



PUBLIC RESPONSIBILITY IN
MEDICINE AND RESEARCH

Chair

Heather H. Pierce, JD, MPH

Vice Chair

Natalie L. Mays,
BA, LATG, CPIA

Secretary

David H. Strauss, MD

Treasurer

Owen Garrick, MD, MBA

Board of Directors

Albert J. Allen, MD, PhD

Barbara E. Bierer, MD

Elizabeth A. Buchanan, PhD

Bruce Gordon, MD

Mary L. Gray, PhD

F. Claire Hankenson,
DVM, MS, DACLAM

Karen M. Hansen

Martha Jones, MA, CIP

Jori Leszczynski, DVM, DACLAM

Vickie M. Mays, PhD, MSPH

Robert Nobles, DrPH, MPH, CIP

Sally Okun, RN, MMHS

Suzanne Rivera, PhD, MSW

Stephen Rosenfeld, MD

Ex Officio

Elisa A. Hurley, PhD
Executive Director

July 30, 2019 Submitted electronically at www.regulations.gov

Norman E. Sharpless, MD
Acting FDA Commissioner
c/o Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2019-D-1264, "Enhancing the Diversity of Clinical Trial Populations-Eligibility Criteria, Enrollment Practices, and Trial Designs; Draft Guidance for Industry" (84 *Federal Register* 26687)

Dear Acting Commissioner Sharpless:

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to comment on the Food and Drug Administration (FDA)'s Draft Guidance for Industry, "Enhancing the Diversity of Clinical Trial Populations-Eligibility Criteria, Enrollment Practices, and Trial Designs," published in the *Federal Register* June 7, 2019.

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, including members and staff of human research protection programs and institutional review boards (IRBs), investigators, and their institutions. Through educational programming, professional development opportunities, and public policy initiatives, PRIM&R seeks to ensure that all stakeholders in the research enterprise understand the central importance of ethics to the advancement of science.

PRIM&R believes the FDA's draft guidance represents a significant and welcome step forward in the agency's efforts to enhance diversity in clinical trial participation, and we applaud the agency's leadership in proactively recommending practical strategies that sponsors and other parties can adopt to advance this important goal.

We furthermore appreciate the comprehensiveness of the draft guidance, touching as it does on a wide range of approaches for ensuring that clinical trial enrollment better reflects the populations that will ultimately be taking a newly approved therapy.

The draft guidance would benefit from more robust discussion of the *ethics of enhancing clinical trial diversity*. Below we elaborate on this suggestion and make a few additional recommendations that we believe will strengthen the guidance as a tool to help research sponsors advance the important goal of diversifying clinical trials.

In the current version of the draft guidance, the rationale for enhancing diversity in trial enrollment is presented almost exclusively as a matter of better reflecting the populations most likely to use the study therapy if approved. While we understand the FDA's focus on the scientific and clinical benefit of increasing diversity in clinical trials, those are not the only reasons to widen eligibility criteria and make other efforts to include populations that might otherwise be underrepresented in trials. There are ethical reasons as well. The Belmont Report's principle of justice demands the equitable distribution of burdens and benefits of research.¹ This means in part that those most likely to receive the benefits of a newly approved therapy ought also to share the burdens of participating in the clinical trial testing that therapy. It also means that the benefits of research—including potential knowledge about and access to new therapies—ought to be fairly distributed among those who have relevant medical needs, including previously underrepresented communities. Those communities ought then to be included in research on those therapies. When a clinical trial's enrollment does not reflect the diversity of the patient population that will ultimately be using the therapy, the post-approval use of the therapy with categories of patients for whom the trial did not develop a proper evidence base about the therapy's safety and efficacy is equivalent to an uncontrolled experiment.

The ethical issue of fair distribution of benefits and burdens of research participation also requires thinking about relevant populations' access to the novel therapy post approval. Translating novel therapies from the clinical trial setting to the real world raises questions beyond effectiveness about whether or not the new therapy will reach all communities where there is need, whether its use or delivery is culturally acceptable, how burdensome receiving the therapy will be, in terms of number and duration of clinic visits, and the like. These issues are relevant to the question of whether the therapy will have its intended effects. The guidance discusses minimizing the burdens of participating in research and engaging with communities to address participant needs regarding research participation, two important factors for enhancing diversity, to be sure. But if utilizing the novel therapy in the real world turns out to involve *additional* burdens for previously underrepresented populations, then that fact should be considered in the determination of whether recruiting those groups into the research provides overall net benefit to them. These considerations should be acknowledged in the guidance.

Furthermore, the FDA should make clearer and help stakeholders understand that the inclusion in clinical trials of previously underrepresented groups may involve ethical tradeoffs. The guidance acknowledges that one reason that members of certain

¹ [The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research \(1979\). Department of Health and Human Services.](#)

populations are intentionally excluded from trials is because they have concomitant chronic conditions. But it pays inadequate attention to the fact that those exclusions often serve specifically as *protections* from the increased risks individuals face as a result of having those conditions. Making a commitment to diversifying trial enrollment and including previously underrepresented groups in research—including those with comorbidities—requires acknowledging and attending to the possibly heightened risks their participation entails. As we have noted elsewhere,² PRIM&R believes we should move away from the practice of reflexively excluding certain populations from research participation as a primary risk-mitigation strategy, because it unjustly excludes those groups from the benefits of research, and that we should instead make efforts to include those groups in research, *provided certain safeguards are met*. It is important to recognize the tradeoffs, in terms of increased risk, that may come with making these efforts at inclusion.

We suggest the guidance's discussion of expanding and enhancing the enrollment of groups who previously may have been excluded on safety grounds include an explicit recognition of these issues. Although the FDA throughout the document touches on ways to mitigate the increased risks that may accompany the recommended efforts to diversify trial enrollment—such as narrowing exclusion criteria to allowing participants with milder forms of comorbid conditions to enroll (lines 108-112); enrolling higher risk participants at sites that have experience working with those specific groups (lines 121-125); and considering staggering enrolment by age in pediatric trials with potential safety concerns (lines 160-162)—we urge the agency to explicitly articulate, early in the guidance, a **broad recommendation that as sponsors work to enroll historically underrepresented groups, they must consider and make plans to address the full range of risks participants might face.**

In that vein, the guidance would benefit from considering some additional protections, safeguards, and oversight that might facilitate inclusion. It could, for instance, discuss how better use of community advisory boards and data and safety monitoring boards could provide additional safeguards for studies where some of these newly included participants may be at increased risk. The FDA should also mention and encourage, in this context, risk-management measures such as site monitoring, reporting requirements, trial personnel training, and implementing a comprehensive risk management plan. Taking such steps is especially important given that investigators may not always have experience working with these new populations. Finally, the FDA should use the publication of this guidance as an opportunity to further encourage the use of risk-based monitoring and refer to its prior guidance on this issue.

² [Response to National Institutes of Health's Request for Information: Inclusion in Clinical Research Across the Lifespan](#). (2017). Public Responsibility in Medicine and Research (PRIM&R). [Response to the Food and Drug Administration's Draft Guidance for Industry. Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients](#). (2019). PRIM&R.

Enhancing communication with and engagement of potential participants and their communities may also help sponsors develop strategies to identify, mitigate, and communicate to participants about risks that may accompany the participation of previously underrepresented populations in research. We therefore agree with the FDA that sponsors should engage patient communities and other prospective participants in the design of clinical trial protocols. We urge the FDA to expand upon its recommendations in this area and align them with other FDA guidance on patient-focused drug development. Sponsors should be encouraged to engage communities across all stages of the research process, including on other aspects of study design, recruitment activities, and dissemination of research findings. To this end, the FDA's commendable [patient-focused drug development resources](#) could be mentioned in section III.B of the guidance.

Finally, we encourage the FDA to consider the following additional recommendations:

- The draft guidance should include in its list of populations that are often excluded without scientific rationale non-English speakers, who can be safely enrolled in research provided certain safeguards are put in place.
- While we understand this guidance originated with CDER and CBER, we encourage the FDA to extend this guidance to include devices, as most of the recommendations in this draft seem applicable to sponsors of device research as well.
- The draft guidance should offer more robust recommendations for decreasing the burden of participating in research for trial participants. For oncology trials, for example, offering to reimburse travel costs or provide payment for participation, as the guidance suggests, may go only part way toward minimizing the financial burden of trial participation. In these trials, sponsors frequently cover the costs of the study drugs themselves but not the administrative costs associated with providing and taking the study drug, or the costs of interventions considered standard of care that may be part of the study. As a result, those without health insurance may be less likely to be able to afford trial participation, which may affect diversity of the trial population. Sponsors should be encouraged to put in place mechanisms that allow those without insurance and who cannot afford trial costs to participate.

Thank you again for the opportunity to comment on this important issue. We are grateful that the FDA is taking a leadership role in enhancing clinical trial diversity, and we stand ready to provide any further assistance or input, should that be of interest. Please feel free to contact me at 617.303.1872 or ehurley@primr.org.

Respectfully submitted,



PRIM&R
Page 5

Elisa A. Hurley, PhD
Executive Director

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