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Re: Docket No. NIH-2011-0003, Comments on “Clinical Trials Registration and Results Submission” 79 FR 69566-680 (Submitted at regulations.gov)

Re: Notice NOT-OD-15-019, Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information (Submitted via email to: clinicaltrials.disseminationpolicy@mail.nih.gov)

The Association of American Medical Colleges (AAMC) is a not-for-profit association representing all 141 accredited U.S. medical schools, nearly 400 major teaching hospitals and health systems, and 90 academic and scientific societies. Through its member institutions and organizations, the AAMC represents 128,000 faculty members, 83,000 medical students, 110,000 resident physicians, and thousands of graduate students and post-doctoral trainees. Our member organizations and their faculty include the nation’s preeminent clinical researchers. The AAMC appreciates the opportunity to submit comments on the above referenced Notice of Proposed Rulemaking, *Clinical Trials Registration and Results Submission* issued by the Department of Health and Human Services (HHS) and the related policy issued by the National Institutes of Health (NIH). Specific comments on both the proposed rule and the NIH draft policy are included in this letter.

The AAMC has strongly supported clinical trials registration and sharing of information from clinical studies. We were a leading proponent advancing the National Library of Medicine’s ClinicalTrials.gov website as the uniform, comprehensive national registry for clinical trials in 2004. In 2007, following a meeting of the AAMC’s Advisory Panel on Research and authorities on issues pertaining to the database, including the ClinicalTrials.gov director, and a journal editor and member of the International Committee of Medical Journal Editors, the AAMC issued a statement urging medical schools and teaching hospitals that conduct interventional studies on human research subjects to amend their own institutional policies to provide for trials registration. The intent of the Association’s statement, which preceded the 2007 Food and Drug Administration Amendments Act (FDAAA), was not only to facilitate compliance with the then-pending legislation, but to reaffirm publicly the view of our member institutions and clinical

investigators that research on human subjects “is ethically justified only to promote generalizable knowledge.”¹

The AAMC is supportive of the proposed rule extending the FDAAA’s requirements to all applicable trials, not only those for which the drug or device has received FDA approval. The AAMC also supports the NIH’s proposed parallel policy to extend requirements to all clinical trials meeting specified criteria funded by the agency.

Implementing both the final rule and the parallel policy should be undertaken with care to ensure the success of the agency’s goals. We encourage the NIH to carefully consider the following, each of which is further discussed below: limitations or difficulty in using the existing ClinicalTrials.gov database; the extent of effort required to submit additional data in comparison with the perceived marginal benefit to patients and the research community; the alignment of incentives and obligations for faculty researchers, particularly with posting negative results; and ensuring that the public-facing interface is both usable and clear in its utility and limitations.

A. Structure and format of the national registry

A key obstacle for posting trial results has been the lack of an effective format in the registration database that would facilitate efforts by other researchers to query and build on those results, especially across many trials, and to maximize the return even on negative results from the contributing investigators and their research. Developing such a format is challenging, and requires striking a balance to include sufficient structure for posting data in a way that enables research, while not imposing an overly complicated structure. The current ClinicalTrials.gov database lacks a structure that renders the reporting of clinical trials results usable to many clinical investigators who wish to build on the reporting and results of their peers. However, the proposed rule may actually go to the other extreme, establishing an overly complicated, “one-size-fits-all” structure.

Institutional users of the current ClinicalTrials.gov system report that limitations of the software infrastructure pose significant barriers to its effective and efficient use. For example, the inability to sort or filter the information or to create reports across one institutional account has been noted by more than one institution.

The AAMC recommends convening pilot projects with researchers and other institutional representatives to evaluate the new system for results posting, and identify the optimal, streamlined format for reporting results and facilitating queries of the data. There may be several models developed which could facilitate revisions to ClinicalTrials.gov.

¹ AAMC statement on clinical trials registration, Dec. 2007.

The success of ClinicalTrials.gov depends not only on the successful entering of data, but on a system that provides patients, research subjects, the public, and health care providers or investigators meaningful, contextual information about its contents. It is only by engaging both the likely and unlikely public users of ClinicalTrials.gov that the NIH will be able to create an improved national database. **The NIH, perhaps through the NLM's outreach efforts, should make a concerted effort to engage patients and the public in the development of a user-friendly and useful public-facing database.**

The inclusion of many additional clinical trials as a result of the NIH draft policy, including Phase I, small volume trials, and behavioral studies, could significantly impact the strain on and complexity of the resulting database. This extent of the additional burden that this policy will impose on investigators and institutions will be driven in large part by the ease of use for the system. Before NIH implements its draft policy to require all NIH-funded trials to follow the requirements of the final rule related to ClinicalTrials.gov, the AAMC strongly urges the agency to ensure that the necessary infrastructure, interface, and context is fully in place. This may mean that a delayed or staggered implementation for certain trials would be in the best interests of the agency, the investigators, and the public. **The AAMC encourages the NIH to get additional input and user testing from both investigators and patients as this implementation begins.**

B. Addressing compliance burdens

The National Science Board, the White House Office of Science and Technology Policy, the Federal Demonstration Partnership, and previous federal initiatives have uniformly expressed profound concern for the aggregate level of effort that investigators expend in complying with requirements related to federally funded research, and how this burden affects research productivity and effectiveness.

A National Research Council committee is now looking at these concerns at the direction of Congress and the NIH, and is charged to help address this situation. Recommendations may include further harmonizing and standardizing requirements across agencies, and clarifying requirements to assist institutions' counsel in precisely responding to obligations. The AAMC has strongly encouraged both federal agencies and the research community to evaluate the effectiveness with which various policies and regulations advance their stated objectives, and consider other and more flexible approaches for achieving these ends.²

The current proposed rule, the AAMC believes, is a case in point. The notice creates definitions that are not specified in the relevant sections of the FDAAA and that differ from those commonly used by IRBs. Many of the timeframes proposed are similarly inconsistent with other reporting requirements, and would be onerous and burdensome for compliance, without

² AAMC testimony to National Research Council, Feb. 13, 2015.

specifying how the particular requirement, as opposed to more flexible requirements, advances the interests of transparency or enabling follow-on research. There is little guidance to explain the rationale for the definitions or context.

The AAMC recommends that the demonstration project or pilot described above also consider whether the definitions and timelines should be modified in implementing the proposed regulation, specifically applying NRC recommendations on administrative burden and the IOM’s recommendations on clinical trial data sharing. A part of this effort should be for HHS and the NIH to specify the intended outcomes of the rule, how the promulgated requirements would meet those outcomes, and appropriate metrics for evaluating success.

To respond to the flexibility required when reporting results from a wide range of clinical trials, the AAMC further recommends that the final rule minimize the required fields and data. However, the NIH should work to develop ClinicalTrials.gov to accommodate a large number of elective fields and formats so that information critical or more relevant to specific trials or types of trials can be readily accommodated. The NIH should work with both investigators and the public through an iterative process to improve the quality and usability of the data.

Specific Recommendations to the Notice of Proposed Rulemaking:

1. The proposed number of updates that must be entered into ClinicalTrials.gov within 15 or 30 days of a change provides a standard that will be difficult to implement and will make full compliance with the regulations a struggle for most institutions. When possible, the timeframe in which changes must be reported should align with the requirements for the IRB review of changes in research with human subjects. These requirements are in place and well understood in academic institutions.
2. Definitions that differ from the same or similar terms in other regulations may lead to confusion or the need to create duplicate or revised processes for ensuring compliance with this regulation. Examples that are of most concern to AAMC member institutions are the proposed definitions for:
 - a. “adverse event,” which does not align with the FDA regulations;
 - b. “clinical trial,” which is very similar to the revised definition issued by the NIH but uses slightly different wording;
 - c. “completion date,” which seems to correspond with the current term “primary completion date” in the current system and may be confusing;
 - d. “intervention,” which includes the phrase “biomedical or other health related outcomes” but does not explain how to identify such a outcomes; and

- e. “study start date,” which is proposed to be the date when the study is open for enrollment or the first subject is enrolled, but is considered by many institutions to be the date of IRB approval and may lead to inconsistent internal records.
3. The AAMC agrees with previous comments that additional documents not currently specified in Section 402(j) of the Public Health Services Act should not be required through this rulemaking process. Requiring the posting of documents such as clinical trial protocols, informed consent documents, or lay summaries of the results could lead to the unintended consequences of causing these documents to be heavily redacted or drafted with the expectation that they would become public, therefore excluding detail that might be confusing to a lay audience but essential to investigators or IRBs.

C. Aligning incentives and outcomes

The optimal path to promoting a comprehensive national clinical trial registry with reported results and other pertinent information is to align incentives among researchers, research organizations, and funding agencies, rather than impose a rigid framework that may result only in *pro forma* compliance. **In addition to the steps noted above, the NIH should: encourage investigators to post negative results and facilitate this submission; facilitate and reward wide sharing of data and information; and recognize investigators and institutions who credit peers who have provided such data.**

The AAMC urges the NIH to use this opportunity to create an environment that supports effective, evidence-based regulation. The AAMC sees the current HHS proposed rule and the parallel NIH policy as part of the continuing effort to strengthen clinical trials by promoting transparency, trust, and usefulness of knowledge from human subjects research. The rule is also consistent with broader efforts to promote data sharing across medicine and science, as underscored by the Institute of Medicine’s recent report on clinical trial data sharing.³

The AAMC is again grateful for this opportunity to comment on the proposals specified in the NPRM. Please feel free to contact me, or my colleagues Heather Pierce, J.D., M.P.H. (hpierce@aamc.org) and Stephen Heinig (sheinig@aamc.org) with questions about these comments.

Sincerely,



Ann C. Bonham, Ph.D.
Chief Scientific Officer

³ Institute of Medicine (IOM). *Sharing clinical trial data: Maximizing benefits, minimizing risks*. Washington, DC: The National Academies Press, 2015.