.

For many practice-based activities, alternative review and oversight mechanisms, several of which we outline here, are equally appropriate as IRB review and probably more effective and hence efficient. In all cases, essential to the protection of the human beings affected is the training of the individual professional in ethical principles related to the conduct of his or her work.

For activities at the “boundary,” attributes can be identified that ethically prepared and attuned professionals may use when evaluating their own work and the endeavors of others to make informed judgments or to offer sound advice about which activities require more formal ethics review. We have outlined a number of such factors here.

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¹ Gonsalus CK, et al. The Illinois White Paper: Improving the System for Protecting Human Subjects: Counteracting IRB “Mission Creep. The Center for Advanced Study. 2005. American Association of University Professors (AAUP). Academic Freedom and the Institutional Review Board. 2006

² See ref. 1, Gonsalus et al. 45 CFR 46.102(d).

³ See ref. 1.

⁴ See ref. 1. Gonsalus et al., 2005. p.12.

⁵ See ref. 4.

⁶ Kass NE, Faden RR, Goodman SN, et al. The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight. *Hastings Center Report: Special Report: Ethical Oversight of Learning Health Care Systems*. 2013; January-February: S4.

⁷ 45 CFR 46.102 (d).

⁸ Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics. *Hastings Center Report: Special Report: Ethical Oversight of Learning Health Care Systems* 2013; January-February: S24-S25.

⁹ Flicker S, Travers R et al. Ethical Dilemmas in Community-Based Participatory Research: Recommendations for Institutional Review Boards. *Journal of Urban Health: Bulletin of the New York Academy of Medicine*, 2007; Vol. 84, No. 4: 486-487.

¹⁰ Gostin LO. Surveillance and Public Health Research Personal Privacy and the “Right to Know.” *Public Health Law: Power, Duty, Restraint*. Berkely: University of California Press, 2008, pp. 308-310. Lynn, J et al. 2007. The Ethics of Using Quality Improvement Methods in Health Care. *Annals of Internal Medicine* 146(9): 670.

¹¹ Baily MA, Quality Improvement Methods in Health Care, in *From Birth to Death and Bench to Clinic: The Hastings Center Bioethics Briefing Book for Journalists, Policymakers, and Campaigns*, ed. Mary Crowley. Garrison, NY: The Hastings Center, 2008, 147-152.

¹² US Department of Health and Human Services. 2011. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators (ANPRM). *Federal Register* 76, no. 143, (July 26): 44512–31.

¹³ The wide range of fact-finding and consensus-engendering strategies, including what was characterized as a “think tank” made up of recognized leaders in the various fields of concern and an open “town hall” discussion at PRIM&R’s annual Advancing Ethical Research conference in 2011, is described in Appendix A which is available on the PRIM&R website. To probe the ideas developed—and to tether the discussion to real-world problems—the project leaders solicited “case” examples from think tank participants as well as from PRIM&R members more broadly; these are described in Appendix B, at the same site. The think tank involved both plenary sessions and parallel sessions of working groups that each explored the unique challenges faced in one of the four domains; their discussions are summarized in Appendix C, at the same site. The process was further informed by broader public engagement on the issues in a variety of forums including national conferences and internet exchanges.

¹⁴ National Research Act. 1974. Title II, Public Law 93-348. Sec. 202(a).

¹⁵ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Washington, D.C. Department of Health, Education and Welfare; DHEW Publication OS 78-0012 1978.

¹⁶ See ref. 13.

¹⁷ See ref. 6. S8.

¹⁸ See ref. 1. Gunsalus et al.

¹⁹ 45 CFR 46.102(d).

²⁰ Selker H, et al. The Common Rule and Continuous Improvement in Health Care: A Learning Health System Perspective. 2011 Institute of Medicine Discussion Paper. Lynn, J et al.. The Ethics of Using Quality Improvement Methods in Health Care. *Annals of Internal Medicine*. 2007; 146(9): 670.

²¹ See ref. 19.

²² See ref. 6.

²³ Lynn J. When Does Quality Improvement Count as Research? Human Subject Protection and Theories of Knowledge. *Quality and Safety in Health Care*. 2004: 13 :67–70.

²⁴ See ref. 23, p. 69.