Dear Commissioner Hamburg:


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.

PRIM&R is committed to the protection of the rights and welfare of human subjects, and we strongly believe that the informed consent process is an essential part of ethical research with human subjects. We therefore commend the FDA’s efforts to further clarify the responsibilities of IRBs, clinical investigators, and sponsors to see that potential subjects in clinical trials receive the information they need to make considered, autonomous decisions about research participation. Similarly, we support the FDA’s goal to enhance the protection of subjects while also reducing the burden on others by harmonizing regulatory requirements across federal agencies, provided always that “where the regulations differ, the regulations that offer the greater protection to human subjects should be followed” (p.2). We also applaud the addition of expanded sections on informed consent with respect to vulnerable populations, as well as the agency’s consideration of the use of new technologies for obtaining informed consent.

Throughout the draft guidance, the FDA emphasizes that informed consent involves more than a form. Investigators, IRBs, and sponsors are encouraged to think of informed consent as a dynamic process that can be adapted to reflect the unique needs of potential subjects, as well as local context. PRIM&R has long championed precisely such a framework for informed consent. We commend the FDA for using this guidance document to foster understanding of informed consent.
Yet, given this document’s potential influence, we believe further guidance could benefit IRBs, investigators, sponsors, and, ultimately, subjects. We therefore offer below a number of broad recommendations, as well as three additional comments.

I. Consent Form versus Consent Process

PRIM&R has long encouraged recognition on the part of policymakers that the purpose of informed consent is first and foremost to help potential subjects become informed decision-makers about whether to participate in research. Being given a consent form to read and sign is only one path—and probably not the best—to that goal. We applaud your agency’s efforts to clarify the distinction between the consent form and the consent process, but several places remain where we believe the FDA could strengthen its recommendations.

As a preliminary point, we strongly urge the FDA to replace the term “consent interview” with the term “consent discussion.” “Consent interview” is used throughout the document to refer to the process by which a clinical investigator or other study staff member discusses participation in a clinical investigation with a potential subject. The term “interview,” however, is misleading and contrary to the goals of informed consent as it implies that conversation is directed by a single party when it ought to be a dialogue in which both parties seek and provide information. When the consent process is working as intended, it allows for open dialogue between research staff and potential subjects about the purpose, risks, benefits, and alternatives to participating in a clinical investigation. Furthermore, it encourages potential subjects to ask questions. The term “consent discussion” thus more accurately and appropriately reflects the tenor of these conversations, and we strongly encourage the FDA to adopt its use.

Second, we suggest that the FDA could go further to clarify the role of the consent form. Many different assumptions exist about the purpose of the consent form. Some believe the form exists solely for the purpose of legal documentation, some believe it to be an educational tool for use during the consent process, some believe its purpose is to guide investigators when they discuss a research protocol with a potential subject, and some believe it is intended to serve as a reference document for subjects. Varying views about the purpose of the consent form result in differences in its content from institution to institution. Therefore, the FDA should pay very close attention to how it explains the purpose of the consent form, as what is said in this guidance document is likely to have far-reaching effects on the content of consent forms.

In the draft guidance, the FDA indicates that one function of the consent form is to “ensure that the subject receives the required information” (p. 3). In some ways, this statement seems innocuous, but it is troubling because it indicates that the FDA believes this is the purpose of the form. A form cannot ensure anything; it is just a piece of paper. It would be very different to say that “the investigator or sponsor should ensure that all the information needed by a potential subject to make an informed choice about participating in a trial has been conveyed in a clear and comprehensible fashion.” There the responsibility is placed on a person or group with the potential to act—in formulating the information in such a way that it can be understood, in conveying that information, and in ascertaining that the potential subject has taken in the information. Such an approach could place the consent form in a more useful role, not as the sole document that “ensures” subjects have all the required information, but as one component of the process of enabling potential subjects to be informed decision-makers.
We appreciate that this language in the draft guidance is drawn from the requirements for the documentation of informed consent, but we urge the FDA to rethink the relationship between the consent document and the required information. When consent forms are used as a mechanism for providing potential subjects with information about any and every risk, benefit, or alternative possibly related to participating in a given clinical investigation (as has become commonplace), the result is a form that is overly lengthy and not understandable by many potential subjects. PRIM&R believes that the primary purpose of the consent form should be to memorialize the outcome of the consent process. Signing a consent form symbolizes that the subject has made the choice to participate in the research and memorializes that decision in a formal document. Of course, the consent form should summarize the points that are most likely to be important to a potential subject’s decision to participate, but placing a full recitation of all the required elements in a legalistic consent form—from an explanation of the details of the intervention being investigated to all the available alternatives, each with its burdens, benefits, and risks—typically overwhelms and confuses potential subjects, deadening rather than sharpening their decision-making. The information relevant to the subject’s decision to participate will often be better conveyed in other documents or electronic media and, of course, through discussion with the investigator, other research personnel, and sometimes with the subject’s other medical care providers.

It must be noted, however, that our recommendation that consent forms be crafted to formalize and memorialize a subject’s decision to participate in research presupposes the occurrence of a robust and purposeful consent discussion that focuses on the information most relevant to that decision. Thus, we urge the FDA to give greater attention to the process of discussion than is now provided by the draft guidance, which focuses largely on delineating the purpose and the content of the consent form. The form and function of the consent discussion, as well as its relationship to the consent form, is left unclear. We encourage the FDA to more clearly set forth the necessary features of the consent discussion and to clarify its relation to the consent form. We also believe the guidance document should emphasize the utility of using other methods—oral and visual as well as written—for conveying information to potential subjects, both to improve comprehension and to keep the consent document focused on its central purpose.

Relatedly, at several points throughout the draft guidance it is unclear whether the FDA is recommending the presentation of information in the consent form, the consent discussion, or both. We urge the FDA to review all recommendations in the draft guidance and to revise them as needed both to provide appropriate specificity as to whether particular types of information are to be addressed in the consent form or consent discussion, and to encourage investigators to rely principally on the consent discussion in preference to the consent form as the means of conveying the wide range of necessary information.

II. Presentation of Risks

In its discussion of the basic elements of informed consent, the FDA indicates that reducing length may increase the readability of consent forms (Section III.B.1 in the draft guidance). It is well established that consent forms have become increasingly long to the potential detriment of subject comprehension. We commend the FDA for recognizing this issue and for its effort to enhance the value of consent forms. However, later recommendations in the draft guidance, specifically the FDA’s call for disclosure in the consent form of any reasonably foreseeable risks associated with the medically recognized standard care and appropriate alternatives, seem likely to perpetuate the problem of overly long and complicated forms (III. B). Respect for persons requires that potential
subjects be provided with the information necessary to carefully weigh the decision to participate in research, but the inclusion of any reasonably foreseeable risks related to standard care and alternatives would undoubtedly be counterproductive to the goals of the informed consent process. PRIM&R believes that the consent form, as well as the consent discussion, should focus on presenting potential subjects with the information that is most likely to be significant to their decisions about whether to participate in research.

In general, clinicians should discuss with their patients the benefits and risks associated with standard care. Thus, when information is being shared with a potential subject about a clinical investigation, that discussion should focus on the purpose of the research, that subjects do not need to take part in the research, and how a subject’s experience in the research context will depart from standard care, in terms of additional procedures, burdens, risks (i.e., potential harms), and potential benefits. In light of this, we urge the FDA to carefully consider its recommendations for the inclusion of any reasonably foreseeable risks associated with standard care and alternatives.

With respect to interventions and procedures required by the study protocol, PRIM&R appreciates and agrees with the FDA’s emphasis on only including those risks that are reasonably foreseeable (III.B.2). To help investigators, IRBs, and sponsors make determinations about which risks are “reasonably foreseeable,” we believe the distinction between “risks” and “side effects” associated with a clinical investigation can be useful. As we have commented previously, side effects are the expected and common effects of an intervention other than those that are desired or sought through the intervention. Along with the requirements for participation in the trial that differ from standard care (such as more frequent visits for additional monitoring), side effects are part of what a subject who enrolls in a clinical investigation is likely to experience. In contrast, the term “risks” refers to a broader range of possible events or outcomes, most of which are unlikely to occur, but some of which are serious enough that the possibility that they could occur should be mentioned. Informing subjects about “side effects” as well as such serious “risks” makes clear to subjects the distinction between what their participation is likely to entail and what more serious outcomes are possible, if rare. Using this framework will strengthen subject protections, while providing greater clarity to IRBs, investigators, and sponsors about what outcomes are appropriate for inclusion in the consent process.

Our recommendations about what information is central to the informed consent discussion and the content of the consent form are not ad hoc. Rather, they rest on the purpose of the entire process, which is to enable potential subjects to be well informed before they make the decision whether to receive care (or diagnosis or prevention) for their condition solely as patients in a clinical setting, or as patient-subjects in a research setting. What, specifically, is entailed in making the latter choice? First and foremost, potential subjects need to realize that they are being asked whether they wish to contribute to answering a scientific question (e.g., about the efficacy of the intervention being tested and its side effects and risks). That choice will depend, in part, on the additional burdens in terms of time, inconvenience, pain, expected side effects, and the like entailed by choosing to enter the trial rather than to receive standard care. Further points that are inherent in entering the trial—and that an informed decision-maker would reasonably want to know—are the likelihood (based on how subjects are assigned to the trial’s active versus control arms) that the subject will receive the active intervention, and what the subject would receive if assigned to the control arm (i.e., an established, effective intervention or a placebo). In contrast are those risks that are not inherent in participating in the trial but that are possible, the salience of which depends not only on their probability and magnitude, but on how they differ from the risks of the care the
subject would otherwise receive. In each case, some of the risks are foreseeable (based on experience with comparable drugs or procedures) albeit somewhat unknown, and some are predictable because the trial involves an intervention (such as anesthesia) that carries a known risk. When a consent form is devoted in large part to a litany of possible risks that are presented without being placed in the context of what a patient-subject is likely to experience if he or she does not enter the trial, the form is not helping the potential subject to make an informed decision. That consideration should guide investigators and sponsors in shaping the informed consent process, as well as IRBs evaluating their plans and efforts in this regard.

III. Investigator Responsibilities

The inclusion of specific sections delineating the respective responsibilities of IRBs, investigators, and sponsors for informed consent is a welcome addition to the FDA’s guidance in this area, and we applaud the FDA for recognizing that each of these groups has an essential role to play in the informed consent process (IV).

We also commend the FDA for recommending that investigators consider the order in which information is presented to potential subjects in the consent form (IV.B.). The goal of the informed consent process is to impart information in a way that empowers potential subjects to make informed research participation decisions. In order to improve comprehension and ensure that consent is truly informed, PRIM&R believes that such an approach should also extend to the consent discussion. To assist investigators in operationalizing this recommendation, we encourage the FDA to seek out—by consulting with experts and reviewing relevant empirical research—and share best practices for imparting information to potential subjects.

PRIM&R also suggests that the FDA support investigators and sponsors who wish to develop alternative approaches to information disclosure that will enhance the consent discussion, such as videos or online resources. Technology-assisted learning methods can be used to increase comprehension, test potential subjects’ understanding, and provide documentation of the consent process. The FDA should make it clear that it is open to accepting these new methods once data establishes their utility.

As a final point, we urge the FDA to consider requiring investigators and/or research staff to attest that they have discussed the risks, benefits, and alternatives and provided the potential subject with an opportunity to ask questions, and that, in their judgment, the potential subject understands the information that has been presented and has voluntarily chosen to participate. The addition of an attestation statement would help reinforce the responsibilities of investigators and research staff charged with facilitating consent discussions.

IV. Understandable Language

We applaud the FDA for recognizing the importance of ensuring that consent language is understandable to potential subjects. It is good that at the outset the draft guidance frames what we already know: the health literacy and numeracy (quantitative literacy) of many US adults are at a basic level (III.A.3). When the informed consent process is working as intended, it reflects, and responds to, this reality.
In order to achieve the ideal of a properly functioning consent process, we recommend strengthening the FDA’s guidance in several ways. First, to ensure that information is presented to potential subjects in a manner that is understandable, the FDA should recommend that scientific and medical terms only be used when necessary and, whenever possible, as parentheticals to ordinary language descriptors. Consent forms often present definitions of scientific and medical terms in the body of the form. When possible and appropriate, we suggest that this process be reversed. Relatedly, when it is deemed necessary or appropriate to use scientific and medical terms, consultation with plain language editors should be sought, so as to ensure that such language is understandable to potential subjects.

Second, low numeracy presents its own challenges, but the draft guidance—having acknowledged the limited quantitative literacy of US adults—fails to provide adequate recommendations for ensuring that quantitative information is understandable to subjects (III.A.3). Discussing probabilities, percentages, and other quantitative information with potential subjects will not enhance and may undercut comprehension, yet the draft guidance calls for elements such as “quantified comparative estimates of risks and benefits” (p. 10). Since clear communications about the likelihood of risks and benefits is essential to the consent process, the FDA should carefully consider how investigators and sponsors can achieve this objective. We believe the FDA will be able to offer more useful recommendations to IRBs, investigators, and sponsors if it engages with experts who can offer guidance and tools for presenting quantitative information to potential subjects.

Finally, some areas of the draft guidance conflict with the agency’s recognition of limited literacy among US adults. Specifically, the only sample language provided by the FDA—language for informing subjects that they have a legal right to seek compensation for research-related injuries—is overly legalistic and complex, and very unlikely to be comprehensible to an individual with limited literacy (p. 11-12). While we applaud and appreciate the inclusion of specific examples in the draft guidance, we urge the FDA to ensure that both its recommendations and any examples it provides are consistent with the reading level of the average US adult. Additionally, the draft guidance should make clear that, when designing consent forms for some studies, the model language offered in the document may have to be adjusted for subjects with below average literacy.

V. Enrollment of Non-English-Speaking Subjects

The principle of justice requires that no specific population either be unfairly excluded from the potential benefits of research or unduly subjected to its burdens. When barriers to enrolling individuals from a specific population, such as non-English speakers, are high, concerns related to the principle of justice arise. Given the changing demographics of the United States, the inclusion of specific guidance on the enrollment of non-English-speaking subjects is a welcome addition to the agency’s guidance document (V.B).

Rather than enhancing subject protections, however, some of the recommendations put forward by the FDA may impose unnecessarily restrictive and burdensome requirements on the enrollment of non-English-speaking subjects. For example, in the event that a non-English-speaking subject is enrolled unexpectedly and the timeframe for enrollment does not allow for the preparation and IRB review of translated consent documents, the draft guidance states that an investigator should consult with the IRB chair in order to determine if there is sufficient justification for the enrollment
of the subject anyway. If it is determined that there is, the investigator can utilize an appropriately translated and IRB-approved “short form” and written summary to enroll the subject (V.B.2).

The aim of such an exception, which is to facilitate the enrollment of non-English-speaking subjects, is undermined by two further requirements in the draft guidance. First, at the time of enrollment, non-English-speaking subjects must be provided with a copy of the IRB-approved English version of the long form. The purpose of providing such subjects with a copy of the long form in English is unclear and reinforces a legalistic view of the consent form that undermines its true purpose. Second, the draft guidance requires that subjects be provided with a translated version of the long form after they are already enrolled in the research, a requirement with costly implications and questionable benefits. PRIM&R believes that subject protections should never be compromised in the interest of reducing costs or administrative burdens. However, we recognize that institutional resources are finite and should be used where they will do the most good; we thus caution against requirements or recommendations that are financially or administratively burdensome when there is little evidence that such requirements will enhance subject protections. In this case, given that subjects have already participated in the consent discussion and enrolled in the research, it is unclear what post-hoc provision of the long form will accomplish from a subject-protections perspective. Indeed, there is some reason to be concerned that institutions, wary of the expenditure required to create such long forms, might be deterred from enrolling non-English speakers in research, raising serious justice concerns. In light of these concerns, we urge the FDA to reconsider this requirement.

We also wish to make a general point about the availability of medical interpreters during the consent process and clinical investigation. Ideally, professionally trained medical interpreters would be available and accessible to all non-English speakers during the consent process and throughout the duration of a clinical investigation. PRIM&R recognizes, however, that such a requirement may be unrealistic given realities faced in the research setting, including the limited availability of properly qualified medical interpreters. We thus encourage the FDA to recommend that investigators and IRBs carefully weigh the complexity and risk associated with individual studies to determine if the presence of a professionally trained medical interpreter is likely to significantly enhance subject protections. In cases where it is determined that the presence of a professionally trained medical interpreter is not likely to significantly enhance subject protections—for instance, because the study is not particularly complex or risky—we recommend that alternative means for enhancing subject understanding be explored, such as the use of more robust, translated short forms, or staff members who can serve as interpreters.

VI. Additional Comments

Finally, PRIM&R offers the following additional comments:

- PRIM&R agrees that the enrollment of subjects in more than one clinical investigation simultaneously, and the enrollment of subjects in the same clinical investigation multiple times, should, in general, be strongly discouraged (V.G.). However, we believe that additional guidance is needed regarding how multiple enrollments should be discussed with potential subjects in the consent form and the consent discussion.

- PRIM&R appreciates that the FDA has clarified that subjects may be informed about whether a product is already on the market and may be prescribed by a healthcare provider
outside of the research context for the labeled indication or for other conditions/diseases that the provider determines are appropriate (III.B.1). We agree that when a drug that is being evaluated in a clinical investigation is also available in the marketplace—with or without a prescription—prospective subjects should be informed of that fact.

- As we noted at the outset, the emphasis on flexibility as a tool for enhancing understanding is one of the strengths of the FDA’s draft guidance. However, in order to make sure that such practices can be operationalized by institutions, sponsors, investigators, and IRBs, the FDA must ensure that parties responsible for monitoring, inspection, and enforcement understand, and are in agreement with, the recommendations that have been put forward. Institutions must not face sanctions for exercising the regulatory flexibility outlined in this and other guidances produced by the FDA.

PRIM&R is grateful to the FDA for the opportunity to comment, and we hope that you and your colleagues will find our input on this matter to be useful as you finalize this guidance. 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