Stakeholder Perspectives Towards Enrolling Representative Oncology Clinical Trials

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Global Cancer Drug Development—A Report From the 2022 Accelerating Anticancer Agent Development and Validation Meeting

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ABSTRACT

Rapidly expanding systemic treatment options, combined with improved screening, diagnostic, surgical, and radiotherapy techniques, have led to improved survival outcomes for many cancers over time. However, these overall survival gains have disproportionately benefited patients in high-income countries, whereas patients in low- and middle-income countries (LMICs) continue to experience challenges in accessing timely and guideline concordant care. In September 2022, the Accelerating Anticancer Agent Development and Validation workshop was held, focusing on global cancer drug development. Panelists discussed key barriers such as the lack of diagnostic services and human resources, drug accessibility and affordability, lack of research infrastructure, and regulatory and authorization challenges, with a particular focus on Africa and Latin America. Potential opportunities to improve access and affordability were reviewed, such as the importance of prioritizing investments in diagnostics, investing health infrastructure and work force planning, coordinated drug procurement efforts and streamlined regulatory processing, incentivized pricing through regulatory change, and the importance of developing and promoting clinical trials that can answer relevant clinical questions for patients in LMICs. As a cancer community, we must continue to advocate for and work toward equitable access to high-quality interventions for patients, regardless of their geographical location.

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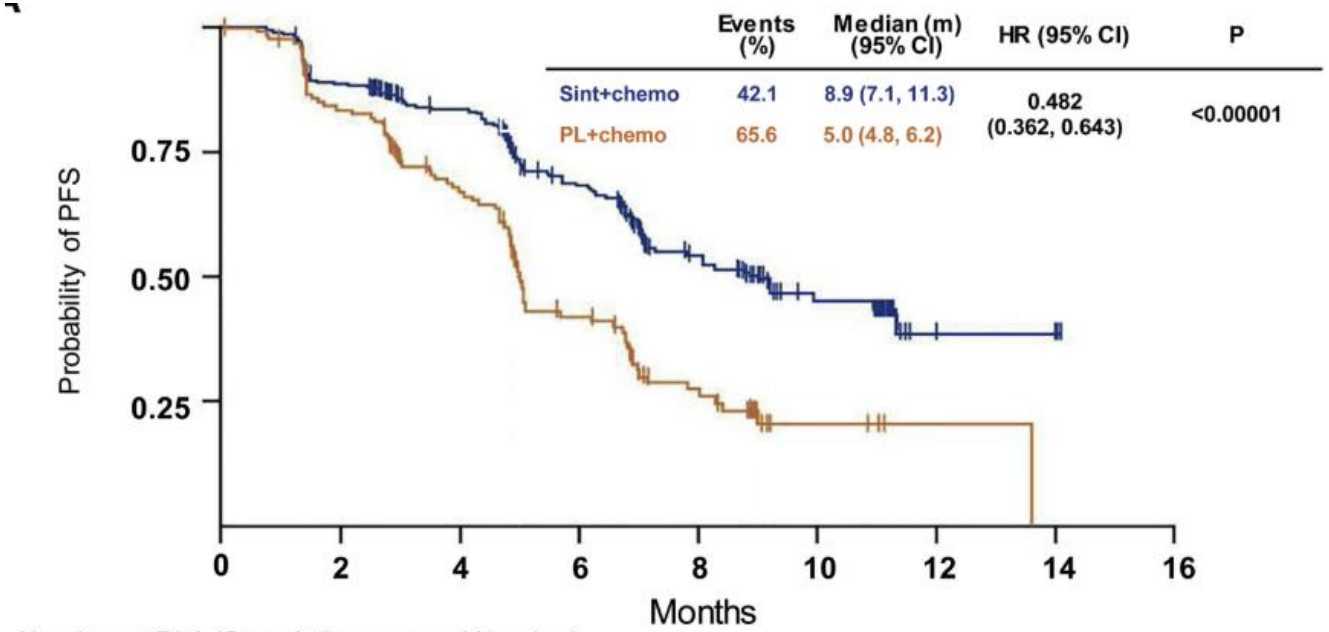
TABLE 1. Key Barriers and Potential Solutions to Improve Global Cancer Drug Development

Key Barrier	Details	Potential Solutions
Lack of diagnostic services and human resources	Limited pathology and radiology services Lack of trained personal (physicians, nursing, surgeons, and supportive staff) Weak and fragmented health systems infrastructure Centralized services creating geospatial barriers to access for patients	Prioritize investment in diagnostics and radiology Invest in training and promote long-term workforce planning Prioritize investment in health care infrastructure and increase care coordination Encourage and invest in solutions that promote decentralization of cancer care delivery
Drug accessibility and affordability	Unstable drug supply chains Unaffordable and lack of value-based drug pricing for LMICs Lack of public funding for cancer drugs (not included in national health coverage plans) Failure to prioritize cancer drugs on national essential medicines lists	Coordinate regional drug procurement efforts Incentivize affordable pricing through regulatory changes Encourage local government investment Prioritize cancer drugs in national health plans
Research infrastructure, regulatory and authorization challenges	Insufficient research infrastructure to support trial development Clinical trials asking questions that are not relevant to clinicians in LMICs Competing time requirements for patient care driven by inadequate staffing and resources Un-necessarily complex regulatory process for drug development and policy	Government and private investment in research infrastructure and encourage novel solutions to current technological barriers Promote and prioritize relevant clinical trial designs Increase funding for clinical researchers and build local capacity for clinical trials Streamline regulatory processes (eg, Project Orbis)

Abbreviation: LMICs, low- and middle-income countries.

The FDA Oncologic Drugs Advisory Committee expressed decisive support for the agency's view that data from trials of checkpoint inhibitors performed in mainland China aren't applicable to the U.S. population.

At a meeting Feb. 10, ODAC voted 14:1 in support of the agency's position that additional clinical trials demonstrating applicability to U.S. patients and U.S. medical care should be required prior to a final regulatory decision for the first such drug to be presented to the agency. *The Cancer Letter: February 11, 2022 Vol.48 No.06*



1.Efficacy and Safety of Sintilimab Plus Pemetrexed and Platinum as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC: a Randomized, Double-Blind, Phase 3 Study (Oncology pRogram by InnovENT anti-PD-1-11)
2.Yang, Yunpeng et al.
3.Journal of Thoracic Oncology, Volume 15, Issue 10, 1636 - 1646

Can solely non-US clinical data support US FDA approvals?

According to briefing documents, applications based solely on foreign data can be approved if they meet these three criteria:

- The foreign data are applicable to the U.S. population and U.S. medical practice;
- The studies are performed by investigators of recognized competence; and
- There is FDA validation of trial data through on-site inspections or other appropriate means.

Failure to meet any of these criteria will result in an application not being approvable based on the foreign data alone. FDA will apply this policy in a flexible manner according to the nature of the drug and the data being considered.

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Data from the ORIENT-11 trial not acceptable

The results from ORIENT-11 are not applicable to U.S. patients or U.S. medical practice based on 21 CFR 314.106. The trial was conducted without FDA consultation or oversight, with a comparator arm and endpoint (PFS) that do not meet U.S. regulatory standards or align with U.S. medical practice. Comparison of sintilimab to an approved drug would ensure that there is no loss in OS advantage.

ORIENT-11 is not reflective of a diverse U.S. population, and does not account for both known and unknown differences amongst populations.

The FDA may apply policies on applicability of foreign data in a flexible manner according to the nature of drug and data being considered. ORIENT-11 closely resembles existing MRCTs, yet was powered for a less clinically meaningful endpoint.

The trial results do not fulfill an unmet need, thus do not warrant regulatory flexibility when considering applicability to a U.S. population.

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PFS data from ORIENT-11 trial not acceptable

Since that time, there have been at least seven approvals [of PD-1 drugs] for non-small cell lung cancer. All of them are based on overall survival. In addition to that, the survival data on pembrolizumab has been updated, which now shows an over-one-year improvement in overall survival.

We strongly believe in the FDA that we should not lose this year of overall survival. That's why we have brought this forward, to make sure that people understand that the world has changed.

Comments that were made at an AACR meeting should not be viewed as regulatory policy. Conversations should be held within the FDA–especially with regards to the submission of an application.

Nevertheless, we believe that the landscape has significantly changed since those comments, especially with the demonstration of the overall survival and the maturation of that over time. So, the landscape has changed here, folks.

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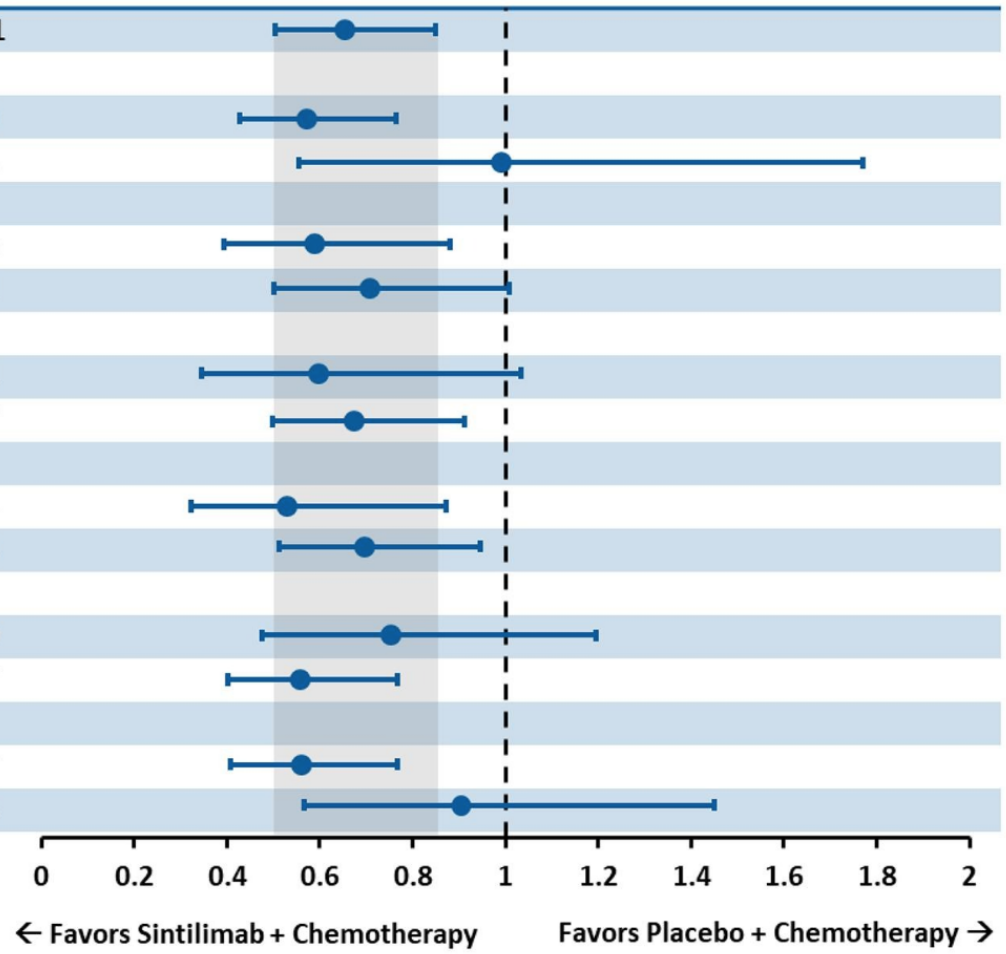
Updated OS data from the ORIENT-11 trial

Subgroup	Sintilimab + Chemotherapy Events/N	Placebo + Chemotherapy Events/N	Hazard Ratio (95% CI)
Total	151/266	92/131	0.65 (0.50, 0.85)
Sex			
Male	116/204	75/99	0.57 (0.43, 0.77)
Female	35/62	17/32	0.99 (0.56, 1.77)
Age group			
≤60 years	62/126	41/60	0.59 (0.39, 0.88)
>60 years	89/140	51/71	0.71 (0.50, 1.01)
ECOG performance status at baseline			
0	35/76	22/34	0.60 (0.35, 1.03)
1	116/190	70/97	0.67 (0.50, 0.91)
Platinum			
Cisplatin	40/71	26/33	0.53 (0.32, 0.87)
Carboplatin	111/195	66/98	0.70 (0.51, 0.95)
PD-L1 expression level (CRF)[a]			
<1%	51/77	29/40	0.75 (0.48, 1.19)
≥1%	94/181	62/87	0.56 (0.40, 0.77)
Smoking status			
Former/Current	96/171	66/87	0.56 (0.41, 0.77)
Never	55/95	26/44	0.91 (0.57, 1.45)



[a] Only includes evaluable patients.
Data cutoff date: 15 Sept 2021.

https://doi.org/10.1016/j.lungcan.2022.07.013

Commitment to diversity in US

Number two, over the past two to three years, especially since the pandemic, this country has experienced significant social change, and there has been a tremendous outcry for diversity in clinical trials and representation. We, as a public agency, the FDA, have to adhere to what patients want in the United States.

As I stated before, we've heard clearly from all patient groups that they want faces like theirs represented in their clinical trials. So, we have a huge commitment to diversity.

Single-country submissions is a step backward in achieving the racial diversity that we need in the United States.

I just want people to understand that this is going to be a major goal of not only oncology submissions, but also submissions throughout the FDA.

The third point I want to address with regards to change in our perception of what we want from international trials, is this issue of multiregional trials. We want to bring China into the multiregional arena.

We feel that we would all benefit by having China participate fully in multiregional trials with the U.S., with Europe, with South America, Central America, and, hopefully, Africa. The world will be a better place with having all countries participate in these multiregional trials.

> Single-country submissions is a step backward in achieving the racial diversity that we need in the United States.
>
> — *Richard Pazdur*

These single-country trials are a step backward in that regard.
We don't want to pit one country against the world. We want to have everyone participate together.

The Cancer Letter: February 11, 2022 Vol.48 No.06

Diversity in clinical cancer research

The population of patients with cancer enrolled in the clinical study(s) demonstrating benefit often consists of a subset of the general population with access to high quality medical care and the economic and social support systems required to participate in clinical research.

The population studied in the clinical trial often differs from the demographics and characteristics of the general population diagnosed and living with the cancer.

Significant gaps in clinical trial participation remain, particularly for minoritized populations that experience health disparities in clinical care and outcomes.

Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OCE) Lola Fashoyin-Aje, 240-402-0205, (CDER) Tamy Kim 301-796-1125, (CBER) Office of Communication, Outreach, and Development, 800-835-4709, or 240-402-8010, or (CDRH), CDRH Clinical Evidence Mailbox, CDRHClinicalEvidence@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Minority Health and Health Equity (OMHHE)
Office of Women's Health (OWH)

June 2024
Clinical/Medical

V. CONTENT OF THE DIVERSITY ACTION PLAN

Under sections 505(z) and 520(g)(9) of the FD&C Act, a Diversity Action Plan must include:[40]

- the sponsor's goals for enrollment in the clinical study, disaggregated by race, ethnicity, sex, and age group of clinically relevant study populations,
- the sponsor's rationale for such goals, and,
- the sponsor's explanation of how the sponsor intends to meet such goals.

Steps Towards Enrolling Representative Oncology Clinical Trials: Stakeholder Perspectives from the 2023 Accelerating Anticancer Agent Development and Validation Workshop

Terrell Baptiste
Stacey Bledsoe
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Chitkala Kalidas
Scarlett Y. Yang
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SUBJECT/METHODS: Proceedings and recommended tools to advance the enrollment of representative oncology clinical trials, a summary from the Accelerating Anticancer Agent Development and Validation (AAADV) Workshop 2023. The 2023 AAADV Workshop assembled a panel to discuss “Steps Towards Enrolling Representative Oncology Clinical Trials.” Academic, pharmaceutical industry, and decentralized trial experts examined approaches from trial development through execution to improve representation and address persistent and inherent barriers. The presentations focused on practical tools to advance evidence generation and improve health outcomes for oncology patients.

STAKEHOLDER PERSPECTIVE: Panelists from academia, sponsor companies, and experts in decentralized trial methods considered the ways to enhance access and enrollment of racial and ethnic minorities in oncology clinical trials. Practical strategies emphasized early trial planning specific to the target product profile, the use of available tool kits and adaptive learning, and the adoption of models from health authority programs.

CONCLUSIONS: Available tools can be utilized to increase representative enrollment with the end goal of matching participation in clinical trials of investigational medicines with the populations who are intended to receive the medication or intervention. Prospective planning, innovation, and continuous improvement aim to achieve sustainable and representative clinical research.

Table 1: Tools to Reach Properly Enrolled Oncology Clinical Trials[i]

Categories: • Participant & Community Engagement • Workforce Development • Study Design, Conduct, and Implementation • Stakeholder Commitments and Accountability
Pre-Study • Form and nurture partnerships with underserved communities. Engage with community physicians, patients, and others (e.g., community and religious leaders, cultural ambassadors, patient navigators, educators) to inform the study question, design, and conduct. • Develop health-literate communications and support educational activities to enhance diverse participant awareness, access, recruitment, and retention (e.g., translation of study materials, participation in local health fairs, engage with community health centers). • Establish processes to minimize burden (e.g., reimbursement and compensation for participation, flexible appointments, geographic flexibility, appropriate accommodations, child- and elder-care, translation services). Consider whether and how decentralized clinical trials, and/or the introduction of decentralized elements into trials, would reduce burden. • Select sites in geographic locations that house and host diverse populations. • Train site and research staff in relevant cultural and linguistic dimensions of communication. • Create/adapt a standard mechanism to collect, record, and track demographic and non-demographic variables of participants screened, offered, and consented into study. • Develop objective screening approaches and systematically collect and record reasons for screen failure. • Periodically analyze/evaluate screen failure data.

On-Study

- Document the basis of the decision to exclude participants from a trial.
- Devise a simple and clear informed consent process for participants that is conducted in a health-literate, culturally and linguistically appropriate manner.
- Provide translation services of the informed consent form and/or interpreter services for individuals with limited or no English proficiency, as applicable.
- Apply accessibility principles to study documents and provide accommodation for people with disabilities as required.
- Allow flexible strategies that enable participants and their caregivers to adhere to the expectations of the study (e.g., amenable clinic hours, locations, virtual visits; provision of childcare, eldercare, and food during study visits; transportation assistance; appropriate reimbursement and compensation).
- Offer regular, open, and respectful communication through the platform of participant preference (i.e., phone, text, email, virtual meeting, etc.) to foster participant understanding.
- Establish a monitoring and evaluation system to ensure timely interventions if actual enrollment does not meet expected enrollment or if the actual enrollment does not reflect the expected demographic(s) intended for the study.
- Monitor retention to study by demographic and non-demographic factors.
- Put practices in place that provide continuous education, support, and outreach to participants and their communities.

- Train all staff interacting with participants and their caregivers in principles of respectful communications, bias, and cultural humility.

Post-Study

- Plan for data analyses that includes sub-group analysis and examination for heterogeneity of treatment effects as applicable to the study.
- Provide clear communication around end-of-study expectations, including transitions of care, potential later outreach, timing of further communications.
- If the study involved an investigational product, anticipate continued access to the investigational product for participants who are benefitting from the treatment and have no other equivalent options for treatment
- Return aggregate and, to the extent possible, individual study results in health literate and understandable language to study participants.
- Return aggregate results, if applicable, to the community in a culturally and linguistically appropriate manner to the community.
- Conduct post-study survey of participants to learn what worked well and areas for improvement.
- Review study performance for lessons learned and to help plan future studies.

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[i] Adapted from: Bierer BE, White SA, Meloney LG, Ahmed HR, Strauss DH, Clark LT. Achieving diversity, inclusion, and equity in clinical research. Cambridge and Boston, MA: Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center). 2020 Sep 22. https://mrctcenter.org/resource/diversity-inclusion-and-equity-in-clinical-research-procedural-logistical-checklist/

Table 2: Pros and Cons of Developing Diversity Plans Early

Stage of Development	Pros and Cons
Early (Target Product Profile, Phase 1-2)	**Pros** • Ability to apply/learn how best to apply technology-enabled decentralized procedures • Allows decision making in early stages which may enable study protocol modifications e.g., inclusion & exclusion criteria • Scientific interest from study investigators • Early identification of trends to generate hypotheses for subpopulations • Planning early costs less than waiting • Ability to include patient/advocacy input to study design and build trust • Allows for the selection of more diverse sites
	Cons • Study team resource (time and money) may be limited • Heterogeneity in clinical trials may limit interpretability if statistical power is not sufficient • May not find best suitable decentralized technology

Table 2: Pros and Cons of Developing Diversity Plans Early

Late (Pivotal, Phase 3)	**Pros** • Will ideally have proof-of-concept and be able to confirm
	Cons • Difficult to modify protocol • Later studies are industry-focused and may not generate scientific interest from study investigators

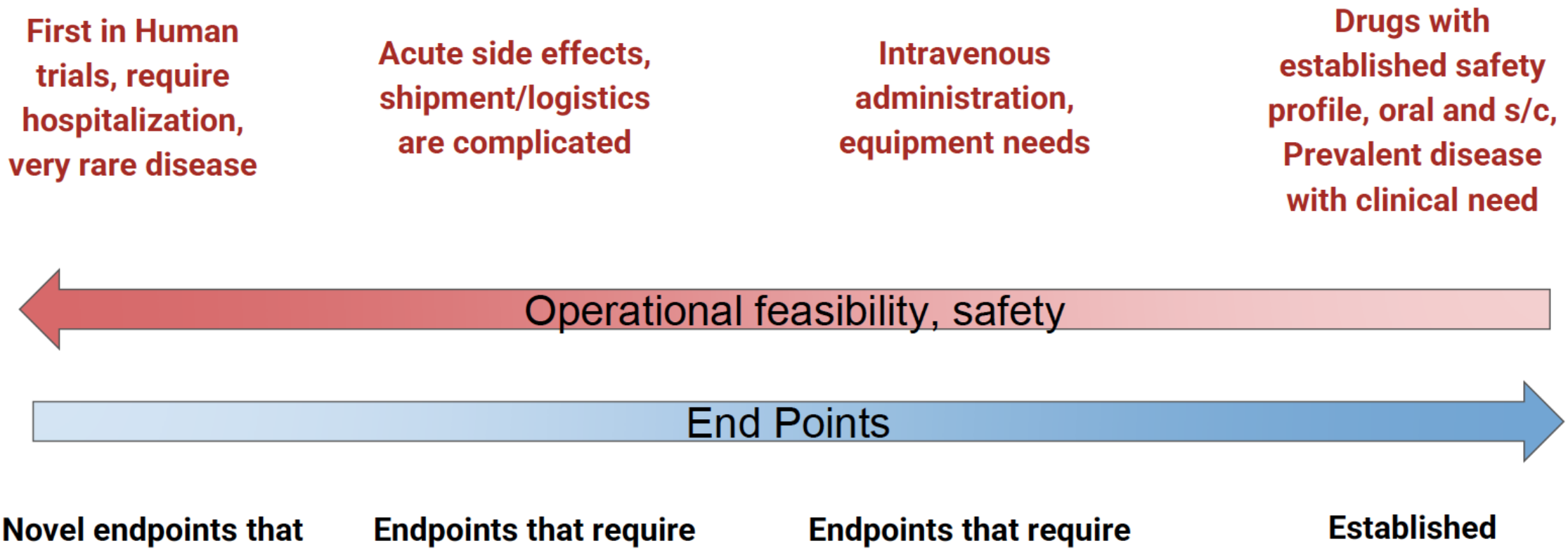
Table 3: Considerations for Representative Clinical Trial Design

Investigator / Site Staff and site selection	Partner with sites to promote awareness of cultural awareness / implicit bias. Encourage presence of site staff that mirror underrepresented patient / community populations.
Patient / Patient Advocate feedback on clinical trial design	Partner with patients and/or patient representatives reflecting patient population (including underrepresented populations) to review clinical trial protocol and patient education materials. Provide feedback to improve overall patient experience during screening and trial duration.
De-risking decentralized clinical trial (DCT) management	Provide patients with options for community based / local assessment. Needs assessment of DCT capabilities at organizational level, to enhance/ progress clinical development programs. Partnership with institutions to implement DCT solutions (e.g., multiple sponsors/ stakeholders to share investment).

Table 3: Considerations for Representative Clinical Trial Design

Availability of standards of care (SoC) / comparator drugs	Sponsors may work with patient groups to support access and reimburse sites / patients where SoC / comparator drugs are not available. Patients on Medicaid may now be reimbursed for clinical trial procedures.
Lack of statistical power in small numbers	Augment with real-world evidence / disease registries (or review of electronic health records) and modeling data. Interaction assessments of race and ethnic groups with treatment can help to rule out effects differential from the treatment effect demonstrated overall in the trial population.
Effect size in treatment experienced subjects	Emphasize estimation of effect and effect size for comparison against the overall cohort's effects, over inferential statistics in smaller race and ethnic subsets.

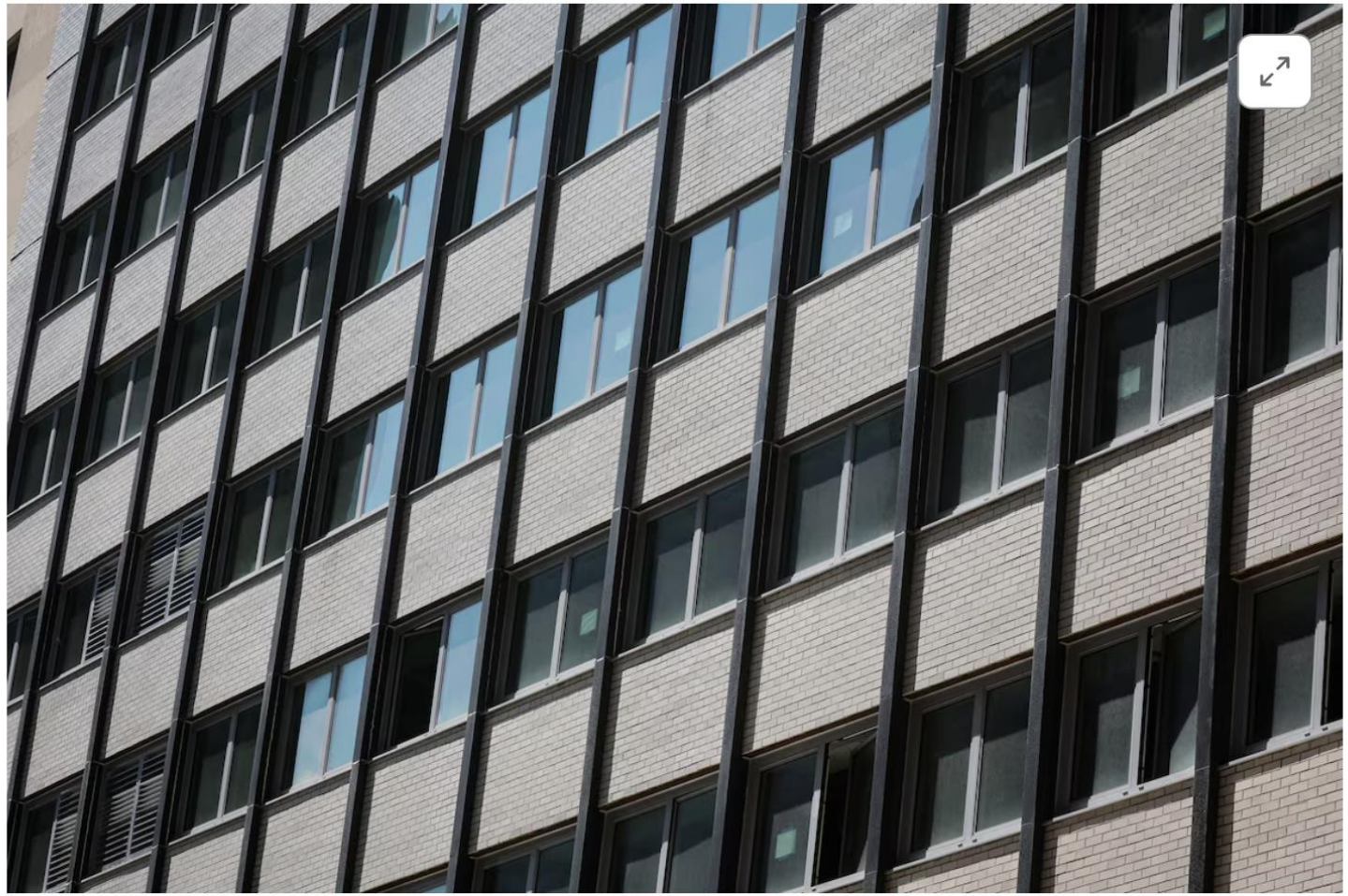
The application of decentralized trial (DCT) methods depends on various factors. The appropriateness should consider: 1) the clinical feasibility as well as its 2) validation in the clinical setting being tested



Key directives in Trump DEI executive order for government, private sector

By **Kanishka Singh**

January 21, 2025 11:55 PM EST · Updated 5 days ago



[1/2] A vacant office building, 5 Hanover Square, is seen in the financial district of New York City, U.S., July 6, 2023. REUTERS/Brendan McDermid/File Photo Purchase Licensing Rights

US FDA drops web pages on improving clinical trial diversity

By **Julie Steenhuysen**

January 24, 2025 3:31 PM EST · Updated 2 days ago

Signage is seen outside of the Food and Drug Administration (FDA) headquarters in White Oak, Maryland, U.S., August 29, 2020. REUTERS/Andrew Kelly/File Photo Purchase Licensing Rights

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Washington, D.C. 20201

TO: Heads of Operating Divisions Head
Heads of Staff Divisions

THROUGH: Wilma M. Robinson, Ph.D., Deputy Executive Secretary

FROM: Dorothy A. Fink, MD, Acting Secretary

DATE: January 21, 2025

SUBJECT: Immediate Pause on Issuing Documents and Public Communications – ACTION

As the new Administration considers its plan for managing the federal policy and public communications processes, it is important that the President's appointees and designees have the opportunity to review and approve any regulations, guidance documents, and other public documents and communications (including social media). Therefore, at the direction of the new Administration and consistent with precedent, I am directing that you immediately take the following steps through February 1, 2025:

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Will a change in US FDA clinical trials diversity guidance impact your clinical development strategy of new molecular entities?

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If the US FDA clinical trials diversity guidance is eliminated, how will your clinical development strategy of new molecular entities change?

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