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October 25, 2011

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Department of Health and Human Services
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Submitted electronically at www.regulations.gov

Re: Docket Number HHS-OPHS-2011-0005, Advanced Notice of Proposed Rulemaking concerning *Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators,* published in the July 26, 2011 *Federal Register* (76 FR 44512)

Dear Dr. Menikoff:

The Association of American Medical Colleges (AAMC) is pleased to have this opportunity to comment on the Advance Notice of Proposed Rulemaking (ANPRM), entitled *Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators*, issued by the Department of Health and Human Services (HHS) and the Office of Science and Technology Policy (OSTP).

The Association of American Medical Colleges (AAMC) is a not-for-profit organization representing all 135 accredited U.S. and 17 accredited Canadian medical schools; nearly 400 major teaching hospitals and health systems, including 62 Department of Veterans Affairs medical centers; and nearly 90 academic and scientific societies. Through these institutions and organizations, the AAMC represents 128,000 faculty members, 75,000 medical students, and 110,000 resident physicians.

AAMC congratulates HHS and OSTP on the decision to take a bold approach to rethinking the regulation of human subjects research. This ANPRM represents a substantial effort and demonstrates an understanding that the current system as codified in the Common Rule (45 CFR Part 46, Subpart A) does not always serve to best protect human subjects, and is not easily applied to a research system that has changed significantly in breadth, approach, technology, and

complexity in the more than 20 years since the Common Rule was adopted by HHS and 14 other Federal departments and agencies.

AAMC is appreciative that HHS chose to provide the public and the research community advance notice not only of the intention to revise the Common Rule, but also of specific proposals that institutions, institutional review boards (IRBs), and investigators can consider and address. This decision has resulted in robust discussions throughout the research community, not only about the merits and challenges of implementing the proposals as set forth in the ANPRM, but also about the appropriate roles of the federal government, institutions, and investigators in protecting human subjects.

I. General Comments

The stated goals behind the ANPRM's proposals are to (i) "better protect human subjects who are involved in research" while (ii) "facilitating valuable research and reducing burden, delay, and ambiguity for investigators." The AAMC understands the second goal to include the development of a system that affirmatively advances the research enterprise and that minimizes unnecessary burden on investigators and the institutions at which the investigators conduct research. The ANPRM implicitly recognizes that these aims should not be at odds, and that facilitating a robust, ethical research system and culture necessarily requires simultaneous consideration of both goals. By better calibrating the level of review to the risks posed by research, we can both better protect subjects and reduce burdens on investigators and institutions by focusing resources where they are most effective.

We commend to HHS the many detailed letters submitted by academic medical centers and teaching hospitals in response to this ANPRM. These institutions have invaluable experience in implementing and ensuring compliance with the Common Rule and a practical understanding of the potential effects or unintended consequences of the proposed changes on the subjects they protect, the investigators who carry out research, and the administrative structures that support and enable the conduct of research.

Several of the proposals in the ANPRM suggest promising concepts, but require significant additional study before being mandated or incorporated into the federal regulatory framework. It is our hope that this rulemaking process is indicative of a thoughtful, stepwise course of action, and that the finalized regulatory changes will clearly incorporate areas of flexibility that can be used to accomplish both aims of the ANPRM. Further, AAMC hopes that the process of evaluating the Common Rule and assessing its effect on the protection of human subjects and on the conduct of research will become a more routine occurrence. In the face of rapidly evolving technology, research methods, discoveries, and scientific understanding, it is no surprise that the

Common Rule needs significant revisions after two decades. While the proposed revisions to the Common Rule should allow for flexibility to address emerging research methods and study design, HHS should take accountability for a regular, rigorous evaluation of the effect and effectiveness of the regulations in accomplishing the two stated goals. While there is a need for clarity and the establishment of appropriate protection standards in the regulations, AAMC suggests that the Department consider addressing some of the identified concerns through guidance and not by increasing the complexity or proscriptive nature of the regulations.

The ANPRM has identified seven broad concerns related to the Common Rule, and presented 74 related questions. AAMC has structured this response letter to address each of the proposals in the seven sections and to reference the specific questions as appropriate. We have addressed those proposals that we believe are ripe for inclusion in revisions to the Common Rule, those that require further study or consideration before being incorporated into regulations, and those that AAMC does not believe should be adopted or implemented as proposed. Many of the elements proposed are interdependent, and the support of one element may depend on the adoption or abandonment of another. We recognize that the ANPRM is presented as a comprehensive proposal for significant changes to the Common Rule, but hope that in light of comments received from the research community, each suggested change will be considered independently for its likely impact on subjects, investigators, and institutions.

II. Ensuring Risk Based Protections

AAMC agrees that a regulatory system that better calibrates the review requirements with the risks of participating in a research study can accomplish both the goals of protecting subjects and reducing burden in the system as a whole. To further this aim, the ANPRM presents five broad proposals: (1) standardizing data security standards based on the identifiability of the research data collected; (2) revising rules for continuing review; (3) updating the categories of research that may undergo expedited review; (4) revising the regulations regarding exempt studies; and (5) requiring written consent for research use of all biospecimens collected for clinical purposes.

Many of the proposed calibration efforts are tied to a determination of whether a particular study is considered *minimal risk*. AAMC notes that the success of any proposal to better calibrate the review level to risks thus depends on a concrete definition of minimal risk. The current definition, which requires an IRB to compare the "probability and magnitude of harm or discomfort anticipated in the research" with "those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests," has not been applied consistently. Consistent with the recommendations proposed by the Secretary's Advisory Committee on Human Research Protections, AAMC suggests that the definition be revised to clarify that (i) the harms or discomforts considered should be those presented by the research

itself, not those anticipated to be experienced by subjects during the timeframe in which the research will be conducted, and (ii) that activities and experiences "ordinarily encountered" by research subjects should not differ based on the characteristics of the subjects themselves or any specific community. For example, review of the "harms and discomforts" of a proposal to study patients who are undergoing chemotherapy should (i) consider the potential effects of the research activity itself, not the risks of the chemotherapy being administered or other medical examinations and procedures undergone, and (ii) compare the research activities proposed with those experienced in the daily life of a healthy individual in the general population, not with the examinations or procedures that become routine for a cancer patient. [*Question 1*]

1. Standardizing Data Security Processes

The ANPRM proposes the creation of a separate review process for "informational risks," those that "derive from the inappropriate use or disclosure of information, which could be harmful to the study subjects or groups." Under this proposal, an IRB would no longer consider informational risks in the assessment of the protocol, but standard data protection requirements would apply to all research and the IRB would not assess the adequacy of the data security. The presumption inherent in the ANPRM is that all informational risks are equivalent. Despite the acknowledgement in the ANPRM that "informational risks are correlated with the nature of the information and the degree of identifiability of the information," the proposal seeks to calibrate the level of required protection to the level of identifiability of the data alone. This assumption does not address the complexity in research and variations in data sensitivity and suggests, for example, that greater data security standards might be applied for an undergraduate class survey on transportation preferences where students were readily identified than for research involving medical records related to HIV status or criminal records if most identifiers were removed.

Although AAMC supports the appropriate protection of sensitive personal data, we suggest that efforts to standardize the approach to informational risks incorporate a level of flexibility to address instances when minimum data protection efforts are insufficient or when the risks associated with the identification of subjects are particularly high. We recommend the development of a tiered structure for data protection and that IRBs are given the authority to determine which standard must be applied to the study, with certain default presumptions. This would incorporate the necessary flexibility to provide additional protections based on the nature of the data, but would address the goal of lessening the burden on IRBs to assess without regulatory guidance whether each protocol has proposed the appropriate data security protections. For example, the regulations could set forth definitions for Minimal, Moderate, and High Security data protection standards and then indicate which types of research should typically be assigned to each tier of protection. This would remove the decision making about informational risks from most IRB reviews and would set forth data security expectations for

investigators, but would allow an IRB to require more stringent data protection methods if needed to protect subjects.

AAMC agrees that there is a need to improve the protection of data associated with research. We recognize that concerns related to data security and information have received national attention in the wake of revelations regarding significant breaches of personal and identifiable data. We do not believe, however, that the HIPAA Security Rule standards are the appropriate model to adopt. The HIPAA Security Rule has broader implications and purposes than the protection of data from disclosure, and many standards such as the HITECH breach notification standards would be onerous to implement across all research. We note that if the research data that have been compromised is from a HIPAA covered entity and relates to protected health information, such a breach would already be covered by HIPAA and the Security Rule would apply. [*Question 59*]

As further described in Section V of this letter, AAMC does not recommend that the definitions from the HIPAA Privacy Rule be used in the Common Rule. The HIPAA definitions have significant drawbacks in the research context that hinder the conduct of research without providing commensurate benefit or increases in the protection of human subjects.

2. Revising Rules for Continuing Review

AAMC recognizes the burden placed on institutions and investigators to conduct continuing review of studies that pose little risk to human subjects, either because of the nature of the initial research, or because the research is closed to further subject enrollment or limited to follow up or data analysis. We strongly support the proposals to eliminate routine mandatory annual continuing review for research that qualifies for the expedited review process. [*Question 2*]. In addition, AAMC supports the proposal that routine annual continuing review could be eliminated for research posing greater than minimal risk once all remaining activities would be eligible for expedited review or would be exempt from the regulations. [*Question 3*] Critical to the success of this revision is the ability for an IRB to determine when more frequent review is necessary to protect human subjects. In addition, the regulations and accompanying guidance must allow IRBs to decide readily and consistently when research has reached the threshold of eligibility for decreased continuing review requirements, so that the current standard of annual review is not maintained simply due to a lack of clarity about the requirements.

3. Revising the Approach to Expedited Review

The ANPRM proposes three changes to the system for reviewing research through an "expedited" process: (1) updating the list of research activities that may undergo expedited

review; (2) creating a default presumption that a research study that includes only activities on the list is a minimal risk study eligible for expedited review; and (3) rethinking whether expedited studies must meet all eight criteria at 45 CFR 46.111. In addition, the ANPRM proposes eliminating default continuing review requirements and documentation requirements for expedited review studies.

The proposals as a whole could reduce the administrative burdens related to the review of studies deemed eligible for expedited review without diminishing protections for human subjects, and AAMC supports the movement in this direction. We encourage the development of regulations that clearly provide an IRB flexibility to modify or waive certain criteria required for expedited review (e.g. through the use of phrases such as "when appropriate"). AAMC also supports the proposal to review and update the list of research activities eligible for expedited review. [*Question 9*]

One of the fundamental premises of the ethical protection of human subjects is the IRB's ability to impose additional requirements or review mechanisms to address specific risks or to protect vulnerable populations or subjects. Requiring an institution to report to OHRP cases in which an IRB has gone beyond the requirements of the regulations or has overridden the default requirements of the regulations to provide additional protections or review steps may not provide OHRP with meaningful information, significantly increases the burden associated with that study, and, most importantly, may create a disincentive for IRBs to override the defaults when it is warranted. OHRP could clarify its expectations by issuing guidance assuring IRBs and institutions that OHRP considers the default requirements to be adequate protections in most cases, absent some other unexpected circumstance. [*Question 13*]

4. Revising the Regulations Regarding Exempt Studies

Under the current regulations and related guidance, activities that fall into one of six categories may be considered "exempt" from the Common Rule and do not require further IRB review. The determination that research meets the criteria for exemption is typically made by a member of the institution's human research protection program. The ANPRM proposes that this framework be substantially revised to eliminate exempt categories and establish "excused" categories of research, which would not be subject to further review under the Common Rule, but would be "registered" with the IRB before the research begins and subject to the data protection standards discussed elsewhere in this letter. AAMC appreciates that IRBs currently spend significant time making determinations of minimal risk and assessing whether research is exempt, but has concerns about the implementation of the ANPRM's proposals.

The ANPRM proposes to shift the decision-making process for determining whether a research study is *excused* from an IRB member to the investigator. AAMC is concerned that this may not accomplish either of the two goals of the ANPRM. Even with clear definitions and guidance, the potential for an investigator to err or misclassify research as *excused* when it should have been reviewed by an IRB remains. Without a clear delineation of responsibility between the investigator and the institution, concerns about institutional responsibility for such errors could easily lead to another review system, in which institutions require the review of all registered studies before research can begin, a system that closely mirrors the current process for determining whether a study is exempt. The ANPRM proposal positions IRBs against investigators, giving the former administrative, review, and audit responsibilities, yet allowing the latter to make decisions without mandated oversight. AAMC recommends that any revisions to the Common Rule delineate specific responsibilities and accountability for investigators as well as institutions. While the refinement of process, criteria, and categories related to exempt studies is warranted and welcome, the concept of exempting certain research from additional regulation should be retained. Should the new categories of excused or registered research be adopted, we recommend a mandatory waiting period to allow institutional review of the filed registrations. [*Question 19*]

Mandating audits of *excused* research after the research has been initiated or completed does not provide additional protections for subjects and serves to increase burdens on investigators, IRB staff, and institutions. Ongoing review of the research activities taking place at an institution is an integral part of a robust research compliance program, but it is not evident how such audits of *excused* research would be conducted, what responsibilities institutions would have after finding problems with the research registration or conduct, and what benefit they would provide if incorporated into the regulations. Each institution should be free to design the quality assurance and research management systems that are most appropriate for its research portfolio, without being encumbered by proscriptive regulations. AAMC urges that the regulations not include required audits of research deemed to be of no more than minimal risk. [*Question 21, 22*]

The expansion of categories of research that qualify for treatment as exempt or excused can decrease burdens on investigators and institutions. Such expansions should be done thoughtfully, with input from experts in the proposed fields of inclusion. AAMC supports the creation of a category to include other critical research that poses no more than minimal risk to subjects. In addition to certain types of social and behavioral research, we recommend that the category include certain quality, health care delivery, public health, and implementation science research. [*Question 15, 24*]

Regardless of how the proposed rules address the areas of minimal risk and exemption, we do not recommend that the term *excused* be used, as it connotes an exception granted from the rules,

as opposed to research deemed to be of low enough risk to not require additional human subject protections. Other comments have proposed "registered" as an acceptable alternative term if the *exempt* category of research is eliminated. [*Question 20*]

5. *Requiring written consent for research use of all biospecimens collected for clinical purposes*

As part of its general description of the proposed move from *exempt* to *excused*, the ANPRM offers specific examples of how it intends the shift to affect existing exempt categories, including the current exemption of certain research involving the use of existing data or biospecimens ("Category 4"; 45 CFR 46.101(b)(4)). We discuss our response to this specific proposal below, as it relates to the proposal to require broad prospective consent for this type of research. In sum, we object to a re-imagining of Category 4 as a new *excused* category for many of the reasons that we object generally to the proposal to move entirely "away from the concept of exempt." With regard to data and biospecimen research where the identity of the source of the information or materials cannot readily be ascertained, we believe that increasing the requirements on such research through the conditions associated with the new proposed *excused* category unnecessarily burdens important research with administrative requirements that do not meaningfully add protection to the individuals from whom such information and materials derive. This research has historically been outside both the definition of human subjects research and the regulatory requirements for activities that qualify as human subject research. Increasing the requirements for such research is contrary to the ANPRM's stated goal of appropriately calibrating the level of review and oversight to the level of risk presented by the research in order to facilitate important research while appropriately protecting human participants. For research on identifiable data and biospecimens, we explain further in Section IV why the current system of protections and waivers works appropriately to balance the protection afforded to subjects' identifiable information against the burden imposed on researchers and the research-review system. Although AAMC would support the slight broadening of the current exemption to encompass certain research involving identifiable data and biospecimens not in existence at the time the research is proposed, this would be conditioned on the protections to ensure that data and biospecimens are not misused.

III. Streamlining IRB Review of Multi-Site Studies

The use of a single IRB of record for multi-site studies has the potential to decrease burden, standardize protections, and reduce delays in approval processes. The ANPRM proposes that a single IRB of record be mandated for all multi-site, domestic trials. AAMC supports the establishment of a regulatory framework that promotes and facilitates the adoption of single IRB review for multi-site studies. Regular use of a single IRB of record in large multi-site trials

could accomplish both goals of the ANPRM if certain considerations, guidance, and clarifications are in place prior to the effective date of such a requirement.

This is an area of great promise, but the process to move towards a mandated single IRB of record needs to be deliberate and thoughtful. AAMC urges OHRP to engage in further discussions on this proposal before new regulations are drafted to identify more clearly the specific elements that would lead to the successful implementation of single IRB reviews without the development of "shadow" local review systems designed to protect against real or perceived institutional liability or risk of enforcement actions. We note that no change is needed in the Common Rule to allow single IRB review of multi-site trials and that the lack of adequate guidance, the history of enforcement actions against institutions that had delegated IRB review to another entity, and uncertainty about the responsibilities of an institution versus an IRB of record have created an environment in which there is substantial hesitation to adopt what could be a successful model. Questions of how the IRB of record would be funded and overseen by OHRP, and how the interactions between local IRBs and the IRB of record will be managed need to be resolved. At least four areas of concern must be properly addressed in any proposed regulations before AAMC can fully endorse adoption of a mandated single IRB of record: (1) the definition of multi-site trial, (2) the IRB selection methodology; (3) clear definition of roles and responsibilities; and (4) the consideration of local context.

1. *Application and definition of Multi-Site Trials*

The establishment of single IRBs of record has been used successfully in several contexts and is currently encouraged or required by the VA system, many industry sponsors, the National Cancer Institute, and the FDA, with respect to multi-site clinical trials under its jurisdiction. Such efforts have not been without some challenges, and AAMC suggests that the experiences and lessons learned by entities involved in those multi-site studies be considered in drafting regulations that would accompany such a mandate. The mandate should not necessarily apply to studies in all disciplines or to all research that takes place at more than one site. As an initial approach, accompanying guidance could clarify the structure or categories of studies that would be subject to this requirement (e.g., studies that involve more than a certain number of sites or subjects or those that were funded by a Common Rule agency, should the regulations be extended to all research).

2. *IRB selection methodology*

Criteria and processes for selecting the IRB of record would be critical to the successful implementation of a single IRB requirement. The regulations should set forth the criteria that the IRB of record must meet, how the selection criteria is applied, and what entity makes the

decision about which IRB will serve in that capacity. Criteria should be based on the competence of the IRB and should include an assessment of the IRB's ability to oversee and coordinate the activities and review through the completion of the study.

3. Roles and responsibilities

Clear delineation of the roles and responsibilities for local sites and for IRB of record are essential. For institutions to embrace the concept and refrain from creating a shadow review system for fear of liability, it must be clear where the regulatory responsibilities and risks lie. Whether or not this proposal is implemented as described, this clear allocation of responsibility among participating institutions, local IRBs, and the identified IRBs of record is critically important and currently missing from federal rules and guidance. When there is a concern or issue with the research as approved or implemented, the regulations and guidance should make it clear which entity is responsible for responding and where OHRP's enforcement actions may be directed. Institutions may conduct internal administrative reviews of all proposed research to ensure that the research can be conducted (from a financial, feasibility, and mission perspective, as well as to ensure review of important correlative issues such as financial conflicts of interest). Thus, having clear expectations for the ethical review of research will help ensure that such local administrative review can occur in conjunction with single IRB review without unnecessarily duplicating efforts.

4. Consideration of local context

Before a single IRB of record can be mandated for studies that take place in many sites and geographic locations, institutions must have clear understanding of how local considerations may factor into the review of a protocol, how those considerations are either communicated to the IRB of record or assessed locally, and OHRP's expectations for ensuring that local context is incorporated in institutional decision-making or review requirements when appropriate. This may be accomplished through a requirement that the IRB of record solicit input from the local sites or independently assess whether the nature of the research or subject population is likely to raise questions of site- or community-specific needs or challenges.

IV. Improving Informed Consent

Improving Consent Forms

Overall, AAMC strongly agrees that consent documents are now used as communication tools, proof of regulatory compliance, shields against liability, and catalogues of extraneous information. Thus, they have increased in length and complexity, often to the detriment of the

informed consent process. This has diluted the fundamental goals of the process: to provide individuals with the relevant information, time, and opportunities to formulate questions about the research and to ensure that the subject has given voluntary, informed consent. Ideally, the consent "form" only serves as written documentation that such a process has occurred. Given this environment, AAMC is pleased that the ANPRM proposes changes to the informed consent process, and posits that regulatory changes can move the research community away from lengthy forms that do not emphasize the elements that are most critical to prospective subjects in deciding whether or not to participate in the research. We note, however, that the ANPRM, like the current Common Rule, maintains the regulatory focus on the document alone, not the process. This focus may have the effect over time of preventing IRBs from allowing the implementation of novel, effective methods of communicating critical study information to research subjects.

While we support the shortening and simplification of informed consent forms and have been involved in efforts to further this goal, we do not believe that imposing specific page limits or other proscriptive formatting requirements is appropriate. Instead, we suggest that the regulations and accompanying guidance stress the flexibility that IRBs have to approve documents that provide all meaningful and relevant information to individuals, including easy access to more information as needed. [*Question 37*]

The ANPRM suggests that OHRP could design templates of acceptable consent documents. Although templates can be helpful tools, we suggest that guidance that reinforces the flexibility in the regulations and provides examples of acceptable language, similar to the approach taken in the recent OHRP/FDA guidance on exculpatory language, is preferable to templates. Once created, and absent other examples, templates tend to take on the importance of regulation. Institutions may subsequently try to convert all consent documents to the precise format, length and content of the template, even when that template is not the most effective or appropriate means of communicating relevant information for the study.

The regulations should dictate required elements of the process but not the precise manner in which the information is provided. Novel document formats, such as a brief summary document followed by a complementary appendix of more detailed information, as has been suggested by several comment letters, should be allowed and encouraged by the regulations.

Proposals Related to Research Involving Existing Biospecimens and Data

The ANPRM proposes to revise the oversight of research on biospecimens and data by reconfiguring the existing exemption category found at 45 CFR Part 46.101(b)(4) into a new *excused* category. This category would apply to all research on biospecimens and data that are

collected for purposes other than the proposed research, thus deeming them "existing" outside the proposed research (even if they have not yet been collected at the time the research is proposed). This excused category would apply regardless of whether the investigator intends to maintain identifiers, provided that there are no plans to return individual results of the research back to the subjects. We understand the proposal to mean that such research, although excused from traditional IRB oversight and research-level informed consent, would nonetheless be subject to the following requirements: (1) complying with the new data and security protections outlined in the ANRPM; (2) registering the research with an institutional office; (3) auditing by the institution (of a subset of the registered research) to ensure that the *excused* category is being used appropriately; and (4) complying with certain informed consent requirements: namely (i) obtaining general consent for the future research use of "existing" biospecimens (whether or not the biospecimens are identifiable), whether originally collected for non-research or research purposes; and (ii) obtaining consent to the future use of any data originally collected for research purposes (whether the data will be identifiable or de-identified for purposes of the future use). We understand that the future use of data originally collected for non-research purposes would only require consent when identifiers are retained.

As a whole, the proposals related to research on existing data and biospecimens do not achieve, and in fact thwart, the overarching goals on which the ANPRM seeks comment. The proposals do not increase protection for human subjects. Conversely, the proposal introducing a broad consent requirement for research involving all biospecimens may *increase* the risk that an individual's identity will be exposed as a result of research involving his or her tissue. Institutions that are required to obtain general consent to future research use from each individual from whom biospecimens are collected during clinical care or for other research, will need to maintain a link between the identified consent and the specimen to ensure future uses of the biospecimen are permissible. Whether by a code associated with the signed consent document or registry of individuals who have provided the general consent to future research, every biospecimen would have a physical or electronic link to a signed consent document containing the individual's name. Under the current rules a biospecimen, once stripped of identifying data, cannot be linked to the individual from whom it was collected. *The ANPRM's proposal would create a new risk of a breach of confidentiality for every single specimen donor.*

The AAMC supports the ANPRM's recognition of the importance of secondary research uses of data and biospecimens collected for other purposes, whether clinical or in the context of other research studies. Appropriate secondary use of existing information and materials promotes efficient use of scarce resources and also avoids unnecessary collections, which are arguably unethical if viable specimens and information already exist. As therapeutic innovation moves increasingly towards an in vitro model, appropriate secondary use of specimens and associated

information can assist in the development of therapies without in vivo testing, thus minimizing risk to human subjects.

We also want to reinforce the critical need for any regulatory changes to be prospective in nature, with a compliance date that is later than the effective date of the regulation, thereby establishing a reasonable implementation period [*Questions 52, 58*]. Retrospective application of any changes ultimately included in the new proposed regulations would be catastrophic for on-going specimen and data research, compromising research that is in progress.

AAMC strongly supports educational efforts regarding the importance of biomedical research to advance medical technology and improve the quality of medical care. These efforts can only be effective if they engage researchers and prospective subjects by respecting the role of the public as active partners in the process of research and discovery. This must be a national partnership, not simply an attempt to inform the public about the research process. [*Question 49*] Academic medical centers and teaching hospitals are uniquely positioned to be instrumental in such activities and AAMC looks forward to partnering with HHS and OHRP in such an important effort. Only through collaboration with the public can we regain and maintain the public trust in the ethics, importance, and promise of the research mission.

AAMC is committed to the principle of obtaining informed consent when it is meaningful and achieves the goal of providing individuals with relevant information that would be material to the decision facing them. If the focus of concern with respect to research on data and biospecimens is (1) protecting the confidentiality and privacy of the individuals from whom such data and materials derive and (2) obtaining informed consent from those individuals for future research use, then the general informed consent articulated in the ANPRM does not accomplish either goal. An individual who is asked to sign a blanket consent document without any information about what type of research might be done in the future and with no opportunity to ask questions about the research that may be conducted (for example, if such consent is obtained just prior to surgery or on admission to a hospital) cannot be said to have provided meaningful informed consent. This could be more accurately characterized as "notice cloaked in consent's clothing," providing individuals with a false sense of individual control when, in fact, there is none. [*Questions 49, 50*]

The ANPRM's stated goal to "conform the rules for research use of clinically-collected biospecimens with the rules for biospecimens collected for research purposes" overstates the current disconnect between these two frameworks. Even biospecimens collected during primary research studies may not have any consent to their specific use in research (for example, an observational study in which specimens will be collected as part of the underlying standard of care procedure being studied), or such consent may be narrowly circumscribed to the clinical

trial in which the specimens are obtained (for example, in a clinical trial where the participant provides consent to certain biomarker testing of a resected tumor but does not express an opinion one way or the other with respect to future uses). Therefore, the new proposed rules do not so much correct a current disparity as impose a "consistent" framework of uniform prospective broad consent.

The ANPRM's proposal to convert the *exempt* categories into a new, broader, *excused* category may reduce the burden on investigators in certain ways (for example, by potentially increasing the types of specimens and data that may be used in research without IRB review and oversight), but it increases the burden on institutions by imposing significant administrative and data security burdens on research that is currently completely exempt from any requirements. Although the *excused* categories are intended to create efficiencies and thus facilitate research, for research on de-identified biospecimens and data, the new requirements of registration, prospective consent, and compliance with data security protections will inevitably complicate and undermine this important source of therapeutic advancement without adding meaningful protection for the individuals from whom the materials derive.

Identifiability of Biospecimens

The ANPRM's proposals appear to be based on the premise that all biospecimen research (regardless of the identifiability of any data associated with the specimen) should be considered research involving identifiable information on the grounds that DNA or genomic data is inherently identifiable. This assumption underlies the ANPRM's proposal of different standards for research involving de-identified data and de-identified specimens, with research on de-identified data collected for non-research purposes permissible without consent while future research on all biospecimens would require consent. AAMC acknowledges the technological advances that allow whole genome sequencing and comparison of genetic material. However, basing a regulatory scheme on the assumption that all biospecimens are easily identifiable creates barriers to research that far outweigh the current risks of identification. Therefore, AAMC favors an approach that can adapt over time, but does not undermine the promise of research with biological specimens.

Currently, biospecimens without attached identifiers can only be re-associated with the individual from whom the specimens were obtained if the researcher actively works to sequence the DNA and has access to a referent database (such as a DNA sequence disease registry or criminal database) that identifies the individual. [*Questions 56, 57*] The rules for data and biospecimens could and should be consistent and depend fundamentally on whether the identity of the individual from whom the information and/or materials was collected can be readily

ascertained either from the data or specimens themselves, or by virtue of other information available to those individuals who may reasonably have access to them. [*Questions 45, 46*]

AAMC strongly favors retaining the Common Rule's existing standard for *individually identifiable*, that an individual's identity "is or may readily be ascertained by the investigator or associated with the information" (45 CFR Part 46.102(f), emphasis added). [*Question 55*] The advantage of this standard is that it can evolve with the development of new technologies and scientific advancements without the need for further regulatory amendment. If in the future researchers may readily ascertain the identity of individuals through the acquisition of a biospecimen without associated identifying data, such specimens would be considered individually identifiable and additional protections would be required. This approach is consistent with OHRP's prior guidance on the status of coded data or specimens, which represent human subjects for anyone with the ability to re-link them to the subject's identity, but which are exempt from the regulations if conditions exist such that re-identification is not reasonably possible.

To clarify OHRP's position on the treatment of biospecimens, the definition of *individually identifiable* could include an explicit reference, such as the following: "when the identity of the subject is directly associated with the biospecimen or may readily be ascertained by the investigators or others with a reasonable likelihood of having access to the biospecimen, including where the biospecimen contains a code in lieu of the identifying information and the investigator or other individual has the ability to de-code and re-link the biospecimen to the individual's identity." With such a definition, the basis for the distinction drawn in the ANPRM between the consent requirements for existing de-identified data and existing de-identified biospecimens collected for non-research purposes falls away.

Applying Notification and Use Limitations in Lieu of Broad Consent

The existing regulatory mechanism of exemption from regulatory oversight of certain research involving existing de-identified data and biospecimens is an appropriate mechanism for facilitation of this minimal risk research. The exemption is currently granted on the finding that it does not involve research on human subjects and/or meets certain criteria such that overview and consent is deemed unnecessary. [*Question 47*]

In lieu of the broad consent requirement contemplated by the ANPRM, AAMC supports an alternative approach of *transparent notification* for individuals who come into a hospital or other treatment environment. Such notification would inform them that if they choose to receive treatment or participate in research at the hospital, such treatment or research may result in data or excess biospecimens that may be put to certain future uses. Specifically, patients could be

informed that such excess information and materials may be retained by the hospital without any information that identifies them directly and may be used for various purposes, including education, research, or quality improvement activities that are central to the hospital's mission. The notification could also outline any restrictions on the future use, such as a prohibition against attempting to re-identify data and biospecimens that have been de-identified, or a limitation on the external entities with which such data and biospecimens may be shared.

AAMC strongly supports the inclusion in the regulations of a default position that investigators be prohibited from attempting to re-identify biospecimens without attached identifiers unless specifically allowed by an IRB. We believe that strong penalties for attempted or actual re-identification in contravention of an IRB decision are appropriate. [*Question 63*]

If the proposal to consider all biospecimens identifiable is included in revised regulations, we note that the current process through which an IRB may grant a waiver for conducting non-exempt research without written consent (45 CFR 46.116(d)) is a more thoughtful and honest approach to the protection of the human subjects from whom a biospecimen is obtained then a blanket consent document. Through this process, an IRB has the opportunity to assess, on a protocol-specific basis, the nature of the proposed research question and the protections in place to prevent re-identification of specimens, as well as the sufficiency of any consent that may have been given previously (for example, for data and biospecimens previously collected during the course of a research study). AAMC supports the continued use of the waiver process, where appropriate, for research on identifiable data and biospecimens.

V. Strengthening Data Protections to Minimize Information Risk

Although AAMC strongly supports the goals of the ANPRM in harmonizing definitions across regulations that impact the conduct of research, AAMC does not recommend using the definitions of "individually identifiable," "limited data set" and "de-identifiable" from the HIPAA Privacy Rule. The definitions, taken from a regulatory scheme meant to apply only to health information, have been difficult to apply in the research context and have not served the research community well. Adapting datasets to meet the HIPAA definitions for "de-identified" or "limited data sets" for example, often render remaining data useless for research purposes. Data that are currently unidentifiable under the Common Rule may be considered identifiable under the HIPAA Privacy Rule because they include a single date or geographic detail. Instead of adopting these unwieldy definitions, AAMC recommends that an appropriate definition of identifiability be codified in the Common Rule and urges the Office of Civil Rights (OCR) to harmonize the research-specific provisions in the HIPAA Privacy Rule with the revised Common Rule.

As further described in Section II, above, AAMC recommends that the Common Rule not adopt the HIPAA standards from the Security Rule. This revision presents an opportunity to set reasonable, protective standards that are practicable and can easily be applied to all research data, not just protected health information collected by a covered entity. AAMC hopes that this opportunity is manifested in definitions and standards that can be emulated or adopted by other agencies.

AAMC understands from presentations made by OCR and OHRP that the intention of the ANPRM is not to extend either the HIPAA Privacy Rule or the Security Rule, and that OHRP, not OCR, will retain enforcement jurisdiction over the Common Rule regardless of the definitions and standards that are adopted. We believe that this is appropriate.

VI. Data Collection to Enhance System Oversight

The ANPRM sets forth three proposals with respect to the collection of safety data: (1) defining standardized data elements for reporting, (2) creating a web-based, Federal-wide portal for electronic submission of required reports, and (3) harmonizing safety guidance across all Federal agencies. These are generally laudable goals and AAMC encourages the further exploration of these potential improvements to the systems for collecting and evaluating critical safety data. AAMC supports the concept of streamlining the collection of safety data and agrees that a centralized system could be helpful for collecting data in certain types of studies. However, coordination between HHS and FDA or other agencies to develop and pilot a tool to ease reporting and collecting of information does not require changes to the Common Rule. We suggest further study to determine whether adverse event data and definitions are consistent enough across all research studies to make a single national database a useful tool or could truly allow for meaningful integrated analysis, including the review of other existing tools and databases. [*Question 69*]

VII. Extension of Federal Regulations

AAMC has supported efforts to ensure uniform protections of research subjects regardless of where research takes place or how the research is funded. Under the current regulatory framework, there are considerable gaps in the rules that govern research with human subjects and AAMC agrees that addressing these gaps requires a national solution. However, the proposal set forth in the ANPRM to extend the Common Rule to all research, regardless of funding source, at those institutions that receive any funding for human subjects research from an agency that has adopted the Common Rule, does not adequately meet either of the stated goals of the ANPRM.

AAMC urges the Department not to include this proposal in the revised regulations. [*Question 71*]

The proposal has three primary drawbacks: (1) the approach does not address the most pressing needs in closing gaps in the protections of human subjects and may not provide significantly increased protections even in the institutions it affects; (2) the potential burden on institutions, particularly if other proposals in the ANPRM are adopted as suggested, could be significant; and (3) the proposal could have the unintended consequences of increasing the number of research studies conducted without regulatory oversight of any kind.

1. *Extending the Common Rule within Federally Funded Institutions Does Not Address the Gaps in the Protection of Human Subjects*

Currently the Common Rule only applies to research that is federally funded or that takes place at institutions that have voluntarily applied the Common Rule and granted OHRP regulatory oversight for all research (by "checking the box" on the institution's Federalwide Assurance). As a matter of policy and practice, however, most institutions that have filed a Federalwide Assurance with OHRP apply the same protections and standards to all research at the institution, regardless of the funding source. Institutional policies that meet the regulatory requirements of the Common Rule are typically implemented throughout the institution. In addition, research involving investigational drugs and devices is regulated by the FDA, regardless of the funding source. Research conducted outside of academic medical centers and other institutions that receive substantial federal research funding presents more problematic potential gaps in the protection of human subjects. Such research, which may take place in private clinics, community hospitals, or dedicated research centers may not be subject to any federal regulation, either under the current regulations or under the proposed change to the Common Rule and OHRP jurisdiction. The AAMC appreciates that HHS is not able to address these gaps through a regulatory revision, but the limited solution proposed here does not present an appropriate response to the Department's concerns.

2. *The Proposal Could Substantially Increase Institutional Burden*

Not only is the proposal unlikely to measurably increase protections at institutions that currently receive federal funding for human subjects research, but the increase in institutional burden from such a regulatory change would likely be substantial. The requirements that institutions promptly report to the Department any "unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance" and any suspension or termination of IRB approval would alone represent an increased reporting burden. There is no cited evidence that these reporting requirements provide any additional protections for human subjects when only

applied to federally funded research. Additionally, if all proposals set forth in the ANPRM are implemented, this extension of the Common Rule to all research would exponentially increase the number of studies that would need to be registered, audited, and subject to standardized security measures; a burden that would be borne only by those institutions already subject to the Common Rule.

3. The Unintended Consequences of the Change Could Decrease Federal Oversight of Some Human Subjects Research

The unintended consequences of extending the Common Rule reach beyond the potential increased burden for institutions. Faced with the potentially onerous requirements of the Common Rule, entities that receive little or no federal funding for human subjects research could opt to decline such funding specifically to avoid the requirements of the Common Rule. These unregulated entities could also be attractive research sites for sponsors seeking a way to avoid the federal requirements and oversight or, in the case of research with investigational drugs or devices, to prevent a study from being regulated simultaneously by the FDA and OHRP. This issue of overlapping jurisdiction and regulatory compliance with two sets of regulations underscores the need for better harmonization across agencies.

VIII. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

AAMC strongly agrees that a single set of guidance documents would be helpful to the research community. The recent draft guidance document on exculpatory language on informed consent, jointly issued by OHRP and FDA on September 7, 2011, represents a notable positive movement in this direction. Harmonizing the regulations regarding research with human subjects is a laudable goal and would serve to decrease ambiguity and regulatory burden. It would be useful to implement a process through which multiple agencies review draft guidance documents prior to publication, and make a determination as to whether each agency whose regulations might be implicated will adopt and sign on to the guidance. In some cases agency-specific variation may be warranted and appropriate. When regulations or guidance cannot be harmonized, a statement or guidance document from the agencies describing the rationale for having varying standards or rules would assist institutions in understanding the variation and implementing the requirements of each set of rules. [*Question 74*]

We encourage the more frequent issuance of guidance as OHRP becomes aware of confusion or inconsistencies in implementing the regulations. Too often, existing guidance documents take on the color of regulation, leading to a decrease in flexibility and a gloss on the regulations that was never intended. Further, as institutions are looking for insight into OHRP interpretation and enforcement priorities, published determination letters have served as a substitute for agency

guidance, focusing institutional review on the procedural elements covered by the most recent OHRP findings and actions.

The inconsistencies between the Common Rule and HIPAA in the treatment of data for research have complicated compliance for research governed by both sets of regulations. As the ANPRM recognizes, the same data can be individually identifiable under HIPAA, but not readily ascertainable and thus not identifiable under the Common Rule. In addition, AAMC recommends that the criteria for waiver of informed consent under the Common Rule be harmonized with the waiver of authorization under HIPAA, and that the regulations be harmonized to treat coded data similarly under both sets of regulations. [*Question 39*]

The Common Rule has facilitated the establishment of institutional policies and procedures by ensuring that the research-related expectations for institutions, IRBs, and investigators were similar or identical to those required by other federal agencies that had adopted the rule. AAMC hopes that HHS will work with the other agencies who initially adopted the Common Rule to ensure that the Federal regulatory framework for research remains consistent across these agencies. AAMC notes that efforts to harmonize both the regulations and guidance present an opportunity for requirements that are truly common to all federally funded research, and hopes that this process is seen as a chance to move towards harmonization of the other subparts of 45 CFR Part 46 as well.

IX. Additional Issues for Consideration

AAMC would like to propose that the following additional issues be considered as the Common Rule is being re-evaluated.

- Definition of Research – Several of the proposals implicitly call into question whether the definition of "research" under the Common Rule is adequate and useable. Specifically, we question whether the standard that the activity is one "designed to develop or contribute to generalizable knowledge" remains a useful standard for differentiating what activities should fall under the regulations, as every academic pursuit or study in any field may be intended to contribute to generalizable knowledge.

- Additional stakeholder input – AAMC recognizes that there is significant pressure to move this rulemaking process forward expeditiously. We urge HHS and OSTP to consider the magnitude of the changes being proposed and to continue to engage a broad spectrum of the research community as the process moves forward and specific proposals are abandoned or included in future iterations or proposals.

In conclusion, the AAMC supports this bold effort to bring the rules governing human subjects research into the 21st century. We hope that the focus remains on harmonization, simplification, and protection of human subjects as well as the advancement of research to improve the health and lives of all. We look forward to working with HHS, OSTP, and OHRP as the regulations are evaluated and revised and would be pleased to offer any other assistance in this ground-breaking process. Please do not hesitate to contact me or Heather Pierce, Senior Director for Science Policy and Regulatory Counsel, at hpierce@aamc.org.

Sincerely,

Ann Bonham, Ph.D.
Chief Scientific Officer