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Response to HHS and OSTP on Human Subjects Research Protections

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October 26, 2011

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

SUBJECT: HHS-OPHS-2011-0005
Enhancing Protections for Subjects and Reducing Burden,
Delay and Ambiguity for Investigators

Dear Dr. Menikoff:

The Council on Governmental Relations (COGR) is an association of 188 research universities and their affiliated academic medical centers and research institutes. COGR concerns itself with the influence of federal regulations, policies, and practices on the performance of research conducted at its member institutions. COGR members perform a significant amount of research involving human participants in partnership with Federal agencies. As a principal performer of human subjects research, we are deeply interested in proposed changes to the regulations governing that activity.

We agree that the current framework, essentially unchanged since it was codified and established, in part [Subpart A, 45CFR46), as the Common Rule in 1991, is worthy of review. Changes in research practices have brought elements of the Common Rule into question and, as a consequence, have required a growing volume of guidance and interpretative documents to address contemporary questions. It is worth observing, however, that the clarity and simplicity of the current regulatory framework argues for a measure of caution before changes are made to the Common Rule. Investigators, their home institutions and their designated Institutional Review Boards (IRBs) have used the guiding principles articulated in the Belmont Report and the flexibility built into the Common Rule to maintain protections for the thousands of subjects that participate in research activities each year. Thus, the current Common Rule combined with the policies and procedures implemented by our research institutions generally provide the intended level of protection to research subjects. The vast majority of subjects who participate safely in research understand their contribution and continue to volunteer to advance our understanding of ourselves and the world in which we live. Areas can be strengthened in light of changes in research and experience with the current regulations to ensure that subjects are protected but those changes must be balanced with

an understanding of the burdens associated with those changes.

This letter offers general observations on the areas described in the Advanced Notice of Proposed Rulemaking (ANPRM); the appendix attached to this letter provides more detailed responses to the seventy-four questions posed in the ANPRM.

Enhancing Protections and Reducing Burden

As we reviewed the proposed changes to the Common Rule, we remained mindful of the goals articulated in the ANPRM – enhancing protections for subjects and reducing burden, delay and ambiguity for investigators and institutions. We share those as guiding principles for any change to the regulations. Throughout our review we asked ourselves in each instance “would the protection of subjects be enhanced or diminished by this change?” If a proposal had no measurable impact on the subjects but increased the burden in any way on the investigator or the institution, we recommend that such change not be implemented. In some cases, changes in the regulations may not be the appropriate response. Clear and concise guidance can often assist the investigators, institutions and IRBs in navigating ambiguities.

Many of the proposed changes are wise and based on a growing body of knowledge built on the experiences of investigators, institutions and IRBs informing the process. If we were able to build the entire regulatory framework new, such a framework would reflect much of what is proposed here. However, many elements in the ANPRM expose institutions to a greater regulatory “risk” without affording greater protections to subjects or relief for investigators.

Ensuring Risk Based Protections:

We endorse a risk-based regulatory framework that relies explicitly on performance-based standards rather than prescriptive regulatory requirements. Giving investigators, institutions and IRBs greater flexibility will ensure achievement of the fundamental goal of protecting subjects. Calibrating protections to the level of risk enables an institution to focus its protection program on those research activities that pose the greatest risk while providing the appropriate level of review and monitoring of minimal risk studies.

From this perspective – risk-based performance standards – we are concerned about the elimination of exempt categories of research. We believe that there are categories of interactions with subjects that should remain exempt from the regulations and the proposed revisions in the current exempt categories can and should be accomplished without the creation of a new “excused” category. For example, limiting or eliminating continuing review unless required by IRB at the initial review will be a significant and appropriate change. Revising the exemption criteria for survey, interview, and other research activities involving competent adults and extending the exemption to additional minimal risk studies will provide significant relief.

We are troubled by the changes proposed related to informational risk including eliminating categories of exempt research and imposing requirements to manage data and information security across the research enterprise. These changes will most assuredly increase the burden on investigators without measurable benefit to the subjects. IRBs have been successfully reviewing research involving confidential information. The proposals advanced in the ANPRM for defining and managing

informational risks would be managed by the investigator and institution outside the IRB process but not outside the human subjects protection program. We are unaware of systemic problems or significant incidents with disclosure, re-identification or breaches of confidentiality that warrant such a significant shift in responsibilities for IRBs. However, we are certain that mechanisms proposed for registration and retrospective audits will not add protections to current subjects but will measurably increase the burden on investigators and institutions.

The cascade of requirements that are proposed as a result of the elimination of exemptions and the introduction of heightened concerns for informational risk is alarming. Currently there is no consent requirement for exempt research and the introduction of this requirement will make the conduct of certain types of research unnecessarily complex without increasing the protection of subjects. Expanding the meaning of “human subjects” by including biospecimens without identifiers within the provisions related to information risk and requiring written consent for research use of de-identified biospecimens reverses long-standing definitions of what constitutes human subjects and undermines the conduct of critical research. The proposed shift to a more regulated enterprise leads to proposing an unnecessary change in the long-established and virtually universally applied definition of research to accommodate clearly exempt activities such as quality improvement and program evaluation.

We recognize that research can have some measure of informational risk but not all such activities pose the same level of information and data security risks. However, we oppose a separate process for the review of informational risk. Such a process would create another burdensome layer of bureaucracy without a concomitant benefit to subjects.

In a manner similar to the current definition of minimal risk, the probability and magnitude of harm from such information risk is likely not greater than the risk encountered daily in our lives as we rely increasingly on transactions and activities conducted through electronic means. We believe that any research that falls solely under informational risk is, by definition, minimal risk and would be categorized, under the current regulations, as exempt. We know that the information and data security requirements as proposed will increase the burden on researchers and the registration and auditing requirements will increase the burden on the institution. We fear that these new requirements could limit, or worse, drive underground some research activity, notably that research conducted by students as a part of their educational experience.

Streamlining Review of Multi-Site Studies

We recognize that there are advantages to establishing an IRB of record for multi-site clinical trials. For the project directors, the coordination under a single IRB providing a common review for all sites including a common informed consent process will increase efficiencies. For many multi-center studies conducted nationally, the value of local IRB review is less critical because it is unlikely that a local context would raise major differences in approach to ethical issues, but local review could, however, raise specific and, in some cases, significant cultural differences associated with a site that may affect operational aspects of implementing the study at that specific site.

There are limits, however, to the efficiencies and streamlining that could result from a requirement for a single IRB of record. We know that determining where inefficiencies affect the initiation of multi-site research is a complex and challenging problem. Many factors impact how quickly and efficiently a multi-site study can begin enrollment, only one of which is IRB review. Typically

participating sites initiate at differing times dependent not only on their IRB review, but many other factors such as contract and budget negotiation, and other national policy and regulatory activities that are coordinated with and have an impact on local IRB review including, as appropriate, pharmacy, radiation safety, biosafety, HIPAA, and financial conflicts of interest policies and requirements. Further, use of central IRBs may only create additional administrative activities that usurp any gain in a more efficient IRB review process.

We see no advantage to mandating the use of one IRB of record. The advantages, like cooperative review and the elimination of multiple redundant reviews can be accomplished through education, guidance and an emphasis on changing the current culture of “over-review” that results from institutions operating out of fear of regulatory non-compliance or legal liability or, perhaps more importantly, from a lack of knowledge of available options related to cooperative review. Concerns related to regulatory and legal liability, whether real or imagined, are a significant contributor to institutions choosing to conduct their own local review. These concerns are shared by institutions across the spectrum of large and small, public and private.

We believe encouraging use of central reviews will be most beneficial in creating a more streamlined review process while maintaining important human subjects protections. As proposed, the IRB of record provides only limited streamlining with regard to such activities. The protection of subjects remains with the local site and, as a consequence, most local sites prefer to describe the protection provisions in its communication with the local investigator. This is an area that is not well served by being incorporated into regulations. We would encourage OHRP to issue guidance and provide access to resources that assist institutions and investigators in assess the strengths and weaknesses of the different approaches to inform a decision that is good for the subjects and good for the study.

Improving Informed Consent

We strongly discourage the regulatory prescription of content and format for the informed consent documents. We know that any “boiler plate” language whether developed by OHRP or another entity will not ensure the conveyance of useful information to subjects in a specific study. We agree that the informed consent documents have become unnecessarily long and complex but we believe that is driven as much by a risk-based assessment by institutions and sponsors to avoid allegations of non-compliance rather than the initiation of more complex studies. All parties to the implementation and enforcement of the regulations need to reconsider what the role of the consent process is as opposed to simply focusing on the documents used in that process and work to assist investigators and institutions to ensure that the information conveyed serves the purpose of informing the subjects.

Institutions routinely include language that addresses subject injury or limits to confidentiality related to submission of payments for income tax purposes. The forms deal with additional regulatory requirements or policy guidance such as FDA requirements to inform subjects about clinicaltrials.gov or the OHRP guidance and requirements to include detailed information regarding Genetic Information Nondiscrimination Act (GINA) of 2008 in the consent document. The consent forms in clinical trials also contain information concerning HIPAA consent notifications as well. All of this information will be unique to the institution, sponsor, and specific study in some cases and will not be served by a prescriptive regulatory approach.

We believe the informed consent process would greatly benefit from the ability to streamline the documents to address key elements of the research study and related activities with the required regulatory, policy and institutional information attached as appendices to the consent document itself. Some of these appendices could be standardized by the institution for particular research units thus reducing the burden of preparation for investigators.

We do not support the proposed informed consent requirements for unanticipated future use and analysis of data or biospecimens collected for research. Data or biospecimens collected for a different research purpose should be permitted for future analysis without specific informed consent. As necessary, the proposed use can be reviewed by an IRB for a determination that the waiver of informed consent is appropriate. We support a general future use provision in consent forms but do not consider it a prerequisite for any and all future research use. The current IRB process for waiving informed consent provides an effective framework for protecting individual subjects without damaging critical research efforts that serve in the best interest of the public as a whole.

We do not support any limitation on the future use of data collected for non-research purposes. A similar general permission for use should provide sufficient protection and notification of individuals to ensure that critical research activities can proceed. We know that obtaining meaningful consent at the time of data collection in non-research activities is ineffectual. We also know that biospecimens and data collected for non research purposes are important sources of information for researchers and reuse of existing data is an efficient mechanism for conducting research without presenting additional risks to the individual.

Strengthening Data Protections to Minimize Informational Risk

We do not support mandatory data security and information protection standards and strongly oppose using HIPAA security and notification standards as a model. Simplified guidelines developed in collaboration with investigators and research institutions would be more appropriate.

The HIPAA Privacy and Security Rules include complex identification criteria and security standards designed to protect private health information. Duplicating these standards for “all” research at institutions would be extremely burdensome for the investigators and institutions without any assurance that the subject-related information would have greater protections. The use of HIPAA as a model assumes that these standards and regulations have been an effective tool but the Institute of Medicine’s 2009 report, *Beyond the HIPAA Privacy Rule*, concludes that “the HIPAA Privacy Rule does not protect privacy as well as it should, and that, as currently implemented, it impedes important health research.”

Of greater concern is the suggestion that these privacy and security rules designed for private health information would be applied across all research activities. First, not all research performers are “covered entities” as defined by HIPAA. As a consequence, those non-covered entities would need to implement, at significant cost, the provisions of HIPAA. HIPAA is a poor model for “research” especially for social, behavioral, and educational research. A requirement that applies the HIPAA framework to define identifiability would expand the scope of what is considered human subjects research under the Common Rule because many more social, behavioral, educational studies would fall under the standard requirements. But as most observers would acknowledge data collected in these studies would rarely lead to any harm even if a breach should occur.

The implementation of HIPAA requirements for all research creates a significant regulatory and financial burden for investigators, institutions, and sponsors obligated to meet these standards. These costs must be justified and balanced with the information risks that the standards are designed to minimize. Research institutions like all institutions and organizations and businesses have broad computing protections in place. Adding significant data security provisions at the HIPAA standards across the campus will be a significant cost for the institutions. The information most at risk – private health information – is already protected under HIPAA; other types of vulnerable information are protected under the provisions of other state and federal regulations. If a breach of confidentiality poses a significant risk, the related research activities would likely not be exempt and the IRB can review and manage the risk with the investigator.

Data Collection to Enhance System Oversight

The challenge that is described in the ANPRM with regard to data collection builds on the observation that research agencies use varying definitions, timelines and elements to collect information on unanticipated problems involving risk to subjects and/or adverse events frustrating integrated or comparative analyses in the interest of more global assessments of the frequency and severity of such problems or events.

As a rule, COGR supports harmonization across agencies to the extent that unique agency needs continue to be met and the most stringent requirements are not applied to low risk research in an effort to apply one rule to all. However, we believe a single approach to data collection that covers all human subject research, from clinical trials to survey research, would not serve the subjects, the investigators or, as suggested, our understanding of such events or problems. As we suggested earlier, a risk-based performance-based approach toward regulation could provide a strong basis for the harmonization of regulations.

We recognize that the reporting of unanticipated problems and adverse events is a critical component to ensuring the protection of subjects and public health and streamlining the currently required reporting to the sponsor, IRB and OHRP, as appropriate, will help ensure that good decisions can be made to protect subjects. Generally, we support efforts to improve the prompt collection of critical, in this case, safety data via a common electronic portal but there can be real problems associated with a proposed web-based portal. As with any electronic system, the quality and validity of the data is only as good as the information provided which remains dependent on the user's understanding and interpretation of what needs to be reported, when.

Nonetheless, we have very real concerns regarding the value in terms of cost and time with amalgamating such data gleaned from diverse studies and sources in order to conduct an integrated analysis. It is unclear how the data is useful beyond its specific study. Patterns of events or problems might be possible but, given that each trial is different, trying to establish these patterns in a large data set from diverse studies will be difficult if not impossible. Many unanticipated problems, particularly from social or behavioral research, are isolated and would offer little application for global interpretation if entered into a central repository.

It is unclear who would have access to the data, how it would be managed and interpreted and who would support the development of such a system. In its current form, it does not enhance protections for human subjects but adds additional reporting requirements for researchers and IRBs contrary to the goals of the ANPRM.

Extension of Federal Regulations

We do not believe the extension of federal regulations to all research at an institution serves to provide any greater protections to human subjects. We particularly oppose the extension under the current and proposed regulatory regime. Most institutions with a Federalwide Assurance (FWA) apply the Common Rule to all research regardless of funding including those institutions that have “unchecked the box.” The latter institutions apply the regulations in principle and generally in practice reserving the right to exercise greater flexibility in such areas proposed for change in this ANPRM, e.g., continuing review, documentation of consent in minimal risk research with competent adults, etc.

Thus, we believe the proposed extension will not enhance the protection of subjects but we know it will greatly increase the costs, burden, and delay of research for institutions that receive Federal support. Ironically, these institutions and the studies they conduct are not the institutions that likely cause the greatest concern for the public. This proposed extension does nothing to reach those organizations and institutions currently operating outside the regulations.

Clarifying and Harmonizing Regulatory Requirements

As we have stated in many comments and reports to the Federal government, we support the harmonization and coordination among agencies in the development and implementation of regulations, policies and guidance. In the case of human subject protections, harmonization among the agencies would simplify training of and promote compliance by investigators because the regulations would be consistent and not agency-dependent. If the regulations were tailored to the risk to subjects and not to the type of research, then one set of regulations could easily address diverse populations and the breadth of research areas.

Nonetheless, we have found that actions of some federal agencies undermine the achievement of real harmonization and the application of common approaches. In many of the cases, agencies add to or alter the common approach to meet statutory requirements or agency-determined program needs. We have found that changes incorporated during the implementation of a common rule or policy result in incremental burdens that when repeated across the agencies defeats the common approach.

The model for the burdensome impact of the accretion of agency-specific policies and approaches is the Common Rule. We have found that in implementing the Common Rule, agencies have taken strikingly different approaches. The difference between FDA regulations and the Common Rule are frequently cited and we appreciate the efforts by the FDA and OHRP to align the regulations as much as possible. But the Department of Justice and the Department of Education also have slight but important different requirements. We have found that maintaining a current FWA does not prevent some agencies from adding additional layers of requirements. The Department of Navy requires an entire Addendum to the FWA and has recently expanded the training requirements for administrative personnel despite the requirement that is part of the FWA process.

The most time-consuming and redundant procedure is the requirement to submit to the Federal agency a research protocol describing the human subject research component that has already been reviewed and approved by the applicant institution’s IRB for yet another review and approval by the agency IRB or, in some cases, by the peer review panels established to recommend the funding of research projects. This duplicate review delays awards and creates ambiguities over which entity – the

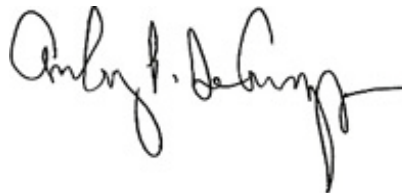
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institution or the agency – is finally responsible for the conduct of the human subjects research. Additional unique reporting, training, and operational requirements create a level of confusion and occasional conflict in maintaining compliance with the actual regulation or policy itself. There is nothing common among these approaches. It's not a problem with the Common Rule; it's the varying implementations of the "Common" Rule that adds significantly to the burden, delay and ambiguity for investigators. We applaud the interest in harmonization and we are hopeful that real harmonization will occur.

The attached appendix provides responses to each of the questions raised in the ANPRM. We appreciate the opportunity to begin this consideration of changes to the regulations providing protection for human research subjects.

Sincerely,

A handwritten signature in black ink, appearing to read "Anthony P. DeCrappeo". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Anthony P. DeCrappeo
President

**Appendix to Letter Dated October 26, 2011
Council on Governmental Relations (COGR)
Responses to Questions 1-74 concerning Proposed Changes to Subpart A of 45 CFR 46
HHS-OPHS-2011-0005**

II. Ensuring Risk-Based Protections

A. Protecting Subjects From Informational Risk

We oppose the ANPRM's proposed changes that effectively remove the review of privacy and confidentiality issues from the IRB and transfer the responsibility to another process within the human subject protection program. We recognize that some research has informational risks (as defined in the ANPRM) but requiring mechanisms to address informational risk to all research data collected, stored, analyzed or otherwise reused will not increase the protection of subjects and will dramatically increase the burden for investigators and institutions. We are concerned that the related registration and auditing requirements would severely limit, or worse, drive underground student research activities that are a part of the educational mission/activities in many departments and colleges.

The ANPRM considers informational risk in the context of unauthorized disclosures of research information and proposes to use the HIPAA Security Rule for security of identifiable data and data in limited data sets and Privacy Rule definitions for identifiable, de-identification and limited data sets. As proposed, the goal of information protection is to prevent breaches of confidentiality through unauthorized access, inappropriate disclosure or reidentification.

We are concerned that using the HIPAA standards for security and privacy for addressing informational risk across the range of disciplines and activities represented by the human subjects research endeavor is an extreme response to a yet-to-be identified problem. Research institutions like all institutions and organizations and businesses have broad computing protections in place. Adding data security provisions at the HIPAA standards across the campus will be a significant cost for institutions, especially for those which are not currently covered entities. The information most at risk – private health information – is already protected under HIPAA. If a breach of confidentiality poses a significant risk, the related research activities would not likely fall under the exempt categories and would receive an IRB review. The IRB can address the management of the data as a part of the approval process.

It remains unclear what problems/incidents with disclosure or breaches of confidentiality OHRP is attempting to address with this proposed change. We are unaware of any such recent incidents and suspect the proposed revisions do not add appreciably to the protection of subjects from informational risk. Retrospective audits will not protect current subjects.

B. Calibrating the Level of Review to the Level of Risk

The ANPRM seeks comments on ways to improve expedited review. We recommend that the current list of expedited categories be reviewed immediately by a panel of experts including researchers, particularly social scientists, IRB members and chairs, IRB administrators, and lay persons knowledgeable about research, such as non-scientific IRB members. The panel should be diverse in background and geography. The panel should serve in an advisory capacity to the

regulators responsible for making changes to the list. The categories should be reviewed at least every five years.

The list of categories should be not be considered exhaustive and we recommend adding a category that would allow the IRB to use expedited review procedures for any additional activities determined by the IRB to be of no greater than minimal risk. For example, the IRB should be allowed to judge whether extra samples taken for research during a clinically indicated test constitutes no more than minimal risk. All areas on the proposed list of new expedited categories could be included in the list, but the IRB should determine which activities that are not part of routine care might increase risk. Much of what is listed as Expedited Categories 5 (data analysis), 6 (collection of data from voice, video, etc.) and 7 (group characteristics – surveys, interviews, etc.) should be reclassified as exempt.

We believe the criteria for IRB approval at 46.111 are appropriate for research that qualifies for expedited review, and that the same criteria should be used for review of both expedited review and full board review. We support adding the phrase “when appropriate” to the introduction of 46.111(a) to allow IRBs additional flexibility.

There should be no mandatory reporting by IRBs when they choose to use full board review for projects that might seem to qualify for expedited review. Such a requirement would add institutional burden without any added protections for subjects.

Question 1: Is the current definition of "minimal risk" in the regulations appropriate? If no, how should it be changed?

The current definition of minimal risk should be modified to:

"The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered by typical individuals in the study population in their daily lives or during the performance of routine physical or psychological examinations or tests".

This would allow consideration of special circumstances relevant to populations such as illegal immigrants; impoverish communities; or people living in high crime or high drug use environments.

Question 2: Would the proposals regarding [eliminating] continuing review for research that poses no more than minimal risk and qualifies for expedited review assure that subjects are adequately protected? What specific criteria should be used by IRBs in determining that a study qualifies for expedited initial review should undergo continuing review?

Yes, continuing review for minimal risk research – whether undergoing an initial full or expedited review – should be eliminated as a regulatory requirement. Eliminating continuing review for studies involving minimal risk, particularly those that initially receive expedited review will still provide subjects with protections. Criteria which an IRB may wish to consider when determining whether to require continuing review could include reports of serious adverse events, unanticipated problems involving risk to subjects or non-compliance identified during monitoring. The IRB

should also have the option to require continuing review, when they have concerns about a specific study.

Question 3: For research that poses greater than minimal risk, should annual continuing review be required if the remaining study activities only include those that could have been approved under expedited review or would fall under the revised exempt (Excused) category?

No, continuing review should not be required for the studies described. Generally, there should be no continuing review of studies that poses greater than minimal risk if research related interactions and interventions with subjects are complete. The IRB has the option to require continuing review when they have concerns about a particular study. However, subjects could still be informed in the event that analysis of data yields a result, which may be of immediate concern/interest to the subjects' wellbeing.

Question 4: Should the regulations be changed to indicate that IRBs should only consider “reasonably foreseeable risks or discomforts”?

Yes the regulations should be so changed. IRB should focus on context and only consider “reasonably foreseeable risks or discomforts.”

Question 5: What criteria can or should be used to determine with specificity whether a study's psychological risks or other nonphysical, non-information risks, are greater than or less than minimal?

The IRB should determine appropriate criteria for risk determination using all the resources available, including literature review, consultation with experts, and precedents established for similar research. Such criteria should not be established in regulation.

Question 6: Are there survey instruments or specific types of questions that should be classified as greater than minimal risk? How should the characteristics of the study population (*e.g.* mental health patients) be taken into consideration in the risk assessment?

There are no instruments or types of questions that should be characterized by risk in the regulations. Characterizing a research tool (a survey instrument) by risk is inappropriate. The IRB is in the best position to review particular instruments, questions and study populations to judge risk on a case-by-case basis and in the context of the study.

Question 7: What research activities, if any, should be added to the published list of activities that can be used in a study that qualifies for expedited review? Should any of the existing activities on that list be removed or revised?

The proposed activities listed below should be included considered minimal risk:

- Allergy skin testing.
- Skin punch biopsy (limited to two per protocol).

- Additional biopsy during a clinical test (*e.g.*, performing an extra colonic biopsy in the course of performing a routine colonoscopy).
- Glucose tolerance testing among adults.

We would add the following activities as minimal risk activities, some of which could be determined to be exempt from the regulations:

Occupational health activities such as walking, deep breathing, mild exercise; fMRI at standard exposure levels; studies of internet behavior; and the establishment of registries for future research purposes should be added to the list eligible for expedited review.

In addition, we believe a general category should be added to allow IRBs to use expedited review procedures for any additional activities determined by the IRB to be of no greater than minimal risk. The IRB should be allowed to judge whether extra samples taken for research during a clinically indicated test constitutes no more than minimal risk. However, the IRB should determine which activities that are not part of routine care may increase risk.

We believe most of the activities listed as Expedited Categories 5 (data analysis), 6 (collection of data from voice, video, etc.) and 7 (group characteristics – surveys, interviews, etc.) should be reclassified as exempt.

Question 8: Should some threshold for radiological exams performed for research purposes, that is calibrated to this background level of exposure, be identified as involving no more than minimal risk?

Yes, a threshold should be established in consultation with medical experts for radiological exams that involve no more than minimal risk.

Question 9: How frequently should a mandatory review and update of the list of research activities that can qualify for expedited review take place?

The list of research activities that qualify for expedited review should be reviewed and, if appropriate, updated every five years by a panel of experts that includes researchers, particularly social scientists, IRB members and chairs, IRB administrators, and lay persons knowledgeable about research, such as non-scientific IRB members. The panel should be diverse in background and geography. The panel should serve in an advisory capacity to the regulators responsible for making changes to the list.

Question 10: Which, if any, of the current criteria for IRB approval under 45 CFR 46.111 should not apply to a study that qualifies for expedited review?

There is no need to change the 46.111 approval criteria for expedited review or full review. The current qualifier, “when appropriate,” provides the IRB the flexibility to apply the appropriate criteria.

Question 11: What are the advantages of requiring that expedited review be conducted by an IRB member? Would it be appropriate to instead allow such review to be done by an appropriately trained individual, such as the manager of the IRB office, who need not be a member of the IRB?

There are no advantages to limiting the expedited review to IRB members. Appropriately trained IRB staff or other individuals should be allowed to conduct expedited reviews. The key criteria should be appropriate training and experience. The IRB should determine and document the appropriate level of experience and training.

Question 12: Changes or additions in documentation:

- a. Are there other specific changes that could be made to reduce the burden imposed in meeting the requirements to submit documents to an IRB, without decreasing protections to subjects?

The requirement for IRBs to review the entire grant proposals, including the budget, to ensure congruence with the IRB application should be eliminated. Institutions can address this concern through an appropriate mechanism such as an attestation on the part of the Principal Investigator that the protocol approved by the IRB and the grant proposal are congruent.

- b. Are there specific elements that can be appropriately eliminated from protocols or consent forms?

The proposed data or information security provisions should not be adopted because, as proposed, the requirements will increase the content of documents and add to the burden on investigators without demonstrable increase in protections.

- c. Which other documents that are currently required to be submitted to IRBs can be shortened or perhaps appropriately eliminated?

The requirement to provide all IRB members with information concerning which studies had been reviewed using the expedited procedure should be eliminated. The process adds no value to the review of minimal risk research [46.110(c)].

- d. Conversely, are there specific additions to protocols or consent forms beyond those identified in this notice that would meaningfully add to the protection of subjects?

Consent documents can be greatly simplified by focusing the consent on the research activities. For example, many procedures included in consent forms are describing the standard of care to which a research drug/activity is added. Focusing subjects on the specific research component rather than long descriptions of standard care will assist in streamlining the preparation of documents and highlight for the subjects what part of their treatment is unique or different.

- e. What entity or organization should develop and disseminate such standardized document formats?

No entity or organization should develop and/or disseminate standardized document formats; nor should such standard document formats be promulgated by regulation. Most institutions have standard formats or templates that have been demonstrated to address IRB criteria and streamline the submission and review of the activities. With any subsequent changes in regulations, OHRP can assist with the guidance that outlines or identifies the key elements for consent.

Question 13: Would it be appropriate to require IRBs to submit periodic reports to OHRP in the instances in which they choose to override the defaults in the regulations? Would [these reports] provide useful information for guidance or the possible need to revise the expedited review list or the continuing review requirements?

It would not be appropriate to require additional reporting from IRBs concerning the exercise of their authorities. Such required reports would greatly increase the IRBs' burden without increasing the protection of human subjects. The current system is largely driven by OHRP guidance and clear guidance and expectations will result in greater consistency. OHRP could consider a mechanism such as a Frequently Asked Questions (FAQ) to provide responses to questions that can be easily disseminated throughout the community.

Moving Away from the Concept of Exempt

The ANPRM proposes major changes to the current exemption categories and review process. The proposed rule would create a new process for “excused research” that would require registration of projects with the institution, but not require review prior to initiating research. The ANPRM proposes retrospective audit to identify problems with the registration process. The changes proposed that address risk-based protections including changing exempt research to excused research and changes within the former exempt categories are built on defining and managing informational risk and related data security as subjects outside the responsibilities of the IRB. This change would eliminate exemptions to the coverage of the regulations. Thus, all research would be subject to informational risk at varying levels.

The proposed changes would increase the burden on institutions in collecting the registrations and conducting retrospective audits of the registered studies. We assume, perhaps incorrectly, that an assessment of informational risk would be expected. The proposed changes may create greater risk of non-compliance for investigators and institutions because institutions are currently held responsible when research is improperly designated as exempt. Finally, this change may decrease the protection of subjects because it relies on a determination that the study is “excused” from investigators who may not be as knowledgeable about the regulations as an IRB staff or Board member who routinely screen projects for exemption eligibility. Using the registration process permits research to move forward without a prior determination of its status by the IRB or institutional designee and eliminates some protections for subjects while increasing institutional liability. If such an approach were considered, OHRP would need to provide additional guidance and better decision-making tools for determining risk categories.

We would strongly encourage the expansion and, as appropriate, clarification of the current exempt categories by a panel of experts including researcher, particularly social scientists, IRB members and chairs, IRB administrators and laypersons knowledgeable about research, such as non-scientific IRB members. We recommend endorsement by OHRP of processes to allow investigators to self-determine exemption status. We believe that with the right tools (decision trees, exemption wizards, smart forms) this process can be automated, but that the institution should oversee the screening process and grant exemption status prior to the initiation of research.

We recommend that the current exemption process be maintained and the current regulations for exempt projects be expanded to include: social networking research, research involving human testing/interfacing with technology like internet behavior, walking, deep breathing, mild exercise research involving only analysis of identifiable data deemed to be minimal risk, and much of what is listed as Expedited Categories 5 (data analysis), 6 (collection of data from voice, video, etc.) and 7 (group characteristics – surveys, interviews, etc.) should be reclassified as exempt.

We recognize that OHRP views this fundamental change as eliminating a burden for investigators but we must assume the reverse is true. The responses to the questions below are provided based on our assumption that we are discussing changes to the *current exempt categories and processes for making exempt determinations*.

Question 14: Are these expansions in the types of studies that would qualify for this exempt [Excused] category appropriate? Would these changes be likely to discourage individuals from participating in research? Might these changes result in reduced protections for research subjects?

We believe that expansions to the current list of exempt categories [proposed as “excused”] are appropriate. This change would not hinder subjects from participating and would not reduce protections. Broadening current exemption categories and maintaining institutional-defined mechanisms for affirming exemption is likely to offer better protection for the human subjects than complete reliance on ad hoc retrospective monitoring of a small number of studies.

Question 15: Are there other types of research studies that should qualify for the exempt [Excused] category? Are there specific types of studies that are being considered for inclusion in these expansions that should not be included?

The current exempt categories should remain in place and be expanded to better encompass social/behavioral research. Suggestions include minimal risk categories for:

- Social networking research
- Research involving human testing/interfacing with technology
- Research involving only analysis of identifiable data deemed to be minimal risk (either secondary data or ongoing analysis of primary data)
- Research involving deception
- Walking, deep breathing, and mild exercise
- Studies of internet behavior

Question 16: Should research involving surveys and related methodologies qualify for the exempt [Excused] category only if they do not involve topics that are emotionally charged, such as sexual or physical abuse? If so, what entity should be responsible for determining whether a topic is or is not emotionally charged?

Yes, surveys and related methodological studies without psychological risks should be exempt. The IRB can be consulted if a project appears to be more than minimal risk based on the proposed research itself. It is not appropriate to excuse research from ethical review if it explores topics which are known to be at least “emotionally charged” for the subject.

Question 17: What specific social and behavioral research methodologies should fall within the exempt [Excused] category? Under what circumstances, if any, should a study qualify for the exempt [Excused] category if the study involves a form of deception (and if so, how should “deception” be defined)?

Scholarly activity is dynamic and defining specific methodologies within regulations has the potential to become prescriptive rather than illustrative. Generally, studies involving minimal risk in social networking research, human testing/interfacing with technology, and research involving only analysis of identifiable data deemed to be minimal risk (either secondary data or ongoing analysis of primary data) should be included as exempt categories. The use of deception is a legitimate scientific strategy and its use can be best addressed through guidance rather than regulation. A definition of deception to distinguish it from concealment and illustrate its acceptable use could be provided in guidance. Some minimal risk deception research may be considered by the IRB for exemption.

Question 18: Currently some IRBs make determinations regarding whether clinical results should be returned to study participants. How should such determinations [to return clinical results to study participants] be made?

Whether clinical results should be returned to study participants should be left up to the participant and research team in consultation with the participant’s physician. If the research anticipates clinical results that may yield important information related to non-research related health and care, a discussion with the participant during the informed consent process is likely the best approach to determine the participant’s interests. A regulatory requirement is not necessary or appropriate in this determination.

Question 19: Regarding the exempt [Excused category], should there be a brief waiting period (*e.g.* one week) before a researcher may commence research after submitting the one-page registration form, to allow institutions to look at the forms and determine if some studies should not be Excused?

We do not recommend adopting the registration process and, therefore, a “waiting period” prior to the commencement of research is not relevant for regulations.

Question 20: The term “Excused” may not be the ideal term. Might a term such as “Registered” better emphasize that these studies will in fact be subject to a variety of requirements designed to protect participants?

We oppose the elimination of the exempt classification of some human subject research activities. Complete elimination of exemptions and the implementation of a ‘registration’ process for “excused” research are not appropriate. These points are discussed elsewhere in ANPRM responses. Current categories of full, expedited, exempt have utility for managing the types/risks of research applications submitted. Some categories could be enhanced and additional guidance could be provided.

Question 21: Is it appropriate to require institutions holding a Federalwide Assurance to conduct retrospective audits of a percentage of the exempt [Excused] studies to make sure they qualify for inclusion in this category?

We do not recommend adopting the registration process and which permits researchers to begin research without a prior determination of its status by the IRB or institutional designee. Therefore the concept of retrospective audits is neither necessary nor warranted for regulation. Institutions should be free to develop their own quality assurance procedures, as necessary.

Question 22: Are retrospective audit mechanisms sufficient to provide adequate protections to subjects? Do researchers possess the objectivity and expertise to make an initial assessment of whether their research qualifies for the exempt [Excused] category? Will the use of a one-page registration form give institutions sufficient information to enable them to appropriately conduct the audits?

Review prior to initiating research protects subject in a way retrospective audit cannot and institutions have mechanisms in place to review and affirm the exempt status of research. A retrospective audit may decrease the protection of subjects because it relies on a determination that the study is “excused” from investigators who may not be as knowledgeable about the regulations as an IRB staff or Board member who routinely screen projects for exemption eligibility. Institutions should have the flexibility to provide standard tools (e.g. smart forms, electronic wizards, checklists) to allow investigators to register projects that meet standards for minimal risk and exempt categories.

Question 23: Under what circumstances should it be permissible to waive consent for research involving the collection and study of existing data and biospecimens? Should the rules for waiving consent be different if the information or biospecimens were originally collected for research purposes or non-research purposes? Should a request to waive informed consent trigger a requirement for IRB review?

We support the waiver of informed consent for the use of any existing identifiable data or biospecimens whether collected for a different research purpose or for a non-research purpose

when an IRB has determined that the waiver of informed consent criteria outlined in [116 (d)] are met.

Question 24: How [should] the Common Rule be changed to clarify whether or not oversight of quality improvement, program evaluation studies, or public health activities are covered.

Yes, it would be helpful for OHRP to provide clarity through guidance, not a change in the regulation, that quality assurance or quality improvement activities (health care operations), program evaluation, and public health surveillance and assessment activities are not research as defined by the regulations. It would be inappropriate for OHRP to redefine “research.” Only research, as generally and currently defined, should be regulated under the Common Rule.

Question 25: Are there certain fields of study [that] were not intended to or should not be covered by the Common Rule?

The determination of IRB purview should not be predicated on a field of study but rather on the activities that involve human subjects.

Question 26: Is the circumstance that a particular demonstration project generates “broad” knowledge incorrectly being used as a reason to prevent certain activities from qualifying for exempt category 5? Would broadening the interpretation of the exemption result in inappropriately increased risks to participants in research?

Broadening the interpretation would not increase risk and the related OHRP guidance should be updated to clarify that quality improvement, program evaluation and general public health activities do not meet the definition of research and, therefore, are not covered by the regulations.

Question 27: Do IRBs correctly interpret [the proscription on considering long-range effects of applying knowledge] as meaning that it is not part of their mandate to evaluate policy issues such as how groups of persons or institutions might object to conducting a study because the possible results of the study might be disagreeable to them?

Many IRBs make the appropriate interpretation but additional guidance or illustration could be helpful.

Question 28: Should the Common Rule include a requirement that every institution must provide an appropriate appeal mechanism?

There is no need for an additional mandated appeal process in the regulations (§46.109(d) requires IRBs to give investigators an opportunity to respond to disapproval). The strength of the current system is that IRBs are able to work independently and without fear that institutional leadership will override IRB decisions. Procedures for managing appeals of IRB decisions should be left to

institutions. If there is a need to encourage institutions to establish reasonable appeals processes, this can be handled through regulatory guidance related to §46.109(d).

Question 29: Would it be helpful to require that each time an IRB [engages in activities beyond regulatory requirements], it must specifically identify that activity as one that is not required by the regulations?

There is no value to the IRB or the investigators in requiring the IRB to maintain a list of exempt determinations or activities undertaken by the IRB outside its responsibilities. IRBs should not review activities outside of their purview. The institution should assist the IRB through training and monitoring to ensure that studies that fall outside the regulations do not come before the IRB for considerations. Institutions use a variety of mechanisms to assist investigators in determining whether research is exempt under the current regulations and the process and procedures for making those determinations should not be established by regulation. Such reporting adds to the IRB and institutional burden without providing additional protections for subjects or relieving ambiguities for investigators.

III. Streamlining IRB Review of Multi-Site Studies

In responding to the OHRP's RFI concerning IRB accountability, COGR noted that the most useful regulatory or, perhaps more directly, enforcement change to encourage the use of a central IRB of record would be to hold the IRBs or IRB organizations – the IRB of record – accountable for compliance with specific aspects of the regulations. We recognize there are significant hurdles to this approach and changes may have the effect of discouraging institutions from having their IRB designated as an IRB of record because of concerns about the risk and potential liability in meeting the obligations of serving as the IRB for a multi-institutional, geographically dispersed project. In weighing the risk and benefits, much would depend on how OHRP responds to allegations of noncompliance.

Question 30: What are the advantages and disadvantages of mandating one IRB of record?

We see no advantage to mandating the use of one IRB of record. The advantages, like cooperative review and the elimination of multiple redundant reviews can be accomplished through education, guidance and an emphasis on changing the current culture of “over-review” that results from institutions operating out of fear of regulatory non-compliance or legal liability or, perhaps more importantly, from a lack of knowledge of available options related to cooperative review.

However, it is important to address advantages and disadvantages from the perspectives of both the researchers involved in and conducting the studies, as well as the IRBs who may have oversight of the research activities. For researchers charged with overall conduct of a multi-site study, such as a coordinating or data management center, there is benefit to having a centralized IRB to provide consistent review for all sites in the study including a consistent informed consent document. This can lead to efficiency in reducing the amount of time needed to obtain IRB approval for all sites. For the individual researcher at a local site, centralized review can relieve some of the administrative

burden of negotiating with a local IRB, but it may actually increase burden if mandated because the individual researcher may now need to interact with multiple “central” IRBs, each with different requirements. However, it may not actually reduce the more important timeline – that of time to enrollment of first subject. Other local review processes such as conflict of interest review and contract negotiations can greatly impact time to first subject enrollment.

As with the individual researcher, the use of a central IRB can reduce the agenda sizes for IRB full board meetings. However, there remains a significant administrative burden on the institution, normally within the IRB administrative office in support and oversight of activities associated with these studies. Assuming all multi-site studies would not use the same central IRB, this necessitates multiple, perhaps unique data and administrative support systems be maintained by the institution in addition to their own IRB system.

Finally, there is the danger that mandating review by a central IRB may lead to “IRB shopping” both in terms of a sponsor seeking out an IRB that will approve the study as proposed as well as the reverse, institutions/sites refusing to participate in studies approved by certain IRBs. This type of manipulation of the process will certainly not increase the protection of subjects.

We believe encouraging use of central reviews will be most beneficial in creating a more streamlined review process while maintaining important human subjects protections. As proposed, the IRB of record provides only limited streamlining with regard to such activities. The protection of subjects remains with the local site and, as a consequence, most local sites prefer to describe the protection provisions in its communication with the local investigator. This is an area that is not well served by being incorporated into regulations. We would encourage OHRP to issue guidance and provide access to resources that assist institutions and investigators in assessing the strengths and weaknesses of the different approaches to inform a decision that is good for the subjects and good for the study.

Question 31: How does local review add to the protection of subjects in multi-site research?

The value of local review is different from mandating an IRB of record for multi-site trials. One has implications for the other but the questions are fundamentally different. As proposed, the IRB of record provides only limited streamlining with regard to such activities. The protection of subjects remains with the local site and, as a consequence, most local sites prefer to describe the protection provisions in its communication with the local investigator. IRB review/approval is just one step in the local review and approval process. Other national policy/regulatory activities are coordinated and have an impact with IRB review including, as appropriate, pharmacy, radiation safety, biosafety, HIPAA, financial conflicts of interest, etc.

For most multi-center studies conducted nationally, the value of local IRB review may be minimal, unless there are specific and significant cultural differences associated with a site. Thus, local context should not include major differences in approach to ethical issues, but rather the cultural differences that may impact operational aspects of implementing the ethical underpinnings. For example, a study reviewed by a central IRB in the Pacific Northwest may be adequate for a majority of sites, but a local site in the Southeast with a majority Latino community may require the knowledge of local culture, educational level and language proficiency. The consequence of mandating central IRB review may lead some local sites to reject participation in a study, thereby, potentially limiting the value of the research if it does not extend to certain populations.

Alternatively, local sites may require an “IRB equivalent” local review mitigating any reduction in local burden.

Question 32: How do concerns about regulatory and legal liability contribute to the reliance on local review?

As noted above, we believe, without mandating the use of an IRB of record, the question of OHRP holding the appropriate IRB accountable has some merit. Concerns related to regulatory and legal liability, whether real or imagined, are a significant contributor to institutions choosing to conduct their own local review. These concerns are shared by institutions across the spectrum of large and small, public and private. However, some would argue that the potential liability that is conveyed through the FWA process is too great to rely simply on a change in enforcement action as described in the OHRP proposal on IRB accountability that COGR endorsed in the past. Thus, this ambiguity around questions of liability combined with the proposal here to expand oversight to all research regardless of funding could heighten the concern that a significant part of an institution’s research (and thus their local participant community) would no longer be directly overseen by local experts in human subjects protections.

Smaller institutions, particularly hospitals that are not connected with an academic medical center but are critical partners in the conduct of research are dissuaded from participation by a required central review. These organizations often are risk averse in terms of liability and are reluctant to cede control to any another entity when it comes to “their patients”. It is not clear that a mandated central IRB review would change this attitude, and it is likely that these organizations still would perform an equivalent IRB review. Alternatively, the mandated central review could have a chilling effect on local and community hospitals willingness to participate in multi-site studies. Given that many institutions choose to ignore currently available options to reduce burden, we do not believe that the proposed changes will address or allay the concerns that exist.

When considering questions of liability, we encourage OHRP to investigate opportunities for reducing the liability of individual members of an IRB as well. The Secretary’s Advisory Committee on Human Research Protections (SACHRP) discussed the issue of IRB member liability in 2004 without, to our knowledge, formulating a specific recommendation. We believe it is timely to revisit that discussion to determine whether a federally mandated grant of immunity for individuals serving on Federally-mandated committees as community volunteers would be appropriate. Currently, civil liability for IRB members is typically addressed in one of two ways; as a general rule, public institutions will provide indemnification for their IRB members as long as they act within the scope of the IRB’s legitimate functions. Volunteer community members – a requirement under the regulations – may or may not be eligible for indemnification. Private institutions, on the other hand, generally handle this risk by insurance. In either case, the IRB member is protected not against being named as a defendant but only against damages; neither approach relieves the IRB member of the possibility of being sued and the attendant burdens that result from providing a defense to the claim. The question of IRB member liability is equally true for other federally mandated review committees including Data Safety Monitoring Boards (DSMB). Nonetheless, member liability may continue to be an obstacle for institutions agreeing to allow their IRB to serve as the IRB of record for research conducted by investigators at another institution.

Question 33: How significant are inefficiencies in local IRB review?

Determining where inefficiencies impact the initiation and conduct of multi-site research is a complex and challenging problem. Many factors impact how quickly and efficiently a multi-site study can begin enrollment, only one of which is IRB review. Typically participating sites start the trial at different times not only because of their IRB review, but because of many other factors such as contract and budget negotiation, conflict of interest reviews, and other institutional start-up activities. The question asks about the significance of inefficiencies in local IRB review, but it is unclear whether these inefficiencies actually significantly impact the overall time to initiation of enrollment. Further, the use of central IRBs creates additional administrative activities that usurp any gain in a more efficient IRB review process. Allowing individual institutions to adapt central IRB review where it is clear that the efficiencies gained in IRB review will lead to real gains in time to startup rather than mandating for all multi-site research would seem a more reasonable first step in revision of current practices.

While review by multiple IRBs certainly creates inefficiencies, there currently are ample options available to local IRBs to minimize the burden associated with local review of a previously approved study. These options can include full reliance on a primary IRB through an IRB Authorization Agreement or conducting a full local review. The current regulations and guidance are clear in stating that these options are available and encouraged. Educating and incentivizing institutions to avail themselves of available options in lieu of full local review allows institutions to reduce regulatory burden without imposing an unproven mandate. It then is up to the involved institutions to decide how best to use their resources.

Question 34: How should an IRB of Record be selected?

The selection of an IRB of record is an issue for the participating sites and/or sponsor. The selection will be self-monitoring because local sites are either willing to use the central IRB or not and, as a consequence, will participate in the study or not. This is not a subject for regulation.

“Reverse” IRB shopping will occur when institutions/sites refuse to participate in multi-site studies based primarily on the IRB of record and not the worthiness of the research study. Institutions having prior negative experiences with certain IRBs may choose to forego participating in a study rather than accept the review of the primary IRB. These circumstances could result in less research being conducted by some of our best and brightest scientists, as institutions choose not to accept projects based on the reviewing IRB. This type of “shopping” may lead to the identification of IRBs that achieve the standards for review and performance that meet the sponsors’ and institutions concerns and result in positive outcomes for investigators and subjects. This process cannot be effectively built by regulation; it will be “market” driven.

The choice of one IRB of record works well when there is an opportunity for involved sites to cooperatively and prospectively decide on the appropriate primary IRB to act on behalf of all. This decision normally is based on a variety of criteria, including where the preponderance of subjects will be enrolled, an IRB’s experience and expertise in reviewing certain types of research, e.g. prisoners, children, genetic research, and institutional resources. There are several consortia around the country that successfully rely on this model; however, the majority of multi-site studies, particularly industry sponsored clinical trials, do not allow for this type of cooperative decision.

IV. IMPROVING INFORMED CONSENT

A. Improving Consent Forms

Question 35: What factors contribute to the excessive length and complexity of informed consent forms, and how might they be addressed?

OHRP and other federal agency compliance letters have included findings and made recommendations that have contributed to lengthy consents. Often this has resulted in sponsors and IRBs including elements of informed consent that are listed in the federal regulations but not applicable to specific studies. For example, the OHRP citation letters regarding tidal volume and pressure in the ICU setting created a great deal of excessive consent language in subsequent consent forms. Many IRBs include an alternative section in their informed consent form regardless of whether the research involves any type of intervention or clinical care. Agency citation letters should only address instances where the intent of the regulations was clearly not met.

Sponsors, cooperative study groups, institutions, and IRBs concern about broad regulatory compliance and institutional boiler plate language designed to reduce legal liability are additional factors that have impacted the length and complexity of consent forms. The regulations pertaining to documentation (.117) should be revised to allow the written consent form to be a summary which succinctly addresses the key issues needed to make an informed decision regarding participation. Details pertaining to the individual elements with auxiliary issues should be included in an attachment, not in the summary consent. Agencies in implementing the regulatory change would need to support the use of a summary consent when issuing compliance findings.

HIPAA authorization requirements have added to length and complexity of consent documents. DHHS should harmonize informed consent and authorization elements to streamline the documents included in consent.

Regulatory requirements or policy guidance has added elements of informed consent that are not needed in the consent documents such as FDA requirements to inform subjects about clinicaltrials.gov, the OHRP guidance and requirements to include detailed information regarding Genetic Information Nondiscrimination Act (GINA) of 2008 in the consent document as well as the HIPAA authorization requirements. The regulations should permit institutions to include detailed information about these and other similar issues in an attachment to a summary consent document.

Question 36: What additional information, if any, should be required by the regulations to assure that consent forms appropriately describe to subjects alternatives to participating in the research study and why it may or may not be in their best interests to participate? What modifications or deletions to the required elements would be appropriate?

Alternatives to Participation

As suggested above, consent forms should include a short summary of alternatives for studies in which this element is appropriate with details concerning alternatives included in an attached document. “Alternatives” is an element of consent that applies in clinical research but rarely applies

in most social, educational, or behavioral research. Social, behavioral and educational IRBs often include a statement in their boiler plate indicating that no alternatives are available except for not participating. This statement only serves to unnecessarily extend the length of the consent. This element should be an optional element rather than a required element. To ensure that IRBs understand that this element is not required, the alternative element should be moved to the additional elements section of the regulations [116 (b)].

Modifications or Deletions

Three of the currently required elements are conditional [46.111(a)(4), (5), (6)], based upon the nature of the research. This approach is appropriate and should be continued but we recommend that these three elements be moved to the additional element section of the regulations included in [116 (b)]. This change will only be effective in reducing length of consents if regulatory agencies in conducting audits/inspections recognize that these elements are “optional”, not required.

Item [116 (a) (7)]: the statement “whom to contact for research related injury” should be optional for studies that do not have risks for research related injuries. This item should be moved to [116 (b)]. This change will only be effective in reducing length of consents if regulatory agencies in conducting audits/inspections recognize that these elements are “optional”, not required.

Other issues traditionally included in consents such as payment should be included in an appendix document for subjects but should not be in the actual consent. Adding payment as a required element is not appropriate because including it in the consent can influence subjects in their assessment of the “benefits” of the study.

For “minimal risk” studies eligible for expedited review, provide IRBs the authority to determine the level and extent of consent using the model found in Subpart D for assent. This strategy would ensure that consents are tailored to the study; minimal risk social, behavioral, and educational research consents often include unnecessary elements that are not applicable to the research but are included because of the requirements in [116 (a)] and concern that [116 (b)] are also required.

As noted in Question 35, the FDA requirements that subjects be provided information regarding how to access the results of trials in which they participate should not be a required informed consent element [21 CFR 50.25 (c)].

Question 37: Would proposed changes improve the quality of consent forms?

Some of the proposed modifications may have potential to improve quality of consent forms depending upon how the proposed modifications are implemented by regulatory agencies. Others would not be useful. Specific comments are included below.

Prescribing required consent with greater specificity: Overly prescriptive requirements will not ensure greater protection for subjects. IRBs are in the best position to review and assess the information provided to subjects in the consent documents and consent process. We recommend reducing the number of required elements [116(a)] and expanding the number of optional elements [116 (b)].

To effectively reduce the length and complexity of consent forms, revisions in [117] are needed. The provisions in [117 (b)(1)] indicate that the written consent form must “embody” the elements of consent. We suggest that the consent form which is signed by the research subject should serve as a summary. Auxiliary or detailed information should be included in an attachment. The provisions in [117] should be revised to clearly specify that the documentation requirements allow a summary of the required elements and, if appropriate, certain additional optional elements. Revisions to the short form option at [117(b)(2)] removing the requirement for a witness may encourage greater utilization of this option. Section [117] should also be revised to consider other options for documentation beyond written signed forms. Technology has changed the manner in which research is conducted and investigators should have the ability to meet the consent requirements using similar electronic mechanisms. Details about options should not be added to [117] but inclusion of a provision that clearly indicates that alternatives to a written form are acceptable would be a useful modification which would improve the quality of the consent process.

Restricting content that would be inappropriate: As with overly prescriptive regulations, overly restrictive requirements would not be appropriate. The current restriction on exculpatory language poses challenges in interpretation for IRBs, investigators, and sponsors. Adding additional such restrictions to regulations could only serve to confuse IRBs, sponsors, and investigators. Guidance in areas of concern would be much more helpful than regulation.

Limiting the length of various sections of the consent form: Setting the acceptable length of sections of the consent form should not be included in regulations. This degree of specificity in the regulations would not serve the best interests of study participants given the broad spectrum of research that falls under the rubric of “human subjects research.”

Prescribing how information should be presented in consent forms including use of appendices: We have recommended that investigators use summary statements, as appropriate, with additional information included in attachments because we believe this modification would improve the quality of consent documents and subject comprehension. The only regulatory change needed is to allow investigators and IRBs the needed flexibility to present the information that meets the needs of the specific study and study participants.

Reducing institutional “boilerplate”: We do not support federal regulation that would intrude into institutional policy. There are state laws, local organizational structures or resources, and local community concerns that must be addressed by the institution. With more focused compliance reviews/audits that result in agencies limiting their citation letters to instances where the intent of the regulations was clearly not met, the need for institutional “boiler plate” will be relieved.

Making available standardized consent form templates: Institutions should have the flexibility to design their consent forms to meet institutional and study needs. Templates designed by Federal agencies would become de facto “required.”

Question 38: Should the regulations require that investigators assess how well potential research subjects comprehend the information provided to them before they are allowed to sign the consent form?

We do not support including a requirement for investigators to assess comprehension in the regulations. Comprehension tests, however well-meaning, will be difficult to implement and how the application of such a test of comprehension would be monitored is unclear. This is an area best left to the institution and/or IRB. The IRB can assess if comprehension of complex studies is an issue and advise the investigator on strategies to overcome potential problems with comprehension.

Question 39: Would conforming changes need to be made to the authorization requirements of the HIPAA Privacy Rule?

Several national groups have pointed out that the HIPAA rules are not appropriate for research. If the goal is simplification, HIPAA “research” provisions should either be radically revised or research should be exempted from the HIPAA requirements. The current review by the HHS Office of Civil Rights should set as a goal harmonizing the Common Rule elements and HIPAA regulations for authorization.

Question 40: Would informed consent be improved if the regulations included additional requirements regarding the consent process, and if so, what should be required?

Such added requirements describing or prescribing steps in a consent process that may be inappropriate for all types of human research would likely only add to the complexity of the process without ensuring greater protections for subjects. The example of disclosing financial relationships is not illustrative of what we understand this question seeks to explore. We believe that information regarding the disclosure of the financial relationships of investigators is a determination of the IRB and the IRB’s authority to require elements in the consent process and forms is sufficient.

Question 41: What changes to the regulations would clarify the current four criteria for waiver of informed consent and facilitate their consistent application?

Recommendations Regarding Waiver of the Documentation of Informed Consent:

- Section [46.116 (d)(1)] should be modified by deleting the word “research” and replacing it with the words “the waiver”, (i.e. the waiver involves no more than minimal risk). One of the factors that contributes to inconsistency is that there are greater than minimal risk studies that have select procedures for which waiving informed consent is ethically appropriate. For example, prospective subjects may be identified through review of medical records or through telephone screening. The screening process in itself is not “greater than minimal risk”.
- OHRP should provide guidance on the interpretation and application of § 46.117(c), using examples as appropriate, with particular emphasis on social or behavioral research. With regard to § 46.117(c)(1), OHRP guidance should clarify that: there would be no links between the subject and the research (e.g., investigator notes) other than the consent form itself; this provision is not limited to minimal risk research, and is appropriate for those studies that involve

greater than minimal risk (e.g., some studies of domestic violence, illegal behavior); and what the term "documentation" used in this section means.

- OHRP should clarify whether the final sentence in § 46.117, regarding the provision of a written statement to subjects, applies to both (c)(1) and (c)(2).
- OHRP should clarify that, when the IRB requires a written statement as described under § 46.117(c), the statement does not need to include the elements of consent required under § 46.116 as long as the elements are addressed orally. This guidance could include examples of situations where the IRB may choose to require a written statement. OHRP should also clarify whether or not the criteria for waiving consent under § 46.116(c) or (d) must be met if some of the elements of consent are not presented either orally or in writing
- OHRP should explore options for modifying or eliminating the requirement under § 46.117(c) (1) that each subject will be asked whether they want documentation linking them to the research. Subjects are not likely in the best position to understand the intent of the question. IRBs can review and approve the elimination of written documentation as a part of its review of the study.

Need for Harmonization

Confusion and inconsistency in applying waivers is to some extent a reflection of the inconsistencies in the federal requirements. FDA, Common Rule, and HIPAA include different criteria for waiver. For the same study using the exact same procedures, an investigator may be asked by the IRB to address waiver for authorization and waiver of informed consent. In addition, the IRB is required to document two different sets of criteria for the same set of research procedures. This confusion and bureaucracy is further exacerbated by the differences in the regulations between FDA and Common Rule. Currently, at COGR member institutions the IRB has struggled with studies which are FDA and Common Rule regulated especially with respect to research procedures pertaining to identification of prospective subjects. FDA regulations do not include the [116 (d)] criteria and do not allow waiver of informed consent. The Common Rule allows waiver of informed consent through [116 (d)]. IRBs spend hours trying to figure out what criteria should be applied when. Often these studies are regulated by HIPAA which further delays reviews, adds to the bureaucracy, and confuses IRBs and investigators. These inconsistencies between HIPAA, Common Rule, and FDA must be addressed.

Question 42: In circumstances where the regulations would permit oral consent, what information should investigators be required to provide to prospective subjects? Are all of the elements of informed consent included at 45 CFR 46.116 necessary to be conveyed, or are some elements unnecessary?

COGR recommends that the following elements be required:

- Purpose of study;
- Statement that the study involves research;
- Description of procedures;
- Expected duration of subject's participation;

- Statement that risks or discomforts are minimal;
- Statement that benefits are for scientific or scholarly knowledge;
- Statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.
- Additional Elements that May or May Not be Necessary depending upon the nature of the research:
 - Optional: Contact for questions about the research or research subject's rights;
 - Optional: Limits to confidentiality;
 - Optional: Identification of individual risks;
 - Optional: Description of Alternatives, if appropriate.

Determination of when these elements are necessary to protect subjects should be determined by the IRB based on the risks of the specific research.

COGR suggests that the following consent elements are unnecessary:

- Detailed description of benefit not necessary for minimal risk research;
- Compensation for injury;
- Contact for injury;
- Element 4 (alternative therapies and related clinical or therapeutic elements) is likely inappropriate;
- Providing orally contact information on the subjects rights isn't the most effective method for conveying information – maybe information available upon request.
- None of the additional elements outlined [116 (b)(1-6)].

Question 43: Are there additional circumstances under which it should be permissible to waive the usual requirements for obtaining or documenting informed consent?

Research in an international setting poses unique challenges for applying the US regulations for obtaining and documenting informed consent. Regulatory changes and/or guidance are needed to allow approval of studies that are consistent with the other culture's concept of autonomy.

Question 44: Are there types of research in which oral consent without documentation should not be permitted? What principles or criteria distinguish these cases?

We have no recommendations.

Consent Protections Related to Reuse of Additional Analysis of Existing Data and Biospecimens

We believe the current regulatory framework for future use of pre-existing data and biospecimens is sufficient to ensure the protection of subjects and requires no revision. We support IRBs applying the waiver of informed consent and support the adoption of standardized notices when collecting non-research data in institutional settings. The proposed revisions to the HIPAA Privacy Rule will bring the HIPAA regulations into alignment with the Common Rule and assist in eliminating any confusion resulting from competing requirements. These safeguards do not require additional regulatory revisions.

We are concerned that the adoption of regulatory requirements for informed consent for future use of data collected for non-research purposes would have a damaging effect on researcher's ability to conduct meaningful research. The practical implications associated with obtaining prior consent create unmanageable logistical demands that will not, in our opinion, provide significantly greater protections for subjects than are currently afforded them by IRB review when appropriate. The suggestions made in the ANPRM to provide options for future use, etc., will create a complex system of tracking that will discourage participation by entities and individuals.

The proposals advanced in the ANPRM if applied across all research conducted at federally funded institutions would sweep non-biomedical data under these general rules. The likely solution to this over-reach would be a system of different requirements for differing types of data making the entire human protection program more complex. It will discourage investigators from pursuing research using existing data and biospecimens.

COGR does support the ANPRM suggestion for a continuing public discussion and education initiative on scientific and scholarly use of data and biospecimens.

Question 45: Under what circumstances should informed consent be required for future use of data originally collected for non-research purposes?

If there is absolutely no link or identifying information collected, then consent should not be required. We believe that data and specimens could be considered de-identified if the investigator has only temporary access to identifiers with the intent of linking specimens with pertinent phenotypic data such as diagnosis.

Individual research studies not associated with repositories: If the data includes identifiers (using the current Common Rule regulations), general informed consent at the time of collection for future use should be obtained unless the IRB waives informed consent based on the criteria included in [116 (d)]. If the data are de-identified (using the current Common Rule regulations), a study utilizing these data is not research involving human subjects based on current guidance and therefore informed consent for future research use is not necessary. De-identified data from repositories should continue to be considered not human subjects research.

Data Repositories Set up for Research Purposes: The repositories' policies and procedures for obtaining data and disseminating data should receive prior IRB review. As part of the review, IRB must consider whether informed consent is required, using [116 (d)] criteria.

Question 46: Under what circumstances should unanticipated future analysis of data that were collected for a different research purpose be permitted without consent? Should consent requirements vary based on the likelihood of identifying a research subject?

Analysis of identified data or biospecimens collected for a different research purpose should be permitted without specific informed consent when an IRB has determined that the waiver of informed consent criteria outlined in [116 (d)] are met.

We support inclusion of general consent provisions for future use in consent forms designed for specific studies. However, we do not believe that general consent for future use should be a necessary requirement for any and all future research uses. IRB application of waiver of informed consent provides an effective framework for protecting individual subjects without damaging critical research efforts that serve in the best interest of the public as a whole.

COGR recommends that HIPAA restrictions prohibiting future use in authorizations should be harmonized to reflect Common Rule’s existing requirements which allow future use in consent forms.

Consideration of the likelihood of identification is already included in the existing federal regulations. In applying the waiver criteria at [116 (d)], the IRB must make a determination whether the research is “minimal” risk and the likelihood of identification can be weighed in the risk assessment.

Question 47: Should there be a change to the current practice of allowing research on biospecimens that have been collected outside of a research study (*i.e.* “left-over” tissue following surgery) without consent, as long as the subject’s identity is never disclosed to the investigator?

We support the current practice. Current practice is appropriate and should be continued when the subject’s identity is not disclosed to the investigator. As noted, we would support the approach that data and specimens could be considered de-identified if the investigator has only temporary access to identifiers with the intent of linking specimens with pertinent phenotypic data such as diagnosis. However, FDA and Common Rule requirements are currently not harmonized because FDA and some of the other Common Rule agencies do not provide for this practice. We recommend that this practice be adopted by FDA, VA and other Common Rule agencies.

Question 48: What, if any, are the circumstances in which it would be appropriate to waive the requirement to obtain consent for additional analysis of biospecimens?

If the biospecimens include identifiers (using the existing Common Rule regulations), informed consent for future use is the preferred approach but the IRB can make a determination that the subsequent use meets the criteria outlined in [116 (d)] (*i.e.* appropriate with an IRB approved waiver.)

If no identifiers accompany the biospecimen (i.e. subject identifiers are not disclosed to the investigator or only temporarily available for linking specimens with pertinent phenotypic data), then it would be appropriate to conduct additional analysis without prior informed consent.

We recommend that this practice be adopted by FDA, VA and other Common Rule agencies.

Question 49: Is it desirable to implement the use of a standardized, general consent form to permit future research on biospecimens and data? Are there other options that should be considered, such as a public education campaign combined with a notification and opt-out process?

We believe that use of a standardized, general consent language for future use, whether the data is collected for specific research purposes or non-research purpose is appropriate and the regulations should allow such practices. Regulation should permit a simple notification procedure as well. A public education campaign or information combined with notification should meet the regulations.

Question 50: What is the best method for providing individuals with a meaningful opportunity to choose not to consent to certain types of future research that might pose particular concerns for substantial numbers of research subjects beyond those presented by the usual research involving biospecimens?

We are concerned that efforts to address issues raised in the ANPRM concerning providing a meaningful opportunity in a non-research setting to choose not to consent to future use or certain types of future use of biospecimens will create a level of complexity in the collection and tracking of specimens that will lead entities holding such specimens to simply “buy-out” of the process and destroy all specimens. Such a reaction will undermine significant future research. It is impossible to anticipate all potential categories of future research and omitting a category could prevent a future use that imposes little or no risk to the subject.

A general notification of practices pertaining to the use of biospecimens can be provided to clinical patients and research subjects in much the same manner that notification of privacy practices is provided now in health care settings.

The current regulations provide mechanisms for IRB review of the use of data and biospecimens if the data or specimens have identifiers. Any additional regulation is not necessary.

We are concerned that such mechanism would sweep across non-biomedical data under these general rules. It will discourage investigators from pursuing research using existing data and biospecimens.

Question 51: If the requirement to obtain consent for all research uses of biospecimens is implemented, how should it be applied to biospecimens that are collected outside of the U.S. but are to be used in research supported by a Common Rule agency? Should there be different rules for that setting, and if so, what should they be? Should they be based on the relevant requirements in the countries where the biospecimens were collected?

The application of such a requirement for the use of specimens collected outside the US will most effectively be resolved through the efforts between US and international bodies to identify and define equivalent protections. US investigators will be unable and should not be expected to affirm that US informed consent mechanisms have been followed in the collection of biospecimens.

Question 52: Should the new consent rules be applied only prospectively, that is, should previously existing biospecimens and data sets be “grandfathered” under the prior regulatory requirements? If so, what are the operational issues with doing so?

We do not support the requirement for obtaining consent for de-identified biospecimens. However, if the requirements were to be adopted, COGR strongly recommends that the proposed consent rules not be applied retrospectively. The impact of applying the requirements to existing data and biospecimens for all research at facilities/institutions that receive federal funds would be very damaging. It would impact potential advancements in all areas of human research.

Question 53: In cases in which consent for future research use is not obtained at the time of collection, should there be a presumption that obtaining consent for the secondary analysis of existing biospecimens or identifiable data would be deemed impracticable, such that consent could be waived, when more than a specified threshold number of individuals are involved?

The number of subjects involved should not be a factor in the IRBs determination to waive the requirements for consent. We believe such secondary uses of identifiable data and identifiable specimens should be reviewed under the current regulations.

V. Strengthening Data Protections to Minimize Information Risks:

We do not support mandatory data security and information protection standards and strongly oppose using HIPAA security and notification standards as a model. The HIPAA Privacy and Security Rules include complex identification criteria and security standards designed to protect private health information. Duplicating these standards for “all” research at institutions would be extremely burdensome for the investigators and institutions without any assurance that the subject-related information would have greater protections. Simplified guidelines developed in collaboration with investigators and research institutions would be more appropriate.

We are unaware of systemic problems or significant incidents with disclosure, re-identification or breaches of confidentiality that warrant such a significant reorientation of the human subject protections regulations from protecting subjects from harm to protecting data. However, we are certain that mechanisms proposed for protecting data will not add significantly to protections to subjects but will measurably increase the burden on investigators and institutions.

Question 54: Will the use of HIPAA Privacy Rule standards for identifiable, de-identified and limited data sets facilitate the implementation of the data security and information protection provisions proposed?

We do not support mandatory data security and information protection standards and strongly oppose using HIPAA security and notification standards as a model. The HIPAA Privacy and Security Rules include complex identification criteria and security standards designed to protect private health information. Duplicating these standards for “all” research at institutions would be extremely burdensome for the investigators and institutions without any assurance that the subject-related information would have greater protections.

Question 55: What mechanism should be used to evaluate and update the meaning of de-identified information? Beyond time, should triggering events such as evolutions in technology or development of new security risks be used?

The de-identification of data is an element of the review conducted by an IRB. Standards for de-identification in one area of research would not necessarily be appropriate in other areas. The standards set for protected health information are not transferable across the research enterprise. The determination of the IRB in its review on a case-by-case basis is the most appropriate approach for the Common Rule.

Question 56: DNA extracted from de-identified biospecimens can be sequenced and analyzed in other ways, with the results sometimes being linked to other available data than may allow a researcher to identify the persons whose specimens were being studied. Should a human biospecimen be considered identifiable in and of itself? What are the advantages and disadvantages of considering all future research with biospecimens to be research with identifiable information?

A human biospecimen should not be considered identifiable in and of itself. To date, the amount of research that has been effectively conducted with discarded specimens without harm to individuals suggests that any change in handling de-identified samples is not justified.

We know that such a change will be detrimental to basic science research because these laboratories do not need identifiers but do need access to samples to analyze biological processes. Classifying de-identified human biospecimens as “human subjects” will create a significant burden for investigators and delay critical basic science research in a set of circumstances that do not represent any risk to the tissue donors.

The requirement of consent will greatly limit the ability of investigators to perform research with rarer conditions and diseases. This is of concern in a number of research areas such as pediatrics research because of the limited number of samples and rare disorders.

The ANPRM does not address nor consider how the requirement for informed consent for human biospecimens would impact the use of pediatric samples when a child turns 18. Currently, OHRP expects that when an individual turns the age of majority informed consent should be obtained or a waiver of informed consent granted if there are identifiers on the samples. The ANPRM proposes that all samples now be considered identifiable and that no waivers would be permitted. For

de-identified samples this means that unless the child can be located and consent obtained, samples collected with parental permission cannot continue to be used. This would result in inability to use valuable pediatric samples and have consequences for future research.

The resources that would be required to broadly implement written informed consent for subjects including maintaining those responses, and tracking samples will be significant. Segments of the research community will not be able to implement or sustain the system which will lead to elimination of vital research. The benefits of the research that will be lost must be weighed against an ill-defined general concern for re-identification of samples.

Question 57: Should some types of genomic data be considered identifiable and, if so, which types (e.g., genome-wide SNP analyses or whole genome sequences)?

Genomic data should not be considered identifiable for research. The possibility to identify someone based on genomic data is remote based on the qualifications and capabilities of most research labs. For those few that have the technology, identifiability is not the intent of the research efforts.

Question 58: Should the new data security and information protection standards apply to all data and biospecimens? How should the new standards be enforced?

We do not support mandatory data security and information protection standards and strongly oppose using HIPAA security and notification standards as a model. The HIPAA Security Rule provides more protection than is necessary or appropriate. The proposal that these standards serve as a model to be applied to “all” research at institutions that accept federal funds means that these standards would apply to low risk studies, where a breach of confidentiality would not necessarily result in harm to subjects. The benefits do not outweigh the risks of impeding research which could have valuable benefits for society. Many institutions that are not “covered entities” as defined by HIPAA and most investigators do not have the expertise or resources to put all of these security protections in place. The HIPAA breach notification standards would be impossible to apply to “all” research at institutions that receive federal funds.

The impact of applying the rule to all data and specimens would be devastating. Currently nationwide there are millions of samples collected and valuable data warehouses set up which are used to conduct critically vital research designed to address the world’s most life-threatening diseases. It would be irresponsible to deny the research community the use of these samples and pre-existing data.

Questions of privacy and confidentiality should remain the responsibility of the IRB. The IRB can determine if a specific research study requires significant security measures and can provide appropriate oversight through continuing review.

Question 59: Would study subjects be *sufficiently* [emphasis added] protected from informational risks if investigators are required to adhere to a strict set of data security and information protection standards modeled on the HIPAA Rules?

Studies involving protected health information likely fall under the current HIPAA protections. In general, study subjects would be over protected for “all” types of research creating an unnecessary burden on investigators and institutions and impeding critical research. HIPAA standards are not appropriate for all types of research including social, behavioral, and educational research. The probability and magnitude of harm resulting from a breach involving social, behavioral, and educational studies is likely insignificant and we are unaware of any such breaches that have resulted in harm to subjects.

No single system or process for addressing privacy and confidentiality will be appropriate for all research activities. The IRB is in the best position to assess the risks tied to a specific study and recommend processes to minimize the risks.

Question 60: Is there a need for *additional standardized* [emphasis added] data security and information protection requirements that would apply to the phase of research that involves data gathering through an interaction or intervention with an individual (e.g. during the administration of a survey)?

Additional standards of data security and information protection at any phase of the research will create additional documentation and require added resources. It is the best practice to use the highest standards across the board for the entire research project rather than utilize different standards for different phases of a single research study.

IRBs carefully review the process and procedures for the collection of data to ensure both privacy and confidentiality of the data. There is no need for additional protection requirements based upon the phases of the study.

Question 61: Are there additional data security and information protection standards [or models] that should be considered?

We recognize that some research may have a measure of informational risk but not all such activities pose the same level of information and data security risks. We believe that for data and information, like the current definition of minimal risk, the probability and magnitude of harm from virtually all such information risk is likely not greater than the risk encountered daily in our lives as we rely increasingly on transactions and activities conducted through electronic means. We know that the information and data security requirements as proposed will increase the burden on investigators and institutions without a commensurate benefit to subjects.

Question 62: If investigators are subject to data security and information protection requirements modeled on the HIPAA Rules, is it then acceptable for HIPAA covered entities to disclose limited data sets to investigators for research purposes without obtaining data use agreements?

Assuming that OHRP determines that HIPAA identifiers must be used as the model, it would be acceptable to disclose “limited data sets” without a use agreement. We would support the proposal that data could be considered de-identified even if investigators see the identifiers but do not record them in the permanent research file.

Question 63: Given the concerns raised by some that even with the removal of the 18 HIPAA identifiers, re-identification of de-identified datasets is possible, should there be an absolute prohibition against re-identifying de-identified data?

It is appropriate to prohibit the re-identification of data unless the IRB has voted to approve the request because it is in the best interest of the subject.

Question 64: For research involving de-identified data, is the proposed prohibition against a researcher re-identifying such data a sufficient protection, or should there in some instances be requirements preventing the researcher from disclosing the de-identified data to, for example, third parties who might not be subject to these rules?

The proposed prohibition on re-identification is sufficient. De-identified data and biospecimens should not be governed by these regulations because such de-identified data and information is not a human subject for regulatory purposes.

Question 65: Should registration with the institution be required for analysis of de-identified datasets so as to permit auditing for unauthorized re-identification?

Institutions have designed mechanisms for the review and determination of the exempt status of research studies. Institutions can be expected, but not required, to ensure that investigators are aware of and understand the meaning of the prohibition on re-identification of de-identified data. Requirements for the auditing of studies that have been determined not to be subject to the regulations are inappropriate.

Question 66: What entity or entities at an institution conducting research should be given the oversight authority to conduct the audits, and to make sure that these standards with regard to data security are being complied with? Should an institution have flexibility to determine which entity or entities will have this oversight responsibility for their institution?

Currently, institutions have the flexibility to determine which entity or entities provide oversight with regard to their general data security policies. Oversight of human subjects research protocols occurs under continuing review. Any additional regulatory requirements for oversight or audits are unnecessary.

Any such requirement for data security audits applied, as proposed, to all human subjects research would be time-consuming, labor-intensive, and require specialized expertise. It is unrealistic that these labor-intensive audits can be applied to all research. We cannot identify a corresponding measure of benefit to subjects.

VI. Data Collections to Enhance System Oversight

The challenge that is described in the ANPRM builds on the observation that research agencies collect information on unanticipated problems involving risk to subjects and/or adverse events using varying definitions, timelines and elements or templates for reporting. The ANPRM authors express frustration with storage in separate databases that lack connectivity and interoperability thus preventing integrated or comparative analyses in the interest of more global assessments of the frequency and severity of such problems or events.

As a rule, COGR supports harmonization of definitions, interpretation standards, and reporting timelines across agencies to the extent that unique agency needs continue to be met and the most stringent requirements are not applied to low risk research in an effort to apply one rule to all. We recognize the challenge in harmonizing reporting requirements. Agency needs differ making complete harmonization of requirements implausible even though the common goal of reporting is protecting human subjects. For example, FDA's reporting requirements are tied to product development which has both the narrow scope of human subject protection and the broad objective of enhancing the safety of medical therapies for the general public. The efforts by FDA and OHRP have greatly improved both the scope of reportable events and the timing requirements for reporting. Both agencies have issued guidance designed to minimize uninformative reports and enhance meaningful, interpretable information. However, a single approach that covers all human subject research, from clinical trials to survey research, would not serve the subjects or the investigators.

In a similar manner, we support the efforts to improve the prompt collection of critical safety data. While development of an electronic portal to facilitate review and analysis by applicable agencies and oversight bodies might serve this goal, we encourage analysis of existing portals such as MedWatch, Adverse Event Reporting System ([AERS](#)), and ClinicalTrials.gov before initiating another, independent effort to determine its usefulness in protecting subjects.

There are real problems associated with a proposed web-based portal. Submission of events via an electronic portal with automated delivery may be convenient for research investigators and would allow for more expedient analysis of events by sponsors, IRBs, applicable agencies, and oversight bodies. However as with any electronic system, the quality and validity of the data is only as good as the information provided which remains dependent on the user's understanding and interpretation of what needs reported when. Standardization and user education would be required before such data could be considered valid for assessment. The implementation issues involved including access, security, and costs to the Federal government as well as the research community need to be carefully considered. Given current financial constraints and the limited usefulness described below, the potential benefit of such a portal justifying the costs is not evident.

We have concerns regarding amalgamating such data gleaned from diverse studies and sources in order to conduct integrated analysis. Conclusions drawn from such assessments may be unreliable taken out of the context of the trial and study population. It is unclear how the data are useful beyond the specific study the data are associated with. Patterns of events or problems might be possible but, given that each trial is different, trying to establish these patterns in a large data set from diverse studies will be difficult if not impossible. For instance, single events reported from blinded studies would be of limited use without un-blinding the data. This will therefore take considerable resources with questionable benefit. Many unanticipated problems, particularly from social or behavioral research, are isolated and would offer little application for global interpretation if entered into a central repository. We question the benefit of reporting unanticipated problems particularly where they do not involve any applicable risks to others.

It is unclear who would manage or interpret the information in a central repository as described in the proposal. It is unclear who would have access to the data, how it would be managed, and who would support the development of such a system. In its current form, it does not enhance protections for human subjects but adds additional reporting requirements for researchers and IRBs, both issues contrary to the stated purpose of the ANPRM.

Question 67: Is the scope of events that must be reported under current policies, including the reporting of certain “unanticipated problems” as required under the Common Rule, generally adequate?

Yes, the current policies are generally adequate. Efforts by FDA and OHRP have greatly improved both the scope of reportable events and the methods for reporting. Both agencies have issued guidance designed to minimize uninformative reports and enhance meaningful, interpretable information.

Question 68: With regard to data reported to the Federal government:

a) Should the number of participants be reported?

It is our understanding that this information is being reported in progress and final reports which routinely provide number of subjects enrolled to the sponsors. Given the cost of implementing and maintaining a centralized authority, we do not see the cost value of setting up a system for reporting and maintaining number of subjects. What purpose would this number serve? There is no correlation between the number of persons involved in research and their protection and the potential benefits of adding another layer of data access and safety monitoring should be considered in tandem with the costs of creating another level of bureaucracy.

b) What additional data, not currently being collected, about participants in human subjects research should be systematically collected in order to provide an empirically-based assessment of the risks of particular areas of research or of human subjects.

Extrapolating from unanticipated problem or adverse event reporting on individual studies to a general assessment of risk associated with areas of research may be interesting from a research

perspective but is not likely to add to the protection of subjects. Thus, the proposed creation of a central repository to collect and attempt an analysis of additional disparate data must be weighed against the costs associated with the increased reporting requirements. Currently, such problems and events are reported to determine the effect of the study protocol on the subjects enrolled. Anything that distracts from or minimizes the time and resources available for the protection of the enrolled subjects must be carefully considered.

- c) To what types of research should such a requirement apply (e.g., interventional studies only; all types of human subjects research, including behavioral and social science research)? In addition, are there other strategies and methods that should be implemented for gathering information on the effectiveness of the human subjects protection system?

If the goal of increased data collection and monitoring by a central authority is heightened safety, then the proposed effort should focus on greater than minimal risk research and interventional studies.

Question 69: Is it desirable to have all data on adverse events and unanticipated problems collected in a central database?

As we noted in the introductory remarks to this section, as a rule, COGR supports harmonization of definitions, interpretation standards, and reporting timelines across agencies to the extent that unique agency needs continue to be met and the most stringent requirements are not applied to low risk research in an effort to apply one rule to all. In a similar manner, we support the efforts to improve the prompt collection of critical safety data.

We note, again, we are talking about individual events in independent studies, thus, without these critical contextual qualifiers it is unclear what purpose a central repository of all problems and adverse events would serve. Currently, despite guidance and education, researchers continue to over report events or incidents which do not rise to the level of required reporting. Adding a repository will not address that problem. The repository information may have a chilling effect on research, suggesting that participation is riskier than previously known.

Before implementing such a central repository, a thorough cost-benefit analysis should be conducted regarding strengths and limitations of similar data repositories. One key element to assess is the validity of the data and ability to draw generalizable conclusions based on data collected from varied sources and contexts.

Question 70: Is the access to information on individual studies provided by ClinicalTrials.gov sufficiently comprehensive and timely for the purposes of informing the public about the overall safety of all research with human participants?

The International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for publication and the Food and Drug Administration Amendments Act of 2007 (FDAAA) have driven compliance with the requirement to register and provide summary results for clinical trials that meet the specific criteria as a designated “applicable” clinical trial. Beyond providing access to clinical research opportunities, much of the impetus for [clinicaltrials.gov](http://ClinicalTrials.gov) was to enhance

transparency in disclosing results. Disclosure was a means to enhance public trust in clinical research. To that end, the database is adequate.

The scope was not intended to capture overall safety of ALL human subject research. Expanding the scope to include non clinical human research would likely offer little benefit relative to safety data.

VII. Extension of Regulations to All Research

Question 71. Should the applicability of the Common Rule be extended to all research that is not federally funded that is conducted at an institution that receives some Federal funding for research with human subjects?

No, we do not believe the extension of federal regulations to all research at an institution serves to provide any greater protections to human subjects. We particularly oppose the extension under the current and proposed regulatory regime. Most institutions with a Federalwide Assurance (FWA) apply the Common Rule to all research regardless of funding including those institutions that have “unchecked the box.” The latter institutions apply the regulations in principle and generally in practice reserving the right to exercise greater flexibility in such areas proposed for change in this ANPRM, e.g., continuing review, documentation of consent in minimal risk research with competent adults, etc.

Thus, we believe the proposed extension will not enhance the protection of subjects but we know it will greatly increase the costs, burden, and delay of research for institutions that receive Federal support. Ironically, these institutions and the studies they conduct are not the institutions that likely cause the greatest concern for the public. This proposed extension does nothing to reach those organizations and institutions currently operating outside the regulations.

VIII. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance.

Question 72. To what extent do the differences in guidance on research protections from different agencies either strengthen or weaken protections for human subjects?

The differences in guidance on research protections from the different agencies do not strengthen the protections to subjects, but rather have the effect of confusing the researchers who deal with more than one agency. Further, some of the guidance issuing from the agencies departs from the intent of the original regulations and has the effect of creating de facto policy without the normal review and comment period from OMB and the public.

Question 73: To what extent do the existing differences in guidance on research protections from different agencies either facilitate or inhibit the conduct of research domestically and internationally?

The variety of guidance from the various federal agencies sponsoring research is confusing and burdensome to institutions. In implementing the Common Rule, agencies have taken strikingly different approaches. For example, research organizations are required to maintain a Federalwide Assurance (FWA) that demonstrates operational compliance with the current federal regulations. Nonetheless, agencies have inserted additional requirements in their implementation. The difference between FDA regulations and the Common Rule are frequently cited. The Department of Justice and the Department of Education also have slightly different requirements. The Department of Navy requires an Addendum to the FWA; it has also recently expanded the training requirements for administrative personnel despite the standing training requirement that is part of the FWA process.

The most time-consuming and redundant procedure is the requirement to submit to the Federal agency a research protocol describing the human subject research component that has already been reviewed and approved by the applicant institution's IRB for another review and approval by the agency IRB or, in some cases, by the peer review panels established to recommend the funding of research projects. This duplicate review delays awards and creates ambiguities over which entity – the institution or the agency – is finally responsible for the conduct of the human subjects research. Additional unique reporting, training, and operational requirements create a level of confusion and occasional conflict in maintaining compliance with the actual regulation or policy itself. There is nothing common among these approaches. There is also no evidence that the variance in the rules better protects human subjects.

In responding to the recent Presidential Commission for the Study of Bioethical Issues' request for comments on the recommendations presented to the Commission by its International Research Panel, we encouraged the ongoing dialogue between US and international bodies to identify areas of cooperation particularly in defining equivalent protections. Resolving the differences between regulatory or ethical requirements and recognizing how other countries' regulatory structures meet US standards will enable investigators to conduct research in a global environment.

Question 74: If all Common Rule agencies issued one set of guidance, would research be facilitated both domestically and internationally? Would a single set of guidance be able to adequately address human subjects protections?

Harmonization among the agencies would simplify training and promote compliance of researchers because the rules would be consistent and not agency-dependent. If the regulations were tailored to the risk to subjects and not to the type of research, then one set of regulations could easily address diverse populations and the large number of research areas. As an interim step, we recommend that one website be created which posts all federal regulations and guidance related to research with human subjects.

Internationally, the application of US regulations does not better protect human subjects because foreign researchers are unlikely to be familiar with them and in many cases, US requirements run counter to the local culture (e.g., the formality of a written consent form or the legalese of many consent elements may make potential subjects wary of participating). The current regulations allow

for each agency head to rule that a foreign government's procedures afford protections that are at least the equivalent of those provided by US policy. We note that the 2003 Report of the Equivalent Protections Working Group provides a framework for evaluating equivalent protections. We recommend that the agencies begin to develop and post such approved equivalencies on the same website as the regulations are posted (see above).

IX. Agency Request for Information

Additional Recommendations to Reduce Administrative Burden

We've highlighted below some areas that we recommend the consideration for revisions:

- We support elimination for the requirement for **annual** review [§46.109 (e)]. IRB should have the flexibility to determine when **continuing** review of approved research is required.
- We recommend eliminating federal guidance that requires IRBs to review funding applications (OPRR, May 31, 2000, IRB Review of Applications for HHS Support). Relying on the 45 CFR 46.103(f) requirement that each application or proposal for HHS-supported human subject research be reviewed and approved by the Institutional Review Board links the actual proposal document to the research. The application is an expression of the research written to meet specific application requirements, e.g., page lengths, type face, section order, etc. The research reviewed by the IRB is often more detailed and includes more information than the application to the agency. We believe the review of the IRB research protocol is sufficient. The investigator is required to promptly report changes in the approved research to the IRB for review and approval [§46.103 (4)(iii)]. If congruence between the funded project and the IRB approval at the time of award requires such modifications, the investigator is required to report those changes before initiating the research.
- The September 22, 2011 OHRP Correspondence concerning engagement/non-engagement in research is an important modification to earlier October 16, 2008 *Guidance on Engagement of Institutions in Human Subjects Research* issued by OHRP. We believe the exception that the awardee institution of the NIH award was not engaged in the non-exempt human subjects research studies when the human subjects research is to be carried out by other institutions under the award is very important and should be incorporated into the Guidance and/or regulations, wherever appropriate.