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Elisa A. Hurley, PhD

Submitted via email to emergencyclinicaltrials@ostp.eop.gov

January 26, 2023

Stacy Murphy

Office of Science and Technology Policy

Executive Office of the President

Eisenhower Executive Office Building

1650 Pennsylvania Ave., NW

Washington, DC 20504

RE: Request for Information – Clinical Research Infrastructure and
Emergency Clinical Trials

Dear Ms. Murphy,

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to respond to the Request for Information – Clinical Research Infrastructure and Emergency Clinical Trials” published in the *Federal Register* on October 26, 2022.

PRIM&R is a nonprofit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served as a professional home and trusted thought leader for the research protections community. Through educational programming, professional development opportunities, and public policy initiatives, PRIM&R seeks to ensure that all stakeholders in the research enterprise appreciate the central importance of ethics to the advancement of science.

We recognize and appreciate the importance of proactively addressing how the research enterprise can be better prepared to respond to and efficiently conduct critical research during a public health emergency. There are lessons to be learned from the flexibility, creativity and ingenuity demonstrated by the research community in the early days of the COVID-19 pandemic. To that end, PRIM&R offers comments related to three specific areas for OSTP consideration:

1. Streamlining institutional review board (IRB) review for research during emergencies
2. Utilization of public health surveillance during emergencies
3. Tension between clinical care and research during public health emergencies.

1. Streamlining IRB review for research during emergencies

Efforts to reduce regulatory burden without undermining the safety of human subjects in such research, such as the use of reliance agreements to streamline IRB review by requiring a single IRB of record (sIRB) for multisite studies, are underway. In the RFI, OSTP requests comment “*on the possibility of developing a framework of key terms ... in advance of an emergency... that can be integrated into clinical trial agreements for emergency clinical trials...*” One of the suggested key terms to be included in such an Emergency Master Agreement is the use of a sIRB.

PRIM&R notes that the use of a sIRB model may well streamline processes for study initiation and be beneficial for research conducted during emergencies. However, given that the sIRB model is relatively new, PRIM&R recommends that OSTP consider gathering evidence to determine if the sIRB model does in fact make the review process more efficient, particularly within the context of time sensitive research conducted during emergencies. For example, OSTP could consult with the Department of Health and Human Services to learn more about its exception to the sIRB requirement for COVID-related research and whether that exception was beneficial in improving the efficiency of multi-site trials during the pandemic. Adopting a flexible approach, initially, by supporting but not mandating sIRB, may provide the research community with an opportunity to learn about the most efficient pathways in future emergencies and make informed choices about the IRB review structure that can best support multisite research during an emergency.

OSTP should also consult with IRBs that have experience serving as the IRB of record for large multisite trials and gather data about experiences of IRB review during the COVID pandemic and other emergencies to learn more about models that have proven effective in both emergency and nonemergency situations and can be built into the clinical research infrastructure. Lastly, OSTP should also consider mechanisms (including funding) to ensure that research oversight systems are poised for rapid response in public health emergencies through the routine use of emergency preparedness simulation exercises.¹

2. Utilization of public health surveillance during emergencies

There are also loopholes in the interpretation of current regulations for protecting the rights and welfare of human subjects that were highlighted during the pandemic, and which should be addressed. For example, the 2018 Federal Policy for the Protection of Human Subjects (also known as the Common Rule) deems public health surveillance activities as falling outside the regulatory definition of “research,” and as such exempt from compliance with the regulatory requirements. However, the regulations do not clearly distinguish between public health activities that constitute *surveillance* and those that

¹ Lowe, A. E., Kraft, C., Kortepeter, M. G., Hansen, K. F., Sanger, K., Johnson, A., Grein, J. D., Martin, Julie, Rouselle, R. Garland, J.A., Spotts, J., Lowe, J. J., Sauer, L. M., Kratochvil, C. J., * Gordon, B. G. (2022). Developing a rapid response single IRB model for conducting research during a public health emergency. *Health Security*, 20(S1), S60-S70. doi:10.1089/hs.2021.0181

constitute *research*.² During the pandemic, IRBs saw a surge in proposals identified as “public health surveillance,” where traditional protections such as informed consent and data confidentiality safeguards were therefore not triggered or required.

While PRIM&R appreciates the importance of not impeding vital public health activities, we believe that the public health surveillance exclusion must be utilized mindfully and in a manner that does not take advantage of the ambiguity in the regulations to intentionally skirt requirements such as informed consent—doing so threatens to further erode public trust in science and medicine, which may already be fragile during public health emergencies. At the same time, given that collection and future use of data is often a common part of public health surveillance activities, we acknowledge that the line between public health surveillance and research is blurry. We therefore believe that, individuals who are subjects of such activities, as well as the general public, should be given general information about the scope and purpose of any public health surveillance activities and potential future uses of data collected as part of those activities. ***PRIM&R recommends that OSTP engage the public in exploring provisions that support public health activities broadly (i.e., both surveillance and research) while ensuring that the rights and welfare of individuals and of the public at large are protected, e.g., via public service announcements/education campaigns as well as, where appropriate, informed consent, respectively. Such provisions will serve the dual purpose of sustaining public health and promoting public trust in science and medicine.***

3. Tension between clinical care and research during public health emergencies

The COVID-19 pandemic also illuminated tensions between clinical care and research during a public health emergency, specifically with reference to the use of the expanded access pathway. Expanded access (EA) to drugs that have not been approved by the Food and Drug Administration (FDA) outside clinical trials is legally permissible only if it does not interfere with drug development. During the pandemic, a large-scale expanded access program (EAP) for convalescent plasma (CCP) raised important questions about the clinical research infrastructure as well as the other real impacts of EA on clinical trials. The EAP for CCP allowed access to an unapproved product for large numbers of patients at treatment sites where the product might not otherwise have been available, perhaps because those sites were identified as not having the infrastructure to support randomized clinical trials. This was a problem, however, because data on the use of CCP in this EAP was not collected in a manner that allowed for scientifically valid assessment of CCP’s safety or efficacy as a treatment for COVID-19. Moreover, the EAP was utilized at sites that did in fact have substantial research capacity: more than one-third of the top 100 NIH-funded institutions

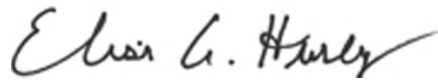
² Beach, M. C., Lederman, H.M., Singleton, M, Brower, R.G., Carrese, J., Ford, D. E., Hansoti, B., Hendrix, C. W., Jorgensen, E. V., Moore, R. D., Rocca, P, & Zenilman, J. M. (2020). Desperate times: Protecting the public from research without consent or oversight during public health emergencies. *Annals of Internal Medicine*, 173(11), 926-928. doi:10.7326/M20-4631

and several hundred sites running Phase 3 COVID-19 trials, including CCP trials.^{3,4} It seems likely, therefore, that at least some of the resources, including access to patients, that were invested in the EAP for CCP could just as well have been directed towards a greater number of properly designed clinical trials, which would have resulted in more rapid, robust prospective clinical data about CCP as a treatment for COVID-19.

Thus, PRIM&R recommends that OSTP urge the federal government to invest in building a better clinical infrastructure so that sites that were recruited only because of the public health emergency will be better equipped to run clinical trials under emergency and non-emergency conditions in the future, promoting clinical trial diversity and equitable access to clinical trials. In addition, there is need for a strong oversight mechanism to monitor EAPs to ensure that such programs are not utilized in a way that is detrimental to the conduct of scientifically robust clinical trials.

Thank you again for the opportunity to provide information on building a robust infrastructure that can support emergency clinical trials. We hope that our comments are useful to OSTP in this effort. PRIM&R stands ready to provide any further assistance or input that might be of use. Please feel free to contact me at 617.303.1872 or ehurley@primr.org.

Sincerely,



Elisa A. Hurley, PhD
Executive Director

cc: PRIM&R Public Policy Committee, PRIM&R Board of Directors

³ Gustafson, M. S., Patel, A., Hong, C., Meline, M., Pena, D., Tang, C., & Lynch, H. F. (2022), Estimated clinical trial capacity of sites participating in the COVID Convalescent Plasma Expanded Access Program. *JAMA Network Open*, 5(10), e2237540. doi:10.1001/jamanetworkopen.2022.37540

⁴ Sullivan, D. J., Gebo, K. A., Shoham, S., Bloch, E. M., Lau, B., Shenoy, A. G., Mosnaim, G. S., Gniadek, T. J., Fukuta, Y., Patel, B., Heath, S. L., Levine, A. C., Meisenberg, B. R., Spivak, E. S., Anjan, S., Huaman, M. A., Blair, J. E., Currier, J. S., Paxton, J. H., ... Hanley, D. F. (2022). Early outpatient treatment for COVID-19 with convalescent plasma. *New England Journal of Medicine*, 386(18), 1700-11. . DOI: 10.1056/NEJMoa2119657