The metrics of success for oncology drug development and approval shifted with the shorter time to approval associated with the US Food and Drug Administration (FDA) 2018 Real-Time Oncology Review (RTOR) program and the newly mandated FDA Diversity Action Plan (DAP) requirements.\(^1\)\(^-\)\(^4\)

The study by Mooghali et al\(^5\) found that premarket evidence for RTOR indications was often drawn from surrogate end points. However, postmarketing requirements to confirm benefit for RTOR indications with traditional approval were infrequent. Mooghali et al\(^5\) conclude that additional postmarketing requirements for trials with surrogate end points may be important to sustain the flexibility of the RTOR program. An active critical test case is how the RTOR program adapts premarketing and postmarketing evidence requirements to meet DAP objectives.

The RTOR program and DAP requirements focus on distinct but complementary aspects of drug development and approval: speed to patient access and equity in data supporting access, respectively. The FDA Oncology Center of Excellence also has implemented other mechanisms, such as Project Orbis and the Product Quality Assessment Aid to expedite drug review and Project Equity to advance clinical trial diversity and evidence generation for historically underrepresented patient populations\(^2\)\(^,\)\(^3\)\(^,\)\(^6\) These initiatives reflect a broader FDA strategy to improve patient outcomes through regulatory efficiency and accurate understanding of outcomes for the intended patient population.

The DAP gained legislative backing as a requirement in late 2022, the same year a draft guidance was issued. The final guidance is pending as of March 2024, and there is limited publicly available experience. In particular, it is unknown how the FDA will assess achievement of DAP goals for RTOR eligibility and the extent of postmarketing studies that are highlighted in the draft DAP guidance.\(^1\)

Despite prior FDA efforts to improve clinical trial diversity, overall recruitment of racially and ethnically diverse patient populations remains disproportionately low. For example, although Black patients account for approximately 20% of all patients with multiple myeloma, they represent approximately 4% of patients enrolled in myeloma clinical trials.\(^1\) Population-level studies confirm racial and ethnic inequities in clinical trial participation across multiple cancer types.\(^7\) The drivers of inequitable trial participation include trial eligibility criteria that disproportionately exclude Black, Indigenous, and people of color; geographic and transportation barriers; earned mistrust of the medical and clinical research system, bias among trial staff, and lack of partnership with Black, Indigenous, and people of color communities in clinical trial design.\(^8\) Several of the multilevel drivers are addressed in the DAP and prior FDA guidance documents related to advancing clinical trial diversity.\(^1\)

Consideration of DAP goals early in the drug development process and early discussion with the FDA is likely the most effective approach to meeting the dual objectives of access and equity. A critical challenge to developing a meaningful DAP is deeply understanding the characteristics of patients who will likely benefit from the therapy. These characteristics extend beyond race and ethnicity to include other historically underrepresented populations based on age, sex, gender identity, socioeconomic status, pregnancy and lactation status, and disability.\(^1\)

Unfortunately, current and detailed epidemiologic information is not always available in research publications, existing incidence databases or disease registries. Availability of data is
particularly challenging for rare diseases, regional or community differences, and specific indications (eg, second-line treatment for metastatic triple-negative breast cancer after a specific first-line chemotherapy regimen). One approach is to leverage data from electronic health records (EHRs) to extract additional patient demographic and clinical details not usually captured in other databases, such as claims and registry data.

To make sense of complex data from disparate EHR sources and to enable efficient drug development and access programs, such as the RTOR, advanced analytic approaches and technology-based solutions are needed. For example, artificial intelligence and machine learning approaches can be applied to EHR data to support DAP enrollment goal-setting for specific indications and settings, optimization of trial eligibility criteria for diversity, and identification of potential trial sites enriched for diverse patient populations. Still, it will be important to assess and mitigate potential algorithmic bias in leveraging artificial intelligence and machine learning in these contexts. Additionally, equitable implementation of decentralized trials and wearable devices could facilitate conduct of research at nontraditional trial sites and enhance recruitment (and retention) of patients experiencing more barriers to care and long-term follow-up. Furthermore, all of these approaches must meet the ethical obligation to prioritize patient privacy and protection, particularly around sensitive health care information that inform DAPs.

There is a clear need to evaluate the combined effects of RTOR and other efforts to accelerate drug approval in the evolving regulatory landscape that now includes DAP requirements. For example, how do overall drug development timelines and execution, from preclinical to registrational studies and from clinical trial design to postmarketing surveillance, best adapt? How will logistical, resource, and regulatory harmonization challenges identified in prior reports for the RTOR program be addressed? Finally, do these programs achieve the ultimate goal of improving outcomes for all patients everywhere?

The dual objectives of the RTOR program and the DAP requirements represent progressive steps toward a more efficient and equitable drug approval process. Significant efforts are required to streamline and balance these objectives. Embracing real-world data, as defined by the FDA,9 and integration of DAP goals into clinical practice may be pivotal to achieving these ambitions, ensuring that treatments are rapidly and equitably available and safe and effective for all intended patient populations.

ARTICLE INFORMATION
Published: May 1, 2024. doi:10.1001/jamanetworkopen.2024.11447
Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2024 Miksad RA et al. JAMA Network Open.
Corresponding Author: Rebecca A. Miksad, MD, MPH, Boston Medical Center, Boston University, 820 Harrison Ave, Boston, MA 02118 (rebecca.miksad@bmc.edu).
Author Affiliations: Boston Medical Center, Boston University, Boston, Massachusetts (Miksad); Flatiron Health, New York, New York (Ryals).
Conflict of Interest Disclosures: Dr Miksad reported previously being employed by Flatiron Health and owning stock in Roche outside the submitted work. Dr Ryals reported being employed by Flatiron Health and owning stock in Roche outside the submitted work.

REFERENCES

Downloaded from jamanetwork.com by guest on 05/03/2024


