PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

October 26, 2011

Jerry Menikoff, MD, JD
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Submitted electronically at www.regulations.gov

RE: Docket Number HHS-OPHS-2011-0005, advance notice of proposed rulemaking on human subjects research protections published in the July 26, 2011 *Federal Register* (76 FR 44512)

Dear Dr. Menikoff:

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to submit comments regarding the advance notice of proposed rulemaking, "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators," published in the July 26, 2011 Federal Register.

PRIM&R is a non-profit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served the full array of individuals and organizations involved in biomedical, social science, behavioral, and educational research. PRIM&R's membership community includes professionals working with human research protection programs, institutional review boards/research ethics committees, institutional animal care and use committees, and institutional biosafety committees, as well as researchers, institutional officials, government personnel, subject advocates, ethicists, policy makers, pharmaceutical and biotechnology employees, and attorneys. Via a wide variety of conferences and other educational activities, PRIM&R provides current, balanced, thorough, and accurate information on a range of ethical and regulatory issues affecting research, while also offering access to certification, networking, professional development programs, and other resources.

I. Introduction

Before providing more detailed comments, PRIM&R wishes to make a few general observations. In several places in the ANPRM, it is suggested that whenever an IRB creates more stringent protections for subjects than those provided in the federal regulations, the IRB needs to register them with OHRP. We think it is essential for all involved in the human subjects protections process to understand that federal regulations set the *minimum standard* for the protection of human subjects, and that no barrier should exist for institutions wishing to adopt rules that they believe enhance such protections. Therefore, we recommend deleting any statement or implication that institutions must provide justifications for enhancing human subjects protections.

A related issue involves the role of IRBs in the human subjects protection system. As is true in much of the literature on human subjects protections, the ANPRM focuses on the IRB and largely ignores the other actors involved in human subjects research. Most notably, the ANPRM rarely refers to either the authority or the obligation of the *institutions* in which research is conducted. IRBs do not adopt stricter research rules, but rather the institutions in which IRBs reside do. It may be that the institution delegates this authority to its IRB, but ultimately any additional rules are *institutional* rules, not IRB rules. Similarly, *institutions*, not IRBs, are responsible for protecting the safety and welfare of subjects.

In that same vein, IRBs neither interact with subjects nor write consent forms. Rather, consent forms are often written by sponsors and sometimes by investigators, who then present them to an IRB as part of its review of the research. IRBs work with what is submitted to them, so we strongly urge that OHRP remind sponsors and investigators that they have an obligation to create clear and understandable consent forms prior to submitting them to IRBs for review, and that *they* are the entities that actually design and conduct research which makes them primarily responsible for protecting human subjects. As discussed below, we recognize that consent forms have become increasingly legalistic documents designed to protect institutions and sponsors rather than to protect human subjects. This is not, though, a problem created by IRBs, and often there is little an IRB can do to correct this in the face of institutional and sponsor pressure. If change is going to come in this area, sponsors and investigators must take primary responsibility for making informed consent forms more useful to subjects than to themselves.

The "Common Rule" as currently written applies to institutions, not to sponsors or investigators. Because of this, sponsors and investigators may have little incentive to take seriously their obligations to protect human subjects, and may instead try to foist their responsibilities onto institutions and IRBs. The most effective way to reverse this reliance would be for OHRP and the FDA to work together to make investigators and sponsors responsible for the quality of work they do in regard to the protections they provide to human subjects. We recognize this may raise some jurisdictional issues in that it is the receipt of federal research funding that triggers the authority of the federal government to regulate an entity in this area, and that the institutions, not

individual investigators, are the technical recipients of federal research funds. However, we suggest there is no barrier to regulating investigators and sponsors whose work is directly supported by federal funding. We suggest that OHRP further investigate the jurisdictional basis for regulating investigators and sponsors with the goal of regulating them more directly. One benefit of this approach would be that federal regulators would no longer have to choose between doing nothing, on one hand, and cutting off funds for entire *institutions* whenever there is a violation of the federal rules, on the other. Intermediate sanctions applicable directly to investigators and sponsors would encourage practices that enhance protections for human subjects more effectively than cutting funding to entire institutions, an approach so draconian that it cannot be applied without wreaking havoc that upends research that other investigators are carrying out ethically and in compliance with the regulations.

An important aspect of human subjects protection that was not addressed in the ANPRM is the need to better train IRB members, chairs, and investigators in the ethics and regulation of human subject protection. Individuals become members of IRBs for a variety of reasons and with a variety of backgrounds. People who volunteer to serve on an IRB out of sense of mission are quite different from people who are required to sit on an IRB by department chairs to fulfill their committee membership obligations. Given this variance in IRB members' backgrounds and motivations, IRB training must go beyond a discussion of the compliance aspects of the regulations and extend to an exploration of the important ethical issues raised by even mundane-appearing human subjects research. In our opinion, what currently passes for adequate training, such as the information on the NIH website, is not sufficient. For many training programs, one cannot even determine who is actually sitting at the computer completing the minimal certification process. While we offer no specific recommendation here, we suggest that revised educational/training requirements be placed on the agenda for further regulation.

There is a semantic point that needs clarifying. The ANPRM and the literature often use the term "IRB review" to include a range of different activities. This phrase could refer to review by a fully convened IRB that meets the quorum requirements, or to an administrative action that is implemented by IRB office staff. Of course, full IRB review is the most burdensome and time-consuming form of review, and so the suggestion of IRB review conjures up delays and bureaucracy. Given the possibility of being misunderstood, it is important to be specific when asking about the desirability of IRB review so that it is clear to what the drafters are referring.

There are two final general points we wish to make before proceeding to the specific elements of the ANPRM. The stated purpose of issuing this ANPRM is to make the process of human subjects protection more efficient. We fully recognize the potential benefits of accomplishing this goal. But we also want to note that efficiency itself is not a moral imperative or even an ethical value; human subjects protection should not be compromised by a desire for increased efficiency, a view we believe OHRP shares. Second, the term "harm" is used throughout the ANPRM, and its use seems to refer mostly to physical harm. The goal of human subjects

protection is not just to minimize the risk of physical or psychological harm, which protects subjects' *welfare*, but also to protect the *rights* and autonomy of current and potential subjects, an imperative that is based on respect for human dignity, not simply regard for physical or psychological welfare.

We turn now to PRIM&R's more specific comments. The comments are organized by broad topic, and we note in the text where we are responding to specific questions posed in the ANPRM.

II. Informed Consent

PRIM&R believes that an effective informed consent *process* is central to the protection of human subjects, whereas the proposals in section IV of the ANPRM focus almost exclusively on the written consent *form*. PRIM&R suggests that OHRP focus on improving the process of seeking and obtaining informed consent, with particular emphasis on the ongoing and iterative nature of the consent process; the responsibilities that investigators bear for ensuring that truly informed consent is obtained and the importance of educating investigators about their role; and methods for determining whether and to what extent a robust consent process actually takes place (addresses Q. 38). OHRP might consider explicitly suggesting that while the investigator is responsible for assuring that informed consent (not just a signed consent form) is obtained, the use of professionals with expertise in patient education as representatives of the investigator in the informed consent process is acceptable or even encouraged. Physicians and principal investigators are often not the best patient/subject educators and are far from neutral when proposing that a person enter a research study for which the investigator needs to enroll a sufficient number of subjects. Another concern is that the ANPRM's emphasis on *forms* inadvertently reinforces the mistaken belief that the forms are what primarily matters to OHRP.

Despite our concerns about an over-emphasis on consent forms, it is PRIM&R's view that forms may serve a meaningful role in a robust informed consent process, and that consent forms can be vastly improved. To do so one needs to recall that the original goal of consent forms was to memorialize what transpired during the informed consent process. They were not intended to be the primary method of informing potential subjects of the risks, benefits, and alternatives to enrolling in the research project. Over time, for reasons that are not entirely clear, consent forms have become longer, more complicated, more "legalistic," and less useful as sources of information to potential subjects. One likely reason for this is that consent forms have evolved from documents that present useful information that was discussed during the consent process to documents that are primarily designed to protect institutions, sponsors, and investigators, and not to educate subjects. To enhance the value of consent forms, this trend should be reversed (addresses Q. 35).

Another reason for lengthy and redundant consent forms is that there seems to have arisen a culture—this includes regulators as well as institutions— that insists that every piece of useful information must be included in the consent form. At the same time virtually no one involved in human research protections thinks current consent forms are useful or appropriate. Surprisingly, given this almost unanimous disapproval of current consent forms, there seems to be widespread reluctance about making any changes to them. Institutions are concerned that if the forms are considered incomplete, OHRP will find them to be out of compliance. Therefore, from their self- interested perspectives, institutions have nothing to lose by using lengthy, comprehensive forms, even if they are incomprehensible to potential subjects. As far as we know, OHRP has never criticized any institution for using consent forms that are too long or complex. It would be incorrect to blame IRBs for this problem as sponsors, institutional lawyers, risk managers, and other executives are primarily concerned with institutional protection rather than subject information. One way to reduce some of this apprehension about changing, clarifying, and shortening consent forms is for OHRP to clarify its minimum requirements for such forms as well as its enforcement methods for consent form inadequacies. OHRP also needs to make clear that varying approaches to the documentation of informed consent are acceptable (addresses Q. 35).

PRIM&R has some specific suggestions about informed consent documents that address ANPRM questions 35, 36, 37, and 40. To improve the informed consent process will necessitate a change to the common understanding of the purpose of its documentation. To facilitate this change, we suggest the documents that contain subject information no longer be called "informed consent forms" or "informed consent documents." Titling them "forms" or "documents" perpetuates the sense that they are for "legal purposes." Asking subjects to sign 15, 20, or 30-page consent forms further perpetuates the understanding that they have primarily legal implications, rather than informational ones. Instead, these documents should be called "educational material for potential subjects." We think this immediately changes everybody's understanding of the purpose of these materials. Furthermore, when they are conceptualized as "educational materials," it becomes even clearer that they should be written in language the "students" can understand. It also makes clear that there may be additional relevant materials provided to the potential subject that are not contained in this one particular document.

One can then consider the purpose and goals of these educational materials. The key point is that not everything that is useful to subjects needs to be in one document. Instead, we suggest that the primary educational document for biomedical research (this would also be applicable to behavioral research with some modification) should contain the following elements in lay language (addresses Qs 32, 36):

1. A clear statement that "you are being asked to be in a research project, which means the primary purpose is not to *treat* you, but to gain new knowledge about your condition…" or "to learn more about whether an intervention might become a treatment in the future."

2. A description of the *research* procedures that describe the interventions a subject would not encounter if she were solely a patient receiving standard treatment. If part of the research involves risks related to the collection of data from tests that would be done for treatment purposes even if the person was not in the research project, those risks need not be disclosed. (Of course, they must be disclosed at the time of the therapeutic intervention by the professional performing the intervention.)

3. The expected side effects of the research procedures. We intentionally use the term "side effects" and not "risks." Side effects are the expected and common effects of interventions. For example, hair loss is a side effect of some chemotherapeutic agents, not a risk, even though some people might not lose their hair. Discomfort while undergoing bronchoscopy is not a risk–it is a side effect.

4. When side effects may come from more than one source (for example, the subject will receive two drugs with similar side effects), the side effects should not be repeated for each drug. From the perspective of the potential subject, which intervention causes the side effect is of little or no interest—what matters is the likelihood of encountering a certain form of discomfort or unpleasant experiences as a result of being in the research.

5. A statement that there are "risks" inherent in the research, where by "risks" is meant bad things that are not expected to happen but which could happen (these would be listed in a separate document—see below).

6. A clear statement that the decision to enroll or to not enroll in the study is entirely voluntary and that all standard treatments will be available if the person does not choose to enroll. We recommend avoiding words like "penalty" in this document, even to explain that there will be no "penalty" for deciding not to participate. Many potential subjects might not even consider this possibility of a penalty until they hear the investigator mention it.

7. A statement that one is free to withdraw from the study at any time for any reason, even though, in some cases, the actual process of withdrawal must be gradual to prevent harm. The document should explain that one can withdraw from the prospective part of the research study, but not from procedures that have already happened. For example, the investigative artificial knee replacement will remain in place unless there are clinically indicated reasons to remove it.

We suggest that no other information be included in the primary educational document. Everything else that is currently considered "boilerplate" and is found in every document the institution uses for research permission should be provided in a separate document, such as a booklet that describes the *rights of all research subjects* to privacy, whom to call with questions or concerns, the non-waiver of rights, and so forth. If there is something special about these matters in a given piece of research, then that should be in the research procedures and risks portion of

the educational materials created for the specific research project. The information in the booklet would be useful information, and while one does not "consent" to these matters, all potential and current subjects should be aware of the protections that are offered to all research subjects (addresses Q. 37).

The question remains of how a potential subject indicates *consent* to research participation. PRIM&R suggests that the way a subject consents is by affirming to the person who is providing the subject with the informational materials what he or she has agreed to do. The *documentation* of consent can be accomplished by the subject's signing a separate brief form that accompanies the educational materials that indicates only that the subject has read and discussed the educational materials and, having done so, agrees to participate in the research (addresses Qs. 36, 37).

Finally, PRIM&R would like to submit the following additional comments in responses to specific proposals made in Section IV the ANPRM:

- There should be no arbitrary limit on length of consent forms or their sections. Rather, narrowing the scope of information included in the documentation of consent will reduce the length of such documents. (See above.)

- While PRIM&R questions whether the federal consent form templates proposed in the ANPRM will be helpful, if they are adopted the regulations must make clear that they provide suggested language only, and that their use is not mandatory. The regulations should further clarify that use of the federal templates will not immunize institutions from citation for failure to adhere to the regulatory and ethical requirements for obtaining informed consent. If templates are made available, it is essential that they be created by bona fide health educators and experts in health communications to patients, not by regulators, lawyers, doctors, or others who routinely use jargon that is unlikely to be understood by those with less education and expertise (addresses Q. 37).

- As stated above, IRBs do not write consent forms. We would like to see OHRP work with sponsors, investigators, and other federal agencies to sensitize them to the need to produce useful documents that will comply with the new requirement to create educational, not legal, documents.

- It appears that the ANPRM's discussion of waivers does not take into account HIPAA requirements for granting waivers. Future versions of this document should take HIPAA rules into account or should suggest changes in HIPAA rules.

- PRIM&R does not support the proposal that written consent be required for all biospecimen research, regardless of whether or not the biospecimens are de-identified and whether or not the research entails analysis of the biospecimen that would allow the

person from whom the specimen came to be identified. PRIM&R favors the status quo, whereby unidentified biospecimens may be used for research purposes without consent. PRIM&R does not believe that the use of such de-identified specimens violates the rights or welfare of subjects, and the requirement that consent be obtained for all uses of de-identified biospecimens would make it prohibitively difficult to conduct much of the research involving biospecimens that is currently being conducted (addresses Qs. 23, 45, 46, 47).

III. Privacy

Protecting the privacy of research subjects is an ethical imperative. PRIM&R agrees with the ANPRM's general suggestion that privacy interests remain largely consistent from study to study, that general standards can be created to protect privacy, and that pre-review is not usually necessary to protect subject privacy if other effective mechanisms exist.

Contrary to the suggestions made in the ANPRM, however, PRIM&R believes that HIPAA provides a poor model for protecting research privacy. It is a particularly poor model as applied to research data because much of HIPAA is concerned with authorizing the release of medical information to insurers, law enforcement, other providers, and so on (addresses Qs 54, 59).

PRIM&R proposes some general standards to enhance protections for research subjects which are based on a sharp distinction between "research records" and "medical records." Medical records are created when *patients* interact with health care professionals to receive medical treatment or advice to maintain or improve health. They may contain test results, pharmaceutical information, and medical history. Such records are appropriately protected under the provisions of HIPAA.

"Research records" contain data that was created in the context of a bona fide research project. Unlike medical records which include a comprehensive and broad array of personal information, the vast amount of data contained in research records is of little or no interest to anyone other than the researchers. As far as we know, there have been no cases of unauthorized research data release, even in the absence of the application of HIPAA rules. Because there is no need to release research records, HIPAA's burdensome requirements are not necessary to adequately protect such data. (Furthermore, while hospitals may be able to interpret, pay for, and apply HIPAA requirements to their patient populations, non-biomedical researchers and their institutions have no familiarity with HIPAA.) (Addresses Q. 54.)

Accordingly, PRIM&R proposes the following. Any data collected in the context of an IRB-approved research project would automatically constitute research data and should be stored separately from medical or other clinical records. The ANPRM proposes that, as long as the privacy rules are clear, prior review by IRBs is not necessary to protect subjects' privacy interests. PRIM&R agrees with this suggestion in part, but suggests that when considering the

appropriateness of IRB review, a distinction needs to be made between the collection of data and the maintenance of data once collected. Given the fact that the collection of data often happens via an interaction with research subjects in which sensitive or disturbing questions may be asked, questions about how, where, in what format, and from whom to safely, securely, and respectfully collect and protect such data, falls within the purview of the IRB. In other words, PRIM&R recommends that considerations about when and how to protect research subjects at the point when information is gathered through interaction with research subjects should continue to be subject to prior review, although not necessarily requiring action by a convened IRB (addresses Q. 60). Once the data has been collected, however, questions about appropriate methods for storing, maintaining, moving, sharing, or destroying the data are matters that need not concern the IRB, again, assuming that there are other effective and enforced privacy rules and mechanisms in place.

For research that does not require IRB approval, a registration system should be created in which investigators summarize their research and provide that summary to institutional officials who certify the records as research records. These officials can be those involved in protecting privacy, such as a privacy officer, not necessarily an IRB staff member. In the absence of IRB approval, a registration system is a transparent way of identifying research data as such and setting expectations that the data is protected in the ways outlined above. It is also a method for identifying and registering bona fide researchers. Release of *any* research data to employers, insurers, law enforcement agencies, marketers, family members, the general public, the press, etc., would *never* be considered a release to bona fide researchers (addresses Qs. 54, 56).

We suggest that primary researchers (i.e., those who collect the data for research) be allowed to share *unidentified* research data with other bona fide scientific researchers (i.e., secondary researchers), without subject consent. This proposal requires a set of criteria outlining what qualifies research data as unidentified for the purpose of protecting the privacy of research subjects, although those criteria need not be as stringent as the HIPAA requirements. We believe it is possible to create a simple list of what makes a research subject reasonably "unidentified," that would function as a more effective tool for protecting research subjects than the HIPAA approach. We have not developed those criteria, but suggest preliminarily that data is adequately unidentified if secondary researchers cannot identify the person from whom the data was derived without taking additional steps (address Q. 59). (Note that we use "unidentified," instead of "de-identified" or "de-identifiable" intentionally, because the latter suggests the ability to reconnect private data with individuals.)

To fortify these protections, we suggest creating a rule that forbids identified data from being released to non-research entities including employers, insurers, law enforcement agencies, plaintiffs, lawyers, and so on without subject consent. This rule differs from HIPAA, which permits disclosures in some circumstances in the absence of subject consent. Given the limited data contained in research records this should have no, if any, effect on the entities listed earlier in

this paragraph. Further, there would no longer be a need for "certificates of confidentiality" under such a rule because all identified research data would be covered (addresses Qs. 54, 56, 61, 64). This reduces the burden on investigators to apply for such certificates.

In order for this proposal to effectively protect subjects, it must be made a serious *crime* for anyone to intentionally release, induce the release of, re-identify, or attempt to re-identify, previously de-identified research data, whether in the form of written records, electronic records, DNA, or biospecimens. Making it a crime to re-identify de-identified DNA specimens should address the technical concern that all specimens are potentially re-identifiable (addresses Qs. 54, 56, 65). Furthermore, these rules and sanctions must apply to individuals as well as to institutions. Making actions that threaten subject privacy a crime deters such transgressions. This process is not without precedent. It resembles that used for the protection of bank records, IRS records, and other important records which does not require pre-review. While we recognize that this would require legislative action, we urge HHS to initiate and advocate for such action. Meanwhile, HHS can use its regulatory authority to remove transgressors from eligibility for current and future funding.

The only exception to a rule outlawing re-identification would be for the rare circumstance in which such re-identification is clearly necessary for the protection of the person from whom the data or specimen was taken, and where it could be concluded that a reasonable person would wish to receive such information. This determination could not be made solely by the researcher, but would be made in accordance with institutional policies that require the involvement of individuals knowledgeable about the relevant science and ethics of such a determination.

PRIM&R's proposal to protect subject privacy goes far beyond the protections of HIPAA while being less burdensome for IRBs and researchers. If the strong protections of privacy we suggest are adopted, these rules could make existing data and specimens available for research without additional review, because there would be no additional interaction with human subjects, and the potential for the unauthorized release of identified research data would be deterred by strong sanctions that should be applied to both institutions *and* the individuals who are responsible for the wrongful release of data (addresses Q. 54).

Existing data or specimens that were collected with explicit restrictions on use imposed by the subject could not be used other than in conformity with those restrictions. While the safety and welfare of this group of subjects would not be damaged by the use of such data or specimens, it would be a direct affront to the previous explicit exercise of their autonomy (addresses Qs. 46, 47).

Finally, with regard to privacy, PRIM&R reiterates that nothing in the federal rules or laws should prevent an institution from adopting stricter rules to protect subject privacy, including an institutional rule that requires preapproval, in addition to registration.

IV. Centralized Review

In principle, PRIM&R favors a system of centralized review for multi-site studies as a means of reducing inefficiencies in the current research review system that do not enhance the protection of human subjects. That said, PRIM&R does not support the proposal to mandate that there be one IRB of record for all multi-site studies.

As made clear in the introduction, PRIM&R supports institutional flexibility in the protection of human subjects and therefore urges that no institution ever be required to justify additional review or any other additional measures it adopts to augment the protection of human subjects. In this instance, then, it is PRIM&R's view that no institution should be excluded from participating in a multi-site study because it refuses to rely solely on external review to protect human subjects (addresses Q. 30). It is also PRIM&R's view that while institutions may voluntarily enter into some sort of central review process, institutions should never be relieved of their ultimate responsibility to protect human subjects within their institution as part of an overall human research protection program (addresses Q. 31). If the federal regulations evolve in the area of centralized review, they should be absolutely clear that review is only one part of a human research protections program and that institutions remain responsible for all research activities that take place within the institution.

PRIM&R suggests a distinction should be made between centralized *review* and a *central IRB*, a distinction not included in the ANPRM. There are several ways that multiple institutions can come together to participate in a process of centralized review of research to be conducted at each of those sites. For example, there is a consortium model that several prominent academic institutions have recently adopted, and that provides a robust centralized review process that all participating sites agree to, but without ceding review responsibility to a completely external body. Each institution may decide, on a protocol-by-protocol basis, not to participate, or to override centralized decisions depending on the nature of the research proposed and the institution's needs.

Where there is one central review board (e.g. a commercial or independent review board), the term "IRB" should not be used. IRBs are "institutional" review boards, and central review boards are not part of the institutions conducting research with human subjects. The use of "IRB" in these contexts is confusing and inaccurate. We would therefore suggest that the term "IRB" be replaced by either "research review committee" or "research review board," names that better reflect the purpose of these bodies.

V. Calibrating level of review to level of risk

Expedited review

The ANPRM proposes revising the current list of research activities that qualify for expedited review, and putting in place a Federal panel that would periodically revisit and refresh the list. PRIM&R is concerned about the creation of an *all-inclusive list* of research activities that qualify for expedited (addresses Qs. 7, 8, 9). We suggest that the regulations set out criteria for what constitutes minimal risk which IRBs could apply to specific proposed research activities and determine if those activities would be appropriate for expedited review. It would, however, be useful for OHRP to create an illustrative (not exhaustive) list of what it believes to be minimal risk research that would be eligible for expedited review along with *its reasoning* for placing these illustrative cases on the list. This would enable IRBs to better understand and incorporate the principles that lead to a legitimate categorization of minimal risk research and a subsequent expedited review determination.

PRIM&R strongly suggests that research subject to expedited review be required to meet all of the criteria for IRB approval of a study at 45 CFR 46.111. Standards for approving research should not vary based on the process for approving research. Expedited review should in no way be seen as less stringent, merely faster, which is what the term "expedited" means. All human subjects should be entitled to the same substantive protections regardless of the method of review. In addition, there are studies that move from expedited to full board review or vice versa, and having separate standards would make that type of movement confusing for both reviewers and researchers (addresses Q. 10).

In response to the ANPRM's question about who should conduct expedited review (Q. 11), PRIM&R recommends that the regulations mandate that expedited review be conducted by an IRB staff person or IRB member. As the individuals within the institution who are most active in protecting human subjects, IRB members and staff are those most qualified to conduct such reviews. The notion of some other "qualified" person only raises the question of what would make this person qualified, whereas IRB membership or staff membership would be an automatic qualification, assuming that the means of education and preparation for IRB members and staff are adequate and clearly stated.

Exempt research

PRIM&R suggests that neither the term "exempt" nor the term "excused" be used to describe research that is not required to meet the 45 CFR 46.111 criteria. Rather the single term "research not subject to review" is a self-explanatory term that would cover what is considered "exempt" or "excused" (addresses Q. 20).

The ANPRM suggests creating a registration and retrospective audit system for research not subject to review (i.e., referred to as "excused" research" in the ANPRM). In such a system, investigators would complete a brief form for research they deem to be "excused," thereby registering it and making it eligible for retrospective audit. In this model, there would be no prospective review of the research, and presumably investigators could proceed immediately with the research, once it is registered. PRIM&R suggests that any proposal that authorizes investigators to make the determination of whether or not a proposed study constitutes "research not subject to review" is unwise and unnecessary. We have serious concerns about authorizing investigators with limited understanding of the regulatory system to make such determinations. We believe that OHRP's current position that investigators are not in the ideal position to make objective decisions about the level of risk or discomfort posed by their research has a sound rationale. PRIM&R suggests that some documentation of the study needs to be prospectively approved by an IRB staff member or a designated IRB member. This would not constitute a "review," since none of the 45 CFR 111 criteria would be applied. Rather the determination would be made that the proposed research actually meets the "research without review" criteria. This should be able to be determined in a very brief period of time with minimal paperwork involved. Since no research needs to be done emergently, a brief delay should cause no problems (addresses Q. 19, 22).

We support the expansion of the current exempt category 4 by re-defining "existing" data, biospecimens, etc. as proposed in the ANPRM, namely, to mean collected for purposes other than the proposed research. We do not see this as negatively affecting subject protections as long as no identifying information is attached to the data or specimens (addresses Q. 15).

Regarding the ANPRM's question about whether the Common Rule should be revised to explicitly state that certain activities that have traditionally not been viewed as research (classics, history, languages, literature, and journalism, e.g.) are not covered (Q. 25), PRIM&R is unaware that the failure to exclude these fields from the Common Rule has ever been a problem for scholars in classics, or literature, etc., and therefore questions whether such a provision is even worth considering. That said, PRIM&R suggests that determinations regarding what is and is not subject to IRB review should be made on the basis of the specific research activity in question, and not on the basis of an investigator's scholarly discipline. This would address some current inconsistencies regarding what type of inquiry gets reviewed (addresses Q. 25).

While it is the research activity and not the discipline that should determine whether and how a research proposal is reviewed, there is a sense in the research community that IRBs have expanded their scope to encompass activities that were not intended to fall under the purview of IRBs, including quality improvement, community based participatory research, public health surveillance, and clinical innovation.

PRIM&R suggests that the resolution of this concern lies in establishing clear delineations of the types of *activities* that do not need to be reviewed, and making clear *why* those activities do not require review (e.g., because they don't involve individual patient/subject contact, or because they don't involve manipulating an individual's environment, etc.). PRIM&R is currently working on definitions of each of the four activity types mentioned above, and would be pleased to share them when they are fully developed (addresses Q. 24).

Assuming that activities such as clinical innovation and quality improvement are determined not to require full IRB review, this does not mean that there are no ethical issues associated with those activities, or that there should not be some other mechanism for ethical oversight of such activities.

Other issues related to risk-based protections

The ANPRM asks whether there are other specific changes, in addition to those the ANPRM proposes, that would reduce documentation burdens imposed on researchers, without decreasing the protections of subjects (Q. 12). In response to this question, PRIM&R suggests the following with respect to continuing review. The regulations should state that the default is for IRBs to annually conduct continuing review, but that an IRB can decide to review less often, as long as it documents a justification for that decision. Similarly, the IRB should be able to require more frequent reviews of research when it deems such a measure appropriate.

The ANPRM asks whether a requirement for a mechanism by which investigators can appeal IRB decisions about research protocols should be inserted into the Common Rule (Q. 28). PRIM&R opposes any such requirement. Current rules provide that institutional officials can determine that a particular study approved by the IRB cannot be conducted at that institution, but that they may not override research that has been disapproved by the IRB. We question whether an additional institutional body would be better qualified than a properly trained IRB to apply the federal regulations and to therefore properly override IRB determinations. Frankly stated, an appeals mechanism is almost certain to be subject to institutional political pressures. Of course, institutions should be allowed, if they choose, to put in place mechanisms whereby an IRB can reconsider its decision. Each institution should handle this according to its unique structure and capabilities.

PRIM&R does not support the suggestion in the ANPRM that institutions be required to report any activity an IRB undertakes that goes beyond what it is required to do by regulation (including overriding provisions for expedited review and requiring full review). As we made clear in our opening comments, PRIM&R believes that institutions should always be permitted to add additional protections to the minimal regulatory requirements as they see fit without special permission or any presumption that doing some makes them "non-compliant" with the federal rules. In the absence of the authority to override the additional protections an institution

adopts, the reporting requirements would have no effect other than to increase the burden on the institution (addresses Qs. 13, 29). As noted earlier, federal regulations should be seen as a minimum set of standards below which institutions may not fall, but should never be viewed as a ceiling an institution cannot surpass.

VI. Post-IRB human subjects protections

Since the promulgation of the Common Rule, increased attention has been focused on the need for appropriate data monitoring plans for human subjects research, including at times having formal Data Monitoring Committees (DMCs). However, there seems to be variability in the quality of these plans and committees, as well as significant confusion about their purpose and proper composition. Accordingly, the proposed rules in section VI of the ANPRM should consider requiring IRBs to review the data monitoring plan for proposed research as well as establishing criteria for determining when a formal DMC should be required. (Currently a DMC is required under the HHS implementation of the Common Rule when there is an exemption from the requirement to informed consent in the emergency setting, but otherwise this is not the case.) As of now, there are no requirements for the composition and functioning of DMCs. Developing minimum requirements for DMC composition and processes, based at least in part on current FDA guidance, would provide additional protections for human subjects.

Thank you again for the opportunity to respond to the proposed changes to the Common Rule. We would be happy to work with HHS as it continues the important and challenging task of evaluating and revising the regulations in its efforts to better protect human research subjects. If you have any questions, or if we can provide any further information, please feel free to contact me at 617.423.4112, ext. 0, or by email at jrachlin@primr.org.

Respectfully submitted,

Joan Rachlin, JD, MPH
Executive Director
Public Responsibility in Medicine and Research (PRIM&R)

Cc: Board of Directors, Public Policy Committee