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October 26, 2011

The Honorable Kathleen Sebelius
Secretary
Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

John P. Holdren
Director
Office of Science and Technology Policy
Executive Office of the President
725 17th Street, Room 5228
Washington, DC 20502

RE: Advance Notice of Proposed Rulemaking (ANPRM) — Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators (Docket number HHS-OPHS-2011-0005)

Dear Secretary Sebelius and Dr. Holdren:

Public Citizen's Health Research Group (HRG) has the following comment regarding the above-referenced ANPRM:

A. General Comments

(1) While the title of the ANPRM suggests that the Department of Health and Human Services (HHS) is proposing changes to current federal regulations that would enhance the protections for human subjects who participate in research, very few of the proposed changes would directly enhance the protections for human subjects participating in greater than minimal risk research, such as clinical trials, which clearly pose the greatest risk of harm to subjects. As a result, HHS appears to be more interested in reducing burdens for investigators than in strengthening protections for human subjects.

The ANPRM is premised on the assumption that reducing the time and effort institutional review boards (IRBs) spend reviewing certain minimal risk research (i.e., decreasing protections for subjects participating in minimal risk research) will allow IRBs to spend more time and effort reviewing greater than minimal risk research, thus enhancing protections for subjects enrolled in such research. However, HHS offers no evidence that this will be the end result if the proposals in the ANPRM are

implemented. It is very likely that if the ANPRM proposals are implemented in a final rule without new additional specific requirements for greater than minimal risk research, many IRBs, already feeling overburdened, will simply spend the same amount of time and effort reviewing greater than minimal risk research as they currently spend, resulting in no enhanced protections for subjects participating in such research.

(2) The ANPRM states that recommendations from the National Bioethics Advisory Commission's (NBAC) 2001 report *Ethical and Policy Issues in Research Involving Human Participants* are one source for the revisions to the Federal Policy for the Protection of Human Subjects (the Common Rule) currently being considered by HHS. However, the ANPRM proposes mainly to adopt those NBAC recommendations that relate primarily to minimal risk research and generally disregards other NBAC recommendations that would be most likely to enhance the protections for subjects participating in greater than minimal risk research, which includes most clinical trial research. We therefore urge HHS to include new provisions in the Common Rule that would implement the following important NBAC recommendations:[1]

> *Recommendation 3.1:* All institutions and sponsors engaged in research involving human participants should provide educational programs in research ethics to appropriate institutional officials, investigators, Institutional Review Board members, and Institutional Review Board staff. Among other issues, these programs should emphasize the obligations of institutions, sponsors, Institutional Review Boards, and investigators to protect the rights and welfare of participants. Colleges and universities should include research ethics in curricula related to research methods, and professional societies should include research ethics in their continuing education programs.
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> *Recommendation 3.3:* All investigators, Institutional Review Board members, and Institutional Review Board staff should be certified prior to conducting or reviewing research involving human participants. Certification requirements should be appropriate to their roles and to the area of research. The federal government should encourage organizations, sponsors, and institutions to develop certification programs and mechanisms to evaluate their effectiveness. Federal policy should set standards for determining whether institutions and sponsors have an effective process of certification in place.
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> *Recommendation 3.4:* Sponsors, institutions, and independent Institutional Review Boards should be accredited in order to conduct or review research involving human participants. Accreditation should be premised upon demonstrated competency in core areas through accreditation programs that are approved by the federal government.
>
> *Recommendation 3.6:* Institutions should develop internal mechanisms to ensure Institutional Review Board compliance and investigator compliance

with regulations, guidance, and institutional procedures. Mechanisms should be put in place for reporting noncompliance to all relevant parties.

Recommendation 3.7: Federal policy should define institutional, Institutional Review Board, and investigator conflicts of interest, and guidance should be issued to ensure that the rights and welfare of research participants are protected.

Recommendation 3.8: Sponsors and institutions should develop policies and mechanisms to identify and manage all types of institutional, Institutional Review Board, and investigator conflicts of interest. In particular, all relevant conflicts of interest should be disclosed to participants. Policies also should describe specific types of prohibited relationships.

Recommendation 3.9: Federal policy should establish standards and criteria for the selection of Institutional Review Board members. The distribution of Institutional Review Board members with relevant expertise and experience should be commensurate with the types of research reviewed by the Institutional Review Board (see Recommendation 3.10).

Recommendation 3.10: Institutional Review Boards should include members who represent the perspectives of participants, members who are unaffiliated with the institution, and members whose primary concerns are in nonscientific areas. An individual can fulfill one, two, or all three of these categories. For the purposes of both overall membership and quorum determinations 1) these persons should collectively represent at least 25 percent of the Institutional Review Board membership and 2) members from all of these categories should be represented each time an Institutional Review Board meets (see Recommendation 3.9).

Recommendation 4.1: An analysis of the risks and potential benefits of study components should be applied to all types of covered research (see Recommendation 2.4). In general, each component of a study should be evaluated separately, and its risks should be both reasonable in themselves as well as justified by the potential benefits to society or the participants. Potential benefits from one component of a study should not be used to justify risks posed by a separate component of a study.

Recommendation 4.2: … Minimal risk should be defined as the probability and magnitude of harms that are normally encountered in the daily lives of the general population. If a study that would normally be considered minimal risk for the general population nonetheless poses higher risk for any prospective participants, then the Institutional Review Board should approve the study only if it has determined that appropriate protections are in place for all prospective participants.

Recommendation 6.1: Federal policy should describe how sponsors, institutions, and investigators should monitor ongoing research.

(3) On March 29, 2007, the Secretary's Advisory Committee on Human Research Protections (SACHRP) made the following recommendations regarding training of individuals involved in the review, oversight, or conduct of human subjects research:[2]

Recommendation 1. SACHRP strongly recommends that the Office for Human Research Protections (OHRP) require that institutions ensure that initial and continuing training is provided for **IRB members**. Such training should include ethical principles and their historical foundation, federal regulations, state and local laws, written IRB procedures, OHRP guidance, and institutional policies relevant to the protection of human subjects. Training should be initiated before members review human subjects research and IRB duties should be commensurate with the level of training completed. Ongoing training should occur in a manner appropriate to assure the continued competence of IRB members.

Recommendation 2. SACHRP strongly recommends that OHRP require that institutions ensure that initial and continuing training is provided for **IRB staff**. Such training should include ethical principles and their historical foundation, federal regulations, state and local laws, written IRB procedures, OHRP guidance, and institutional policies relevant to the protection of human subjects. IRB duties should be commensurate with the level of training completed. Ongoing training should occur in a manner appropriate to assure the continued competence of IRB staff.

Recommendation 3. SACHRP strongly recommends that OHRP require that institutions ensure initial and continuing training for the **Institutional Signatory Official and the Human Protection Administrator** (e.g., Human Subjects Administrator or Human Subjects Contact Person). Such training should include ethical principles and their historical foundation, federal regulations, state and local laws, and institutional policies relevant to the protection of human subjects, and the terms of the institution's federal assurance. Ongoing training should occur in a manner appropriate to assure the continued competence of these institutional officials.

Recommendation 4. SACHRP strongly recommends that OHRP require that institutions ensure initial and continuing training for **investigators and other members of the research team with responsibility for conducting human subjects research**. Such training should include ethical principles and their historical foundation, federal regulations, state and local laws, professional standards, and institutional policies relevant to the protection of human subjects. Initial training should be completed before investigators are allowed to conduct research that involves human subjects. Ongoing training should

> occur in a manner appropriate to assure the continued competence of investigators.
> [emphasis in original]

We are disappointed that the ANPRM included no proposals to adopt these important SACHRP recommendations. In order to enhance the protections for subjects participating in greater than minimal risk research, the Common Rule should be revised to adopt these recommendations.

B. Specific Comments and Responses to Questions

(1) In section II (**Ensuring Risk-Based Protections**), B (*Calibrating the Levels of Review to the Level of Risk*), 2 (Revise Approach to Expedited Review), (a) (Eligibility for Expedited Review), iii (Determination That the Study Meets All of the 45 CFR 46.111 Criteria), HHS proposed the following:

> *Given that a study is eligible for expedited review only if it involves minimal risk, and only if its activities are limited to those that appear on the published list, it is not clear that the study should be required to meet all of the criteria for IRB approval at 45 CFR 46.111. Currently, before an IRB may approve a research study, including research that is being reviewed under an expedited procedure, the IRB must find that the following criteria have been satisfied as required by 45 CFR 46.111 … Accordingly, we are considering whether all of those criteria should still be required for approval of studies that qualify for expedited review, and if not, which ones should not be required.*

HHS provides no sound rationale for eliminating any of the criteria required for IRB approval under 45 CFR 46.111 for research undergoing expedited review, and we oppose the elimination of any of these requirements.

All of the criteria for IRB approval of research under 45 CFR 46.111 are appropriate for research eligible for expedited review. Furthermore, the current criteria for IRB approval already include language that allows appropriate flexibility when an IRB reviews research under an expedited review procedure. In particular, the criteria under 45 CFR 46.111(a)(4) and (5) permit waiver of the requirements for obtaining and documenting informed consent, respectively, if certain conditions are met, and the criteria under 45 CFR 46.111(a)(6) and (7) already begin with the conditional phrase “When appropriate,” thus allowing an IRB to determine that these two criteria are not necessary for IRB approval of research reviewed under an expedited review procedure or even by the convened IRB. Further exclusion of any of these criteria for research eligible for expedited review would inappropriately weaken protections for human subjects.

(2) In section II (**Ensuring Risk-Based Protections**), B (*Calibrating the Levels of Review to the Level of Risk*), 2 (Revise Approach to Expedited Review), (c)

(Streamlining Documentation Requirements for Expedited Studies), HHS proposed the following:

> *Under the current Federal regulations, researchers typically must submit the same documents including a detailed protocol, informed consent documents, and any other supporting documents, regardless of whether the study will be reviewed by a convened IRB or be approved by the expedited review process. Although it is important to document why research qualifies for expedited review, it is unclear whether the time and effort expended in such preparation activities result in increased benefit in terms of protecting subjects.*
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> *Ideally, standard templates for protocols and consent forms and sample versions of those documents that are specifically designed for use in the most common types of studies would facilitate expedited review. Such forms would need to be carefully designed to eliminate those elements that are of relevance only in studies that pose greater than minimal risks and to substantially reduce the current burden of researchers involved in producing these documents and of the IRB members who review them.*

HHS again fails to provide any rationale for this proposal. The purpose of IRB review under an expedited review procedure is not to document why the research qualifies for expedited review, but rather to ensure that the rights and welfare of subjects who will participate in the proposed research will be adequately protected. This is accomplished by the IRB reviewer ensuring that the research satisfies the criteria for approval under HHS regulations at 45 CFR 46.111, which requires a complete and well-written protocol and informed consent document.

Furthermore, the drafters of the ANPRM appear to be poorly informed about current IRB practice: most protocols submitted to IRBs for expedited review today generally are significantly shorter than research protocols requiring review by the convened IRB, because of the nature of the research.

Finally, given the extremely wide range and diversity of research that is, or would be, eligible for expedited review, the HHS proposal to develop standardized templates for protocols and consent forms is irrational and unworkable.

(3) HHS *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?*

The current definition of minimal risk is not appropriate. It should be revised as follows:

> *Minimal risk* means that 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 lives **of healthy individuals** or during the performance of routine physical or psychological examinations or tests **in healthy individuals**.

The current definition of minimal risk at 45 CFR 46.102(i) is ambiguous and creates a slippery slope that permits vulnerable individuals already suffering from serious diseases or disorders to be exposed to greater levels of risk — without corresponding increases in human subjects protections — than would be permitted for healthy subjects.

(4) HHS *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?*

If the proposal to eliminate some of the criteria for IRB approval of research under HHS regulations at 45 CFR 46.111 for research undergoing expedited review were implemented, there would *not* be assurance that subjects are adequately protected, as discussed in comment B(1) above.

(5) HHS *Question 4: Should the regulations be changed to indicate that IRBs should only consider "reasonably foreseeable risks or discomforts"?*

The ANPRM provides no context for why HHS is asking this question, nor any rationale for making such a change. Presumably, the question is being asked with respect to the following two criteria for IRB approval of research under HHS regulations at 45 CFR 46.111(a)(1) and (2):

- Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

For both criteria, the phrase "risks to subjects" is without any modifiers. For both criteria, this phrase should not be changed to "reasonably foreseeable risks or

discomforts to subjects" because doing so would substantially weaken protections for human subjects. In particular, the modifier "reasonably foreseeable" would create ambiguity and narrow the scope of risks that IRBs would consider in determining whether risks to subjects are minimized and reasonable in relation to anticipated benefits, if any, and the importance of knowledge that may reasonably be expected to result. Many IRBs likely would exclude from consideration risks of important, serious, but very low probability, harms if the threshold for considering risks were only those that were "reasonably foreseeable."

(6) HHS *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?*

SACHRP submitted recommendations to the Secretary of Health and Human Services that provided a clear and reasonable approach for IRBs to assess whether any type of risk is greater than or less than minimal. Their recommendations including the following steps:[3]

(a) The regulatory intent of minimal risk is to define a threshold of anticipated harm or discomfort associated with the research that is "acceptably-low" or "low enough" to justify expedited review or waiver of consent.

(b) The IRB's evaluation of the harms and discomforts of the research should consider the nature of the study procedures, other study characteristics, subject characteristics, and steps taken to minimize risk.

(c) In its estimate of research-related risk, the IRB should carefully consider the characteristics of subjects to be enrolled in the research including an evaluation of subject susceptibility, vulnerability, resilience and experience in relation to the anticipated harms and discomforts of research involvement.

(d) To satisfy the definition of minimal risk, the estimate of the anticipated harms and discomforts of the research for the proposed study population may not be greater than an estimate of "the harms and discomforts ordinarily encountered in daily life or during the performance of routine medical and psychological examinations or tests."

(e) While the harms and discomforts ordinarily encountered differ widely among individuals and individual populations, an ethically meaningful notion of "harms and discomforts ordinarily encountered" should reflect "background risks" that are familiar and part of the routine experience of life for "the average person" in the "general population." It should not be based on those ordinarily encountered in the daily lives of the proposed subjects of the research or any specific population. [Note that per comment B(3) above, we would substitute "in healthy individuals" for "the average person in the general population" in SACHRP's approach.]

(f) In summary, minimal risk should be applied in manner that recognizes that risks are procedure-specific and population-dependent, but that the notion of "acceptably-low" risk is fixed. When the harms and discomforts of the proposed research as they are anticipated to impact the study participants are judged to fall below this acceptably-low risk threshold, the research is said to be "minimal risk."

(7) HHS *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?*

With regard to the second part of question 6, of course IRBs must consider the characteristics of the expected study population when assessing risk of any research study, even when it involves survey procedures. The mental health and age of the expected subject population would be two of many factors that the IRB should take into consideration when doing its risk assessment for such research.

(8) HHS *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.*

Allergy skin testing, skin punch biopsies, and additional biopsy during a clinical test (such as an extra colonic biopsy during a routine colonoscopy) all would involve risks posing a greater probability and magnitude of harm or discomfort than those ordinarily encountered in the daily lives of healthy individuals or during the performance of routine physical or psychological examinations or tests in healthy individuals. Therefore, such procedures involve more than minimal risk and should not be included on the list of research procedures eligible for expedited IRB review.

(9) HHS *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?*

Prescribing through regulation a specific frequency for reviewing and updating the list of research activities that qualify for expedited review is unnecessary and would provide no additional protections for human subjects. Furthermore, HHS offers no evidence that the absence of such a regulatory provision has adversely impacted the protection of human subjects.

(10) HHS *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?*

As we stated in comment B(1) above, all of the current criteria for IRB approval of research under 45 CFR 46.111 should apply to research eligible for expedited review.

(11) HHS *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?*

Expedited review of human subjects research always should be conducted by an IRB member, and HHS offers no compelling reason for doing otherwise. Besides it being a statutory requirement that an IRB review and approve biomedical and behavioral research involving human subjects conducted or supported by HHS, maintaining expedited review within the sphere of the IRB appropriately centralizes the responsibility for reviewing and approving human subjects research within a well-defined authority that is easily identified and recognized by investigators, human subjects, and regulators. Furthermore, decentralizing the authority to conduct expedited review to individuals external to IRBs would create circumstances where the expedited reviewers are more likely to be subjected to inappropriate influence and pressure by investigators, institutional officials, and others. Such a proposal would weaken the protection of human subjects.

(12) HHS *Question 12: … 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?*

These questions again suggest that the drafters of the ANRPM are unfamiliar with the current text of the Common Rule, because the regulations do not prescribe any specific elements of information that must be included in research protocols. Thus, institutions already have great flexibility under the current regulations in determining what information must be included in protocols submitted to their IRBs.

The HHS regulations at 45 CFR 46.116(a) do specify the basic elements of informed consent that must be provided to each subject when consent is sought, unless these requirements have been appropriately waived by the IRB. For most research, each of these basic elements provides important information directly relevant to a

potential subject's decision to participate in research, and none of them should be eliminated from the regulations.

The HHS regulations at 45 CFR 46.115(a) require that investigators provide the IRB with copies of research proposals; scientific evaluations, if any, that accompany the proposals; sample consent forms; progress reports; and reports of injuries to subjects. The HHS regulations at 45 CFR 46.103(a) also require that investigators report to the IRB any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB. The requirement for investigators to submit all of these documents and reports should be retained.

Finally, given the extremely wide range and diversity of research that is, or would be, eligible for expedited review, the HHS proposal to develop standardized templates for protocols and consent forms is irrational and unworkable.

(13) In section II (**Ensuring Risk-Based Protections**), B (*Calibrating the Levels of Review to the Level of Risk*), 3 (Moving Away From the Concept of Exempt), (c) (Consent Rules for Excused Research), HHS proposed the following:

> *Second, with regard to the researchers' use of pre-existing data (i.e., data that were previously collected for purposes other than the currently proposed research study):*
>
> *… b. If the data was originally collected for research purposes, then consent would be required regardless of whether the researcher obtains identifiers. Note that this would be a change with regard to the current interpretation of the Common Rule in the case where the researcher does not obtain any identifiers. That is, the allowable current practice of telling the subjects, during the initial research consent, that the data they are providing will be used for one purpose, and then after stripping identifiers, allowing it to be used for a new purpose to which the subjects never consented, would not be allowed.* [emphasis in original]

We strongly endorse the proposed change because requiring informed consent in such circumstances would be more consistent with the basic ethical principle of respect for persons.

(14) In section II (**Ensuring Risk-Based Protections**), B (*Calibrating the Levels of Review to the Level of Risk*), 3 (Moving Away From the Concept of Exempt), (c) (Consent Rules for Excused Research), HHS noted the following in its discussion of research with biospecimens:

> *Participation in a research study (such as a clinical trial) could not be conditioned on agreeing to allow future open-ended research using a biospecimen.*

We strongly agree that participation in a clinical trial must not be conditioned on a subject's agreement to allow future open-ended research using biospecimens obtained from that subject because imposition of such a condition would constitute coercion to participate in the open-ended research using the biospecimens.

(15) HHS *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?*

Not only should HHS require a brief waiting period to provide an institution with the opportunity to review the registration form and confirm that the study is appropriately categorized as "Excused," the regulations should also include a requirement that such reviews be performed before the proposed research is initiated by an individual with appropriate training, expertise, and independence from the investigator.

(16) HHS *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 recommend that HHS adopt the term "registered" instead of the term "excused," since the former calls attention to the fact that some new requirements will still attach to these studies.

(17) HHS *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?*

Given the HHS proposal to expand the categories of research activities that would be considered excused or exempt, it is important that there be mechanisms in place to hold institutions and investigators accountable for making decisions regarding whether research appropriately qualifies for exempt or excused status. Requiring institutions to conduct retrospective audits of a minimum percentage of such research studies would be one appropriate mechanism for ensuring such accountability. Random and nonrandom mechanisms for selecting studies for audit would be useful. OHRP and other federal agencies also should plan to conduct periodic audits of such research studies.

(18) HHS *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? 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?*

For secondary research involving use of data or biospecimens that were originally collected with informed consent for another specific research purpose — regardless of whether the researcher obtains identifiers with the data or biospecimens — informed consent for the secondary research should be required, and it should not be permissible to waive informed consent for such research. For other research activities described in Section 3(a)(3) of the ANPRM, waiver of informed consent should be permissible provided the research satisfies the requirements of HHS regulations at 45 CFR 46.116(c) or (d). Requests for waivers of informed consent should be reviewed by the IRB.

(19) HHS *Question 24: The Common Rule has been criticized for inappropriately being applied to — and inhibiting research in — certain activities, including quality improvement, public health activities, and program evaluation studies. Regarding quality improvement, for example, these activities are in many instances conducted by health care and other organizations under clear legal authority to change internal operating procedures to increase safety or otherwise improve performance, often without the consent of staff or clients, followed by monitoring or evaluation of the effects. It is far from clear that the Common Rule was intended to apply to such activities, nor that having it apply produces any meaningful benefits to the public. Indeed, its application to such activities, and requiring IRB review and compliance with informed consent requirements, might have a chilling effect on the ability to learn from, and conduct, important types of innovation. 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 are aware that OHRP for years has expressed serious concerns to the senior leadership of HHS that many HHS agencies, including the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention, the Centers for Medicare and Medicaid Services, and the Substance Abuse and Mental Health Services Administration (SAMHSA), among others, repeatedly skirted the HHS regulations for the protection of human subjects by incorrectly determining that many activities conducted or supported by these agencies did not meet the definition of human subjects research or qualified for exemption. Many of these activities involved non-exempt human subjects research in the areas of public health, quality improvement, and program evaluation. The agency officials making these incorrect determinations frequently had conflicts of interest and were interested in reducing the regulatory burdens faced by their intramural or extramural researchers. For example, SAMHSA officials have repeatedly asserted that many research studies testing interventions for treating drug abuse did not involve non-exempt human subjects research, when in fact OHRP concluded otherwise.

HHS regulations at 45 CFR 46.101(d) define *research* as follows:

> *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for the purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Given this definition, the scope of activities covered by the Common Rule clearly was intended to be broad, and many public health, quality improvement, and program evaluation studies meet this definition, involve human subjects, and do not qualify for the current or proposed exempt/excused human subjects research activities. The fact that there is a legal mandate for institutions to conduct quality improvement or public health activities is not a sufficient argument for claiming that such activities, when they involve non-exempt human subjects research as defined by the regulations, do not involve research. We note that the National Institutes of Health (NIH) also is legally mandated to conduct and support human subjects research, but this does not exclude NIH human subjects research from the requirements of the Common Rule.

More importantly, many quality improvement and public health activities that meet the current definition of research involve interactions or interventions with human subjects that pose risks to subjects that are similar to the risks posed in clinical research. In addition, many quality improvement research activities involve manipulations of patients' medical care for research purposes in order to test a hypothesis or answer a scientific question.

Therefore, we strongly oppose any revision of the regulatory definition of research that would exclude those quality improvement, public health, and program evaluation activities that meet the current definition of non-exempt human subjects research.

Finally, with regard to quality improvement activities, not only would it not be useful to adopt the distinction made by the Health Insurance Portability and Accountability Act (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” — such action would be detrimental to the rights and welfare of human subjects involved in quality improvement research.

(20) HHS *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?*

HHS regulations at 45 CFR 46.109(d) currently stipulate the following:

> An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

This provision provides adequate opportunity for an investigator to understand and respond to an IRB’s decision to disapprove a proposed research study. Revising the regulations to require that every institution provide an appeal mechanism would undermine the IRB’s authority and weaken the protections for human subjects. Institutions that currently allow investigators whose proposed research is disapproved by one IRB to seek approval from another IRB are essentially promoting “IRB shopping.”

(21) In section III (**Streamlining IRB Review of Multi-Site Studies**), in arguing for regulatory changes that would promote review of multi-site studies by a single IRB, HHS notes the following:

> *Many commentators claim that multiple IRB reviews do not enhance the protection of human subjects and may, in fact, divert valuable resources from more detailed reviews of other studies. Relevant local contextual issues (e.g., investigator competence, site suitability) pertinent to most clinical studies can be addressed through mechanisms other than local IRB review. For research where local perspectives might be distinctly important (e.g., in relation to certain kinds of vulnerable populations targeted for recruitment) local IRB review could be limited to such consideration(s), but again, IRB review is not the only mechanism for addressing such issues. The evaluation of a study's social value, scientific validity, and risks and benefits, and the adequacy of the informed consent document and process generally do not require the unique perspective of a local IRB.*

Later in section III, HHS states the following:

> *This change [i.e., mandating that all domestic sites in a multi-site study rely upon a single IRB as their IRB of record for that study] is being considered only for domestic sites in multi-site studies. In most cases, independent local IRB reviews of international sites are appropriate because it might be difficult for an IRB in the U.S. to adequately evaluate local conditions in a foreign country that could play an important role in the ethical evaluation of the study.*

The HHS position that relevant local contextual issues pertinent to most clinical studies can be addressed through mechanisms other than local IRB review for any domestic site but not for foreign sites in multi-site studies is dangerously flawed. The drafters of the ANPRM appear to be ignorant about the tremendous diversity across the U.S. population in terms of cultural norms, community attitudes, race, ethnicity, spoken language, religion, educational level, and many other factors relevant to judging whether a research project is ethical and satisfies the requirements of the Common Rule. To assert that such local factors are not relevant to considerations made by IRBs for domestic sites in a multi-site study but are relevant to considerations made by IRBs for foreign sites is not a defensible position.

(22) HHS *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?*

One major disadvantage of this proposal is that it promotes the dangerous misconception that consideration of local context issues are important for IRBs at foreign sites but not for IRBs at domestic sites, as discussed in our prior comment, B(21).

Moreover, regardless of the regulatory language HHS might adopt to mandate one IRB of record for domestic multi-site research studies, HHS appears to have no legal authority to prohibit an institution from requiring review by its local IRB before allowing the research to proceed at that institution. Therefore, the regulatory changes being contemplated would have no practical impact on the status quo.

(23) HHS *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?*

HHS regulations at 45 CFR 46.103(d) require the following to be considered when the agency evaluates an assurance of compliance:

> The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, ... and the size and complexity of the institution.

HHS regulations at 45 CFR 46.107(a) require the following regarding IRB membership:

> The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects … the 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 and practice.

Furthermore, HHS regulations at 45 CFR 46.111(a)(3), 46.111(a)(4), 46.111(b), and 46.116 require that IRBs ensure the following criteria, among others, are satisfied before approving proposed research:

- Selection of subjects is equitable.
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

- Informed consent shall be sought in language understandable to the subject and under conditions that minimize the possibility of coercion or undue influence.

With respect to an IRB's knowledge of local context, OHRP's long-standing position has been the following:[4]

> Institutions have a profound responsibility to ensure that all IRBs designated under an [OHRP]-approved Assurance possess sufficient knowledge of the local research context to satisfy these requirements. This responsibility endures regardless of the IRB's geographic location relative to the institution and the research. It is particularly critical where the research involves greater than minimal risk to subjects or vulnerable categories of subjects.

The regulatory provisions and the OHRP policy position cited above clearly articulate the importance of an IRB, regardless of location, taking into account local factors when reviewing proposed research. The consideration of these local factors has direct relevance to how well subjects will be protected. Under the HHS proposal mandating that all domestic sites in a multi-site study rely upon a single IRB, a single IRB composed of five members could convene a meeting of three members and review and approve a complex multi-site clinical trial involving several hundreds of sites across the U.S. with two members voting for approval.

Given the diversity of the U.S. population, it is impossible for a single IRB — even one composed of many more than five members — to have sufficient knowledge of the local research context at all study sites involved in a large multi-site study and satisfy the regulatory requirements cited above.

The public clearly should be concerned that a centralized IRB reviewing a multi-site study will not have adequate knowledge of the many institutions' specific perspectives or the needs of their populations and that a centralized IRB may not share each institution's views or interpretations on ethical issues. The mandate proposed by HHS likely would adversely impact the protection of human subjects without additional clearly specified regulatory requirements that adequately address local context issues for each institution.

(24) HHS *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?*

Assuming HHS can address concerns regarding how to ensure adequate consideration of local contextual issues by an IRB for all sites participating in a multi-site study, the process for selection of a single IRB of record must include safeguards for preventing IRB shopping. One mechanism to prohibit shopping in the initial selection of an IRB would be to require the selected IRB to be at the institution that is either (a) the primary awardee on the grant, contract, or cooperative

agreement funding the study; (b) the employer of the overall principle investigator for the study; or (c) the coordinating site for the study.

In addition, measures should be taken to prohibit subsequent IRB shopping if the initial IRB disapproves a multi-site study protocol. This would be best accomplished by prohibiting submission of the same protocol – with or without revisions – to a second IRB after disapproval by the designated IRB of record.

Furthermore, whenever any IRB – whether the IRB of record or other IRB – disapproves a multi-site study, information regarding the IRB's disapproval, including the reasons for the disapproval, should be disseminated to all study sites for the proposed research, reported to OHRP and the federal agency funding the research, and posted on a publicly available website, such as ClinicalTrials.gov. At a bare minimum, if the regulations fail to prohibit submission of the same protocol to a subsequent IRB after disapproval by the designated IRB of record, the overall principal investigator for the study must be required to report the disapproval and the reasons for it to the new IRB in its subsequent submission.

(25) In section IV (**Improving Informed Consent**), HHS notes the following in its discussion of informed consent issues:

> *In addition, consent forms may frequently fail to include some of the most important pieces of information that a person would need in order to make an "enlightened decision" (to quote the Nuremberg Code) to enroll in a research study. Instead of presenting the information in a way that is most helpful to prospective subjects — such as explaining why someone might want to choose not to enroll — the forms often function as sales documents, instead of as genuine aids to good decision-making.*

We agree with HHS's comment. Too often, the informed consent process for research, particularly clinical trials, fails to provide sufficient information regarding the procedures involved in the research, research risks, alternatives to participation in the research that may be advantageous to the subjects, and how these alternatives compare to the procedures the subject will undergo in the research.

(26) In section IV (**Improving Informed Consent**), HHS also notes the following in its discussion of informed consent issues:

> *While the regulations have changed in only relatively modest ways since 1974, the average length of consent forms has been increasing since then, and the forms have become excessively long and legalistic, even for relatively routine and low risk research studies. For example, it is not uncommon for the documents to stretch to 15 or even 30 pages in length. Moreover, studies have shown that the reading level of many of these documents is above the desired 8th grade level. Length and high reading levels may inhibit people from reading the full document and from understanding relevant information.*

The number of pages of consent forms is not a useful measure for evaluating the adequacy of informed consent, nor does an increasing number of pages of consent documents indicate a problem. For example, there are many reasonable explanations for why informed consent documents have increased in page length over the past several decades, including the following:

- Many IRBs have required increases in the consent form font size, margins, and spacing in an effort to improve readability.
- Reducing the complexity of a consent form to a lower grade level, also required by many IRBs, generally necessitates using more words to explain complex topics.
- The complexity of research, particularly clinical trials, has increased over the past several decades, resulting in the need to convey more information in order for the consent process to be adequate.

We believe that anecdotal complaints about the length of consent forms, as measured by number of pages, are not sufficient evidence of a problem with informed consent. The average length of consent forms (in terms of number of words) would be a more appropriate parameter for assessing consent form length, but HHS appears to have no empirical data addressing the change in this parameter over time. Even if data existed showing an increase in consent form length as measured by word count, there are reasonable explanations for such a trend, as discussed above.

Investigators have the ultimate responsibility for ensuring that potential subjects fully understand all aspects of the proposed research. Asking subjects to read a consent form, regardless of length, for many research studies would not constitute adequate informed consent. Adequate informed consent, particularly for complex clinical trials, may require hours of discussion between the investigator and the potential subject. The consent form is just one component of a rigorous and meaningful consent process.

(27) In section IV (**Improving Informed Consent**), A (*Improving Consent Forms),* HHS indicates that it is considering the following modifications to the regulations to improve consent forms:

> *(1) prescribing appropriate content that must be included in consent forms, with greater specificity than is provided in the current regulations; (2) restricting content that would be inappropriate to include in consent forms; (3) limiting the acceptable length of various sections of a consent form; (4) prescribing how information should be presented in consent forms, such as information that should be included at the very beginning of the consent form, or types of information that should be included in appendices and not in the main body of the consent form; (5) reducing institutional "boilerplate" in consent forms (that is, standard language that does little to genuinely inform subjects, and often is intended to primarily protect institutions from lawsuits);*

> *and (6) making available standardized consent form templates, the use of which could satisfy applicable regulatory provisions.*
> [emphasis in original]

Most of the modifications proposed by HHS are either unnecessary or will be detrimental to the protection of human subjects. The current elements of informed consent required under HHS regulations at 45 CFR 46.116(a) and (b) provide appropriate detail and address the key elements of consent that need to be covered when obtaining a subject's consent. Given the wide range and diversity of human subjects research, attempting to prescribe content with greater specificity and prohibit certain content deemed to be inappropriate for all research would be foolhardy. Likewise, limiting the length of certain sections of consent forms for all research is a ridiculous proposal; for each individual study, each section of the consent form should be as long as needed to provide the appropriate information to potential subjects.

For most institutions, boilerplate language in consent forms constitutes a minority of consent form content and HHS is not well positioned to judge whether any particular boilerplate language is appropriate or not. Finally, given the wide range and diversity of research studies being conducted, it is not feasible for HHS itself to create standardized consent form templates that would provide adequate informed consent. Such templates ultimately would be so skeletal that they would be useless.

These proposals would weaken the protections for human subjects and should be abandoned.

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

As discussed in our comment B(26) above, the premise that consent forms are excessively long has not been well established by HHS, and there are many reasonable explanations for why some consent forms need to be long.

Regarding excessive complexity in consent forms, in most cases, this results from IRBs approving consent forms that include overly complex terminology, complex sentence and paragraph structure, and poor organization. In many cases, addressing such complexity requires longer consent forms.

(29) HHS *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*?

For clinical trials where the interventions being tested in the research are available to patients outside the research study, the regulatory provision regarding alternatives to

participation in research should explicitly require that subjects be told of such availability and the reasons why not participating in the research may be more advantageous to them.

There should be no deletions of the other elements of informed consent required under the current regulations.

(30) HHS *Question 37: Would the contemplated modifications improve the quality of consent forms?*

Per our comment B(27) above, the contemplated modifications to consent forms would weaken the protections for human subjects and should be abandoned.

(31) HHS *Question 38: Should the regulations require that, for certain types of studies, investigators assess how well potential research subjects comprehend the information provided to them before they are allowed to sign the consent form?*

For research involving more than minimal risk, particularly clinical trials, investigators have an ethical obligation to ensure that potential subjects understand all the information provided under the required elements of informed consent before allowing them to enroll in the research study. Regulatory provisions requiring investigators to ensure such comprehension before subject enrollment should be added to the regulations.

(32) HHS *Question 40: Would informed consent be improved if the regulations included additional requirements regarding the consent process, and if so, what should be required? For example, should investigators be required to disclose in consent forms certain information about the financial relationships they have with study sponsors?*

We would endorse a requirement for investigators to disclose to subjects information regarding the financial relationships they have with study sponsors. Such transparency would allow subjects to make better informed judgments about participation in research.

(33) In section IV (**Improving Informed Consent**), B (*Waiver of Informed Consent or Documentation of Informed Consent in Primary Data Collection*), HHS stated the following regarding waiver of the requirements for documentation of informed consent:

> *IRBs, under the Common Rule (45 CFR 46.117(c)), also may waive the requirement for the investigator to obtain a signed consent form for some or all subjects. The current criteria for such a waiver may not be flexible enough for dealing with a variety of circumstances, such as when Federally-sponsored research is conducted in an international setting where for cultural or historical reasons signing documents may be viewed as offensive and problematic.*

There have been numerous reports, particularly in foreign countries, of subjects being enrolled in research without their knowledge, let alone their consent. In many such cases, the absence of consent forms signed by the subjects corroborated subjects' claims that their consent had not been obtained by the investigators. Thus, the requirement for investigators to document subjects' informed consent, particularly for greater than minimal risk research, is an essential protection for subjects.

If HHS plans to expand the circumstances under which the requirement for documentation of informed consent with a signed consent can be waived, such circumstances should be extremely limited, and an alternate procedure for documenting that the subjects' informed consent was appropriately obtained should be required. For example, the regulations could require that the consent process for each subject be documented by a videotape of the complete consent discussion between the investigator and the subject and that copies of the videotape be provided to the subjects and retained by the investigator.

(34) HHS *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? If some elements should not be required for oral consent, which ones are unnecessary?*

In circumstances where the regulations permit oral consent, the same elements of informed consent required under HHS regulations at 45 CFR 46.116(a) and (b) should be provided to the subjects.

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

See our comment B(33) above.

(36) HHS *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 support implementation of the use of a standardized, general consent form to permit future unspecified research on biospecimens and data that includes tiered options for excluding consent for certain research that the subject would find objectionable. Public education campaigns combined with a notification and opt-out process are likely to be ineffective in reaching substantial proportions of the potential subject population and therefore would not be an appropriate option.

(37) HHS *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?*

The best method for providing individuals with a meaningful opportunity to choose not to consent to certain types of future research would be to use a consent process that includes tiered options for excluding consent for certain research that the subject would find objectionable. Individuals also should have the option of identifying additional categories of research that they would not allow on their data or specimens.

(38) HHS *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 same requirements for obtaining consent for research with biospecimens should apply regardless of where the biospecimens are collected. There is no good ethical justification for doing otherwise.

(39) In section V (**Strengthening Data Protections To Minimize Informational Risks**), HHS proposes the following:

> *As noted above (Section II(A)), a solution we are considering is to mandate data security and information protection standards that would apply to all research that collected, stored, analyzed or otherwise reused identifiable or potentially identifiable information. This would include research with biospecimens, survey data, and research using administrative records as well as secondary analysis of the data. However, we are considering applying these new protections only to prospective collections of data and biospecimens after the implementation of any changes to the Common Rule and not retrospectively to research involving existing data, including stored biospecimens and their subsequent analysis. Further, it is envisioned that these data security and information protection standards would be scaled appropriately to the level of identifiability of the data.*

We endorse the proposal to mandate data security and information protection standards that would apply to all research involving the collection, storage, analysis,

or other reuse identifiable or potentially identifiable information or biospecimens. These standards should apply to any research ongoing when the changes to the Common Rule are implemented and at any time thereafter, regardless of when the specimens and data were initially collected.

We also agree that the data security and information protection standards should be scaled appropriately to the level of identifiability of the data.

(40) HHS *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. How should Federal regulations manage the risks associated with the possibility of identification of such biospecimens? 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?*

The federal regulations should manage the risks associated with the possible identification of biospecimens by uniformly considering all biospecimens to be identifiable and implementing appropriate data security and information protection standards for all research involving biospecimens. The advantage of considering all future research with biospecimens to be research with identifiable information is that the privacy and confidentiality of the individuals from whom those biospecimens were obtained will be adequately protected.

(41) HHS *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? How should the new standards be enforced?*

Yes, the new data security and information protection standards should apply to all research involving data and biospecimens, regardless of when the data and biospecimens were collected. Such a uniform application of the standards will avoid massive confusion regarding which data and specimens are covered by the new standards and which are not.

These new standards should be enforced by periodic random audits of research studies using data and biospecimens and by civil monetary penalties for intentional or unintentional violations of the standards, similar to the penalties imposed for violations of the HIPAA Privacy Rule (45 CFR Part160 and 45 CFR Part164, Subparts A and E).

(42) HHS *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)?

The same standardized data security and information protection requirements should apply to all types of human subjects research.

(43) HHS *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?*

Yes, there should be an absolute prohibition against re-identifying de-identified data.

(44) HHS *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?*

Yes, such registration should be required.

(45) HHS *Question 68a: With regard to data reported to the Federal government, 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?*

Yes, the number of participants in federally funded human subjects research should be reported to the federal government. This could easily be accomplished by including a field for such information for trials registered on the ClinicalTrials.gov website.

(46) HHS *Question 68b: With regard to data reported to the Federal government, 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?*

All deaths and serious adverse events, as defined by FDA regulations, occurring in subjects enrolled in research conducted or supported by the federal government should be reported to the federal government.

(47) HHS *Question 68c: With regard to data reported to the Federal government, 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?*

The requirements referenced in questions 68a and 68b should apply to all types of non-exempt or non-excused (or non-registered) human subjects research.

(48) HHS *Question 69: There are a variety of possible ways to support an empiric approach to optimizing human subjects protections. Toward that end, is it desirable to have all data on adverse events and unanticipated problems collected in a central database accessible by all pertinent Federal agencies?*

Yes, all data on adverse events and unanticipated problems occurring in subjects enrolled in human subjects research conducted or supported by the federal government and clinical trials regulated by the FDA should be collected in a central database accessible by all pertinent federal agencies.

Moreover, this data, at the level of individual subjects, should be accessible to members of the public in a format that is easily searchable, with redaction of subject identifiers.

(49) HHS *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?*

No, access to information on individual studies provided by the ClinicalTrials.gov database is not sufficiently comprehensive or timely for the purposes of informing the public about the overall safety of all research with human participants.

Our informal review of a non-random sample of clinical trials posted on ClinicalTrials.gov found that trial results were posted for less than 15% of all completed industry-sponsored clinical trials posted between January 1, 2006, and January 1, 2011. Moreover, the amount and quality of information posted varies greatly by trial. The ClinicalTrials.gov entries often contain sparse protocol descriptions that fail to describe protections for human subjects. The regulations should be revised to include specific requirements for reporting trial results, rather than simply requiring summary results. The Common Rule should be amended to require that investigators post detailed trial protocols and sample informed consent documents on ClinicalTrials.gov.

See also our response to the preceding question.

(50) HHS *Question 71: Should the applicability of the Common Rule be extended to all research that is <u>not</u> Federally funded that is being conducted at a domestic institution that receives some Federal funding for research with human subjects from a Common Rule agency?* [emphasis in original]

Yes, the applicability of the Common Rule should be extended to all research that is not federally funded that is being conducted at a domestic institution that receives

some federal funding for research with human subjects from a Common Rule agency. Such a change is long overdue.

(51) In section IX (**Agency Request for Information**), HHS invited general comments on the current system of protections for human research subjects. We therefore offer the following additional recommendations:

- The Common Rule should be modified to include civil monetary penalties for violations of any provisions of the Common Rule.
- The Common Rule should include additional provisions to ensure that IRB members have appropriate knowledge and expertise regarding the research reviewed by the IRB, and that investigators provide the IRB with all relevant information regarding the interventions to be studied in proposed research studies. Too often, IRB members lack up-to-date knowledge and relevant expertise necessary for the IRB to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. Likewise, investigators frequently withhold information that is relevant to these determinations and that might lead the IRB to disapprove the research. As a result, human subjects are frequently enrolled in research that is unethical and places them at risk of unnecessary harm. For example, IRBs frequently approve research that involves inappropriate randomization of subjects who have serious illnesses to placebo groups that are denied standard treatments proven to be effective.
- The Common Rule should include a requirement that all non-exempt and non-excused human subjects research be registered in the ClinicalTrial.gov database.
- The Common Rule should include a requirement that once federally funded human subjects research is approved by an IRB, the IRB-approved consent form must be posted on a centralized, online database accessible to the public, such as the ClinicalTrials.gov database. This would improve transparency for the public and better inform the public about the types of human subjects research projects being funded by the federal government.
- The provision under HHS regulations at 45 CFR 46.101(h) allowing a department or agency head to approve the substitution of procedures normally followed in foreign countries to protect human subjects in lieu of the procedures required under the Common Rule should be eliminated. This provision creates an unacceptable double standard for the protection of human subjects in research conducted in foreign countries supported by the U.S. government.

Thank you for the opportunity to comment and for taking our comments into consideration.

Sincerely,

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cc: Dr. Jerry Menikoff, Director, Office for Human Research Protections

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