



PUBLIC RESPONSIBILITY IN  
MEDICINE AND RESEARCH

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The Hon. Howard Koh, MD, MPH  
Assistant Secretary for Health  
Department of Health and Human Services  
Suite 200  
1101 Wootton Parkway  
Rockville, MD 20852

RE: **Docket HHS-OPHS-2013-0004**, Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions (78 FR 38343).

Dear Dr. Koh,

Public Responsibility in Medicine and Research (PRIM&R), a nonprofit educational and professional development organization, appreciates the opportunity to submit comments on matters related to the protection of human subjects of research when studying standard of care interventions, as requested in the June 26, 2013 *Federal Register* notice.

For 39 years, PRIM&R has been dedicated to advancing the highest ethical standards in the conduct of research. We accomplish this goal by serving the full array of individuals and organizations involved in biomedical and social science/behavioral research, particularly the members and staff of human research protection programs (HRPPs) and institutional review boards (IRBs). Through conferences and other educational activities, PRIM&R provides balanced, thorough, and accurate information on a range of ethical and regulatory issues affecting research. As a result, we have developed a good sense of what is important to the frontline defenders of ethical research practices.

## I. INTRODUCTION

Before making specific recommendations for the Office for Human Research Protections (OHRP) guidance to IRBs, we wish to make a few preliminary points.

First, PRIM&R believes that protecting the rights and welfare of human subjects should never be compromised in the service of the desire to expedite research, regardless of how valuable that research may be. Nothing about the work that is the topic of the present notice, “research studying standard of care interventions,” justifies departing from this basic precept. A primary mechanism by which such protection is operationalized is informed consent. When it is working as it should, the informed consent process provides in a clear, well organized, and accessible way the information a potential subject needs to make a considered decision about whether or not to enroll in a research study. While the Common Rule lays out required elements of informed consent, we believe it is essential that all those involved in human subjects research understand that adherence to a regulatory formula is not the same as achieving voluntary and informed agreement, which involves a process, appropriate to the level of risk and burdens implicated in the research, that is

thorough, transparent, and sensitive to the situation of each potential subject, particularly those who are also patients.

Second, investigators who undertake research with patients must be especially vigilant about potential gaps in or failures of understanding, and must thus be sensitive to the circumstances that may exacerbate such gaps or failures. Written consent forms alone are rarely if ever adequate for informed consent. Additional, creative efforts to assess and ensure adequate comprehension of the options around enrolling in research may be called for, and obtaining consent from patients or other vulnerable subjects (or their surrogates) commonly requires devoting substantial time and energy to an ongoing consent conversation. Investigators and their research teams should be expected to make this effort.

## II. GUIDANCE FOR IRBs EVALUATING STUDIES INVOLVING STANDARD-OF-CARE COMPARISONS

Given these precepts, we propose a framework to guide IRBs when they are asked to review research involving random assignment of patient-subjects to interventions all of which fall within the “standard of care” provided to patients outside a trial. Our terminology follows that of the *Federal Register* announcement. First, we use the term “intervention,” which encompasses diagnostic and preventive as well as therapeutic measures, since all may be the subject of comparative study. One difficulty with the term “intervention,” however, is that in some situations, it might suggest that what is being compared is an individual item (*e.g.*, one type of syringe versus another). By medical interventions we have in mind not such individual items but clinical regimens (sets of procedures designed for particular clinical ends). Single items may need to be evaluated for their efficacy and safety, but comparative effectiveness trials usually involve multipart regimens. Furthermore, we assume that what is being studied involves something about which patients usually choose among alternatives, that is, the sorts of changes in routine care that are first discussed with patients by the physician because they would be material to patients.<sup>1</sup>

The other phrase in the *Federal Register* announcement, “standard of care,” could also be criticized in the present context. Since a common use of “standard” is a rule set by an authority (*i.e.*, a bureau of standards), it seems hard to explain why one would intentionally deprive patients of an intervention that embodies the “standard.”<sup>2</sup> A good deal of evidence—particularly evidence of efficacy derived from clinical trials conducted with a carefully select group of subjects—exists for

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<sup>1</sup> Other sorts of matters—how the facility maintains hygienic conditions, how nurses distribute medication, which scalpel is used in an operation, and the like—are covered by the general consent (implicit as well as explicit) that patients give upon entering a healthcare facility. Of course, even within this ambit, physicians, nurses, and healthcare administrators are responsible for the consequences of the professional choices they make, and if a change they have made unreasonably increased the risk of injury they can be found liable for any resulting harm, though not based on the failure to have received informed consent for the change.

<sup>2</sup> A similar criticism was raised when “standard of care” was used to indicate the care that had to be used in the control arm of a clinical trial of a drug for which treatments already exists. This alternative to using a placebo control was often taken to mean the best treatment for the condition in use anywhere, although the National Bioethics Advisory Commission argued that it would be acceptable to give any “established effective” intervention to control arm subjects in a setting where little or no treatment for a condition is generally available. National Bioethics Advisory Commission, *ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH: CLINICAL TRIALS IN DEVELOPING COUNTRIES* (2001), pp. 22 ff. “Established effective” would, however, seem inapt in the present context, when interventions are subjected to comparative study precisely because their relative effectiveness has not been established.

many of the interventions routinely used in medical treatment. What is missing, however, is adequate information about the effectiveness of many interventions as they are generally used, often for indications and in populations for which clinical trials have not been conducted, much less trials that would allow interventions to be compared reliably to one another. In these circumstances, a range of interventions are all within the standard of care. Thus, despite the potential ambiguity with the term, we follow the Department's lead and use "standard of care" to refer to medical interventions that are routinely used by a recognized group of qualified practitioners in treating the condition being studied in the relevant population. Trials of this sort are conducted when uncertainty exists about which of two or more widely used interventions better achieves a particular set of outcomes.

Below are six questions we recommend that IRBs ask concerning protocols and informed consent processes in such trials. We provide further explanation and justification for each question.

**1. Have the investigators established that the medical interventions being compared are within the accepted "standard of care" for the population being studied and that doubt exists concerning their relative effectiveness?**

In reviewing a study comparing standard-of-care interventions, the IRB should ensure that the investigators have adequately supported two threshold points: (1) that the interventions being studied are indeed within the accepted standard for the proposed study population, and (2) that adequate evidence is lacking as to which intervention is most successful in producing particular outcomes, including considerations of burdens and potential harms and benefits. Typically, the first will involve the investigator providing the IRB with professional practice guidelines, data on actual physician practices, or other evidence from peer reviewed journals and medical textbooks relevant to establishing the accepted use of the interventions in the population in question (which should include information on the safety and effectiveness of the interventions).

The second point can be addressed by published commentary on the existence of disagreement regarding the superiority or inferiority of the interventions or any other legitimate source of information that justifies the need for the comparative research. An IRB may need to consult experts in the relevant field of practice for advice on the completeness and persuasiveness of these materials in order to answer these two threshold questions, but in some cases, the answers may be inferred from the very fact that the protocol involves a multi-site study funded by a national medical research body which has subjected the protocol to extensive peer review before being willing to fund it. In examining the two threshold issues, the IRB is not setting itself up as a scientific review body, because deciding whether those with expertise are satisfied that adequate justification exists to provide these particular standard-of-care interventions in a research rather than clinical context is ultimately an ethical judgment.

**2. How will potential subjects be informed about the nature and potential harms, burdens, and benefits of the medical interventions being compared?**

In providing interventions in the context of ordinary care, physicians are generally expected to engage patients in a discussion about the nature of the intervention and any other routinely used alternatives and their relative burdens and potential harms and benefits. In a research study involving the comparison of one or more standard interventions, the IRB should be satisfied

that someone will have engaged potential subjects in the process of discussing the nature, potential benefits, harms, and burdens of the interventions being compared in the trial. This would usually be a member of the research team providing the interventions, but sometimes the discussion of the alternatives in a therapeutic context may initially be carried out by the patient's treating physician before the patient is referred to the research team to discuss entering a trial that will compare two or more standard-of-care interventions for the patient's disease or condition. From an informed consent vantage point, the central concern is that all the relevant factors about each intervention (and especially its potential harms or burdens) be conveyed in as clear and comprehensible way as possible to the patients (or surrogates) who are being solicited to become subjects in a study of those interventions.

Investigators should explain how this process will be carried out, and IRBs should consider such descriptions carefully but also creatively. Guidance rather than regulations is needed because this process of disclosure and discussion can vary from setting to setting and from intervention to intervention, based on the disease or condition being treated, diagnosed or prevented, the relative complexity or familiarity of the interventions, the nature of their potential harms and benefits, the clinical setting, and the prior relationship, if any, of the participants (patients, physicians, investigators, and so forth). The process may involve explanatory materials, written consent forms, oral presentations (with the points to be covered specified, but the exact sequence and format shaped by each particular physician-patient encounter), or other forms of communication (such as interactive media).

Before they become research subjects--indeed, preferably before they are invited to become research subjects--patients should have a clear picture of the risks that inhere in the interventions when they are used in routine medical care. This understanding is especially important when these risks differ in type--that is, when the potential harms of the alternative interventions involve trade-offs among different categories or degrees of harm. In such a situation, a patient may strongly prefer one set of burdens and potential harms and benefits over the other, and thus would probably not want to be in a research project in which he or she has an equal likelihood of being assigned to receive the intervention that is more likely to produce the disfavored risks.

**3. How will the potential subjects be informed that they are being asked to be part of a study comparing two medical interventions and that if they do not wish to participate in (or, later, to continue in) this study, they will instead receive standard care?**

The essential predicate for a patient being enrolled in a study comparing two or more standard interventions is that the patient knows what will be entailed in entering the study: namely, that the intervention he or she receives will be determined under the protocol (typically by random assignment), that the person providing it will be an investigator rather than simply a treating physician, and that the research may impose particular burdens and potential harms beyond those involved in receiving the interventions solely as ordinary care (a point addressed in question #5 below). The IRB should ensure that there is a plan or process in place for informing potential subjects that they are being asked to participate in research. Furthermore, in order for subjects to make an informed decision about participating, they must be made aware of what it *means* to become a research subject in this particular context. For research that involves randomizing subjects between standard-of-care interventions, the basic choice facing potential subjects is whether they wish to have the intervention that their physician recommends based upon the physician's best (albeit less than fully supported) clinical

judgment or whether they—out of a desire to help develop medical knowledge or frustration with the lack of adequate comparative information to guide them and their physician in making choices about their own care—are willing to have the intervention chosen by a process governed by the rules laid out in the study protocol.

For the IRB, the central goal should be to ensure that the investigator has set forth how potential subjects will come to understand that they have a *choice* as regards the specific interventions being studied between remaining in a therapeutic, doctor-patient relationship, or entering an investigator-subject relationship, in which case their physician will not routinely be making personalized clinical decisions about the use of the interventions under study. The usual reassurance given to potential subjects—that the decision to decline participation in a study will not adversely affect their treatment—is particularly pertinent here because patients who decide not to enroll in a trial comparing two standard-of-care interventions should still be able to get either intervention outside the trial since they are routinely used in clinical practice, in contrast to the situation in trials of new drugs and devices that are not yet in general use. As always, patients who choose to enroll must also be told that they can choose to terminate their participation in the study at any time, in which case they will return to having their care governed by the best judgment of their physician(s).

**4. How will the potential subjects be informed of any available alternatives (and their potential harms and benefits) to the interventions being offered in the study?**

In order for consent to participate in research to qualify as informed, potential research subjects must be adequately apprised of the alternatives to participating in the study. When the alternative to participating in research is receiving one or more treatment that is also the object of the study, there is greater potential for confusion about the differences between participating and not participating in the research. These differences must be fully explained to the potential subject, a responsibility that falls to the investigator. It is incumbent upon the IRB, through its oversight function, to ensure that both the informed consent process and the form include a very clear statement that the alternative to enrolling in the study—where the specific intervention a subject receives will be decided randomly—is to leave the choice in the hands of a physician using his or her best clinical judgment. At the same time, it is important for prospective subjects to understand that, given the lack of definitive evidence about which intervention is best, a physician—however good his or her intentions—cannot know whether the intervention he or she recommends will actually serve the patients’ interests better than the alternative. These statements should be accompanied by an explanation of what is known about the potential benefits and harms (per #2 above) of each possible intervention.

**5. What burdens and potential harms—beyond those of the two or more interventions being compared—are added by participating in the study?**

Deciding when a study involves potential harms beyond those that inhere in each intervention when provided as part of standard care requires complicated and nuanced assessment. An IRB must determine whether the investigators (1) have thoroughly examined and identified the added burdens and potential harms to subjects that are added by participation in the study, over and above the risks of receiving either of the standard-of-care interventions being compared, and (2) have developed an adequate description of those added risks for the informed consent process. The specific potential harms added by research participation will necessarily be case-

dependent. However, we urge OHRP to provide guidance to IRBs about how to identify and then evaluate those additional burdens and risks, as illustrated by the following examples:

- Some burdens and potential harms may arise because subjects in the study will undergo additional testing and monitoring (ranging from extra blood-draws and spinal taps to diagnostic imaging), which may create new burdens and potential harms to which patients receiving the intervention as ordinary care would not be exposed.
- Some potential harms may arise because in the course of ordinary care the level or type of a specific intervention would be modified in light of an individual's response to the intervention or what the physician knows about the patient's preferences, whereas in research the study interventions will be given according to the protocol which may or may not provide much flexibility for investigators to respond to the evolving situation of individual subjects. In general, study protocols tend to be more rigid than management by one's personal physician, so it will be important for the IRB to be satisfied with the point specified by the investigator when a subject's response will be judged to be so far off the expected range that the subject will be withdrawn from the study and treated simply as a patient. As part of the obligation to minimize harm to subjects, physician-investigators always retain the authority to exercise their Hippocratic duties to subjects as patients and change the interventions being used when necessary to protect the patient's well-being.
- As a result of procedures that mask certain data sources, a physician-investigator may not receive information he or she would have received when providing ordinary treatment, giving rise to additional risk.
- All studies with random assignment also pose the risk that, should the intervention that a patient-subject would have received outside the research (*i.e.*, the intervention usually recommended by the patient's physician) be proven by the research to be the superior one, the subject has an even chance of not having received that intervention. Of course, the obverse is also true: should the intervention the patient would have received outside of research turn out to be the inferior one, the study will have offered the patient-subject an even chance of getting the superior intervention. The question for a potential subject is thus whether he or she would find it easier to accept a bad outcome that results from a medical intervention that was chosen by the physician and patient than if it were produced by having been randomly assigned to the group that received that intervention.

**6. How will the potential subjects be informed of any such additional risks?**

Similar to our response to question 2, subjects in studies comparing two or more standard interventions should be informed of risks using methods traditionally employed to obtain informed consent from all potential research subjects. The IRB should ensure that, if and when additional risks of research participation are identified, the informed consent process and form include (1) a clear statement that participating in research involves potential harms over and above those receiving one of the interventions outside of the research, and (2) a clear and complete description of those additional risks.

### III. RESEARCH TO ACHIEVE A “LEARNING HEALTH SYSTEM”

The activity that provoked OHRP’s present enquiry—namely, comparative studies of standard-of-care interventions—is part of a broader, and growing, interest among clinicians, health systems researchers, and healthcare funders (including the Federal government) to improve the efficiency and effectiveness of health care by remedying the alarming lack of evidence for much of what happens in medical practice. A variety of activities designed to address this gap and compare the effectiveness of health interventions have recently emerged across the healthcare landscape. The type of research on which DHHS is seeking guidance for IRBs is just one of many such activities. Others include pragmatic clinical trials engaging large health care systems and learning healthcare systems that aim simultaneously to provide care, study outcomes, and improve practice. As the Patient-Centered Outcomes Research Institute (PCORI) gains momentum, we will see a move toward a healthcare system that mandates large-scale projects, including retrospective examinations of health data and interventions designed to determine the optimal standard of care.

As these activities become more widespread, it will be important to establish appropriate oversight systems. Only some of these activities qualify as research under the current regulatory definition, but all face a number of regulatory and ethical challenges including what, if any, type of ethical review is required and what to do when it is not feasible to obtain individual informed consent. It is unclear how to re-conceive models for appropriate oversight for circumstances such as these in which risk, if any, may be minimal but benefit for society is potentially great.

PRIM&R is already involved in several projects identifying and examining the ethical issues that arise for activities designed to learn from the results of providing routine health care and initiating clinical innovations, and we hope to provide guidance to the HRPP/IRB community as our work progresses. We encourage OHRP to use its considerable authority to anticipate the need for ethical guidelines around these emerging learning activities.

### IV. CONCLUSION

Practicing medicine on a strong evidence-base is essential if scarce resources are to be used in the most patient-centered manner possible. Seeking to fill gaps in our knowledge about the relative merits of different, accepted interventions for a particular condition is an important tool for adding to that evidence-base. However, research to improve our understanding of the correct standard of care (often called comparative effectiveness research) is not unique from the perspective of research protections. Those seeking to enroll patients in a study to compare standard-of-care interventions must explicitly tell them that they are being asked to participate in research and what this means for them. Unless a study meets the criteria for an informed consent waiver or exemption, prospective subjects must be informed in a comprehensive and transparent way about the nature, risks, and benefits of the interventions being studied and about any added potential harms or burdens presented by the research, as well as about alternatives to research participation. It may be more complicated for IRBs and investigators to apply the Common Rule and general ethical guidelines about risk and informed consent when research involves standard-of-care interventions, given the added complexities of identifying the relevant standard, of clearly separating the potential harms of the existing interventions from those added by enrolling in the study, and of adequately explaining to subjects the differences between receiving an intervention as a physician’s *patient* and receiving possibly that same intervention as the *subject* of a clinical trial.

We hope that our specific suggestions for how IRBs should be encouraged to think about trials comparing standard-of-care interventions so as to ensure that they meet the high ethical

expectations of the Common Rule, as well as our framing comments in sections I and III, are useful to the Department and to OHRP as you develop guidance or propose modifications in the regulations. As always, PRIM&R stands ready to assist the Department and OHRP with the development of a framework for the ethical oversight of research with human beings that is appropriate to the particular types of research being proposed and carried out. We look forward to an opportunity to discuss this goal with you and to collaborate with the Department and with OHRP on achieving it, which is a matter of central importance to our members.

Respectfully Submitted,

A handwritten signature in cursive script, appearing to read "Alex M. Capron".

Alexander M. Capron  
Chair, PRIM&R Board of Directors

cc: Board of Directors, Public Policy Committee