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Submitted electronically at www.regulations.gov

Re: Docket Number HHS-OPHS-2015-0008, Notice of Proposed Rulemaking: *Federal Policy for the Protection of Human Subjects*, published in the September 8, 2015 *Federal Register* (80 FR 53933)

The Association of American Medical Colleges (AAMC) appreciates the opportunity to respond to the Notice of Proposed Rulemaking (NPRM), entitled *Federal Policy for the Protection of Human Subjects*. The AAMC is a not-for-profit association representing all 145 accredited U.S. allopathic medical schools, nearly 400 major teaching hospitals and health systems, including 51 Department of Veterans Affairs medical centers, and 90 academic and scientific societies. Through these institutions and organizations, the AAMC represents 148,000 faculty members, 83,000 medical students, 115,000 resident physicians, and thousands of graduate students and post-doctoral trainees in the biomedical sciences.

The AAMC realizes the significance of bringing 16 federal agencies and offices to consensus on changes to regulations as complex and broad-reaching as the Common Rule. This collective, intensive activity reflects the considerable commitment of those involved and we are appreciative of this effort. As the preamble to the NPRM describes, in the nearly 25 years since the regulations were promulgated research has changed dramatically, not only how it is conducted but also the settings where research occurs, the volume of data collected, used, and shared, the technology employed, and the level of public engagement in and understanding of research.

Although the AAMC is supportive of many of the proposed changes or approaches, we have strong concerns about the most significant changes to the Common Rule, namely the requirement to obtain consent for all research with unidentified biospecimens and the requirement for approval by a single institutional review board (IRB) for all cooperative research. As further described here, **we urge the revisiting or withdrawal of these proposals and the overall**

simplification of this proposed rule, which has confused and frustrated a very engaged and thoughtful community of investigators, institutions, and ethicists. The AAMC has structured this letter to respond to the major proposed changes in the NPRM and to reference the NPRM's 88 specific questions for public comment as appropriate.

I. General Comments and Observations

The AAMC offers these comments with the goal of assisting the departments and agencies in achieving the stated goals of increasing human subjects' ability and opportunity to make informed decisions, reducing the potential for harm and increasing justice, and facilitating current and evolving types of research. We agree that these considerations should be guiding the revisions to the regulations and note that the NPRM's three goals represent a slightly different approach to balancing potentially competing interests than the 2011 Advance Notice of Proposed Rulemaking (ANPRM)[1] issued by the Department of Health and Human Services (HHS) and the Office of Science and Technology Policy. The ANPRM discussed balancing (i) the protection of human subjects with (ii) facilitating valuable research and reducing burden, delay, and ambiguity for investigators. One of the primary shifts in this approach was the discussion of research subjects as active participants and partners in research, not simply individuals in need of protection. The AAMC agrees that the revision of the Common Rule should recognize the evolving nature of these relationships and facilitate the engagement of individuals and communities while maintaining the highest ethical standards for research and understanding the obligations of investigators and institutions to protect the welfare of human subjects.

The NPRM describes the Common Rule as a framework for weighing the 1979 Belmont Report's core ethical principles of beneficence, respect for persons, and justice, and asks those responding to the proposed changes to consider whether the revisions "strike a reasonable balance" among these principles. In this complicated NPRM, few individual proposals seem to strike such a balance, but fall entirely on one principle to the exclusion of the other two. This disconnected approach makes the assessment of whether the proposed changes "will achieve the objectives of (i) decreasing administrative burden, delay and ambiguity for investigators, institutions, and IRBs, and (ii) strengthening, modernizing, and making the regulations more effective in protecting research subjects"[2] difficult to comment on as a whole. [*Question 1*] Some of the minor proposals would effectively decrease administrative burdens without decreasing the protections for human subjects (e.g., changes to continuing review requirements). Others would increase regulatory requirements for investigators with no obvious increase in the protection of human subjects (e.g., requirement to publish informed consent documents). The proposals to redefine human subjects to include biospecimens, mandate a single institutional review board (IRB) review for cooperative research, and extend the Common Rule to all clinical trials at

[1] 76 Fed. Reg. 44512 (July 26, 2011).
[2] 80 Fed. Reg. 53942 (September 8, 2015).

federally funded institutions have significant foreseeable burdens with insufficient evidence as to their benefits to human subjects or institutions. **Overall, the increase in administrative burden and cost, the complexity of the proposed rule which is already raising disagreements about its intent and requirements, and the lack of flexibility in the proposed rule's mandates lead the AAMC to conclude that the proposed changes will not achieve the objectives of the NPRM.**

The AAMC is concerned that the NPRM represents less of the thoughtful, comprehensive overhaul of the regulatory framework suggested by the tone of the ANPRM than the imposition of far-reaching, significant changes through the modification of existing language and structure. This leads both to uneven changes to the review and conduct of research and many missed opportunities to address problematic aspects of the current rule. Key missed opportunities include: the decision not to revisit and revise the definitions of research, minimal risk, and legally authorized representative; the continued focus on the documentation of informed consent instead of the process; the failure to incorporate investigator responsibilities into the regulations; the failure to provide meaningful delineation between research that should be subject to the Common Rule and continuous quality improvement; and the inclusion of evaluation metrics to assess the effect and effectiveness of the rule after its implementation. The AAMC has recommended all of these changes to HHS in its comments to the ANPRM, and renews these recommendations here.

It is essential that a regulatory framework to protect human subjects provide institutions, investigators, and research subjects with *clarity* to ensure consistency of interpretation from institution to institution and study to study, and *flexibility* to allow the rule to be applied to atypical situations, emerging technologies, and complex research methods. The NPRM as a whole demonstrates significant shortcomings, lacking clarity in some key areas and lacking flexibility in others. The stated goal to "facilitate current and evolving types of research … through reduced ambiguity in interpretation of the regulations," is not realized through most of the NPRM's proposals. In many cases the proposed revisions attempt to reduce ambiguity by reducing flexibility, imposing rigid mandates on all research regardless of structure, design, or actual risk to subjects. The AAMC questions whether too many issues that could have been addressed through guidance were addressed through regulation, leaving the Common Rule less able to adapt and respond to evolving research design and technology.

II. Biospecimens

A. General Comments

The treatment of biospecimens in the NPRM is concerning to the AAMC and its member institutions, and the many provisions that address treatment of research with biospecimens fail to achieve any reasonable balance between informing subjects, reducing potential for harm,

increasing justice, and facilitating "current and evolving types of research." Indeed, the proposals as a whole would greatly increase institutional cost and burden and impede research without increasing meaningful understanding by or protection of human subjects. **The AAMC recommends that the approach to research with biospecimens be substantially revised to better address the potential for actual harm and to reflect an understanding of the extraordinary stresses implementing these changes would put on the research community as a whole.**

While the ANPRM focused on the risk of re-identification as the driving force in proposing changes to how biospecimens are treated in research, the NPRM instead characterizes the proposed revisions as responsive to the wishes of individuals to better understand and have some degree of control over when their biological materials are used for research. The AAMC agrees that as a research community we can and should do a better job of engaging patients and communities in the role they can play in advancing discovery and medical care for future patients and generations. Indeed, it may be the case that few individuals who receive care at teaching hospitals and academic medical centers appreciate how research with large numbers of clinical biospecimens that would otherwise be discarded following surgical procedures or other interventions are improving lives and health every day. It is incumbent upon us to better inform individuals about how and when biospecimens are used in research and revise the current environment in which patients in clinical settings are unaware that biospecimens (without associated identifiers) are routinely used for research.

As many have noted in the time since the NPRM was released, the treatment of biospecimens in the proposed rule is complex, and the requirements for the use or future use of any biospecimen is linked to the circumstances under which it was collected and the intent of the researcher, not the risk of re-identifiability or of the research itself. The AAMC shares the concerns that this varied approach to the approvals and processes required in different situations unnecessarily adds to the complexity of the rule and foreseeable difficulties in implementing the rule uniformly across institutions and investigators.

B. Revising the Definition of Human Subject

The AAMC does not support the NPRM approach of revising the definition of *human subject* as a means to ensure that all research with biospecimens, whether or not otherwise identifiable, is covered by the Common Rule. Defining a human subject as "a living individual about whom an investigator (whether professional or student) conducting research … obtains, uses, studies, or analyzes biospecimens"[3] unnecessarily complicates the implementation of the

[3] As included in the proposed revision to §__.101(e)(1).

rule, and sets up a problematic and misleading regulatory precedent. A de-identified biospecimen is not a human subject.

The Common Rule as currently implemented can already address the concern that biospecimens may become identifiable without any associated identifiers, through the use of sequencing technologies and referent databases that may become more available to researchers or the public. Without adding biospecimens to the definition of human subject, the identifiability of biospecimens could be covered by the current definition of a human subject as "a living individual about whom an investigator (whether professional or student) conducting research … obtains, uses, studies, analyzes, or generates identifiable private information." Research with "de-identified" biospecimens currently does not involve *identifiable private information*, because only when associated data links the biospecimen to the individual from which it was derived can the identity of an individual "be readily ascertained by the investigator." If available technologies and publicly available referent databases allow investigators to "readily ascertain" the identity of individuals from biospecimens alone, the current definition of human subject would suffice to bring that research under the Common Rule. **The AAMC strongly recommends removing the proposed additional provision to the definition of *human subject* and retaining the definition of *identifiable private information* or augmenting to clarify that when the identity of the individual from whom a biospecimen was derived becomes readily ascertainable *by the investigator*, the research would be subject to the Common Rule.** [*Question 3*]

If inappropriate re-identification remains a concern, the 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.

The AAMC notes that treating all biospecimens as human subjects, regardless of the identifiability or associated information may have the unintended consequence of disincentivizing de-identification, greatly increasing privacy risks. In fact, the need to verify whether broad consent was properly obtained, not expired at the time of collection, and what version of the document was signed would likely encourage investigators and institutions to retain associated identifiers or closely link individual and biospecimen codes in a single database to avoid potential barriers at the time of application for future research.

C. Broad Consent for Collection and Storage of Biospecimens

The proposal to require written, documented "broad consent" for every biospecimen collected in a clinical or research setting for the purpose of storage for future research, regardless of identifiability, is the proposal with the greatest impact to institutions with the least benefit to individuals whose biospecimens may be used in future research. **For the reasons detailed in this section, the AAMC strongly recommends that the regulations include a *robust notice* requirement in lieu of the proposed broad consent provisions. This approach is more respectful of individuals and better grounded in core ethical principles than a nonspecific**

document that may satisfy documentation requirements but provides no real opportunity for education, discussion, or meaningful understanding.

The proposal to require broad consent for the collection and storage of all biospecimens for future research suggests that individual autonomy outweighs all other ethical principles or practical considerations, but fails to promote individual autonomy in a meaningful way. When addressing the ethical principle of respect for persons, the NPRM preamble itself appropriately describes informed consent as "designed to ensure that each individual approached to participate in a research study fully understands the risks and potential benefits of the study so that they have sufficient information to make an individualized calculation as to whether or not the tradeoffs inherent in participation are worth it for them to participate."[4] Broad consent, as envisioned in the NPRM, cannot be designed or implemented in a manner that allows for meaningful understanding, the ability for knowledgeable individuals to answer questions about the research, or to facilitate the individualized calculation that is so fundamental to informed consent.

An informed consent document is the written record of a process that should facilitate understanding and provide opportunities for discussion and answering questions. By removing both the word and the concept of an "informed" subject from the broad consent model and requiring the use of template language that cannot be tailored to particular subjects or populations, we are left with a burdensome and costly process that does not lead to meaningful consent but greatly increases the potential for regulatory noncompliance and re-identification. Requiring a signature on a document that may provide the same language and information to each person for every instance of biospecimen collection is more of a *pro forma* exercise to ensure compliance and reduce the risk of future challenges to the outcomes of research than respecting an individual's desire to engage in the research process and understand how research with biospecimens contributes to medical advancement. It is important to note that the requirement to obtain broad consent as proposed in the NPRM moves the research consent process into the clinical context, where there may be no individual familiar with research practices able to answer questions about future research, or who regularly discusses research studies with prospective subjects.

The proposed broad consent process creates an unrealistic expectation that biospecimens will in fact be collected from each individual and used for research. In the clinical care context, an institution will not have made a determination in advance whether a particular individual's biospecimens might be collected and stored for future research use. Thus, it is reasonable to assume that every person receiving care will be asked to sign a broad consent upon arrival, in case there is a later decision to collect and store biospecimens for future use. All individuals signing that document would reasonably expect that their biospecimens would be collected,

[4] 80 Fed. Reg. 53941.

stored, and used for research. This is not consistent with actual practice, in which large quantities of biological materials are discarded and are never stored for research purposes. Similarly, institutions have noted that research is only conducted on a small percentage of stored biospecimens. This demonstrates a fundamental and relevant distinction between a study-specific research informed consent and the proposed broad consent: those individuals who sign study-specific informed consent documents are relatively assured that they are participating in research and making a contribution to the research process, while broad consent simply allows for a collection and storage that may never occur. If an individual has signed a broad consent and later decides to withdraw this consent, an institution may not be able to tell that person whether any biospecimens were ever collected, stored, or used for research. This situation is antithetical to both respect for persons and to meaningful consent. **A robust notice requirement would inform individuals about the research that takes place at the institution using biospecimens without creating an expectation that each person who signs the broad consent is an actual participant in research.**

The AAMC is concerned that the need for tracking the consent and individual attached to every specimen collected or stored is not only potentially profoundly burdensome, requiring the costly development of new tracking and recordkeeping systems at hospitals and academic medical centers, it also creates a new privacy risk. What was previously a set of unidentified biospecimens in a biorepository will now be linked to a physical or electronic database of private information about each subject. Although representatives from the Office for Human Research Protections (OHRP) have suggested that the tracking of individual consent could be separate from the database tracking biospecimens, the requirements for tracking and verifying consent for each biospecimen will undoubtedly link the two in many systems.

AAMC member institutions have voiced concerns that the broad consent and tracking requirements, with the concurrent risk of regulatory noncompliance, will dissuade many smaller or less well-resourced care facilities from continuing to participate in the collection and storage or transfer of non-identified biospecimens for future research. This runs counter to the ethical principle of justice by limiting subject selection and the ability to contribute to future research based on whether the facility where an individual receives care has decided to implement these new procedures. Not only does this result fail to increase autonomy, it may decrease justice by establishing biorepositories for future research that represent a more homogenous population or excluding individuals from certain geographic regions, socioeconomic status, or underserved populations from the pool of biospecimens used for research. This has implications both for the research that can be conducted and for the applicability of research findings across a broader population and the ability to use the results of this research to assess and ameliorate health disparities and inequities.

The tracking of biospecimen consent raises additional complexities in the research context for large institutions. While clinical records for individuals are often consolidated into a single

electronic health record at an institution, that is not the case for research records, which are largely decentralized. It is unlikely that a single system will be developed to track all biospecimens used or stored in every department, lab, or affiliated institution, necessitating a constellation of tracking systems, each of which has an independent risk of being inappropriately accessed, compromising subject privacy and increasing the risk of harm through re-identification.

The future development of a template broad consent document raises important tracking and process issues that are insufficiently addressed in the NPRM. If the template is presented as a framework into which institutions must enter information based on their understanding at the time of the general types of research that might be conducted, sophisticated tracking systems will be required to link each stored biospecimen to a particular consent form or, at least, a particular version of a consent form. Although the future research with these stored biospecimens would be exempt under the proposed rule, presumably there would need to be an IRB review not only of whether broad consent had been obtained using the approved template, but also whether the proposed research is consistent with the description of research for the relevant version of the document *for each biospecimen*.

The cost to institutions of implementing this consent and tracking requirement is overwhelming. The NPRM regulatory impact analysis predicts that it will cost the regulated community billions of dollars to implement the processes and systems required for this proposal. Institutions that have attempted to predict what it would cost to implement the broad consent requirements, including tracking systems, fear that the numbers presented may well underestimate the cost to institutions. It is incumbent upon us to ensure that enacting a requirement of this magnitude justifies the costs by providing a commensurate or essential benefit. The AAMC does not believe that such a benefit is realized by implementing broad consent measures.

In a report issued just after the NPRM was published, the National Academies' Committee on Federal Research Regulations and Reporting Requirements noted that "proposed changes to the Common Rule would require researchers to obtain written consent to use biospecimens, even those that have been de-identified, creating additional administrative burden without adding to the protections of human research participants,"[5] a sentiment echoed in the comments to the ANPRM issued by the HHS Secretary's Advisory Committee on Human Research Protections and by the AAMC. In 2011, the AAMC wrote that requiring informed consent for all biospecimens collected in a clinical context "unnecessarily burdens important research with administrative requirements that do not meaningfully add protection to the individuals from whom such information and materials derive." The NPRM has not addressed these significant and well-founded concerns. As the AAMC wrote in 2011, "In lieu of the broad consent

[5] "Optimizing the Nation's Investment in Academic Research: A New Regulatory Framework for the 21st Century: Part 1" National Academies Press 2015, p. 65.

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." This approach is more honest than broad consent and could incorporate all critical elements of the consent document without the tracking systems contemplated. If appropriately implemented, a notice requirement would help individuals understand that they are part of a research community engaged in a social contract, not participants selected for a specific planned research study.

D. Waivers

As described above, the AAMC does not support the requirement for broad consent for all biospecimens. There should be greater transparency to individuals and to the general public about how and why research with de-identified biospecimens occurs and the role those individuals may be playing in the research enterprise.

The NPRM, through preamble language and proposed regulatory text, adds additional criteria for the granting of waivers to the requirements of informed consent when research involves biospecimens, and indicates that such waivers should be granted very rarely. The AAMC agrees with previous recommendations from SACHRP and others that the current waiver process at 45 CFR 46.116(d), when conducted in a thoughtful and deliberative process with clear criteria, can be more protective of human subjects than a non-specific broad consent document. Through this deliberative process, an IRB can weigh the relative implications of beneficence, respect, and justice in the context of a particular study. [*Question 67, 68*] **The AAMC supports the continued use of the current waiver process, where appropriate, for research on identifiable data and biospecimens.**

E. Transition Provisions

The AAMC agrees that research with biospecimens collected prior to implementation of the final rule should not be subject to the new requirements of the regulations. The prohibition on research with existing biospecimens unless individually identifiable information is removed, however, is problematic and has the potential to halt or disrupt research without better protecting human subjects or increasing autonomy. The provision as written would require stripping identifiers from biospecimens even if individuals had provided informed consent for the research or investigators were granted a waiver in accordance with the current regulations. **The AAMC recommends deleting the requirement that research involving biospecimens collected prior to the regulation compliance date must occur only after removing individually identifiable information (§___.101.(k)(2)(ii)).**

III. Exclusions and Exemptions

A. General Comments

In general, the AAMC is supportive of the creation of "excluded" activities and the classification of activities as excluded or exempt. We are concerned, however, that the structure of this new framework will be difficult to implement consistently across institutions and IRBs. Under the current regulations, activities either meet the definition of research with human subjects or they do not, and certain activities that meet the definition are exempt from all requirements under the rule. In contrast, the proposed revision requires the analysis of whether an activity meets the definitions or not, then whether it is an excluded activity, and if not, whether it is exempt from some, but not all of the requirements of the rule. It is clear in the current rule that activities not mentioned as exempt might still be outside the regulations. As further described below, the existence of "excluded" activities, and the exceptions to those exclusions are being interpreted as definitive statements on what *is* considered research, not just what is *not* covered by the rule.

The AAMC also notes that the NPRM allows for more decision making by investigators if activities are excluded or exempt (with a decision tool). If investigators are going to be making decisions about whether research is excluded from the rule entirely, or exempt from most oversight provisions, the rule or guidance available before its effective date must ensure comprehension through language that is clear and unambiguous, so that institutions can have confidence in the consistent application and interpretation of these rules.

The AAMC commends to OHRP the many letters submitted by our member institutions who have provided specific examples and details about how the proposed categories would reduce burden or lead to greater ambiguity. We address only a few specific proposals below: the exclusion of certain quality assurance and quality improvement activities, research with stored biospecimens, and the exemption determination decision tool.

B. Exempt Activities: Quality Assurance and Quality Improvement (QA/QI)

The routine evaluation of practices and continuous incorporation of knowledge into patient care is fundamental to a learning health system and should be facilitated, not impeded, by a revised regulatory framework. The Common Rule as currently implemented provides insufficient guidance to determine the dividing line between research and expected or novel improvement in care delivery in a consistent and predictable manner. The revision of these rules presents an opportunity to explicitly recognize that efforts to improve care by evaluating both the utilization of an accepted practice and the *effect of that implementation* are not research that should be regulated under the Common Rule.

The AAMC strongly supports the concept of excluding quality improvement activities from mandated IRB review. The exclusion as proposed at §__.101(b)(1)(iv), however, is too narrow,

and is likely to have the effect of subjecting more activities to IRB review rather than less. Further, it does not meet the real need for greater guidance on QA/QI activities, maintaining or even expanding the "gray area" between research and care delivery that has been so troublesome.

The distinction that the proposed rule asks institutions and clinicians to make is between evaluating the "effects on the utilization of the practice" (which would be excluded) and "evaluation of an accepted practice" (which would not be excluded). Although exclusions in the rule are designed to identify activities that are not research and presumably other activities would need to be assessed individually, the reasonable assumption by the research community is that this exclusion is designed to indicate that *all* QA/QI activities other than altering utilization of an accepted practice through implementation should be considered research and be overseen by an IRB. The examples included in the NPRM provide a disincentive to continually assess the impact of implemented changes in a care delivery setting. It assumes that "accepted practices" do not warrant continuous evaluation. It does not make sense that a cluster randomized study assigning staff at half of the institutions to receive training on a practice to reduce the likelihood of infection when inserting a central line would be excluded if it looked at whether the practice was utilized more often when staff were educated, but would not be excluded if that activity also looked at infection rates at the same time.

A better approach would be to identify the criteria that would make an evaluation of a practice itself research, rather than assert that evaluation of a practice would not be excluded. **The AAMC recommends that the limitation on the exclusion at §__.101(b)(1)(iv) be deleted and the exclusion be made broader, to incorporate the evaluation of the effectiveness or outcomes of that implemented change, unless the intervention itself foreseeably increases the risks to those affected by the change.**

C. Exempt Activities: Research with Stored Biospecimens

Of particular concern to the AAMC is the carve out from the exemption at §___.104(f)(2) that deems research with stored biospecimens ineligible to be considered exempt if the investigator anticipates returning research results to individual subjects. This could be interpreted as prohibiting the return of clinically relevant research results to individuals at any time if the research had initially been deemed exempt. This approach demonstrates neither respect for persons nor the facilitation of research. **The AAMC recommends that this carve out when an investigator anticipates returning results to individuals be removed from the exemption and that instead there be guidelines or a designated review process for returning clinically relevant results to individuals.** [*Questions 54, 55*] With the potential of research advances through activities such as the Precision Medicine Initiative, what an investigator anticipates at the time of approval should not create an actual or perceived barrier for returning results to individuals in the future if warranted by the situation and deemed appropriate.

D. Exemption Determination Tool

The proposed rule discusses the future development of an online tool that would assist in making determinations as to whether research activities are exempt from most of the requirements of the rule. The AAMC notes that many institutions have developed processes, flow charts, and decision tools to help investigators and IRBs better understand the criteria and considerations that would indicate whether a particular activity could be deemed exempt from the requirements of the rule. The AAMC encourages the departments and agencies working to develop such a tool to engage the community and review the format, usability, and adaptability of these tools that have already been created. The experiences of these institutions will be invaluable in developing a useful decision tool.

The exemption determination decision tool that the government will be developing purports to create a "safe haven" from enforcement actions related to the appropriateness of the determination of exemption for institutions,[6] but the safe haven will only protect an institution if an investigator enters the information into the tool correctly. Without oversight or review of that determination process, an institution may not be comfortable relying on this presumption. Thus, a tool designed to increase efficiencies and decrease institutional burden may be either seldom used or increase institutional processes by causing institutions to implement additional internal reviews to verify the accuracy of the information entered into the tool. Whether an institution would allow an investigator to use the tool unaided or implement additional reviews prior to accepting the tool's determination would depend in large part on whether the tool developed was easy to use, reliably resulted in the same outcome for the same research study when used by two different investigators acting in good faith, and was the same or nearly identical for various funding agencies. [*Questions 27, 29*] Without an opportunity to review the tool in advance of the NPRM comment deadline, it is difficult for any institution to comment with specificity on whether the tool would be used, useful, or reliable, or whether it would provide comfort to institutional officials, investigators, or the public in the determination of exempt research. [*Questions 27-31*]

The NPRM preamble states that Federal departments or agencies "will develop one or more exemption determination tools,"[7] suggesting that each Common Rule agency might have a different system on which investigators may rely to ascertain whether research is exempt from many of the regulations' requirements. The development of meaningful and reliable decision aids can help to realize efficiencies in research. In the interest of harmonization and reproducibility, the AAMC urges all Federal departments and agencies adopting this regulation

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[6] "Institutions may rely on use of the federally developed tool by investigators as a 'safe harbor' for this determination: So long as the information that was provided to the tool was accurate, result of the application of the tool will be presumed by the federal departments or agencies to be an appropriate determination of exempt status." 80 Fed. Reg. 53956.
[7] 80 Fed. Reg. 53956.

to agree to develop and use a single exemption determination decision tool. **The AAMC urges HHS, should it move forward with the development of this tool, to engage researchers and institutions who have been engaged in making exemption determinations to help design and thoroughly vet it.**

IV. Cooperative Research

The AAMC appreciates that institutions and investigators can realize research efficiencies, reduce delays, and standardize consent processes and subject protections through the thoughtful use of a single IRB for certain multi-site trials. The assumption the NPRM makes, however, is that mandating a single IRB of record for all multi-site trials will result in significant cost savings, reductions in the time from proposal to subject recruitment, and standardized (and therefore better or more protective) reviews. This is an erroneous assumption. There are successful examples of multi-site trials that benefitted from a single IRB review, but that does not indicate that all research involving more than one site will benefit from a single IRB review.

The AAMC response to the ANPRM noted that four key areas of concern prevented the Association from recommending the implementation of a broad mandate for single IRB review of multi-site trials: the definition of multi-site trial; the IRB selection methodology; clear definition of roles and responsibilities; and the consideration of local context. The AAMC appreciates that all four of these issues were addressed or answered to some extent in the NPRM, but remains concerned that there is insufficient evidence to warrant the mandate without additional narrowing of scope, clarification of roles, and flexibility in issuing exceptions.

Recognizing that the NPRM's mandate is reflective of a significant desire to move the research community towards more regular use of single IRBs (as evidenced by the National Institutes of Health (NIH) draft guidance document implementing a similar requirement for NIH-funded research[8]), **the AAMC recommends that an increase in single IRB use for multi-site trials: 1) be accomplished through incentives and documented advantages, not a mandate, 2) incorporate flexibility for both funders and institutions in implementing the requirements, including exceptions, 3) be implemented in stages, and 4) incorporate specific measures to evaluate the effect and effectiveness of the approach.** [*Question 74*]

As the AAMC wrote in comments responding to the NIH draft policy[9]:

> Despite our support for the increased use of single IRBs for multi-site trials, we believe that the implementation of this policy as drafted will not accomplish the NIH's laudable

[8] National Institutes of Health Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research Notice number NOT-OD-15-026.
[9] AAMC Comment Letter "RE: Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (Notice number NOT-OD-15-026)", January 29, 2015.

goals, but may instead increase costs, shift administrative burdens, and encourage the development of "shadow" IRB reviews to fill in the gaps left by insufficient guidance on how to create many simultaneous reliance agreements and relationships.

Our concerns raised in the comments to the ANPRM and the NIH draft policy remain significant. The AAMC notes, as in the response to the NIH draft policy, that there are many additional ways of accomplishing the stated goals that do so with more information. The AAMC suggests that HHS could:

- run a pilot program with a select group of institutions and studies to measure the true costs, benefits, and consequences of greater adoption of single IRBs;
- issue a regulation that facilitates single IRBs in multi-site research with incentives for voluntary adoption;
- determine the attributes of studies that are most readily adaptable to single IRB review and either limit the policy to those studies or begin a phased-in implementation of a broader mandate starting with these studies; or
- create or fund resources and tools that facilitate collaboration, cooperation and greater efficiencies, perhaps allowing the central review of multi-site studies through an online platform.

We note that the NIH has recently funded research on "the principles and characteristics for central Institutional Review Boards (IRBs)"[10] and encourage HHS to postpone the mandate for single IRB review in multi-site research until it can be informed by the results of those studies. In the event the mandate is implemented as proposed, continuous evaluation of its impact should be a priority for the Common Rule agencies. Whether through federally funded research or in depth assessment of institutional data regarding the implementation of the requirement, as the agencies collect information about the costs, advantages, and drawbacks to implementing this requirement broadly it may become evident that certain types or sizes of multi-site trials realize greater benefits than others under a single IRB review, that local review is particularly important in some unanticipated ways, or that for some trials or types of research the added cost and burden of coordination across institutions for a single IRB review outweighs the benefits. In these cases, there should be a well-defined mechanism for institutions to request, and funding agencies to approve, additional exceptions to the requirement. [*Question 77*]

The NPRM appears to overestimate the cost savings of a single IRB mandate without fully understanding the upfront costs and duplication of efforts with each new cooperative research study. The NPRM itself recognizes the shortcomings in its cost analysis, stating that "because of

[10] NIH Funding Opportunity: Empirical Research on Ethical Issues Related to Central IRBs and Consent for Research Using Clinical Records and Data, RFA-OD-15-002 (available at http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-15-002.html).

the lack of available data about IRB effectiveness and how IRBs function operationally, many of the estimations in this analysis are based on anecdotal evidence."[11]

In addition to the recommendation for more flexibility, the AAMC suggests a phased approach to implementation by identifying current models and types of research that are most likely to demonstrate the benefits of single IRB review. As described further below, the extension of the Common Rule would impose this requirement on research not currently subject to the regulations without any funding mechanism to support this requirement. **The AAMC recommends that if the Common Rule is extended to all clinical trials regardless of funding source[12] at institutions receiving federal funding, the requirement for cooperative review by a single IRB not apply to those multi-site trials regulated only as a result of the extension of the regulations.**

V. Informed Consent

The AAMC appreciates the extended discussion in the proposed regulations about the information an individual should have in order to make a decision about participating in research and the emphasis on providing this information in a manner or format that facilitates the prospective subject's understanding. The codification of these ethical considerations, however, reduces flexibility and mires the informed consent process in additional requirements. Reorganization of the document would not address fundamental concerns that the current regulations regarding informed consent opt to focus on documentation compliance instead of ensuring meaningful understanding.

With the major revisions to the Common Rule, there is an opportunity to re-envision the informed consent process and provide investigators and institutions with the flexibility to ensure that critical information is delivered in a way that is understandable to the research subject. Although the proposed changes to the informed consent document are not harmful, they are focused on rearranging and adding to a written document, not setting forth the types of information that it is important for prospective subjects to know and giving investigators and IRBs the flexibility to determine how best to communicate the information and ensure understanding, given the research design, level of inherent risk to participants, target study population, and best evidence for effective communications.

The NPRM preamble accurately notes that "there is also a growing body of literature that suggests informed consent forms have grown too lengthy and complex."[13] Despite this assertion, no required or additional elements of informed consent are removed from the regulations and four new elements have been added. The AAMC agrees with the idea that "the information must

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[11] 80 Fed. Reg. 53996.
[12] Unless the clinical trial is already regulated by the FDA, as proposed in §___.101(a)(2).
[13] 80 Fed. Reg. 53971.

be presented in sufficient detail relating to the specific research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or representative's understanding of the reasons why one might or might not want to participate."[14]

The AAMC does not see a meaningful benefit to research subjects, institutions, or investigators of requiring consent forms to be posted to a single website within 60 days of closing recruitment for a trial, as proposed in §___.116(h)(1) and strongly recommends the deletion of this proposed provision. Not only does this requirement increase investigator and institutional burden without any commensurate benefit to research subjects or the general public, it further reinforces the Common Rule's expectation that meaningful informed consent is always best accomplished through giving a prospective subject a paper document. Evolving best practices using the principles of adult learning and attempts to facilitate meaningful understanding by providing individuals with information in the most effective format and method are discouraged by this mandate. For example, an investigator could not post to a website an interactive online consent process that tests understanding throughout and gives individuals opportunities to engage with the information through videos, audio recordings, or optional additional modules to facilitate comprehension.

VI. Extension of the Common Rule to All Clinical Trials

As in the response to the ANPRM, the AAMC remains concerned that the proposed approach to expand the reach of the Common Rule fails to accomplish the stated goals, and if implemented as proposed would result in unintended consequences. We appreciate both the concern that certain research is not covered by any regulation and the restrictions the agencies face in being able to extend jurisdiction over that research. The AAMC is supportive of the standardization and implementation of ethical research practices and robust protections for all research subjects, regardless of where they reside, what entity funded the research, or where the research is taking place. The proposed change does not appreciably narrow gaps in the coverage of currently unregulated research, as it can only apply to institutions that receive federal funding, the vast majority of which already have policies that cover all research conducted at the institution, regardless of whether that research falls under federal oversight. What the proposal would do, is impose the additional requirements of the rule, such as a required single IRB review for multi-site research, on research not currently subject to this requirement. These requirements would result in an increase in administrative costs without any additional protections of human subjects. [*Question 85*] **The AAMC does not see an appreciable benefit to implementing this extension of the Common Rule to all clinical trials and does not recommend that the extension be implemented as proposed.**

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[14] 80 Fed. Reg. 54052.

In response to a question raised at a town hall meeting, a representative from OHRP confirmed that the option to "check the box" on an institutional federalwide assurance, providing a commitment that all research with human subjects conducted by that institution regardless of funding source, would be rendered moot by this new approach and would no longer be an option. The AAMC notes that this would have the effect of decreasing the number of research studies currently subject to the regulations at these institutions, as the extension of jurisdiction is limited to clinical trials. Further, there are state laws that require compliance with state regulations on human subjects research for all research not already regulated or overseen by a federal regulation.[15] In these states, institutions that have not been subject to state law requirements would now have to implement new procedures for the subset of research with human subjects that would not constitute a "clinical trial" under the revised rule.

VII. Additional Considerations and Recommendations

A. Safeguards for Protection of Biospecimens and Identifiable Private Information

The AAMC has significant concerns about the proposal to codify the requirement that institutions and investigators implement specific "reasonable and appropriate safeguards … to protect biospecimens or identifiable private information that they collect, obtain, receive, maintain, or transmit for research" as proposed in §___.105(a), when these safeguards *have yet to be developed by HHS.* The failure to include draft safeguards that can be reviewed in the NPRM itself makes it impossible to assess whether the proposal strikes the right balance between protecting sensitive information from disclosure and reducing burdens that do not provide commensurate protection for human subjects.

The NPRM provides researchers with the option to use either these yet undefined standards or the standards from the HIPAA Security Rule. This is not an effective stopgap measure until the new safeguards are developed. In response to the ANPRM, the AAMC strongly opposed the use of the HIPAA Security Rule as a model for safeguarding identifiable information in research. We note that the NPRM itself recognizes that in response to the ANPRM proposal, "a majority [of commenters] expressed serious concerns about the merits of requiring all investigators to meet standards modeled on certain HIPAA standards, such as those in the HIPAA Security Rule."[16]

Instead of including specific safeguards in regulation, the AAMC suggests that examples of reasonable safeguards, presented within a tiered, risk-based framework, be issued as guidance. This approach would preserve the flexibility that institutions and IRBs have effectively employed to address different types of data collected through research. Consistent

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[15] See, e.g., Section 2445 of Article 24-A of the New York Public Health Law: "The provisions of this article shall not apply to the conduct of human research which is subject to, and which is in compliance with, policies and regulations promulgated by any agency of the federal government for the protection of human subjects."
[16] 80 Fed. Reg. 53979 (September 8, 2015).

with the NPRM's commitment to harmonizing agency approaches to the protection of human subjects, the AAMC recommends that such a document be issued as joint guidance by all Common Rule departments and agencies. [*Question 43*]

B. Continuing Review

The AAMC supports the NPRM proposal to eliminate mandatory continuing review for research that was eligible for expedited review, that has progressed to data analysis or accessing clinical data from follow-up care, or has undergone the limited IRB review for use of stored biospecimens or identifiable private information (§___.109(f)). The proposed language, which retains the ability for an IRB to determine when continuing review is necessary to protect human subjects even if the stated criteria are met, is appropriate. This regulatory simplification, with the explicit opportunity to require more protections when needed is a good example of common sense flexibility within the rules.

C. Harmonizing Agency Guidance

The AAMC applauds the agencies' efforts to harmonize regulations and guidance, as demonstrated by the inclusion of all Common Rule agencies in the publication of the NPRM, the recent draft guidance documents issued by OHRP and FDA, and the proposed provision at §___.101(j) requiring the consultation, when feasible, of other Common Rule agencies before issuing guidance. The AAMC suggests that the provision move one step closer to true harmonization by requiring that the Common Rule agencies issue joint guidance interpreting these regulations whenever possible. [*Question 73*]

VIII. Conclusion

It is time to modernize and update the regulations for research with human subjects to better meet the challenges of new technologies, ways of communicating, data needs and opportunities, and the connectedness of people, systems, and the world in ways that were not contemplated at the time of the original drafting of the Common Rule. To do this effectively requires sweeping changes and visionary thinking. The proposals in the NPRM have allowed stakeholders to assess the likely impact and outcomes of the concepts contemplated in the ANPRM and have provided invaluable feedback through public meetings and formal comments. The AAMC appreciates the time constraints that may be driving the desire to finalize this rule, but urges all the departments and agencies involved in this process to use the comments and feedback in response to the NPRM to critically evaluate which proposals truly accomplish the objectives of the regulations in an appropriate balance and which need to be reframed, redrafted, or removed. A committed and knowledgeable community of researchers, institutional representatives, ethicists, and community representatives could be further engaged to help develop a new rule that protects human subjects, engages patients and populations, and facilitates important research.

The AAMC is concerned that the NPRM as a whole includes too many new mandates not based on evidence that any additional protections to human subjects, increase to autonomy, or maintenance of public trust in the research community justify the burdens. It has conflated reducing ambiguity with decreasing flexibility. Finally, the NPRM represents too complex a proposal to achieve a meaningful reduction in ambiguity of interpretation.

The dozens of large-scale community discussions, webinars, multi-day conferences and town hall meetings have demonstrated not only significant concern with the proposals but fundamental disagreements about what the proposed rule means, how certain provisions would be implemented, and how it would accomplish its stated goals. Compounding these concerns are frustrations with what has been perceived as a process entirely closed to members of the research community that could be providing useful and meaningful assistance with designing the tools, standards, and lists contemplated by this rule. Whether this rulemaking process proceeds to a final rule or the publication of a new simplified and significantly revised proposed regulation, the AAMC urges the Common Rule agencies to take the written comments seriously and engage individuals, institutions, and investigators in developing workable solutions to identified problems or concerns. This is a truly unique opportunity to reframe and modernize the Common Rule and to capture the promise and potential of research breakthroughs while recognizing that individuals want to understand the commitments and contributions they are making to move science and health forward.

The AAMC is committed to improving the health of all. Facilitating research while engaging participants in the social contract of research and protecting research subjects from harm is core to the AAMC and its member institutions. We commend to you the many thoughtful and detailed letters from medical schools and teaching hospitals across the country who can provide you with their perspectives on the benefits, burdens, and impact of these revisions on their institutions. We appreciate the opportunity to be a part of this historic change. If you would like more information about these comments or if we can be of assistance in this process as the next stage progresses, please contact Heather H. Pierce, Senior Director and Regulatory Counsel at hpierce@aamc.org.

Sincerely,

Ann Bonham, Ph.D.
Chief Scientific Officer