ACRO Innovate Advocate Collaborate

Submitted via email to cures.rfi@mail.house.gov

August 2, 2024

The Honorable Diana DeGette (CO-01)
2111 Rayburn House Office Building
Washington, DC 20515

The Honorable Larry Bucshon, M.D. (IN-08)
2313 Rayburn House Office Building
Washington, DC 20515

RE: Next Generation Cures RFI

Dear Representatives DeGette and Bucshon,

Thank you for the opportunity to provide feedback to your reinvigorated 21st Century Cures effort. The Association of Clinical Research Organizations (ACRO) and its members are encouraged by your commitment to this important work.

ACRO is made up of the world's leading clinical research and technology organizations. Our member companies are involved in the majority of industry-sponsored, FDA-regulated clinical trials in the United States and around the world. ACRO members provide an array of specialized services across the entire spectrum of drug, biologic, and medical device development—from discovery, pre-clinical, proof of concept, and first-in-human studies, through post-approval and pharmacovigilance research.

ACRO was pleased to be involved in the drafting of both the 21st Century Cures and Cures 2.0 Acts, to which we provided language and expertise on issues including increasing adoption of decentralized clinical trial elements, improving diversity and representativeness in clinical trial populations, the collection and utilization of patient experience data, and further increasing the use of real-world evidence in drug development.

General Comments

With the enactment of the 21st Century Cures Act and the introduction of the Cures 2.0 Act, we have seen tremendous progress in the drug development industry. Keeping the goal of getting the right treatments to the right patients at the right time in mind, ACRO members are committed to innovating at every step along the drug development process.

An essential piece of the drug development enterprise is regulatory stability. Recent decisions by the Supreme Court, most notably the *Loper Bright Enterprises v. Raimondo* decision to overturn the *Chevron doctrine*, and the related *Corner Post Inc. v. Board of Governors of the Federal Reserve System* decision, threaten longstanding FDA decisions and authorities that ACRO member companies, and American citizens, rely upon.

In 1962, the Food, Drug, and Cosmetic (FD&C) Act was amended to stipulate that drugs being evaluated for approval are not only safe, but *effective*. The statute states that effectiveness must be established by "substantial evidence," which is further defined as:

> "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[1]

Since that amendment, the FDA has approved 1582[2] new drugs and has consistently employed the statutory standard of safety and effectiveness as laid out in the FD&C Act in making those approval determinations.

To guard against FDA approval determinations being relitigated in courts, we believe that the next iteration of Cures should include language that clarifies that the FDA has correctly interpreted Congressional intent regarding its delegated responsibilities and authorities over the last 60 years, and that Congress remains confident in the Agency's science-based decision making. Failure to do so will cause instability and uncertainty for biopharma and drug development companies and, more importantly, our patients—who must be confident that the drugs and medical products they use are safe and effective.

Specific Comments

Question 2: What elements might be missing that are essential for further progress?

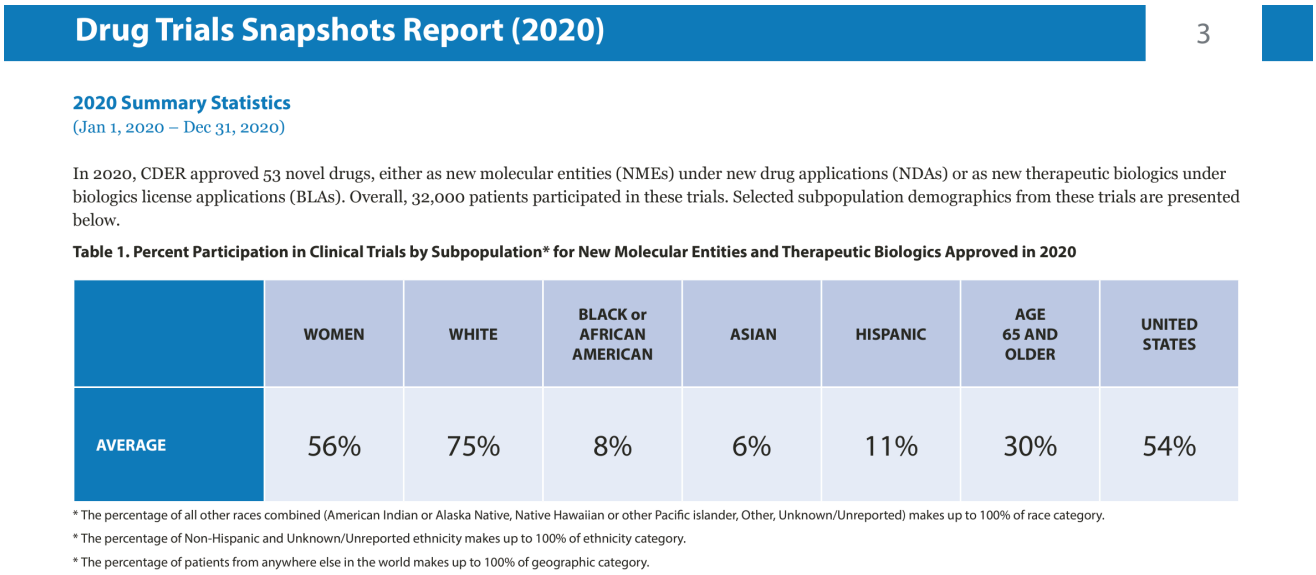
Diversity, Equity, and Inclusion in Clinical Research

ACRO and its members were pleased that Cures 2.0 included provisions aimed at improving the representativeness of clinical trials in the United States. It is important to build on the work that has been done to improve racial and ethnic diversity of clinical research by expanding that lens to include other facets of representativeness (e.g., age, gender, geographic location, etc.).

Providing demographic data for each year's approved novel drugs, the FDA Drug Trials Snapshots have been a useful tool for measuring diversity since 2015, however, the Snapshot reports no longer include the summary statistics for the overall participation demographics in clinical research nor for each therapeutic area. The 2020 Snapshots Report was the last report that provided this breakdown, as seen below in Figure 1. The 2020 Snapshots Report was also the last to include a demographic breakdown for each therapeutic area, as seen in Figure 2. The subsequent Snapshots Reports have included demographic breakdowns for each individual novel drug approved in each year, but the

[1] Food, Drug, and Cosmetic Act, Sec. 505(d) (21 U.S.C. § 355(d)).
[2] Summary of NDA Approvals & Receipts, 1938 to the present. https://www.fda.gov/about-fda/histories-fda-regulated-products/summary-nda-approvals-receipts-1938-present.

higher-level breakdown by each therapeutic area is no longer included.



Drug Trials Snapshots Report (2020) 3

2020 Summary Statistics
(Jan 1, 2020 – Dec 31, 2020)

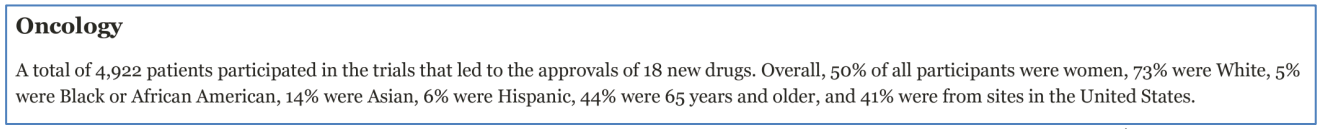
In 2020, CDER approved 53 novel drugs, either as new molecular entities (NMEs) under new drug applications (NDAs) or as new therapeutic biologics under biologics license applications (BLAs). Overall, 32,000 patients participated in these trials. Selected subpopulation demographics from these trials are presented below.

Table 1. Percent Participation in Clinical Trials by Subpopulation* for New Molecular Entities and Therapeutic Biologics Approved in 2020

	WOMEN	WHITE	BLACK or AFRICAN AMERICAN	ASIAN	HISPANIC	AGE 65 AND OLDER	UNITED STATES
AVERAGE	56%	75%	8%	6%	11%	30%	54%

* The percentage of all other races combined (American Indian or Alaska Native, Native Hawaiian or other Pacific islander, Other, Unknown/Unreported) makes up to 100% of race category.
* The percentage of Non-Hispanic and Unknown/Unreported ethnicity makes up to 100% of ethnicity category.
* The percentage of patients from anywhere else in the world makes up to 100% of geographic category.

Figure 1. Demographic breakdown of trial participants across all approved novel drugs in 2020.[3]



Oncology

A total of 4,922 patients participated in the trials that led to the approvals of 18 new drugs. Overall, 50% of all participants were women, 73% were White, 5% were Black or African American, 14% were Asian, 6% were Hispanic, 44% were 65 years and older, and 41% were from sites in the United States.

Figure 2. Demographic breakdown of trial participants across all approved novel oncologic drugs in 2020.[4]

These broader demographic breakdowns across the entire collection of that year's approved novel drugs are extremely important for tracking participation rates across various demographic groups to ensure we can measure progress.

The next iteration of Cures should include provisions that require the FDA to include the overall summary statistics for the percent population in clinical trials by subpopulation for new molecular entities and therapeutic biologics approved that year, as well as an overall breakdown by therapeutic area (not just by individual novel drug) in each year's Drug Trials Snapshots Report going forward.

Artificial Intelligence/Machine Learning (AI/ML) in Drug Development

ACRO's AI/ML Committee has outlined principles for the responsible use of AI/ML in clinical trials.

[3] *2020 Drug Trials Snapshots Summary Report*, U.S. Food and Drug Administration, February 2021. https://www.fda.gov/media/145718/download.
[4] *2020 Drug Trials Snapshots Summary Report*, U.S. Food and Drug Administration, February 2021. https://www.fda.gov/media/145718/download.

As the FDA has reported, participants in the AI drug development continuum are accelerating adoption of AI-based solutions that deliver meaningful benefits, including drug discovery and image analysis. In doing so, we expect to see more medicines available to more patients with unmet need faster. While the promise of AI/ML tools used in drug development is great, we want to ensure that these tools are developed and used responsibly.

Congress should direct the FDA to regulate the use of AI/ML tools in drug development in a risk-based manner, meant to assure the safe, effective, and ethical applications of these technologies. The FDA should promulgate a clear and consistent regulatory framework that provides guidance on the development, validation, and use of AI/ML models in drug development and supports innovation. This includes collaboration with regulatory bodies to align on standards and best practices. Key elements of such regulation should include:

1. **Good Machine Learning Practices (GMLP):** Establishing and adhering to GMLP is critical to ensure the reliability and robustness of AI/ML models. This includes rigorous validation, continuous monitoring, and adherence to high standards of data quality and integrity.
2. **Ethical Considerations:** AI/ML applications must uphold ethical principles such as fairness, transparency, and accountability. This includes mitigating bias in AI models, ensuring explainability of AI decisions, and maintaining human oversight.
3. **Responsible Data Usage:** Ensuring that AI/ML models are trained on diverse, high quality data sets that are representative of the patient populations they are intended to serve. This also includes maintaining data privacy and security.

Decentralized Clinical Trials and Telehealth

ACRO was encouraged by the focus Cures 2.0 put on provisions to continue to decentralize clinical trials and make them more accessible to patients. Ensuring access to telehealth services is an essential component of access. Rollbacks in telehealth interrupt continuity and access for patients trying to participate in clinical trials, and their regular clinical care. We would suggest the next iteration of Cures includes provisions to further make available patients' access to telehealth services.

Patient Experience Data

ACRO echoes our comments from our 2021 Cures 2.0 letter in which we suggested to following edit to Sec. 204(b)(1)(B)(i) of H.R.6000, the Cures 2.0 Act: "…in particular, collecting data on patient experience with regards to the use of various technologies and decentralized trial elements, as well as engaging the patient early on in trial planning and design to build the patient's voice into the trial from inception, with the aim of incorporating patient-centricity by design in the future." We would also suggest revisiting the provisions in Sec. 407 and 408 and broaden them to include all patients, not just pediatric patients. For a truly patient-centric design, all patients should have access to biomarker testing and

genomic sequencing for empowerment in shared decision making, which would include clinical research as a care option.

Question 3: What additional reforms, support mechanisms, or incentives are needed to enhance or improve the effectiveness of the steps already taken, including any structural reform to agencies, offices, or programs involved?

DEI in Drug Development

As mentioned previously, we need to be doing more to improve the representativeness of clinical trials in the United States. A large part of that is removing unnecessary barriers to participation. One such barrier is the persistent lack of renumeration and logistical support to patients for their participation in clinical trials. If we are serious about increasing the participation among under-served, rural, and under-represented populations, the next piece of Cures legislation should include provisions that ensure participants are compensated for their time and that they receive support with transportation, childcare, eldercare, lodging and meals.

Any future Cures legislation should also exempt payments received for clinical trial participation from a participant's taxable income.

Congressman Bucshon's H.R.8412, the Clinical Trial Modernization Act, should be included in this next version of Cures as it neatly supports these two issues, incentivizes and makes possible participation by those who are largely unable to participate in clinical research, and would help to bolster steps already taken by previous Cures efforts.

AI/ML in Drug Development

To further enhance the progress made by the 21st Century Cures Act, ACRO suggests the following reforms and support mechanisms as they relate to AI/ML:

1. **Standardization of Practices:** Encourage the development and adoption of standardized practices for AI/ML in drug development, including data sharing protocols, model validation standards, and ethical guidelines.
2. **Cross-Agency Collaboration:** Facilitate cross-agency collaboration to harmonize AI/ML regulatory approaches and share best practices.
3. **Transparency and Accountability:** Ensure transparency in AI/ML model development and decision-making processes, and fund research related to the evaluation and monitoring of model performance, with mechanisms for accountability and continuous improvement.

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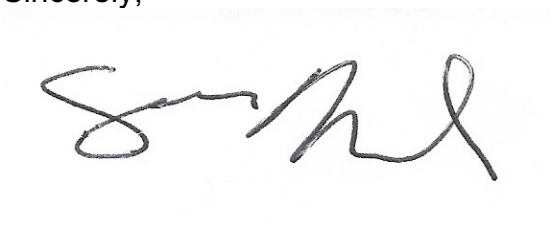
Conclusion

Thank you again for the opportunity to comment on the path forward for Cures and its essential priorities. We are at a critical moment as we work to modernize drug development and are encouraged by Reps. DeGette and Bucshon's attention to these important issues.

If you would like to discuss any of these issues further, please do not hesitate to get in touch.

Sincerely,



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