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Office for Human Research Protections
1101 Wootton Parkway, Suite 200
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RE: Document 2014-25318, Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care (79 Federal Register 63629)

Dear Dr. Menikoff:

Public Responsibility in Medicine and Research (PRIM&R), a nonprofit educational and professional development organization, appreciates the opportunity to submit comments in response to the “Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care,” published in the *Federal Register* on October 23, 2014, by the United States Department of Health and Human Services’ Office for Human Research Protections (OHRP).

For 40 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, behavioral, and social science 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.

The appropriate use of healthcare resources depends on practitioners having, and correctly using, a robust evidence base about medical interventions. Research that identifies the comparative effectiveness of commonly used interventions is essential to creating such evidence. As such research becomes more common, it is imperative that all people involved in it—particularly investigators, healthcare practitioners, and IRB members and staff—understand how oversight rules and mechanisms apply to such endeavors.

In the wake of the controversy surrounding the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), it has become increasingly clear that there is confusion in the research community about how the federal regulations for the protection of human subjects apply to research evaluating alternative interventions that all meet the standard of care for preventing, diagnosing, or treating a particular condition. Given the importance of this issue, PRIM&R appreciates the OHRP’s efforts to foster public discussion and provide the research community with guidance on how to ensure adequate protections for human subjects in research evaluating one or more interventions that are within the standard of care. We do not, however, believe that the current document provides the comprehensive assistance needed by investigators and IRBs, and we hope that it can be rewritten to provide clearer guidance.

Concerns Regarding the Current Draft Guidance

The draft guidance appears to be limited to research whose *purpose* is to evaluate the *risks* of two or more “standard of care” interventions. The guidance indicates that it “focuses on research studies whose purposes include evaluating *risks* of treatments or procedures that are medically recognized standards of care” [emphasis added]. This focus does not, however, present a comprehensive picture of comparative effectiveness research (CER). CER studies are often designed to evaluate several outcomes simultaneously. Indeed, studies of marketed drugs are typically designed to compare efficacy/effectiveness or benefits, as opposed to differences in risks. The draft guidance can be read as not applying to such cases, even though it would be more sensible to suggest that even when a study is *designed* to compare therapeutic outcomes/potential benefits, investigators, patient-subjects, and IRBs should consider possible differences in the risks associated with the interventions being compared.

The following passage from the OHRP document illustrates three related points of confusion:

The key issue is not whether an intervention provided to subjects is within a standard of care, but whether the treatment a subject receives (and thus the risks they are exposed to) is different from that which these subjects would have been exposed to outside of the research study. The risks that result from such a difference in treatment are risks derived from participation in the research study. Patients randomized to different standards of care in a comparative effectiveness trial should accordingly be made aware of the risks of the standards of care that are being compared. OHRP agrees that the distinction between receiving clinical care and participating in research must be made clear to subjects.

One cause for confusion is that the draft guidance often uses terms inconsistently. The quoted paragraph begins, correctly we believe, by speaking of whether an “intervention” is “within a standard of care.” It then substitutes “treatment” for intervention, raising the question of whether that excludes research on preventive or diagnostic as well as therapeutic measures. Further, the paragraph uses a phrase that appears in the title of the draft guidance and repeatedly thereafter: “different standards of care.” However, the differences are in the interventions, all of which meet the applicable standard of care. We are also concerned that the guidance creates confusion around the definition of risk in CER. For instance, at times the guidance refers to the standard regulatory language of “reasonably foreseeable risks,” and at other times, “risks.” The varying characterization of “risk” throughout the draft guidance may result in confusion and misunderstanding of how “risk” is interpreted by the OHRP. Moreover, the term “risk” is sometimes used to describe types of research interventions, and not just the chance of harm, which is potentially misleading.

Second, interventions may be “different” without “thus” exposing subjects to different risks. Indeed, one reason for conducting comparative studies can be to untangle whether the general impression among clinicians that different interventions have similar outcomes and risks is accurate; thus different interventions may be thought to expose patient-subjects to very similar (or potentially identical) risk profiles. Conversely, despite an *a priori* expectation that no differences exist in potential harms—and hence, the study could be meant instead to compare the effectiveness of the interventions or the relative costs of providing those interventions—the study itself might reveal that such differences actually exist. It is therefore important for the guidance to apply to all CER, not solely to studies designed to study differences in risk.

Third, the draft guidance repeatedly states that any significant differences in the “foreseeable risks” of the research must be disclosed. While we agree, it seems that a shift in emphasis would better achieve the OHRP’s main goal, namely, “that the distinction between receiving clinical care and

participating in research must be made clear to subjects.” This could be achieved by placing less emphasis on risks and focusing instead on the need for investigators to make clear to potential subjects that they have a choice of whether to receive one of the interventions in a clinical context, or to assist investigators in learning more about comparative benefits, risks, costs, and so forth by receiving one or another of the interventions on a randomized basis in the trial. When there are significant differences in the potential harms of the interventions being compared, those differences are likely to affect potential subjects’ decisions of whether or not to participate in the trial. But when the differences in potential harms are much smaller, or are even thought to be nonexistent, no implication should necessarily arise that there is nothing left to decide (and hence consent might be waivable), because the fundamental issue remains the same: Does a patient wish to be a patient-subject and contribute to answering a question about the relative effectiveness, side-effects, harms, costs, and so forth of different interventions that are routinely used for a particular medical indication?

Given the importance of providing guidance in this area, we strongly urge the OHRP to use this opportunity to reformulate the draft guidance. As we have indicated in past comments to the OHRP, PRIM&R’s view is that the central concern in research evaluating one or more accepted interventions should be ensuring that potential subjects understand (a) that they are being asked to participate in research, (b) the nature of the research question being investigated, and (c) how their care as research subjects may differ from care they would receive in the clinical context.

Recommendations for Future Guidance

To assist the OHRP with the process of rethinking and reformulating its guidance in this area, we make several recommendations that we believe should guide the review and conduct of comparative effectiveness research in order to protect human subjects.

First, when reviewing protocols involving the comparison of two or more interventions that meet the relevant standard of care, investigators, sponsors, and IRBs should ensure that the protocol makes clear what question(s) are being studied (e.g., comparison of the foreseeable potential harms and potential benefits; comparison of costs; etc.), as well as the importance of the question(s) under study. IRBs should also ensure that the study, as designed, can provide answers to those questions.

Second, it is incumbent upon IRBs, investigators, and sponsors to ensure that information provided to potential subjects during recruitment or consent for research evaluating one or more standard-of-care interventions adequately convey, in an understandable fashion, what is being studied (e.g., relative potential harms, potential benefits, costs, etc.), the importance of the question under study (e.g., to improve clinical practice, to ensure the appropriate use of resources, etc.), and how a potential subject’s care may differ in the clinical research context, as opposed to the clinical context alone. Additionally, potential subjects should be made aware of how interventions will be assigned (e.g., randomly) and that, when so specified by the protocol, neither they nor their health care practitioner will select the intervention they receive. Such information will enable each potential subject to decide whether he or she prefers to receive one of the interventions as patients or to be assigned to receive an intervention as a patient-subject and thereby help answer the question(s) under study.

Third, it is essential that IRBs be attuned to the fact that adequate and appropriate review of comparative effectiveness research will necessarily depend on the nature of the research question(s) posed, as well as the potential risks and benefits of the interventions being compared. For example, while the draft guidance puts forward an example—differences in doses of radiation for the treatment of childhood cancer—where significant differences in risk are possible, other

evaluations of standard interventions, such as which type of exercise bicycle is more effective for knee surgery rehabilitation, may create a much less significant risk differential. As we indicated in the prior section, the explanation provided to potential subjects should reflect the magnitude of the potential risks and benefits associated with the interventions under study, while ensuring that they are provided with all of the information necessary to make an informed decision.

PRIM&R is grateful to the OHRP for the opportunity to comment, and we hope that you and your colleagues will find our input on this matter useful as you finalize this guidance. We believe this is a very important issue, and we hope that the OHRP will use this opportunity to step back and reconsider the draft guidance in light of our concerns.

If you have any questions or require any further information, please feel free to contact me at (213) 740-2557 or PRIM&R's executive director, Elisa A. Hurley, PhD, at (617) 423-4112 or ehurley@primr.org.

Respectfully Submitted,



Alexander M. Capron
Board Chair

cc: Board of Directors
Executive Director