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*Submitted via email to the White House Office of Science and Technology Policy:*
*emergencyclinicaltrials@ostp.eop.gov*

**Re: OSTP Emergency Clinical Trials RFI**

The Association of American Medical Colleges (AAMC) appreciates the opportunity to respond to the Office of Science and Technology Policy (OSTP) Request for Information: Clinical Research Infrastructure and Emergency Clinical Trials (87 Fed. Reg. 64821).

The AAMC is a nonprofit association dedicated to improving the health of people everywhere through medical education, health care, medical research, and community collaborations. Its members comprise all 156 accredited U.S. medical schools; 14 accredited Canadian medical schools; approximately 400 teaching hospitals and health systems, including Department of Veterans Affairs medical centers; and nearly 80 academic societies. Through these institutions and organizations, the AAMC leads and serves America's medical schools and teaching hospitals and the millions of individuals across academic medicine, including more than 191,000 full-time faculty members, 95,000 medical students, 149,000 resident physicians, and 60,000 graduate students and postdoctoral researchers in the biomedical sciences. Following a 2022 merger, the Alliance of Academic Health Centers and the Alliance of Academic Health Centers International broadened the AAMC's U.S. membership and expanded its reach to international academic health centers. Learn more at aamc.org.

From the onset of the COVID-19 pandemic, the AAMC's member medical schools and teaching hospitals were at the front lines of the response, treating patients, developing diagnostics, studying and administering therapeutics and working to address the needs of underserved communities. We agree with OSTP's assertion that the inability to fully and rapidly coordinate efforts on a national scale hampered the COVID-19 pandemic response on many fronts, including the lack of aggregated clinical data that could have sped our understanding of the infectious disease's transmission, assessment of whether certain treatments were effective, and development of diagnostics and therapeutics. In particular, the opportunity to study and understand the virus' impact through large-scale clinical trials was lost with the initiation of many local research protocols that often were poorly designed or insufficiently powered to provide meaningful actionable information. These inadequate trials represented a lost opportunity, and also raised ethical concerns by enrolling human subjects in trials that could

never have yielded meaningful, generalizable results. In addition, the exclusion of communities and populations that have been historically marginalized and who are generally underrepresented in clinical research served to increase the disparate impact of COVID-19 on these communities. For all these reasons, we welcome the current efforts by OSTP to develop new models or strengthen existing networks to organize coordinated clinical trials in advance of a "nationally or internationally significant biological incident."

Here we offer general comments on the RFI and the types of inquiries that we recommend be the focus of the next conversations in an ongoing effort and each of the four broad topics addressed by the RFI.

**General Comments**

The ambitious scope of this project, as OSTP has explicitly recognized, presents challenges to successful implementation. As OSTP and federal agencies begin to move forward, the AAMC urges OSTP to continue a transparent, multisector approach. This strategy should be aided by existing scholarship and previous efforts to find consensus on clinical trial agreement terms, as previous efforts have been hampered by impasses. There should be meaningful, bidirectional engagement with the communities the effort seeks to involve as active participants. The activities should reflect the lessons learned and documented regarding the successes and challenges of research on COVID-19. Finally, the efforts should leverage existing networks of connected institutions and researchers and engage them in stepwise actions through pilot studies to assess the feasibility and effectiveness of a larger effort prior to its implementation.

The listening sessions OSTP held to discuss this RFI were both promising examples of transparency in the development of OSTP's thinking and clear reminders of the extraordinary breadth of opinions, concerns, and considerations this effort raises. Although a range of national and international experts provided worthwhile perspectives and cautions in those sessions, we urge OSTP to include additional voices who could provide much needed direct community feedback early in this process. As has been demonstrated countless times in the context of clinical research, efforts to incorporate community voices in a way that demonstrates trustworthiness must commence at the beginning of the project and facilitate genuine partnership throughout.[1]

To this end, and as referenced below, the AAMC suggests the formation of one or more multi-sector groups tasked with taking a systematic approach to proposing the governance structure for this effort and criteria for the activation of clinical trials through the resulting network. This effort requires the voluntary and active participation of many organizations, including those that have not previously participated in federally-overseen clinical trials. The answers to the

[1] See, e.g., the AAMC Center for Health Justice's co-developed *Principles of Trustworthiness*, available at: https://www.aamc.org/trustworthiness.

important questions posed in the RFI require not only the input of experts, but also engagement and buy-in from across the biomedical research community. Early and broad engagement to arrive at consensus, rather than a "top down" approach from a panel of federal representatives alone will accomplish these two goals in parallel.

Additionally, we note that when the RFI was issued there was some concern in the biomedical research community about describing this work as "emergency clinical trials." It is worth considering that "emergency research" is well understood to describe a relatively uncommon situation when, for a particular protocol or individual, pre-planned research reviewed by an institutional review board can move forward in the absence of informed consent.[2] We suggest that an alternative term such as "coordinated clinical trial readiness" be used instead to avoid suggesting to the public that clinical research during a pandemic or other related incident would be undertaken in all or most cases without the need for informed consent.

**Governance for Emergency Clinical Trials Response**

The governance and primary coordinating structure, including robust cross-agency management and engagement, will be an essential component of a coordinated clinical trial response. We note at the outset that in the face of a pandemic, this coordination would have to be fully integrated into the national pandemic response. All stakeholders in this clinical trial response would benefit from reassurance that the data elements for protocols being developed would be aligned with any data being requested of hospitals and health departments to capture information about the spread and impact of the threat. To the extent possible, the clinical trial's data requirements should match those required for public health purposes. Because the same organizations that would be asked to implement these clinical trial protocols will also be addressing the pressing health needs of the impacted communities, all actions taken to facilitate an effective scientific and clinical response to the biological threat must be working toward a common goal. Similarly, consideration of required data formats and repository access should be undertaken in collaboration with the Centers for Disease Control and Prevention (CDC) and other federal agencies well before an emergency to facilitate streamlined and consistent data transfer to address both public health and clinical research needs. As with many aspects of this initiative, the thorny issues of electronic system interoperability and privacy will need to be addressed.

The AAMC notes that in the section of the RFI on "governance," the set of questions and proposed responsibilities seem to address two disparate sets of activities: 1) those required to develop the procedures and technical specifications to set up the initiative and 2) the decision-making and oversight activities that would take place during a pandemic or other public health emergency. The AAMC recommends that a federal entity should serve in a coordinating role for

[2] See FDA Guidance, *Exception from Informed Consent Requirements for Emergency Research*, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-research.

the first set of activities and retain primary responsibility for the second set of activities, engaging the multisector partners described below as advisors.

This section of the RFI asks for specific criteria or responses to issues that are essential for the successful implementation of a national effort. While we agree that each must be addressed, we suggest that they be answered through the establishment of multisector working groups with the specific charge to propose such criteria and present a consensus viewpoint for more efficient responses from the broad community. We recommend that OSTP look to the Department of Health and Human Services' Office of the Assistant Secretary for Health's Federal Plan for Equitable Long-Term Recovery and Resilience for a model on how to coordinate both federal resources and the local organizations and assets that represent all the vital conditions communities need to thrive and that would be useful in ensuring that this effort is maximally successful.[3] In addition to the relevant federal agencies, including the National Institutes of Health (NIH), Department of Health and Human Services Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) and CDC, the groups should include participants from across all sectors that will be expected or invited to participate in this initiative. The institution-specific and sector-specific responses to this RFI, along with the input provided directly to OSTP through listening sessions, could serve as a starting point for these groups, rather than for a final set of criteria issued by OSTP.

Once a widely supported governance and decision-making structure has been created, the process for developing the clinical trial protocols will be, in our estimation, the most important factor in the success of the initiative as whole. This process must provide all partners, from established research institutions to federal agencies to community clinics to the general public, the opportunity to understand, well in advance of a public health emergency, how those protocols will be created. Any institution that considers entering into an Emergency Master Agreement will need to have the confidence that the clinical trial protocol or protocols developed and activated under the agreement have scientific validity, the ability to answer the most important clinical questions, feasibility, generalizability, a mechanism to address protocol revisions based on new information, considerations for international collaborators or subjects, and a way to address institution-specific concerns. We suggest that the framework for this process be prioritized for development, as this would likely be an element that would take time to build broad community consensus.

One approach a governance group could consider is whether, instead of or in addition to a single clinical trial protocol implemented across all participating sites, a national effort could rapidly identify the most essential key data elements and endpoints that any clinical trial protocol should collect to be part of a national data collection effort. A scientific protocol working group could

[3] See the framework and resources at: https://health.gov/our-work/national-health-initiatives/equitable-long-term-recovery-and-resilience.

set criteria that a clinical trial would need to meet to be eligible to contribute to the data repository (e.g., inclusion criteria, whether an investigational agent was being studied), and then develop the specific fields, metadata, and format that would be required. By making these data requirements publicly available, it might broaden the reach of this effort to organizations that had not previously entered into the Emergency Master Agreement or that had elected not to solely implement the distributed protocol.

**Identifying and Incentivizing Research Institutions and Networks**

The RFI correctly identifies the key barriers to the monumental shift from a decentralized clinical trial approach with some collaboration across networks of institutions to the development and implementation of a single clinical trial protocol implemented simultaneously across many types of organizations. Although there is wide recognition of the need to improve clinical trial infrastructure as a whole, especially in the context of a biological threat, it will be a challenge to incentivize the voluntary participation of a host of organizations with vastly different levels of research experience, number of research staff, existing clinical trial infrastructure, and motivation to take on new research activities in the face of a threat on the scale of COVID-19.

The first steps in building the network of sites that could participate in such an effort should be to identify the existing networks and connections that could be readily activated. Not only can these networks and consortia extend the number of potential research sites, they can also provide OSTP with considerable information about the advantages and challenges with implementing a single protocol or process across a set of organizations with already-established connections. As one key example, the Clinical and Translational Science Awards (CTSA) program administered by the National Center for Advancing Translational Sciences (NCATS) was developed to address precisely the kinds of challenges and inefficiencies in translational research that OSTP seeks to address with this current effort. Engaging with both NCATS and CTSA institutions would be instrumental in assessing the utility of using this network or working to create new models for connecting institutions.

As further discussed below in the context of building clinical trial infrastructure through "warm base" research, a more complete model will need to include information about how this research and the contemplated infrastructure would be funded. Incentives for joining this network through a master agreement will need to go beyond the ability to participate in a novel mechanism for gathering data in a pandemic to a more sustainable engagement in the clinical research ecosystem as a whole.

The AAMC applauds OSTP for considering as a priority the inclusion of organizations that serve underrepresented populations and can engage underserved geographic and demographic communities. As OSTP is exploring ways to increase this participation, leveraging the

connections between academic institutions and their community and public health partners could open additional avenues of communication and sources for working group participants.

**"Warm Base" Research**

As described in the RFI, a core component of an accelerated clinical trial response to an infectious disease outbreak or other public health emergency is the rapid distribution of one or a small number of key protocols for many sites to implement simultaneously. In order to maximize the reach of these trials to all impacted geographic areas and underserved areas, the RFI raises the possibility of supporting or facilitating so-called "warm base" research. This is described as a mechanism through which staff at a site unexperienced with some or many aspects of conducting clinical trials gain familiarity with the regulations, procedures, and data collection methods of clinical trials in advance of the need to activate a specific protocol in the context of a public health emergency.

At its core, what this describes is the concept of research capacity building, a sorely needed and resource intensive endeavor. The AAMC is supportive of efforts that build clinical trial capacity and urges OSTP to consider how these efforts might be initiated and funded at sites that currently have little or no capacity to conduct clinical research. We caution too that even simple data collection trials created to build this capacity through "warm base" research must themselves be ethically and scientifically sound, and conducted and overseen by trained research staff. Such training and capacity building efforts are welcome but might constitute a heavy lift for a federal initiative that is simultaneously developing the governance and process for the initiation of a coordinated clinical trial initiative. As with many aspects of this effort, testing the feasibility of supporting the research through pilot studies will be most beneficial.

**Emergency Master Agreement**

A core structural component of the effort being discussed is the so-called "Emergency Master Agreement," which would seek to settle core contract terms well in advance of a biological threat. A laudable goal, we note similar efforts over decades to settle on key terms in clinical trial agreements have had limited success. Beginning the process with a comprehensive look at the impact of these harmonization efforts would be of use to OSTP. In many cases provisions such as indemnification and subject injury have been difficult to resolve even in more successful templates.

The effort seeks to engage many types of organizations beyond academic medical centers to carry out one or more protocols. The necessary terms, provisions, and capacity assessments may vary by type of organization and type of trial. Observational studies, medical record reviews, and interventional trials with known or investigational agents will each require very different infrastructure and expertise. It may be necessary to create a tiered set of agreement provisions,

allowing each institution to opt in to a threshold set of terms based on its current capacity for conducting clinical trials.

A question that will need to be addressed is how the nationally developed protocols will be coordinated with (or in some cases prevent) other clinical trials developed simultaneously by industry, academic health centers, or other organizations that have signed the Emergency Master Agreement. A threshold issue for many institutions will be whether, by signing the agreement, that institution would be contractually prohibited from initiating or participating in other clinical trials. Without knowing in advance what the agreed-upon trials would seek to answer, this might have a chilling effect on the willingness of some organizations to participate.

The AAMC and its member institutions stand ready to assist the OSTP and federal agencies in considering how greater coordination and the building of clinical trial infrastructure could help us better respond to the threat posed by another infectious disease outbreak or public health emergency. Please feel free to contact me or my colleague Heather Pierce, Senior Director for Science Policy and Regulatory Counsel (hpierce@aamc.org) about these comments or other ways in which we can help.

Sincerely,

Ross McKinney, MD
Chief Scientific Officer

cc: David J. Skorton, MD, President and Chief Executive Officer