October 26, 2011

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

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

Dear Dr. Menikoff:

The Johns Hopkins University (JHU), in partnership with the hospitals and physicians of The Johns Hopkins Health System (JHHS), leads the nation in medical research. JHU consistently ranks first in research spending among all U.S. universities; in 2010 JHU received more than two billion dollars in federal research funding, with the largest portion originating from the Department of Health and Human Services (DHHS). Within JHHS, our hospitals and practice groups both support JHU’s translational human studies and manage a portfolio of their own federally-funded research.

Across the Hopkins systems we operate several Institutional Review Boards (IRB) comprising more than nine full IRB committees. In addition there is the Privacy Board of the Johns Hopkins Medical Institutions that was established in 2003 to meet compliance requirements of the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). The Privacy Board reviews retrospective studies involving archival sources containing health information held by the HIPAA covered entity of Johns Hopkins. Also, the JHU Bloomberg School of Public Health and the Homewood Campus operate IRBs that oversee sizeable portfolios of Common Rule research.

Collectively, the Hopkins IRBs and our research compliance community welcome this DHHS initiative. Revisions to the Common Rule are long overdue, and we look forward to improvements that will make human subjects protections more efficient, transparent, and effective. We caution, however, that merely revising the Common Rule will not solve the broader systemic problems that impede research, and we urge DHHS not to impose new mandates that may inadvertently increase regulatory burden.
We also emphasize that the most important goal of the Common Rule is the protection of human research participants. It is unclear how DHHS will judge whether regulatory change advances this objective. We note that DHHS is contemplating significant regulatory changes in the absence of reliable data to assess the current quality of IRB review or useful metrics to determine whether proposed regulatory changes will increase research protections. In response, we suggest that DHHS support further scholarship and consensus-building around these questions.

We agree that the Common Rule and DHHS guidance should be modernized to target compliance resources toward areas of greatest risk, to ensure privacy protection in the digital age, and to accommodate differences in oversight requirements for social science and biomedical research.

With those objectives in mind, our response to the ANPRM questions reflects the following themes:

1) Cooperation between local and central IRBs. We believe that central IRB review should not be mandated for all multi-center research. We do not believe central IRB review can replace local review entirely; further, central IRB review alone will do little to address the more complex issues associated with delays in protocol initiation in a multi-center trial.

Rather, if roles are defined clearly and prospectively, local and central IRBs can work in partnership, with the central IRB serving as “IRB of record” for review of a protocol in a multi-site study, but with a requirement for that IRB’s review to incorporate feedback from local sites, and a delegation of certain responsibilities (as described below) to the local site’s IRB. Our views are informed by extensive service as both local site and central IRB in multi-center trials, and by our experience in forming the multi-center, multi-state Johns Hopkins Clinical Trials Network.

We urge DHHS to recognize that in multi-center trials, local and central IRBs must cooperate to meet the many federal, state, and even local requirements that apply to human research. As the Common Rule acknowledges, compliance does not relieve an institution of the obligation to know and follow locally applicable laws and regulations. 45 CFR §46.101 (f); IRB review must also be sufficiently cognizant of both applicable law and local context (“[T]he IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct . . .45 CFR §46.107(a)).

Even if a single, central IRB is competent to evaluate scientific merit and overall protocol design for a multi-center trial, that single IRB is not well-positioned to assess areas of local concern, such as the following:
• The qualifications and clinical credentials of investigators and study team members at local sites (especially local sites whose investigators are physicians in private practice);

• Interpretation of state law, such as statutes or regulations that affect who may give consent for research participation, (especially for research involving minors and adults who lack capacity to consent); consent requirements for genetic, STD, and HIV testing; or the licensing or certification required under state law to perform various research procedures;

• Policies and practices of the local jurisdiction concerning enrollment of foster children, prisoners, and others in state custody;

• Determining whether a particular treatment or intervention is standard-of-care or investigational in accordance with local institutional policies; and

• Ensuring that the consent form includes institution-specific language mandated by other federal policies or regulations (e.g., HIPAA Privacy Rule, the federal Certificate of Confidentiality Program), or site-specific language on topics such as payment for injuries or clinical billing, whether developed as a condition of the Association for the Accreditation of Human Research Protection Programs (AAHRPP) accreditation or negotiated with research sponsors or funders.

We suggest that DHHS consider how best to allocate roles between the central and local IRBs. For example, DHHS might consider inclusion of specific regulatory language to address delegation of a single IRB as the IRB of record for review and approval of the protocol, and delegate to local IRBs the responsibility for oversight of the recruitment and consent processes, credentialing of investigators, and compliance monitoring.

DHHS should also consider the problem of central IRB selection in a multi-center trial. IRBs vary in their local context and their competence to review various types of research; it is unclear under the proposed changes who would select the central IRB or which criteria would govern the selection. For example, would sponsors be permitted to require institutions to accept the review of a commercial IRB of the sponsor’s choice as a condition of participation in a multi-center trial? It may even be the case that for certain studies, no single IRB has sufficient depth of expertise or breadth of experience to perform an optimal scientific and ethical review, and DHHS might consider a mechanism by which several IRBs could work in concert to produce one “of record” review.
Further, any cooperative model must recognize the practical limits on how completely one institution may assume responsibility for other institutions when serving as the central IRB. Liability is one such limitation. Liability avoidance is neither a minor nor a parochial concern, since regulatory fines, tort judgments, settlement payments, litigation fees, and the resulting increase in insurance costs impose a very real tax on every research institution, diverting resources that could otherwise support more science.

Hopkins has learned through experience that even for minimal risk studies, when we serve as an external IRB we must negotiate with local sites to obtain sufficient liability protection for our institution. Both the institution and individual IRB members have liability exposure when they review and approve research; therefore, indemnification and insurance to cover indemnification obligations are a necessary part of any arrangement to assume this responsibility. The DHHS proposal to sanction central IRBs directly may complicate already difficult discussions about liability, and as a result, we may be less likely to accept the many requests that we receive to serve as a central IRB. We question the assumption, reflected in the DHHS proposal, that institutional liability concerns would be lessened if DHHS asserted greater sanction authority over central IRBs.

2) **Harmonization and clarification.** Almost everyone recognizes that often it takes too long and involves too much paperwork to initiate a research study. We should not, however, view this problem only through the narrow lens of IRB review and Common Rule requirements. Research institutions don’t just operate IRBs; in the terminology of AAHRPP, they conduct research within a “human subjects protection system,” with numerous regulators and overlapping, sometimes inconsistent requirements. A single protocol may be subject to requirements emanating from the Office for Human Research Protections (OHRP), Food and Drug Administration (FDA), Office of Civil Rights (OCR), Centers for Medicare and Medicaid Services (CMS), and National Institute of Health (NIH) (or another funding agency) covering not only human subjects, but investigational products, privacy, clinical billing, conflict of interest, biosafety, radiation review, research integrity, and so on.

To reduce burden and make research regulation more effective, the federal government should try harder to harmonize all the existing requirements that apply to research. Short of a government-wide effort, there are still many specific instances in which DHHS alone could make efficiency gains through harmonization. For example, it makes little sense for OCR to require detailed Privacy Rule authorization verbiage when a study uses a consent form that is already subject to the Common Rule obligation to disclose privacy risks; doing so increases the length of the consent form substantially and confers no appreciable additional protection for subjects. Likewise, requiring IRBs to conduct separate waiver reviews under the Common Rule and the Privacy Rule wastes time and institutional resources.
We are encouraged to see that DHHS is moving toward modernizing biospecimen research requirements, and agree that a streamlined, prospective consent process with adequate privacy protection is a viable model for research using clinical specimens, as well as unanticipated future uses of specimens collected specifically for research. Again, we would like to see federal regulators adopt a consistent approach to biospecimen research – one that permits waiver of consent for FDA-regulated studies of biospecimens when appropriate under existing Common Rule criteria (current FDA guidance outlining “enforcement discretion” with respect to consent in In Vitro Diagnostic (IVD) studies is too narrow and not entirely consistent with the Common Rule).

We appreciate the DHHS request for comments about the effectiveness of genetic de-identification. The decision about whether human genome research involves information that is identifiable per se is difficult, and deserves careful consideration. We were concerned by language in the ANPRM suggesting a consensus view that genomic information is identifiable. If this is the current position of OCR, much genomic research at academic medical centers will be impacted, and HIPAA-covered entity institutions and providers will no longer be able to disclose “de-identified” genomic data to research databases such as those maintained or funded by the NIH (which requires grant recipients to certify that genomic data are de-identified).

Following a recent OCR workshop on de-identification, and in view of the number of commentators who argue that de-identification is not a workable concept for genomic data, the research community has been waiting for OCR to issue guidance on this topic. We would like to see OHRP and OCR harmonize their interpretation of “identifiability” and their position on genetic de-identification in a coordinated guidance document.

More generally, we believe that much of the variability in IRB review outcomes, particularly in pediatric studies, could be reduced if DHHS and FDA adopted existing Secretary Advisory Committee on Human Research Protections (SACHRPP) recommendations to define or further clarify regulatory terms (such as “minimal risk,” “minor increase over minimal risk,” and “condition”) that IRBs must interpret without sufficiently objective criteria. Listing specific “minimal risk” procedures, as the ANPRM proposes, may lend some clarity, but is not a substitute for better definition of terms (since no federal list can anticipate every procedure, and because, for liability reasons, institutions may be unwilling to rely solely on federal designations when assessing risk). We also emphasize that when assessing risk, IRBs must consider the possibility of harm that may result if a minimal risk procedure, such as certain diagnostic tests, is performed incorrectly or mistakenly, in an ineligible subject whose contraindications place him or her at greater risk.
3) **Do no harm.** New regulatory mandates, including the new auditing and data security requirements discussed in the ANPRM, can create significant administrative burdens for the institutions that must design processes and forms to implement them. The more prescriptive the mandate, the greater the burden associated with implementation in terms of paperwork and staff time. Broadly-applicable and specific security requirements, such as encryption of all research data, whether identifiable or not, across all schools in an institution (including departments of history, social science, and biomedical engineering, where there is already disagreement about which activities should constitute “human subjects research”) would be controversial to implement and burdensome to enforce. *These negative consequences could offset efficiency gains from the proposed reduction in continuing reviews and expansion of the exempt (or “excused”) categories.* In addition, unless there are established, uniform and clear standards that apply to all proposed research, IRB members may feel that they lack the expertise to evaluate electronic security risks.

We strongly urge OHRP to adopt a model in which institutions are required to design data security and audit plans for Common Rule research, but are permitted flexibility to tailor these plans to the risk profile of the research portfolio and the resources available to the institution.

It is not realistic to expect that all researchers can meet the standards that apply to covered entities under the HIPAA Security Rule. OHRP could, however, remind IRBs that the Common Rule’s risk-benefit analysis includes an assessment of risks to privacy, and encourage IRBs to include as members (or engage as consultants) IT staff who can help to evaluate specific projects and identify best practices. For example, Hopkins Medicine has instituted a process in which a physician with IT expertise evaluates many proposed research uses of large Electronic Medical Records (EMR) datasets, and advises the IRB about risk mitigation strategies.

**Other responses to specific ANPRM questions are listed below:**

**Question 1:** Is the current definition of “minimal risk” in the regulations (45 CFR 46.102(i) -- research activities where “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests”) -- appropriate? If not, how should it be changed?

We do not consider the definition to be appropriate. The concept of “daily life” in 2011 is vastly different from the concept of daily life that existed when the regulations were finalized in 1978. The terms “probability and magnitude of harm or discomfort” have always been difficult for IRBs to interpret. We suggest that these terms, if retained, be clarified further in the
It would be useful if the regulations or guidance could provide a list of “routine” examinations, similar to the list of tests that currently exists as those which qualify for an expedited review process.

**Question 2:** Would the proposals regarding 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 that qualifies for expedited initial review should undergo continuing review?

Studies that pose no more than minimal risk and were initially reviewed as expedited should continue to be reviewed within a specified timeframe, but the timeframe could be more infrequently than annually, such as biannually or every three years. In addition, if the study risk profile and procedures have not changed since the initial review, then it would be far less burdensome and no lessening of subject protections if continuing review of the protocol could be an administrative review conducted by an IRB staff member rather than a full review by an IRB member.

If a study has had unanticipated problems, adverse events, or noncompliance since the last review, then it may be useful to conduct a complete review of the protocol at continuing review. Otherwise, once a study reaches data analysis stage, the IRB merely needs to know whether the analysis is “active.”

**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 described in section 3, below (e.g., a study in which a physical intervention occurred in the first year, all subjects have completed that intervention, and only annual written surveys are completed for the next five years)?

Because we believe that there is benefit to participants and to the institution to continue IRB oversight so long as there are interactions with participants, we would prefer to retain annual review.

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

We do not think requiring IRBs to only consider “reasonably foreseeable” risks or discomforts would improve the efficiency of the IRB process, nor increase protections for study participants. In fact, we think adding this modifier without any interpretation guidance would only lead to
increased IRB discussions regarding what is “reasonably foreseeable” and inconsistent determinations amongst IRBs. Moreover, it is unclear what risks DHHS would consider “reasonably foreseeable.” For example, when a study includes both research procedures and routine care, it is not clear to what extent are the risks of the routine care procedures or drugs “reasonably foreseeable” for the purposes of research consent.

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?

Psychological risks will vary from person to person. It is important to remember that examining the questions or assessments alone cannot be the only way to assess risk. It may be even more important to assess the context in which the questions are asked (computerized, interview with privacy, skill of interviewer) and whether there is any opportunity to discuss reactions to the questions outside of the study. For example studies whose participants have been victims of a painful experience (e.g. combat or torture in wartime), or have underlying conditions involving psychological discomfort or pain (e.g., depression or anxiety disorder), could involve greater than minimal risk to participants.

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?

Yes, there are surveys that include sensitive questions that should be classified as greater than minimal risk. Examples would be studies involving participants who are HIV+, are sex workers, injection drug users, or engage in criminal activity. We feel greater than minimal risk should attach to studies whose participants may be placed in legal jeopardy by virtue of their participation or their responses, as well as studies where participants, due to an underlying psychological or cognitive vulnerability (childhood, mental illness, dementia) may be harmed by the experience of participating or answering certain questions.

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? For instance, should the following be included as minimal risk research activities:

- 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 support the proposal to expand the list of activities that may qualify for an expedited review process. We suggest that DHHS and FDA provide a draft revised list for comment to allow expansion of the possible tests and that it clearly distinguish adult and pediatric populations to which the tests apply. We also caution, as noted above, that DHHS should recognize the importance of assessing the risk that procedure will not be performed correctly.

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?

We support the proposal to expand the expedited review criteria to allow a defined subset of radiological procedures that qualify as minimal risk research and that would qualify for an expedited review process. Suggested tests could include the following: a single chest or limb x-ray; one routine DEXA scan, and one routine mammogram.

Question 9: How frequently should a mandatory review and update of the list of research activities that can qualify for expedited review take place? Should the list be revised once a year, every two years, or less frequently?

The list should be reviewed at least every two years.

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?

a. Risks do not need to be “minimized” if they are already “minimal.”
b. “Risks should be reasonable” (e.g., if risks are “minimal” there is no need to compare those risks with “anticipated benefits” )
c. Selection of subjects should be reasonable
d. Consent should always be required if there is an interaction with the participant, but rarely would it need to be documented by signature.
e. If the risk is minimal, there is no need for data safety monitoring.

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? If not, what are the disadvantages of relying on a non-IRB member to conduct expedited review? If so, what would qualify as being “appropriately trained”? Would
the effort to make sure that such persons are appropriately trained outweigh the benefits from making this change?

We are not opposed to delegating review responsibilities to “appropriately trained” staff if the regulations define the minimal training and level of experience that should apply to such staff. The option of allowing institutions to delegate this responsibility to staff would be a useful addition to the regulations.

We have found, however, that minimal risk studies, particularly those conducted in other countries or cultures, do not equate to “minimal complexity.” Studies involving the secondary use of data, though often deemed “minimal risk,” may require specific security precautions to minimize risks. Staff who conduct expedited reviews must have sufficient training in a number of areas, including cultural sensitivity, privacy, and data security.

Question 12: Are there other specific changes that could be made to reduce the burden imposed on researchers and their staffs in terms of meeting the requirements to submit documents to an IRB, without decreasing protections to subjects? Are there specific elements that can be appropriately eliminated from protocols or consent forms? Which other documents that are currently required to be submitted to IRBs can be shortened or perhaps appropriately eliminated? 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? What entity or organization should develop and disseminate such standardized document formats?

The current DHHS regulations do not include references to specific documents that must be submitted for IRB review, but OHRP guidance and determination letters do include references to required documents for review. The DHHS and FDA regulations should provide more specificity and be harmonized in this area. We do not believe that adding regulatory requirements regarding protocols or consent forms would reduce the burden of document submission or reduce the time for approval of an application. If the OHRP and FDA regulations are not harmonized with regard to document requirements, the review process will necessarily remain more complex and less efficient for studies governed by both sets of regulations.

Question 13: Given the problems with the current system regarding wide variations in the substance of IRB reviews, would it be appropriate to require IRBs to submit periodic reports to OHRP in the instances in which they choose to override the defaults described in Sections B(1), B(2)(a)(ii), and B(2)(b) above? Should IRBs have to report instances in which they require continuing review or convened IRB review of a study which involves only activities identified as being on the list of those eligible for expedited review? If an IRB that chose to override these defaults was required to submit a report to OHRP, would this provide useful information about any lack of appropriate consistency among IRBs so that clarifying guidance
could be provided as needed, or provide useful information to OHRP about the possible need to revise the expedited review list or the continuing review requirements?

We appreciate the effort to find out why different IRBs make different decisions about the level of review, and understand that OHRP does not currently have a method for collecting information about those decisions. Adding tracking and reporting requirements would expand the burden placed on IRBs and institutions. Unless such reports to OHRP would produce meaningful, real time feedback to IRBs on the expedited and convened review decisions, the information submitted would not be useful to institutions. Establishment of an OHRP website to allow institutions to submit requests to revise and expand the list of protocols eligible for expedited review would be useful.

**Question 14:** Are these expansions in the types of studies that would qualify for this Excused category appropriate? Would these changes be likely to discourage individuals from participating in research? Might these changes result in inappropriately reduced protections for research subjects, or diminished attention to the principles of respect for persons, beneficence, and justice?

We request that DHHS and FDA regulations be revised to incorporate the same excused or exemption categories to assist IRBs at institutions that review research covered by both sets of regulations. We agree that the proposed changes to Exempt Category 4’s definition of “existing” data or specimens would be beneficial, as it would permit inclusion of medical record information and repository or pathology specimens collected on an ongoing basis.

Further, if the regulations were clarified regarding what is expected of an IRB in relation to ‘exemptions’, IRBs may be able to assist in reducing the burden to investigators. Currently, many institutions conduct a full review of exempt studies to ensure participants have the greatest protections possible and that the regulations are being met.

**Question 15:** Beyond the expansions under consideration, are there other types of research studies that should qualify for the Excused category? Are there specific types of studies that are being considered for inclusion in these expansions that should not be included because they should undergo prospective review for ethical or other reasons before a researcher is allowed to commence the research?

The ‘Excused’ (better renamed as suggested below) category could include non-sensitive surveys with competent adults, regardless of the collection of identifiable information. In addition, the regulations should make clear that certain fields of study, such as those in the humanities, including classics, history, language, journalism, as well as certain specific
activities, such as focus groups and public health surveillance, are not considered human subjects research and therefore do not need to be reviewed by an IRB.

**Question 16:** Should research involving surveys and related methodologies qualify for the 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 should only be ‘excused’ if they do not involve sensitive topics and if they involve “competent adults”. We think there are some topics that are so benign, such as food choice or entertainment preferences, that IRB oversight is not required. Any other study that solicits a personal opinion or personal information should be stratified by risk, and the IRB is the only entity experienced enough to make that determination.

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

It would be useful if the regulations explicitly defined or listed research areas of design involving deception that would not qualify as excused research. Social and behavioral research methodologies should fall within the Excused or Exempt category if they involve benign interventions or interactions with competent adults. Those methods involving deception should be submitted to the IRB for a review to ensure that the manner and need of deception is appropriate.

**Question 18:** Currently some IRBs make determinations regarding whether clinical results should be returned to study participants. How should such determinations be made if the study now fits in the Excused category? Can standard algorithms be developed for when test results should be provided to participants and when they should not (e.g., if they can be clinically interpreted, they must be given to the participants?).

The issue of return of research test results and the definition of when a research test result is a “clinical result” are currently problematical. Proposed changes in regulations to address the issue of return of research test results should address and be harmonized with the requirements of the Centers for Disease Control and Prevention (CDC) Clinical Laboratory Improvement Amendments (CLIA) to assure that conflicting standards are not issued.

**Question 19:** Regarding the 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?
It has been our experience that a one page document rarely provides sufficient information to determine if proposed research is currently eligible for an exemption determination or an expedited review. It is not clear how a registration form would be useful in making a determination about excused research. The regulations should allow institutions to adopt the notification method and waiting period that fits the organization.

**Question 20:** The term “Excused” may not be the ideal term to describe the studies that will come within the proposed revision of the current category of exempt studies, given that these studies will be subject to some protections that are actually greater than those that currently exist. 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 welcome other suggestions for alternative labels that might be more appropriate.

We agree that “excused” is not the best term and multiple categories starting with “ex-“ will lead to confusion among research teams and IRB members. If the regulations are modified to use the term “Registered” it might be better to categorize the research as “Registered Only.”

**Question 21:** Is it appropriate to require institutions holding a Federalwide Assurance to conduct retrospective audits of a percentage of the Excused studies to make sure they qualify for inclusion in this category? Should the regulations specify a necessary minimum percentage of studies to be audited in order to satisfy the regulatory requirements? Should some other method besides a random selection be used to determine which Excused studies would be audited?

The current regulations do not require audits or monitoring of research determined to be exempt from requirement for IRB review. We do not support development of a new regulation that would impose an audit process for excused research, as this would add to regulatory burden. It is not clear what would be the consequences of a retrospective audit of a project that has been completed and then found not have met the criteria for an excused research project. At most, we see mandated audits as a temporary, time-limited (perhaps for one year) means to assess the impact of the proposed regulatory change.

**Question 22:** Are retrospective audit mechanisms sufficient to provide adequate protections to subjects, as compared to having research undergo some type of review prior to a researcher receiving permission to begin a study?

No, except for narrowly-defined categories of research.

**Might this new audit mechanism end up producing a greater burden than the current system?**

Yes.
Do researchers possess the objectivity and expertise to make an initial assessment of whether their research qualifies for the Excused category?

Yes, with training and education from the institution.

Are there nonetheless specific categories of studies included in the proposed expansion for which this change would inappropriately weaken protections for subjects? And will the use of a one-page registration form give institutions sufficient information to enable them to appropriately conduct the audits?

Retrospective audits are not sufficient to provide protections and will only create additional burdens on the IRB and investigators. Some researchers may possess the objectivity and expertise to make the assessment as to whether their research fits into an excused category, but there may be some investigators who do not make the correct decision and do not consult the IRB or institution. Those who do not make the correct decision could put the participant at risk, albeit low risk.

Rather than create an ‘excused’ category, it is preferable to clarify the definition of ‘not human subjects research’, expand and clarify the exemption categories, and specify the level of detail that must be provided by the investigator to the IRB regarding exemptions and the level of review that must be conducted by the IRB for an exempt study. Many institutions conduct a complete review of exempt studies in order to protect the participants and the institution, which takes away resources from the greater risk studies. In addition, it would be beneficial to reduce or eliminate the annual renewal of expedited studies.

Question 23: Under what circumstances should it be permissible to waive consent for research involving the collection and study of existing data and biospecimens as described in Section 3(a)(3) above?

For research that meets the definition of minimal risk, the waiver seems appropriate.

Should the rules for waiving consent be different if the information or biospecimens were originally collected for research purposes or non-research purposes? No.

Question 24: We seek comment on whether and, if so, how, the Common Rule should be changed to clarify whether or not oversight of quality improvement, program evaluation studies, or public health activities are covered. Are there specific types of these studies for which the existing rules (even after the changes proposed in this Notice) are inappropriate? If so, should this problem be addressed through modifications to the exemption (Excused) categories, or by changing the definition of “research” used in the Common Rule to exclude some of these studies, or a combination of both? And if the definition of research were to be changed, how should the activities to be excluded be defined (e.g., “quality improvement” or
“program evaluation”)? Are there some such activities that should not be excluded from being subject to the Common Rule because the protections provided by that rule are appropriate and no similar protections are provided by other regulations? With regard to quality improvement activities, might it be useful to adopt the distinction made by the HIPAA Privacy Rule (45 CFR 164.501(1)), which distinguishes between “health care operations” and “research” activities, defining “health care operations” to include “conducting quality assessment and improvement activities, including outcomes evaluation and development of clinical guidelines, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities”?

We do not believe quality improvement and assessment activities or program evaluations should be covered under the Common Rule. The goal of QA/QI activities is to define best practices and disseminate such knowledge to positively impact health care and services delivered to patients. In many cases, publication or presentation of results is essential to the dissemination of such knowledge, but is often viewed, inappropriately, as a proxy for being engaged in research. It is also important to note that as QA and QI become more rigorous, their methods often resemble those used in research. We do not believe that the term “generalizable knowledge,” without further definition, has proved useful as a means to differentiate research from QA/QI activities.

Simply stating that certain activities are excluded from the category of “research” does little to address the problems inherent in distinguishing them from research, particularly given the similarity of methods. DHHS should focus its efforts on developing meaningful guidance in this area.

Question 25: Are there certain fields of study whose usual methods of inquiry were not intended to or should not be covered by the Common Rule (such as classics, history, languages, literature, and journalism) because they do not create generalizable knowledge and may be more appropriately covered by ethical codes that differ from the ethical principles embodied in the Common Rule? If so, what are those fields, and how should those methods of inquiry be identified? Should the Common Rule be revised to explicitly state that those activities are not subject to its requirements?

The Common Rule should specify that projects in certain fields, such as classics, history, political science, languages, literature, and journalism, do not fall under the Common Rule. The work in these fields should be governed by the ethical codes and requirements of the particular field. Rigid application of the Common Rule and Privacy Rule to studies in these fields is unworkable, and poses a particular challenge when the project involves data held in a covered entity’s medical archives.
Question 26: The current exempt category 5 applies to certain research and demonstration projects that are designed to study or evaluate public benefit or service programs. Is the circumstance that a particular demonstration project generates “broad” knowledge incorrectly being used as a reason to prevent certain activities (including section 1115 waivers under Medicaid) from qualifying for exempt category 5? If so, how should this exemption (as part of the new category of Excused research) best be revised to assure that it will no longer be misinterpreted or misapplied? Would broadening the interpretation of the exemption result in inappropriately increased risks to participants in research? If so, how could such risks be mitigated? Also, is there a need to update or otherwise revise the “OPRR Guidance on 45 CFR 46.101(b)(5)”?

We support development of guidance on the topic of research and demonstration projects, as the concept of “public benefit and service programs” has changed since 1978 when the regulations were adopted.

Question 28: For research that requires IRB approval, the Common Rule does not currently require that the researcher always be allowed some form of appeal of a decision (e.g., disapproval of a project). Some institutions have voluntarily chosen to provide appeal mechanisms in some instances, by, for example, allowing the researcher to present the project to a different IRB, or by having it reviewed by a special “appeal” IRB that is composed of members chosen from among the membership of the institution’s other IRBs. Should the Common Rule include a requirement that every institution must provide an appropriate appeal mechanism? If so, what should be considered acceptable appeal mechanisms? Should such appeal mechanisms, or different ones, be available for appeals asserting that the investigation is not research, or that the research does not require IRB approval?

We suggest that the regulations not include a defined requirement for an appeal mechanism. The regulations should allow institutions the flexibility to incorporate an appeal mechanism into the standard operation procedures, rather than prescribe a mechanism. We recognize that investigators want and deserve a process through which to obtain answers to questions about the IRB process, and to respond to questions or controverted issues. DHHS can encourage institutions to develop sufficient process to accomplish these goals, but should be cautious not to call into question the final authority of the IRB to withdraw or withhold approval of human research.

Question 29: As noted above, IRBs sometimes engage in activities beyond those that are required by the regulations. For example, an IRB might review some studies for the purpose of determining whether or not they qualify for exemption (the new Excused category), or might review studies involving the analysis of data that is publicly available. Would it be helpful, in furtherance of increased transparency, to require that each time an IRB takes such
an action, it must specifically identify that activity as one that is not required by the regulations?

We do not think this requirement would improve the efficiency of the IRB process, nor increase protections for study participants.

**Question 30:** What are the advantages and disadvantages of mandating, as opposed to simply encouraging, one IRB of record for domestic multi-site research studies?

See page 1 for general comments regarding the proposed mandate. We fear that this approach would actually decrease the number of sites willing to participate in a multi-center trial, due to a perceived lack of sufficient control over the review process.

We see few advantages to mandating a single IRB. There is a hypothetical argument that one IRB would be more careful in the review but there are no data to support this. Mandating a single IRB with no process for selecting which IRB would be the single one IRB is not acceptable.

**Question 31:** How does local IRB review of research add to the protection of human subjects in multi-site research studies? How would mandating one IRB of record impair consideration of valuable local knowledge that enhances protection of human subjects? Should the public be concerned that a centralized IRB may not have adequate knowledge of an institution’s specific perspective or the needs of their population, or that a centralized IRB may not share an institution’s views or interpretations on certain ethical issues?

See page 1 for general comments regarding the proposed mandate.

**Question 32:** To what extent are concerns about regulatory and legal liability contributing to institutions’ decisions to rely on local IRB review for multi-site research? Would the changes we are considering adequately address these concerns?

See page 1 for general comments.

**Question 33:** How significant are the inefficiencies created by local IRB review of multi-site studies?

Very few data exist that would permit DHHS to evaluate what factors contribute to delays in IRB approval at all sites participating in multi-center trials. There are anecdotal references in the literature, and we do not advocate changing the regulations without additional data on “inefficiencies.” Local review requirements imposed by institutions vary from site to site and would be difficult, if not impossible, to regulate for all participating sites.
Increasing communication between IRBs in relation to review would also help substantially. DHHS should consider how best to encourage investigators and sponsors to develop a coordinated trial strategy with communication among reviewing sites, rather than an ad hoc approach in which new sites are added in an uncoordinated fashion.

**Question 34:** If there were only one IRB of record for multi-site studies, how should the IRB of record be selected? How could inappropriate forms of “IRB shopping” — intentionally selecting an IRB that is likely to approve the study without proper scrutiny — be prevented?

We do not support a regulation that would mandate designation of only one IRB as the IRB of record. If such a regulation were implemented, and an institution found the IRB of record unacceptable, this would effectively exclude the institution from participation. A guidance on IRB reviews for multi-site studies is preferred over a regulatory requirement that would not have the flexibility needed for institutions to judge whether research may be conducted at the local site.

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

The factor that makes the greatest contribution to complexity and the least contribution to subject comprehension of risks and benefits is the Privacy Rule requirement for a specific research authorization containing seven specified elements. We urge DHHS to allow covered entities to meet the authorization requirement in Common Rule research with a single statement in the consent form that describes risks to privacy. In our experience, the detailed research authorization requirements under the Privacy Rule are largely redundant with Common Rule requirements, are terribly confusing for subjects, lengthen consent forms significantly, and produce no increase in subject protections.

DHHS should also consider the extent to which mandated statements, such as NIH-required language describing Certificates of Confidentiality and FDA-mandated statements about clinical trial registration add to the length and complexity of the consent form.

**Question 36:** What additional information, if any, should be required by the regulations to assure that consent forms appropriately describe to subjects, in concise and clear language, 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?

We do not support changes in the regulations that will require a subjective judgment applied to research to determine for participants “why it may or may not be in their best interests to participate.”
Question 39: If changes are made to the informed consent requirements of the Common Rule, would any conforming changes need to be made to the authorization requirements of the HIPAA Privacy Rule?

Any changes made in the Common Rule consent requirements should have conforming changes in both FDA consent regulations and the HIPAA Privacy Rule requirements for authorization. We feel research protections would be enhanced, due to increased clarity (and consent/authorization forms could be shortened significantly) if DHHS determined the authorization requirement under the Privacy Rule is met by a single statement in the consent form that describes risks to privacy in the research.

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

We request revision or removal of the criterion “(3) The research could not practicably be carried out with the waiver of alteration.” IRBs struggle with the concept “practicably be carried out” as clear guidance is not available to apply to determine what meets the test of “practicably.” Further, it is not clear why criterion “(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.” should remain in the regulations when the waiver may only be applied to minimal risk research.

Question 44: Are there types of research involving surveys, focus groups, or other similar procedures in which oral consent without documentation should not be permitted? What principles or criteria distinguish these cases?

As long as the topics do not include sensitive information and the participants are adults, then oral consent without documentation should be permitted.

Question 45: Under what circumstances should future research use of data initially collected for non-research purposes require informed consent? Should consent requirements vary based on the likelihood of identifying a research subject? Are there other circumstances in which it should not be necessary to obtain additional consent for the research use of currently available data that were collected for a purpose other than the currently proposed research?

We believe this question is difficult to answer in the absence of DHHS guidance on the difference between research and non-research (e.g., quality improvement and quality assessment) uses of clinical data. We urge DHHS to pursue consensus-building activities and to publish guidance on this topic.
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?

No, but DHHS should recognize that de-identification may no longer be a workable concept for biospecimens, and conform its regulations to avoid impeding biospecimen research through the rigid application of outdated criteria and standards.

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?

We are uncertain whether this question signals a change to the existing waiver criteria. We would not support further restrictions on waiver of consent.

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?

It is not clear what OHRP envisions as a “public education campaign” (a national effort, a local effort at each institution, public forum, or other mechanism?). It is difficult to envision that a general consent document would be able to address state law requirements in the U.S.

We agree that a single consent process cannot fully anticipate all future uses of biospecimens. Requiring institutions to describe in more detail institutional policies and to answer questions from participants could help provide a more valid informed consent process. This goal could be accomplished through face-to-face meetings, webcasts, or other means through which participants can engage in dialogue with IRB members and institutional officials.

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? How should the consent categories that might be contained in the standardized consent form be defined (e.g. an option to say yes-or-no to future research in general, as well as a more specific option to say yes-or-no to certain specified types of research)? Should individuals have the option of identifying their own categories of research that they would either permit or disallow?

Tracking individual preferences and responses regarding future research would impose substantial burden on investigators and institutions.
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?

Yes, we believe the requirement should be applied to all research, including research specimens collected outside of the U.S.

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?

Yes, the rules should be applicable to the setting and requirements of individual countries.

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? Yes.

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 terms “impracticable” and “impracticability” should be replaced with clear and concise words that are easily understood and can be more easily interpreted by IRBs and researchers.

Question 54: Will use of the HIPAA Privacy Rule’s standards for identifiable and de-identified information, and limited data sets, facilitate the implementation of the data security and information protection provisions being considered? Are the HIPAA standards, which were designed for dealing with health information, appropriate for use in all types of research studies, including social and behavioral research? If the HIPAA standards are not appropriate for all studies, what standards would be more appropriate?

Social and behavioral research which does not collect Personal Health Information (PHI) should not be subject to the HIPAA standards. Institutions should be allowed to set their own standard for data security when PHI is not used in a research project.

Moreover, DHHS should attempt to address the special circumstances of medical archives. When an archive that holds PHI attempts to comply with HIPAA by granting access pursuant to Privacy Board waivers, the Privacy Board may find that many proposed projects of scholarly significance have been exempted from IRB review on the grounds that they are oral history, single-subject biography, or otherwise not human subjects research. DHHS should make clear
that the Privacy Board is authorized to grant waivers to all projects of scholarly merit, even those that do not meet the definition of “human subjects research.”

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)?

See our general comments in the introductory paragraphs on page 3. What is most important is that OCR and OHRP provide prompt, consistent guidance on this point.

Question 58: Should the new data security and information protection standards apply not just prospectively to data and biospecimens that are collected after the implementation of new rules, but instead to all data and biospecimens? Would the administrative burden of applying the rule to all data and biospecimens be substantially greater than applying it only prospectively to newly collected information and biospecimens?

The regulations should allow institutions to determine the standards that are applied to research and the method the institution will follow to determine that the standards are followed. The regulations should not be expanded to include enforcement standards. We suggest that DHHS set minimal standards that can be followed by all researchers, regardless of the size of the institution in which the research is conducted.

Question 59: Would study subjects be sufficiently 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? Are such standards appropriate not just for studies involving health information, but for all types of studies, including social and behavioral research? Or might a better system employ different standards for different types of research? (We note that the HIPAA Rules would allow subjects to authorize researchers to disclose the subjects’ identities, in circumstances where investigators wish to publicly recognize their subjects in published reports, and the subjects appreciate that recognition.)

As we note below, the HIPAA Security Rule does not specify particular security measures. We suggest that DHHS not attempt to do so in the Common Rule, because data security is a rapidly evolving concept.

One important issue is determining who will be responsible for reviewing informational risks and ensuring the plan is adequate, especially if the IRB is not the appropriate committee to make this determination. It is not clear if the proposed change would require assembling another committee to conduct the reviews; and if it does, would add an additional burden for investigators.

HIPAA rules are not appropriate for social behavioral research, notwithstanding the ability of subjects to authorize disclosures under the Privacy Rule.
Question 60: Is there a need for additional standardized 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)?

No. There should be one standard applied, regardless of phase of the research.

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?

Unlike the HIPAA Privacy Rule, the HIPAA Security Rule does not impose specific requirements that are consistent from institution to institution, so this suggestion would be difficult to implement. Nonetheless, DHHS could greatly facilitate research by permitting two Common Rule institutions to exchange data containing PHI under a simplified data use agreement that requires the recipient to protect privacy and security without mandating the terms of a HIPAA DUA.

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?

No. There may be circumstances in which an IRB determines that re-identification is necessary to protect participant safety. DHHS lacks jurisdiction under the Common Rule to extend prohibitions to many of the third parties (e.g., thieves and hackers) who might undertake unauthorized re-identification.

Question 65: Should registration with the institution be required for analysis of de-identified datasets, as was proposed in Section II(B)(3) for Excused research, so as to permit auditing for unauthorized re-identification?

We do not support expansion of the regulations to require auditing in general for excused research and do not support creating an additional monitoring or review burden that applies only to de-identified datasets or biospecimen research.

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?
Yes, institutions vary in their nature and structure, and should have flexibility about who will have this oversight as well as the responsibility to determine if audits need to be conducted. Not all research involves sensitive information or HIPAA-protected health information. Audits should not be required unless the institution determines that in the context of the research it conducts, an audit program is necessary to achieve compliance with applicable standards.

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.

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

a. Should the number of research participants in Federally funded human subjects research be reported (either to funding agencies or to a central authority)? If so, how?
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 research more globally?
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?

We do not support imposing a new reporting requirement that would add burden to institutions without adding to the protections afforded to human subjects. OHRP initiatives to gather data or information about the effectiveness of the human subjects protection systems at institutions should not be codified in regulations.

Question 70: Clinical trials assessing the safety and efficacy of FDA-regulated medical products (i.e., phase II through IV studies) are generally required to register and, following study completion, report summary results, including adverse events, in the publicly accessible database ClinicalTrials.gov. Is the access to information on individual studies provided by this resource sufficiently comprehensive and timely for the purposes of informing the public about the overall safety of all research with human participants?

Not all research involves medical safety issues, particularly social science and behavioral minimal risk research. A regulatory requirement to register all research would not necessarily serve the goal of providing additional medical research safety information to the public.
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 and regulations produce confusion in the review process and do not strengthen the process.

Best regards,

[Signature]

Daniel E Ford, MD, MPH
David M Levine Professor of Medicine and Psychiatry
Director, Institute for Clinical and Translational Research
Vice Dean for Clinical Investigation
Institutional Official Johns Hopkins Medicine
Johns Hopkins School of Medicine