

October 26, 2011

Jerry Menikoff, M.D., J.D.
Office of Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway
Suite 200
Rockville, MD 20852

Docket ID#: OPHS-2011-0005

Dear Dr. Menikoff:

I write on behalf of Yale University to offer comments on the Department of Health and Human Services' (HHS) and the Office of Science and Technology Policy's (OSTP) Advance Notice of Proposed Rulemaking (ANPRM), entitled *Human Subjects Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay and Ambiguity for Investigators*, concerning modifications to regulations for the protection of human research participants.

Yale applauds HHS and OSTP for this landmark proposal, and the opportunity to participate in the review and revision of the Common Rule, with the goal of enhancing the protections for research participants by improving the effectiveness of the federal oversight system and focusing resources on higher-risk research interventions. Trust in the human research enterprise is essential to our ability to maintain public support and to recruit altruistic participants in the ethical conduct of research. It is our firm belief that the Common Rule can continue to provide a basic system of protections to ensure the safety, privacy and autonomy of human research participants while minimizing the administrative burden on research institutions.

Over the past 20 years, the regulatory system has grown in size and complexity, frustrating good practice and raising questions concerning the adequacy and the appropriateness of the system of protections. At the same time, research has increased in volume and diversity, making it essential for the regulatory system to be responsive to changes

in research methods and to be informed by the perspectives of those who must follow it. A guiding principle for any proposed modification to this system of protections should be to build on the fundamental premises of the Common Rule in a flexible way that does not impede scientific discovery. Going forward, the Common Rule should better support the consideration of individual circumstances and other contextual issues in the conduct of human subjects research. Equally important, the Common Rule should be subject to continuing review – at least once every five years – to reduce or eliminate outdated requirements and to evaluate any changes to the system and their effects. We believe the proposals which comprise the ANPRM are an important first step in this historic effort to streamline and improve this system of protections.

We have reviewed and considered the areas of proposed change in the ANPRM and have the following comments; we provide a summary discussion of the seven aspects of the current regulatory proposal followed by more extensive comments in response to the concepts and many of the questions posed in the ANPRM. We have concluded that the broad proposals on the risk-based protections, the single IRB for multi-site studies, and the improvements to informed consent are ripe for inclusion in the forthcoming NPRM. The other proposals are interesting and worthy of consideration, but they require additional study and refinement before they should be incorporated into rulemaking. We hope that the proposals in the ANPRM are severable. Broadly supported efforts to strengthen and modernize human subjects protections should not be delayed by more complicated, less well-developed issues. We also hope that this process will lay the foundation for the future development of proposals to review and revise other subparts of the human subjects protections regulations.

Executive Summary

Risk-Based Protections

Generally, we support efforts to calibrate the type of review to the level of risk posed by the research study. Regulations in this area should establish a minimal standard for risk, with institutions provided the flexibility to determine a level of review and continuing oversight commensurate with study's degree of risk. As part of the proposed modifications, we believe that it is essential to establish a concrete definition of minimal risk and to make clear that the IRB should identify and evaluate risks that are directly related to the research activity. Risks associated with standard of care procedures should not factor into the risk classification. In addition, we support the elimination of the continuing review requirement for minimal risk research studies, but any proposed modification should allow IRBs to establish local standards for reporting progress on minimal risk research. For "excused" research, we support the concept of requiring that an individual other than the researcher review the registration form. Although this individual should be knowledgeable about the possible risks posed by the research, the guidance should make clear that the reviewer need not be a member of the IRB. We also support a brief waiting period before excused research can begin, as investigators sometimes mistakenly believe that their research is exempt when it is not.

Although we appreciate the proposal to expand the categories that are eligible for expedited IRB review, the list itself is a historical artifact – and one that will never be fully complete. Instead of attempting to capture the range of activities that pose a minimal risk to human participants, we urge HHS to eliminate the expedited categories from the regulation and instead allow institutions to define those activities that are appropriate for expedited review. This would provide much needed flexibility in responding to interventions that are well-known to the institution but may not appear on the current list. To prevent inconsistent application across institutions, examples of minimal risk activities that are appropriate for expedited review could be discussed in guidance.

IRBs should not be required to submit periodic reports to OHRP when they choose to implement more stringent review processes. Reporting is an important mechanism for ensuring the protection of subjects, but this level of additional reporting in the aggregate appears to serve no real purpose and convey no additional benefit. Before we could agree to these periodic reports, we would have to be convinced that they benefit human subjects, as they would impose a significant administrative burden on institutions.

Single IRB for Multi-Site Studies

We support the general concept of using a single IRB of record for multi-site studies, but a number of issues require additional attention before unproductive, duplicative reviews are eliminated and the goal of an improved timeframe from protocol review to implementation is achieved. To facilitate this process, we support the clarification of primary and local IRB roles and responsibilities, especially as they relate to regulatory responsibility and local context considerations.

At this time, we believe that roles and responsibilities are not sufficiently well-defined to mandate a single IRB of record for all multi-site studies. If, however, the NPRM moves forward with this mandate, we believe a tiered approach would be the most appropriate way to proceed, at first limited to robust, established IRBs, such as the NCI's Central IRB, in federally-funded studies.

Informed Consent

We agree that many informed consent documents are too lengthy and complex, and we support efforts to abridge and interpret these documents for research participants. We believe that participant self-determination and informed decision-making can best be achieved through the creation of a summary consent document of no more than two pages. This document, which would be signed by the participant, would describe in clear and concise language the research, its risks and benefits, and the alternatives to participation. Although the full consent package would be included as an appendix, the summary document would provide the most important points to the research participant in a language that he or she can comprehend.

We oppose the development of standardized templates for consent documents issued by OHRP. Although language recommendations can be helpful to investigators, advisory guidance tends to take on the force of regulation over time. To avoid any such federalization, which would limit the ability of institutions to tailor language and documents to meet the needs of local participant populations, we believe the regulations should make clear that the responsibility for informed consent documents resides with the institution. To assist institutions in the simplification effort, OHRP should provide best practices for illustrative purposes but institutions should not be bound by those examples.

For data and biospecimens, we propose a middle ground which involves *notification* about the potential for the future use of remaining or left-over samples in research. We believe notification satisfies the ethical requirement of respect for persons, and a national campaign could help educate and further notify the general public on the importance of biospecimens to biomedical research and advances in health care.

Strengthening Data Protections

The proposal to consider all research that meets a mandated data protection standard as qualifying for “excused” status fails to address all risks that may be associated with a given research project. Further, such an approach does not take into consideration those studies where participants neither desire nor require confidentiality. Although the idea of using data security standards to minimize information risks and to ease IRB review burden has significant merit, we believe that HIPAA does not have the necessary flexibility to serve as the correct standard. The future development of any security standards should be considered in light of the breadth of data covered by the Common Rule, and they should provide the necessary flexibility to address the range of data sets involved.

Conceptually, we understand that biospecimens or data could be identified and the donor put at informational risk. In practice, however, the re-identification of biospecimens or data is usually impracticable for most individuals, and, in our opinion, is not a high risk area. For these reasons, we oppose any effort to consider all samples identifiable at this time, as it creates a significant institutional burden for very little gain. In the future, we would advance the general idea of treating biospecimens as identifiable based on a “contemporary technology” standard. As science progresses, and there is growth in the availability of identified sequence information, additional protections could be developed and the regulations could be amended accordingly.

Data Collection and System Oversight

For the most part, we believe the goals of this section are laudable, but caution that there are variations in the types of safety data and the accompanying regulatory requirements for good reason. Not all research studies are alike nor do they all generate safety data that can be meaningfully aggregated for analysis. In our view, it would be exceedingly difficult to achieve the goal of simplification and standardization while attempting to create a system that would consolidate many disparate factors.

It is important to recognize that some of the different reporting requirements are applicable to different parties – and should continue to be. For example, IRBs require the reporting of unanticipated problems, which was clarified by OHRP in 2007 to mean serious, unanticipated events thought to be related to the study. The FDA, on the other hand, is building a toxicity profile of an investigational drug so reporting on all adverse events is required. Although comprehensive reporting is essential to the purpose of FDA, it is not relevant to the IRB. These different reporting requirements are logical and should be preserved.

We believe that the scope of the events that must be reported under the Common Rule, including the reporting of unanticipated problems, is adequate. For this section, we recommend against the implementation of the proposed changes as they do not appear to be feasible or beneficial to human research subjects.

Extension of Federal Regulations

We do not agree that the proposed extension of the Common Rule to non-federally funded research adds value to human research protections. Institutions with Federalwide Assurances (FWAs) already subscribe to the principles of the Belmont Report or a comparable statement of ethical principles, which binds these institutions to the ethical review and oversight of research involving human participants. The extension of the Common Rule to non-federally funded research at institutions with FWAs serves only to impose additional administrative burdens on institutions and OHRP, without corollary benefit. Moreover, the proposal would not extend these protections to institutions or entities that do not receive federal support, which are the very institutions this proposed extension is intended to address. For these reasons, we caution against the extension of the Common Rule and urge HHS to exclude it from the forthcoming NPRM.

Clarifying and Harmonizing Federal Guidance

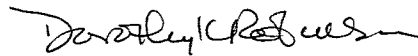
We support harmonization, but it is unclear how to achieve this goal while preserving individual agency expertise. Generally, uniformity is desirable among departments and agencies to eliminate unnecessary regulation and promote understanding of and compliance with regulations involving human participants. That said, we believe that it is warranted and even necessary for these same departments or agencies to impose specific additional requirements that are tailored to certain types of research, especially where the Common Rule is silent.

Instead of limiting the authority of agencies under the Common Rule, we urge the federal government to develop an internal mechanism to review and, if appropriate, harmonize guidance before it is issued to the public. Under this process, the sponsoring agency would justify its proposal and ensure that it does not contradict existing guidance or regulation.

In conclusion, Yale applauds HHS and OSTP for this historic opportunity to reimagine the federal regulations governing human research participants. As noted earlier, we believe that modifications to the Common Rule should be effectuated in a manner that supports institutions' authority to exercise flexibility in protocol review, based on risk, with consideration of individual circumstance and local context. Such flexibility promotes open consideration of ethical issues in human research protections, without impeding scientific discovery. We thank you for this invaluable opportunity to provide initial comments and suggestions, and we look forward to the development of proposed changes to the Common Rule.

We offer below detailed comments and responses to questions posed in the ANPRM. We have annotated our responses to identify the specific questions posed in the Notice.

Sincerely,

A handwritten signature in black ink, appearing to read "Dorothy Robinson". The signature is fluid and cursive, with a long horizontal stroke at the end.

Dorothy Robinson

Detailed Comments and Response to Questions:

II. Ensuring Risk-Based Protections

Calibrate the Level of Review to the Level of Risk

We appreciate the effort to calibrate the extent of review to the level of risk posed by the research study and believe significant efficiencies can be achieved without placing the rights and welfare of research participants at risk. Below we provide suggestions to refine the ANPRM to facilitate these goals. Under this section, we believe there are a number of issues that should be addressed through better guidance, not additional or revised regulation. It is our belief that the inconsistencies among IRBs and level of administrative burden arise from the interpretation of the regulations rather than from the regulations *per se*.

Defining Minimal Risk (questions 1, 5, 6)

Currently “minimal risk” is defined as research activities where “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests”. This definition plays an important role in protecting human subjects yet the concept is ambiguous. Daily life risks are a relativistic interpretation and different populations encounter different risks in the course of daily life. Moreover the average healthy person takes many different risks on a regular basis, such as travel and employment.

The Secretary’s Advisory Committee on Human Research Protection (SACHRP) recommended in 2005 that HHS use a “healthy person” standard when applying the federal definition of minimal risk. We believe that the federal definition should incorporate the healthy person standard to provide needed clarity and consistency in application. In addition, it is important that any discussion of this definition make clear that the IRB evaluates the research activity itself rather than standard of care activities in determining the overall risk level of the study. Further guidance is needed on how study risks can be compared to risks encountered in daily life. That said, any definition of risk should not be so rigid as to prevent the IRB from considering individual circumstances or other contextual issues. For example, there may be no risk in having the status or opinions of public figures disclosed, but the release of information for other private individuals, intentional or not, could have devastating consequences. We support efforts to afford IRBs the latitude to review research for risk, especially as attitudes about and tolerance for risk tends to change over time.

When considering the criteria used to determine greater than minimal risks, we are concerned that any effort to define these criteria in regulation will result in the over- or under-representation of study interventions. Risk is often dependent on contextual and population issues, and we believe that guidance would be the appropriate format to demonstrate how to balance and assess the probability and magnitude of potential harms, including non-physical and non-informational harms. Similarly, with respect to the specific surveys or types of questions that should be classified as greater than minimal risk, we believe it would be

counterproductive to list in regulation the specific questions or surveys which may be problematic as the risk is dependent on both the measure itself and the population as well as any synergistic effects. We recommend that guidance discuss the areas of questioning which should be assessed for potential to be greater than minimum risk, such as those interventions that touch on areas of mental health which can lead to rumination on negative aspects of self and risk taking behavior.

Revise the Common Rule Governing Continuing Review (questions 2, 3)

The ANPRM proposes three changes with regard to the expedited review process: 1) it revises the criteria for eligibility; 2) it eliminates routine, annual continuing review; and 3) it streamlines the oversight process. On the whole, we agree with the default presumption: well-documented activities that pose no more than minimal risk should qualify for expedited review; expedited review provides adequate protections for participants in those activities. Annual continuing review is not necessary for these studies, as adverse events and unanticipated problems would still be reported as they occur. To confirm that there are no emergent issues, we believe that institutions should be encouraged to develop a policy by which the IRB would receive annually a one page summary on study progress. In cases where the summary suggests that the study is not progressing as planned, the IRB should have the discretion to pursue further review of the project. We believe this approach strikes a reasonable balance between the need to protect research participants and the need to streamline the burden associated with continuing review on an annual basis of projects that pose only minimal risk.

We agree that for studies closed to enrollment or those limited to follow up and/or data analysis, it would often be appropriate to remove the annual review requirement. Yet, it is important for the continuing review requirements to be determined on a case by case basis. In our experience, there are some technically expeditable studies that employ novel or complex interventions, particularly in the behavioral sciences. In these cases, we would want the IRBs to have the flexibility to choose to conduct more rigorous and regular study oversight. However, by not mandating review every 12 months, the IRB, based on its knowledge of the research and any local caveats, could better utilize its resources to focus on those studies that determined to warrant further examination.

Review Requirements (questions 4, 11, 12, 13)

Many IRBs are under the impression that all unanticipated events which are not documented initially in the protocol or consent documents are reportable to OHRP. As a result, every possible incident, effect, and outcome that could possibly be related to the study is listed in advance, thereby diluting consideration of those events that are reasonably foreseeable risks and discomforts.

Since the requirements for document and protocol submission are not detailed in regulation, it would be useful for guidance to emphasize the IRB's discretion in terms of what elements are required – and what might be eliminated. For example, we suggest that detailed interview protocols or scripts be eliminated from the list of required documents, so long as the concepts to

be covered are adequately summarized to acknowledge how ethnographic interviews are conducted.

In terms of the potential advantages of requiring expedited review by an IRB member, we view membership as a reasonable requirement, as there is nothing to preclude staff from being named an IRB member. IRB membership reinforces the seriousness of the IRB responsibilities. Also, many such designated staff members receive considerable training and acquire notable expertise during extended service to the IRB. We believe that certain approval criteria should be revisited and more flexibility should be provided to the IRB to determine those protocols which qualify for expedited review. For example, the equitable selection of subjects is meaningless where subject selection is not and cannot be expected to be random, as often happens when an anthropologist seeks to study a particular culture. We also believe that the requirement for full, documented consent is not always appropriate for surveys, interviews and similar study mechanisms. In these cases, the requirement for the IRB to review the protocol and issue the waiver in order to allow for a verbal consent process becomes an exercise in bureaucracy – not human subject protection. In addition, the requirement to consider the relationship of risks to anticipated benefits in minimal risk studies is moot as long as there is some putative benefit. Lastly, in a minimal risk study, there is little to be gained from efforts to ensure and monitor the subject safety. In sum, we recommend that the IRB should be provided the flexibility to waive adherence to the 45 CFR 46.411 requirements on a case by case basis for minimal risk research.

Review Categories (questions 7, 8)

Rather than listing specific activities or radiological levels as eligible for expedited review, we recommend that the list of expeditable categories be eliminated from the regulations. Instead, we recommend that use of local experience with a given technique or procedure be permitted to be evaluated by the IRB under expedited review. This approach would allow institutions to use an expedited process where a procedure is routinely performed under set conditions without inducing harms, while preserving full board review for those institutions where the same procedure is relatively novel. As an initial step, full board review could be used to define the circumstances and controls necessary to minimize risk for a given procedure. Once these are established and the institution has developed experience with the constraints necessary to minimize risk, further review by the larger board may not be an appropriate use of resources. In this instance, research involving such procedures should be reviewed via an expedited mechanism as long as the proposed procedure remains within institutionally documented limits and meets the minimal risk criteria. However, if the proposal to eliminate the list of categories is not incorporated, we welcome changes to the expedited review categories as outlined in the ANPRM should it be deemed necessary to maintain a list of appropriate activities.

IRB Activity Reports (question 13)

We believe that IRBs should not be required to submit periodic reports to OHRP when they choose to implement more stringent review processes. Although we agree that reporting is an important mechanism for ensuring the protection of subjects, this level of additional reporting

in the aggregate would appear to serve no real purpose and convey no additional benefit but would impose a significant administrative burden on institutions.

Move Away from the Concept of Exempt (questions 14, 15, 16, 17)

Currently, six enumerated types of studies involving human participants are exempt from the Common Rule's requirements, although OHRP has issued guidance recommending that exempt studies undergo some sort of institutional review. The ANPRM moves away from the concept of exempt research in favor of "excused" research, with proposed modifications to the types of studies that qualify, tracking and auditing requirements, and consent rules. For the most part, the expansion of the types of studies in the new "excused" category under the ANPRM is appropriate, but we are concerned that it presumes that surveys and related methodologies are limited to informational risks, which can be managed through data security, and ignores fundamental IRB concepts of respect for participant autonomy and justice. We recognize, however, that the ANPRM seeks to create a floor that would allow institutions to institute practices to address these issues, and we appreciate that the proposed expansion would grant institutions the ability to "excuse" research for which more detailed review does not enhance participant protections.

As part of this discussion, we believe there are other types of research that should be excused, particularly in the social and behavioral fields. These include non-invasive, routine activities, or those activities that are similar to routine activities such as video games, video viewing, carnival type games, reading responses, public interactions (e.g. mystery shoppers), and mood indications, and these activities should be added the list of excused studies for competent adults. Also, we believe that deception, defined as omission, not fabrication, should be excused so long as the deception itself is not potentially harmful. We agree that surveys and related methodologies should not automatically qualify for the excused category of research if they involve emotionally charged topics, such as sexual or physical abuse. Depending on the interaction between the measure and the population, these studies can lead to risk, and IRB oversight may be appropriate in some circumstances. For this reason, we believe the level of review for these studies is best determined locally and with a consideration of the study specifics.

Return of Clinical Results (question 18)

The ANPRM seeks to lift the current limitation on research involving data with retained identifiers unless there are plans to return the results to the research participant. We support the proposal because it would permit the use of identified as well as de-identified data and biospecimens that were obtained for purposes other than the proposed research. We would question whether the requirement that no results be returned can always be upheld, since, in some future study, there could be an overriding ethical need for reporting incidental findings. Generally speaking, we do not think it is appropriate for researchers to routinely return clinical information. Clinical results should be returned to research participants only if the results are compelling and actionable as determined by IRB review.

Waiting Period; Terms (question 19, 20)

Under the process proposed in the ANPRM, researchers would file a one-page registration form with their institution or IRB that provides essential information about the study, such as the purpose and the name of the principal investigator. After filing the form, the researcher would be authorized to begin his or her study. We would advocate for a brief waiting period between the filing and the start of the research. Some researchers mistakenly believe that their research is exempt when it is not, and we believe that a waiting period will give IRBs time to examine the brief filing to confirm that the excused determination is correct. Although a one-week waiting period would be reasonable, we would hope that the length would be determined at the institutional level – not in the regulations.

With respect to terminology, we believe that “excused” may have the same problems as the term “exempt”, as both suggest that researchers can independently determine whether or not IRB review is required. We prefer the term “registered,” as the term underscores the requirement that even research that is excused from full board review must register with the IRB.

Retrospective Audits for Excused Research (questions 21, 22)

With respect to the appropriateness of and the minimal requirements for retrospective audits, we believe that this should not be an issue required by regulation. Rather, guidance would be useful, but the nature of the guidance needs to be responsive to the scope of the studies at the institution and the qualifications of the researcher. For example, if the institution has a large number of the same types of projects, it may need to inspect fewer protocols. In terms of protections for subjects, we believe that retrospective audits and/or initial review of excused filings will be important, given the discrepancies between what is thought to be exempt by the research community what is actually deemed to be exempt by an IRB. That said, in cases where an exemption is filed erroneously, our experience suggests that the project is likely to pose only minimal risk to participants. We believe that audit/review requirements should be commensurate with this expectation in order to not drain resources from the rigorous review needed for studies posing greater than minimal risk.

Existing Data and Biospecimens (question 23)

The use of existing data (and biospecimens) collected for non-research purposes may not merit the need for consent, even if it is identified. For example, some studies require identifiers to be conserved to link data sets, but they are otherwise conducted anonymously. The initial retention of identifiers under a reasonable data security plan should not in and of itself require institutions to re-contact the data source to obtain consent. Furthermore, if the HIPAA definitions for identifiability are adopted, there is very limited data that would qualify as “not identified” while still being useful. For example, data that include the date of service for a common procedure would be considered identifiable under HIPAA, but it would be very difficult for the researcher to determine the identity let alone contact information to allow consent to be obtained. In fact, any requirement to collect additional identifiers for the purpose of future consent could have the unintended effect of increasing risk to the donor.

Even with more direct identifiers, it can be impracticable to reinitiate contact with subjects. We believe that a request to waive informed consent should not trigger an IRB review if there are routine data handling practices that can be defined where obtaining consent would be of little value in respecting the rights and welfare of participants, such as using minimal identifiers to link data sets and/or having coded data and keeping code longitudinally to access clinical information.

Common Rule Exclusions (questions 24, 25)

There are certain activities which should not be covered by the Common Rule, and we believe researchers would benefit from the clearer exclusion of these activities. Specifically, activities such as program evaluations, quality improvement activities, and historical archives should be specifically excluded, even if they have the potential for future research analysis. We believe that additional guidance that demonstrates how to identify projects that are not generalizable, and thus could be excluded from IRB approval, would be useful.

III. Single IRB for Multi-site Studies

(questions 30, 31, 32)

Over the last several years, there has been growth in alternative IRB models for multi-site studies, such as the NCI Central IRB, the Multicenter Academic Clinical Research Organization, and the Biomedical Research Alliance of New York. For U.S. sites in a multi-site study, we believe that HHS should encourage – not mandate - the use of these alternative models. A single IRB of record could reduce bureaucratic complexities and eliminate delays, but these advantages will be realized only if clear guidelines are in place. To facilitate the use of a single IRB of record and to streamline the review of multi-site studies, we urge HHS to develop an IRB model that addresses the following issues: the types of studies that qualify for single IRB review, a clear delineation of responsibilities for the IRB of record and the local institution, and a clear and specific definition of the elements to be considered as local context.

If HHS decides to mandate the use of a single IRB of record for multi-site studies, we recommend a tiered approach to implementation. Initially the mandate should be limited to already established central IRBs for multi-site studies. After the model IRB is developed and responsibilities are clearly defined, use could be expanded to established IRBs that meet the requirements of the model. Also as an initial matter, we recommend that protocols identified for single IRB review be limited to federally-funded clinical trials, conducted at more than three sites. We believe broader implementation should wait until the success of the model is evaluated and any needed modifications are enacted.

Currently, IRBs have a broad understanding of what they consider local context issues. It is critical to define and mandate the local context requirements to be reviewed, so that time spent locally will be reduced. For example, local IRBs should not review and approve the study design or protocol, but they should be able to modify the consent form to meet the needs of

their patients, comply with local laws, and update the local contact and other locally relevant information. Specifically, we believe that evaluation of the following areas is appropriate for local review:

- Researcher conflict of interest
- Training of research personnel
- Qualifications of local principal investigator
- Storage and handling of research drugs
- Local billing issues
- State laws regarding notification of specific conditions
- Any known community issues that may affect the conduct of research locally
- Any known local issues involving vulnerable populations

Review can be further streamlined by limiting the time in which the local IRBs may review and provide feedback to the primary IRB. In addition, research should commence as soon as the IRB of record has approved the study and the first local IRB has reviewed and accepted the protocol.

We also believe that HHS should clearly define the responsibilities of the IRB of record in a multi-site study from initial review through study completion. This includes the development of a standard, nonnegotiable agreement between the IRB of record and the participating sites, and whose modifications include only those alterations to the consent form that local context review requires. We are concerned that too much time is lost in institution-specific negotiation on memoranda of understanding or IRB authorization agreements.

We recommend that the IRB of record be responsible for the following activities: (a) ensuring the completion of local institutional review and execution of an MOU prior to initiation of protocol at the local site; (b) reviewing locally generated amendments to determine whether they may be applicable to multiple sites; and, (c) serving as the clearinghouse for adverse and unanticipated events. The local institution should be responsible for the following activities related to the local conduct of research: (a) review and approval of personnel added to the study; (b) review of local adverse and unanticipated events submitted to the IRB of record; and, (c) review of all local subject complaints. The local institution also should retain responsibility for the investigation of local compliance issues, in coordination with the IRB of record.

Serving as IRB of record for a multi-site study necessarily involves added administrative and financial burden. This burden should not fall to the IRB without appropriate reimbursement. In the absence of reimbursement, qualified and appropriate institutions may be reluctant to take on this responsibility. We strongly recommend that the costs of serving in this capacity be included in the study budget as a direct cost.

(question 34)

Considering the importance of the primary IRB, one must consider how the IRB of record is selected. As noted above, our recommendation is that for the initial studies, existing IRBs, such as the NCI's Central IRB, be used for federally-funded studies. With the evolution of the system, we believe the funder should choose the IRB of record, based on its knowledge of their experience and expertise. This selection process should be used whenever a single IRB is used, either mandated or optional for the local IRB. Although we believe that the resolution of the definitional issues and responsibilities identified above will help overcome reluctance by institutions to rely on an IRB that is not within their own institution, there may be issues and concerns that persist. This includes the potential for smaller institutions to decline participation in studies. Many hospitals in particular are protective of their patient population and may be slow to accept a study for which they did not have full review or approval authority. Another issue is the concern or potential that the primary IRB might fail to identify something of consequence in its review that may have been found by having the protocol reviewed by more than one IRB. We believe these potential disadvantages can be overcome by clearly defined roles for the IRB and the institution, educating the research community about the primary IRB and its expertise, and preserving a limited role for local IRBs.

IV. Informed Consent

Improving Consent Forms (questions 35, 37)

Informed consent should promote participant self-determination, ensure informed decision-making, and provide protection from harm, and we support efforts to improve documentation to better achieve these goals. Currently, many informed consent documents are too lengthy and complex, with readability levels that make it difficult for potential participants to fully comprehend unfamiliar medical and scientific information. In addition, these documents – through guidance and determinations in allegations of noncompliance – have grown to incorporate redundant language and terminology to provide protection to the sponsor and/or research institution. This protective language often comes at the cost of overall document clarity. Lastly, consent documents include non-research related procedures, drugs and side effects and details such as participant visit schedules, the procedures for each visit and the length and timing of each and every procedure. Taken together, these elements have contributed to document length and complexity in a way that has frustrated usability and served primarily to protect the researcher and the institution, not the research participant.

To restore the consent document to its rightful place as a protective and informational mechanism for the participant, we suggest that the signed document be a summary of no more than two pages. The elements of the summary consent document should track back to the Common Rule, describing in clear and concise language the research, its risks and benefits, and the alternatives to participation. In this way, the summary document would be similar to the verbal presentation of key points which is currently provided to the potential participants prior to study enrollment. The page limit would have to be required and provisions for inclusion in the summary document would have to be narrowly defined to reduce sponsor and institutional

tinkering and to encourage the elimination of legalistic terminology. To further improve document clarity, the summary document should be written at a reading level appropriate to the targeted participant population.

Under this revised format, the summary document would serve as a complement to a longer consent document, which would be provided as an appendix. As the appendix will likely be fairly long, we believe there are additional steps which should be taken to ensure that the document conveys the information that is most useful to the research participant. Specifically, we believe there should be a presumption against the inclusion of information in the appendix that is unrelated to the research, as it only serves to confuse and add unnecessary volume. To prevent the inclusion of unrelated or irrelevant information, the regulations should specifically disallow any non-research related information regarding risks and procedures unless the IRB determines that this information will be valuable to the participant, such as a clear delineation of standard of care procedures. Also, there are instances where a sponsor seeks to restrict the participant's discussion of the research with his or her team of caregivers by marking the consent document 'confidential'. This should be specifically disallowed. There should be nothing in the consent summary or appendix that would preclude participants from considering options with family, friends and physicians. In this way, the summary document, with attached appendix, will serve the purpose of informing the consent process while continuing to be a reference for participants and caregivers during the research study.

Finally, we oppose the development of standardized templates for consent documents issued by OHRP. Although recommendations can be helpful for researchers, we believe the responsibility for the consent documents should reside with institutions, as they are best able to tailor language and format to meet the needs of local participant populations. It would be valuable, however, for OHRP to provide examples of the model consent forms, for IRB reference, with instruction that institutions are not required to adopt or use the sample forms.

Waiver of Informed Consent; Documentation of Informed Consent in Primary Data Collection (questions 41, 43)

Under 45 CFR 46.116, the IRB is authorized to waive the requirement to obtain informed consent, including all mandated consent elements, only if the research involves no more than minimal risk to the subjects *and* the IRB determines and documents that the waiver (or alteration) will not adversely affects the rights and welfare of the subjects, that the research could not practicably be carried out without the waiver or alteration and, whenever appropriate, the subjects will be provided with additional pertinent information after participation. If there is no more than minimal risk to the subject, we believe that these categorical limits should not govern. Instead, the IRB should be permitted to make a determination concerning the appropriateness of the waiver if the anticipated harm or discomfort falls below an acceptably low-risk threshold.

If the above recommendation is not enacted, we believe that regulations should clarify and standardize the current criteria for waiver of informed consent by defining the term

“practicable” as it relates to the performance of research in the regulation, as recommended in the January 31, 2008 letter from the Secretary’s Advisory Committee on Human Research Protections to the HHS Secretary (<http://www.dhhs.gov/ohrp/sachrp/sachrpletter013108.html>). By defining this term in regulation, we believe there will be more consistent application of the waivers.

Further, under 45 CFR 46.117(c), the IRB is permitted to waive the requirement to obtain a signed consent form if the research presents no more than minimal risk to the subject and the principal risk to the subject would be the potential breach of confidentiality. At issue in the ANPRM is whether written informed consent is required to document participants' consent. There are times when it is inappropriate to obtain consent through a signed document, and we believe that IRBs should have the flexibility to waive documentation under certain circumstances on a case by case basis, *regardless of the level of risk* to the potential research subject. Specifically, we believe the IRBs should be authorized to waive documentation of consent in cases where subjects could be vulnerable to legal, physical or other harms if it is discovered that they are participating in a research study, regardless of the level of risk of the overall study. For example, where there is an atmosphere of fear, as experienced by a woman in an abusive relationship, the act of signing one’s name to a document introduces a significant element of risk to the subject. In cases like this, the IRB should be afforded the flexibility to waive written consent.

Consent Protections Related to Reuse or Additional Analysis of Existing Data and Biospecimens (questions 45, 46, 47)

The ANRPM proposes to require written consent for the research use of biospecimens, whether or not the specimens were collected for non-research purposes, and notwithstanding the removal of identifying information regarding the source of the specimens. According to the ANPRM, such consent “need not be study specific” and could include “open-ended future research.” This change would be in marked contrast to current HHS policies, which allow the use of de-identified human biospecimens in research to be considered “not human subjects research”. Therefore, under current practice, consent is not required. Although the ANPRM suggests that this new Common Rule policy would apply prospectively, we are concerned that it would result in burdensome new requirements for clinical facilities in the future.

The ANPRM states that participation in a research study cannot be conditioned on a participant’s agreement to “allow future open-ended research using a biospecimen.” This prohibition on conditioning participation would be similar to the current HIPAA restrictions that prohibit conditioning treatment on an individual signing an authorization for the use or disclosure of identifiable health information for future, unspecified research. The proposal leaves open whether participation may be conditioned on specified uses of biospecimens.

In general, we believe that the ethical principle of respect for persons, on which voluntary informed consent is founded, supports the view that **notifying** individuals of the potential future use of biospecimens and data collected both clinically and for research purposes is

appropriate. That said, we believe this process should distinguish between samples that are expressly drawn for research and samples that are leftover, either from previous research or from clinical sampling.

From an ethical perspective, the use of a standardized, general consent form to permit future research on biospecimens and data has been criticized as not being meaningful and not fully informing research participants. Much of the problem is that a general consent form would have to be sufficiently broad to cover all data and biospecimens to be collected related to a particular set of encounters with the institution. As discussed below, research institutions should notify clinical patients that data and/or biospecimens may be used without their consent, provided reidentification is not likely based on existing technologies.

Patients admitted to hospitals benefit from the resources made possible by research conducted on specimens and data that came from the patients before them. This benefit extends beyond the patients of a teaching hospital, as research results inform clinical practice globally. Biospecimens stored at or linked to hospitals represent a great number of human biological materials and they are tremendously valuable to research. Yet limitations on the use of these biospecimens are a major barrier to groundbreaking research. The general public should be better educated about the importance of biomedical research and the role of clinical data and biospecimens in advancing and improving patient care.

Notification could in part be achieved by a series of federally-supported public service announcements and a national education campaigns, which would inform the public about the enormous potential held by biological research made possible through the willingness of individuals to provide samples. The national campaign would be especially helpful in explaining coding, confidentiality and the honest broker system in a way that a majority of patients can understand. Such an educational campaign could solve the related problem with the timing of the individual notification. Studies have shown that patients are generally willing to provide biospecimens for research purposes, but they are often focused on their pending medical care or surgery and may be less willing to confront complex issues of consent, especially when future use is not known. A nationwide education campaign serves as notification to individuals before they are in a pressured situation.

A distinction should be made for samples drawn for planned research purposes. In research studies, informed consent would always be required because the planned research can be explained to subjects in a way that is meaningful. Informed consent becomes difficult to obtain, however, when the future use(s) of the biological materials is not known at the time of their collection, because researchers cannot provide the subjects with complete information regarding the undetermined future use(s). On a related note, all subjects enrolling in research should be informed that their biospecimens and data may be used in a de-identified manner in future research, and some of these uses may occur without their explicit consent. For this reason, notification might include a general description of the types of research supported by the

institution and its potential benefits to the public. In rare instances, where the research might raise unique concerns, the notification might warrant the inclusion of check-off boxes, allowing a separate yes/no for things like the creation of cell lines or reproductive research.

For future research use of data collected either for research or for nonresearch purposes, the requirement to obtain informed consent for use of biospecimens should be based on re-identification ability. The concept of 'readily ascertainable' as currently included in the Common Rule, should be preserved. Specifically, the regulations should allow informed consent to be waived if re-identification is unlikely, based on technologies available at the time the consent is waived or the new use of the samples is proposed. Consent also should be waived if the investigator has no plans to re-identify the individual with the specimens.

(questions 48, 49)

Although the ANPRM argues that informed consent should be required in all instances because genetic testing has the potential to make everything identifiable, science has not progressed to a point where we should distinguish between identifiable and non-identifiable samples for the purposes of informed consent. We believe the regulation should be written to allow flexibility in the present and to afford modification in the future, should re-identification become easier using contemporary techniques. It also may also be appropriate to waive the requirement to obtain consent for additional analysis of biospecimens after a certain number of years. This sort of "statute of limitations" would be appropriate when obtaining consent would be impracticable if the subject has been lost to follow up, no longer have a relationship with the investigators or clinical facility, or is unavailable to consent and the data remains de-identified. This also would be an appropriate mechanism to allow research on biospecimens that were collected outside of a research study (e.g. "left-over" tissue following surgery) without a research consent, so long as the subject identity is not disclosed to the investigator.

(questions 50, 51)

The ANPRM seeks comment on the best method to provide individuals a meaningful opportunity to withhold consent for future research projects. Although we want to be respectful of those who have strong ethical or religious objections to specific areas of concerns, the difficulty remains that we are unable to conceive fully the future possibilities in research. As discussed above, we believe the public should be educated about biomedical research and notified of the possibility of their participation, but specific choices that may restrict future options should be avoided. Also, for practical reasons, any new regulations with respect to consent for biospecimens and data sets should be applied prospectively, as retroactive application could impede research and threaten years of work. With respect to biospecimens collected outside of the U.S., we believe these rules should be applied consistently, regardless of where the research is being conducted, as inconsistent application will only lead to animosity in these foreign countries.

(question 53)

Finally, for cases in which consent for future research is not obtained at the time of collection and obtaining consent for secondary analysis of existing biospecimens or data would be impractical, the presumption should be that consent has been waived. In determining the factors or threshold numbers that determine impracticability, we support the Secretary's Advisory Committee on Human Research Protections' (SACHRP) January 31, 2008 recommendations to the Secretary (<http://www.dhhs.gov/ohrp/sachrp/sachrpletter013108.html>). In summary, SACHRP suggests a definition of the term practicable and establishes criterion for when the scientific integrity would be compromised or ethical concerns would be raised if consent were required, such as a skewed sample size or the risk of psychological, social or other harm, or if there is a scientifically and ethnically justifiable rationale why the research could not be conducted with a population from whom consent can be obtained. Also, we support SACHRP's recommendation that practicability should not be determined solely by considerations of convenience, cost or speed.

V. Strengthening Data Protections to Minimize Informational Risks

Characterizing Information with Respect to Potential for Identification (questions 54, 55, 56)

We applaud the plan to harmonize data identification terms across the Common Rule and HIPAA as there is currently significant confusion. Although harmonization will not in and of itself improve data security, it will facilitate standardization of IRB practices and improve the consideration of whether or not data security plans are commensurate with risks associated with identifiability of the data.

With respect to when and how to evaluate what is identifiable, we believe that time and triggering events should be considered. For example, changes in technology or availability of linked data sets may create an emergent risk necessitating reconsideration of identifiability. With respect to biospecimens, we believe that the present risk of harm from re-identification of the samples is rarely an issue and not a high risk area, although one exception would be DNA samples of criminal offenders. Generally, however, assuming all biospecimens to be identifiable creates a significant burden for very little gain. In the future, if biospecimens can be identified based on "contemporary technology", the standards could be re-evaluated as to whether biospecimens should be considered identifiable. As science progresses, and there is growth in the availability of identified sequence information, additional protections could be considered and the rules amended accordingly.

Standards for Data Security and Information Protection (question 59)

The ANPRM proposes to prospectively apply new data security and information protection standards to all research that involves collection, storage, analysis, or reuse of identifiable or potentially identifiable information, in place of IRB review of informational risks. The proposal would model the new data security standards on the HIPAA security rule, and it would adopt HIPAA privacy standards for determining what constitutes individually identifiable information and de-identified health information. All biospecimens would be considered

identifiable information and subject to heightened protection. For research using limited data sets or de-identified information, investigators would be strictly prohibited from attempting to re-identify the subjects of information.

We appreciate the efficiencies that may be gained by standardizing data protection to minimize informational harm. We also acknowledge that the IRB is not always the optimal resource for evaluating data security plans, and standardization would likely streamline at least one aspect of IRB review. However, we do not believe that HIPAA security standards are appropriate. Moreover, we do not believe a single standard exists which could remove from IRBs the burden associated with considering the adequacy of data security plans. The HIPAA security rule is designed to address data integrity and availability in addition to confidentiality. As a result, HIPAA requirements, such as those related to audit trails, contingency plans, emergency operations, and access controls, are tailored more broadly than those that would offer protection from inadvertent disclosure. For example, the adoption of the HIPAA standard would require breach notifications. This would be a costly and burdensome requirement which would not be clearly meaningful or useful to those who would receive the notification, as much of the research data has little value outside the research context (*c.f.* Report to Congress on Breaches of Unsecured Protected Health Information prepared by DHHS Office of Civil Rights August 15, 2011). We support the current practice whereby IRBs have the ability to determine if notification would mitigate risks to subjects, based on the data involved and the circumstances of the breach. HIPAA HITECH breach standards, on the other hand, would be far less flexible.

The scope of data collected in the course of human research includes data that is currently afforded different levels of protection under state and federal laws. At one end of the spectrum, there are stringent protections for health information under HIPAA and state law with regard to information of use in identity theft. At the other end of the spectrum, there is ethnographic data for which the research participants actively request attribution. The proposed application of a unified data security standard for all human research, including “excused” research, confounds the issue by including data that may not merit this level of security. We believe that it is essential for IRBs to maintain sufficient flexibility to ensure that the data security requirements are appropriately matched to the degree of informational risk.

Instead of a single standard, we believe a far better approach would be the development of guidance on best practices for the security of data which poses low, intermediate and high informational risk. We also wish to stress that care must be taken to ensure that other risks are not overlooked in the adoption of any proposed data security requirements. For example, the ANPRM presumes that managing informational risks will be adequate to minimize risks in most excused and expedited review projects. Although informational risks are common in social science and behavioral research, they are not the only potential harms to participants. Further, minimizing informational risk is not the sole criterion for the approval of human subjects research. Through the creation of better protections for informational risks across the

full spectrum of human subjects data, it is our hope that the IRB will be better able to focus consideration on any other risks associated with a given study.

VI. Data Collection to Enhance System Oversight

(questions 67, 68)

The ANPRM proposes changes to the way in which adverse events are reported during clinical trials to “simplify and consolidate” such reporting. The changes involve the use of a “standardized, streamlined set of data elements,” the development of a web-based federal agency-wide portal, and the harmonization of safety reporting guidance across federal agencies. The ANPRM also proposes to create a central data repository to store adverse event information received by all federal agencies.

For the most part, we believe the goals of this section are laudable, but caution that there are variations in the types of safety data and the accompanying regulatory requirements for good reason. Not all research studies are alike nor do they all generate safety data that can be meaningfully aggregated for analysis. For example, clinical trials generate the largest number of adverse events, but they often involve factors which confound the analysis of, and therefore the meaningfulness of, combined data. These data will have meaning for the select group of enrollees only, as the study is defined by inclusion/exclusion criteria, age spectrum and allowance or prohibition of concomitant medications. Further complicating matters is the fact that reports of adverse events can occur while the study drug is blinded, and it is therefore not known at the time of reporting which substance the subject has received. Finally, dose, route of administration, length of exposure, and a host of other factors contribute to the analysis of an event, which could be lost in aggregation. It would be exceedingly difficult to achieve the goals of simplification and standardization in trying to create a system that could consolidate these disparate elements.

In addition, it is important to recognize that some of the different reporting requirements are applicable to different parties – and should continue to be. For example, events of relevance to the IRB are unanticipated problems, clarified in 2007 OHRP guidance to mean serious, unanticipated events thought to be related to the study. On the other hand, government agencies, such as the FDA, require reporting of all adverse events, since the toxicity profile of an investigational drug is in the process of being built. Additionally, reporting of all adverse events to a sponsor is essential in order to capture the evolving toxicity profile. These different reporting requirements are logical and should be preserved.

We believe that the scope of the events that must be reported under current Common Rule requirements, including the reporting of unanticipated problems, is adequate. OHRP and FDA have issued clarifying guidance in 2007 and 2009 respectively, with further revisions to the FDA adverse event regulations in 2010. We believe these efforts underscore the notion that uninterpretable reports, containing the confounders mentioned above, are neither useful nor helpful to IRBs in their protection of human subjects. Current FDA regulations require

sponsors to analyze events and put them in context for researchers and IRBs. Sponsors must also analyze in the aggregate events that are not interpretable as single cases and report them only if there is an observed imbalance between the drug treatment and control groups, suggesting that the event is caused by the drug. FDA also defines the term “reasonable possibility” to mean that there is evidence to suggest a causal relationship between the drug and the adverse event. Taken together, these changes are intended to reduce the previous excessive reporting by sponsors.

(question 68)

With regard to data reported to the federal government, we acknowledge that it has been a frequent criticism that the number of research participants in federally funded human subjects research is not known, counted or reported. The criticism notes that it is difficult to evaluate adverse events if the number of exposures (or “denominator”) is unknown. Even if this were possible, we are concerned that the count would not be meaningful. The main issue is how to count participants. Currently, there is a lack of consensus regarding when and how to count human participants. For example, should the count be based on the number of participants who sign the consent form? Or the number who after consenting are determined to meet the study’s eligibility criteria? Or should it be the number of participants who receive the intervention? If we decided to count those receiving the intervention, should it include those who receive one dose, more than one dose or who have completed all the interventions? In each case, there are different definitions and different implications for generating denominator data, which would frustrate a meaningful count. This is further complicated by the fact that many clinical trials involve commercially available products. Because of these questions and overall variability, we believe counts of denominators are nearly impossible to derive and provide little useful information.

(questions 69, 70)

The current scope of focus of the Common Rule is the reporting of unanticipated problems to IRBs and to other bodies, with different requirements to serve different purposes. Although it may be desirable to have a central database on adverse events and unanticipated problems, this requirement seems to extend beyond the focus of the Common Rule. IRBs need to concentrate efforts on unanticipated problems, which could require revision to the protocol, procedures or consent form to protect human subjects. IRBs cannot process, nor react in real-time to, accumulating adverse event data that would be compiled in a comprehensive on-line database. For these reasons, the proposal appears to add significant burden without enhancing human protections.

With respect to the timeliness and comprehensiveness of individual studies on [ClinicalTrials.gov](https://clinicaltrials.gov), we support the goals of the publicly accessible database, but it is onerous and data is made available after the study has been completed. It is unclear to us how one might effectuate real-time data reporting, especially with respect to blinded studies, and improve the safety of human research participants during the trials.

VII. Extension of Federal Regulations

(question 71)

The ANPRM proposes to expand mandatory compliance with the Common Rule to all human subjects research at domestic institutions that receive federal funding from a Common Rule signatory agency. Even if a particular study does not involve federal funding or funding from a department or agency that has adopted the Common Rule, the institution would be required to follow the Common Rule for the study.

We support the goal of protecting the welfare and well-being of individuals who participate in research, and it is our understanding that most research institutions have elected to extend the applicability of the Common Rule to all human subjects research conducted at their institution, regardless of whether it falls under federal research regulations. In fact, an institution that is engaged in human subjects research that is conducted, supported or otherwise subject to regulation by a Common Rule agency is required to have a Federalwide Assurance (FWA), which commits the institution to using the Common Rule for most federally funded research and encourages its use for all other research. Equally important, the FWA requires the institutions to review *all* research under a set of principles acceptable to OHRP, such as the ethical principles articulated in the Belmont Report. This serves to foster a culture of ethical conduct and provides uniform protections to all human subject participants under the purview of the FWA institution.

For those institutions that choose to limit the applicability of regulations by “unchecking” the Common Rule and/or Subparts B, C and D boxes, non-federally funded research will remain subject to the ethical principles acceptable to OHRP. The only difference is that these institutions may choose to have greater flexibility on matters such as continuing review intervals and expedited review. In fact, many of the proposals in the ANPRM have their origins with those who sought the flexibility to limit the applicability of the FWA while providing equivalent or better protections to research participants.

For FWA institutions, the extension of the Common Rule will not offer additional or better protections for research participants. It might, however, apply regulatory procedures in a narrow way when, in the past, there has been flexibility to innovate. In addition, the extension of the Common Rule to all studies will likely increase the volume of documentation and reporting requirements, creating a significant fiscal burden which does not produce a measurable improvement in protections.

Most important, institutions that do not have a FWA would not be subject to the proposed extension of the Common Rule. As an initial matter, the ANPRM does not specify what would constitute “Federal funding from a Common Rule agency for research with human subjects.” Does this mean that the extension of the Common Rule would apply only to institutions that receive federal funding for specific human subjects studies? Or would apply to institutions that receive federal funding that supports human subject research programs generally? More

practically, the ANPRM would not reach those institutions that conduct human research studies exclusively with industry or other private sources of funding. Although some of these institutions may choose to apply the Common Rule and/or other Subparts to their research projects and have their own IRBs and requirements for IRB oversight of research, an infraction of these institutional policies would not itself constitute a breach of federal policy. Even under the extension envisioned under the ANPRM, federal agencies would not have the jurisdiction to conduct oversight or enforce compliance with these institutional policies.

VIII. Clarifying and Harmonizing Federal Guidance

(questions 72, 73, 74)

Although some studies may not be subject to any federal oversight, the ANPRM notes that some studies are subject to multiple regulatory schemes which may be inconsistent and unnecessarily complex. As discussed in the ANPRM, this has led to IRB and investigator frustration as well as variation in the way different IRBs approach oversight of the same study. For example, the Common Rule, HIPAA, and FDA regulations have meaningfully different approaches to (1) determining when information is identifiable and what that determination means for the review process; and (2) regulating the creation of, maintenance of, and withdrawal from biospecimen and data repositories. As discussed in the ANPRM, there are a number of initiatives underway to begin to address these inconsistencies. We support these efforts, when possible, but we also recognize that there are instances when distinct agency approaches and requirements are warranted due to the agency's mission or the nature of its research programs.

In general, uniformity is desirable among departments and agencies to eliminate unnecessary regulation and promote understanding of and compliance with regulations. We believe that it is warranted and even necessary for these same departments or agencies to impose additional requirements that are tailored to certain types of research, especially where the Common Rule is silent. For example, the Department of Defense has special prohibitions concerning research involving Prisoners of War (POWs). This sort of tailoring is supported by the Common Rule itself, which states in two separate places that agencies reserve the right to issue guidance beyond the Common Rule. In addition, agencies have different relationships with their research programs, stemming from their distinct missions and different types and phases of research, that support agency specific requirements tailored specifically to particular types of research. Finally, the act of achieving consensus across the entire federal government may be arduous, if not impossible, and it could prevent the timely issuance of guidance to investigators, IRBs and institutions.

Instead of limiting the rights of agencies under the Common Rule, we believe the federal government should develop an internal mechanism to review and, where possible, harmonize guidance before it is issued to the public. Under such a process, the sponsoring agency would be required to justify its guidance and ensure that it does not contradict existing guidance or regulation. Inconsistent policies could be corrected before they are issued, or at least clearly noted as inconsistent. One recent issue that would have benefitted from this type of review is

the NIH policy addressing Genome-Wide Association Studies (GWAS). The policy inhibits the use of coded human data that would otherwise be regarded as “not human subjects” per OHRP guidance by requiring specific consent from persons for the use of the data. Under the GWAS policy, IRBs are required to review and certify an investigator’s plans for submission of data to the GWAS data repository, including the adequacy of consent forms for data submission plans despite the acknowledgement by NIH that the data are “not human subjects” and not subject to IRB review or determination under OHRP guidance. If agreement between OHRP and NIH had been reached on how to regard this type of coded human data before the NIH policy were enacted, confusion and frustration among IRBs and investigators would have been avoided, and compliance with these institutions’ requirements would have been facilitated.

(questions 72, 73)

As discussed in the case of the DOD’s prohibition on research with POWs, some differences in guidance on research protections from the federal agencies strengthen protections. Other differences serve to decide the applicability of Subparts B, C, and D to the research conducted by Common Rule signatories. For example, the National Science Foundation, which funds a significant amount of social, behavioral, and educational research, expressly states that Subparts B, C and D are not adopted, as their application may not be necessary to approve social, behavioral and educational research with vulnerable populations. This type of flexibility in allowing IRBs to decide the applicability of the Common Rule Subparts has been helpful in approving meaningful and ethically sound research.

On the other hand, differences in guidance from different Common Rule agencies could weaken human subject protections if the additions or exceptions to the regulations are not apparent. Of course, all Common Rule agencies and departments include identical Subpart A language in their separate regulations, but each agency is permitted to issue its own guidance on the meaning and application of the regulations found in Subpart A. For this reason, labeling these agencies as “Common Rule” agencies can be misleading, and it can create compliance challenges since guidance often has the force of regulation. We believe it would be more accurate if agencies and departments are identified as having signed on to Subpart A, instead of the Common Rule. Subpart A agencies could be further categorized by their implementation of any exceptions or additions to Subpart A. This would aid in compliance because institutions and IRBs would know that they should search for agency specific guidance.

(question 73)

We support the goal of harmonization but it is unclear how to achieve this goal while preserving the agency specific guidance for specific research needs. We believe that additional clarification and justification of guidance that deviates from the Common Rule can help ensure compliance while continuing to protect vulnerable populations. We also believe that this could be an opportunity to better communicate the intent of guidance, especially when it conflicts with or narrowly interprets regulation. This is especially important because the intent of guidance is often misunderstood and yet, as a practical matter, it is given the force of regulation.

Among the federal laws and regulations that relate to the protection of human subjects that are inconsistent with the Common Rule, HIPAA is one that should be harmonized. It is our hope that working definitions, especially for terms such as individually identifiable, de-identified and coded, will be clarified and simplified for subjects, investigators and the IRB, and the criteria for waiver of authorization will be harmonized with the criteria for the consent waiver.

Finally, a single set of guidance issued by all Common Rule agencies – and updated on a regular basis or as changes occur – would be helpful in reducing confusion and enhancing compliance. Unfortunately, that would only apply to agencies and departments that sign on to Subpart A, leaving other agencies to continue to issue their own guidance. A different option would be to establish the regulations at 45 CFR 46 and their attendant guidance as the preemptive rule for all federal agencies and departments that conduct human research. Any guidance pertaining to specific agencies could be limited to issues that are not expressed in these documents.

IX. Important issue not addressed in the ANPRM: Proposal-protocol consistency

We believe that clarity is needed with respect to IRB certification of the project or proposal, per 45 CFR 46.103(f). OPRR guidance, issued May 31, 2000, states that the regulations require IRBs to certify that a funding application or proposal is entirely consistent with any corresponding protocols submitted to the IRB. NIH has issued similar guidance. Yet, in our experience the likelihood that a proposal compares identically to a protocol at any arbitrary single point in time is remote. This requirement is nearly impossible to meet, as human research often requires several protocols under one funding proposal or one protocol under several funding proposals. If the intent of the regulation is to require IRBs to approve funding proposals, then proposals must be written with sufficient specificity to address the required approval criteria under 45 CFR 46.111. Currently, funding proposals are not written with such necessary specificity.

We understand that this mandate in 2000 resulted from OPRR's having identified numerous instances in which human subjects research described in an application for HHS support differed significantly from the IRB-approved protocol that was claimed by the investigator to constitute the research in the application. To ensure that important elements such as the targeting of vulnerable subjects, additional treatment arms, different drug dosages, and additional collaborators, are reviewed and approved by the IRB before implemented, the regulatory requirement should simply state that the human research described in each application or proposal for research covered by the assurance and by 45 CFR 46.103 of this policy has been *or will be* reviewed and approved by the IRB *before the human research is allowed to commence*.