REAGAN-UDALL FOUNDATION FOR THE FDA

Improving Oncology Multi-Regional Clinical Trials

ROUNDTABLE DISCUSSION AND RECOMMENDATIONS SUMMARY REPORT | Issued October 2025

ABOUT THE REAGAN-UDALL FOUNDATION FOR THE FDA

The Reagan Udall Foundation for the FDA (Foundation) is an independent non-profit created by Congress to advance regulatory science to help the U.S. Food and Drug Administration accomplish its mission. The Foundation manages a suite of programs that assist the FDA in engaging with external stakeholders and that facilitate evidence generation, improve public understanding of the FDA, and deliver more accessible health information to the public.

FUNDERS

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Contents

Executive Summary

On September 4th, 2025, the Reagan-Udall Foundation for the FDA (Foundation) convened an invitation-only Roundtable discussion with representatives of the biopharmaceutical industry, oncology clinical trial sites, clinical research organizations, and cancer-focused non-profits. Participants articulated challenges in activating and conducting multi-regional clinical trials (MRCTs) for oncology treatments and discussed solutions needed to improve the operational and policy environment to significantly advance oncology clinical trial efficiencies.[a] Specifically, the agenda was designed to examine ways to improve trial clarity, consistency, and efficiency with a focus on what the sponsors of trials (biopharmaceutical companies and CROs), clinical trial sites. FDA, and global regulators might realistically address.

The discussions brought to light the significant reform efforts and activities underway, some for many years, by both sponsors of trials and clinical trial sites to address multifactorial root causes of sub-optimal clinical trial enrollments, site activation, and start-up times, especially in the United States (U.S.). Efforts to identify and resolve barriers and improve the oncology clinical trial ecosystem continue. Additionally, patient and research organizations have been working with both sites and sponsors to improve the efficiency and effectiveness of clinical trials. Roundtable participants discussed how systemic and sustainable reforms will require creating task-oriented, cross-stakeholder collaborations focused on operationalizing solutions. Lastly, the participants observed the need to advance short-term solutions that can be applied to clinical trials that are underway and long-term solutions that will improve the clinical trial ecosystem moving forward.

Specifically, the group developed recommendations to:

- Unlock the potential of network approaches;
- Improve enrollment and study start up timelines by advancing more patient-centric, rather than trial-centric, approaches;
- Explore common budget and contract processes for U.S. trial sites;
- Ensure utilization and deployment of technology yield benefits;
- Align on training needs and minimize duplicative activities;
- Develop scientific principles for representativeness targets and adapt for disease-specific application; and
- Manage heterogeneous and continuously evolving standard of care by articulating contextualized regulator/researcher understandings for discrete cancer areas.

A common thread underscoring each recommendation is the importance of ensuring modernization and reform efforts focus on improved efficiency, effectiveness and outcomes for clinical trials (i.e., do not add complexity without benefit). Lastly, it was noted that without the support of federal and state policy makers to address additional reforms necessary to optimize the U.S. medical research ecosystem (e.g., tax reform, funding of medical research facilities, coverage policies etc.), the full potential impact of these recommendations may be limited.

The paper is divided into two main sections: the first addressing activation, enrollment, and study start up timelines and the second addressing science-based approaches to clinical trial representativeness targets and generalizability analyses. Each section discusses challenges, relevant efforts and activities, and recommendations to advance prioritized solutions. A complete list of these recommendations, with identified stakeholders, and estimated time frames are provided in Appendix A and Appendix B. The intent of this project is to serve as a platform to stimulate focused activities on the recommendations.

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a MRCT is defined as a trial that is conducted in more than one region under a single protocol with region defined as a geographical region, country or regulatory region (FDA. 2024. Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs; Draft Guidance for Industry.

Meeting Purpose

Multi-regional clinical trials (MRCTs) are a cornerstone of oncology drug development and are critical for building the evidence base for product safety and efficacy as well as expanding patient access to new therapies. However, prolonged timelines for trial site activation and patient enrollment, as well as regional variability in site needs and approaches pose significant challenges and create inefficiencies across the domestic and global clinical trial ecosystem. Moreover, limited infrastructure outside major hospital systems constrains the number of clinical centers currently offering clinical trials, and those systems are facing additional financial strain. Misalignment in standards of care, such as differences in time to diagnosis, variability in availability or preference for specific treatments and/or access to emerging new treatments, in different U.S. regions, as well as globally, complicate clinical trial designs, data interpretation, and comparability of efficacy and safety outcomes across regions. Addressing these challenges requires science-driven and harmonized approaches to representativeness targets and generalizability assessments. Researchers in the U.S. and other countries are exploring solutions to increase patient access to, and compress timelines for, conducting studies, such as streamlining site operations and reducing burdens on patients. This report delves into the challenges and solutions discussed for each of the key topics raised by attendees and aims to stimulate focused activities to implement these reforms.

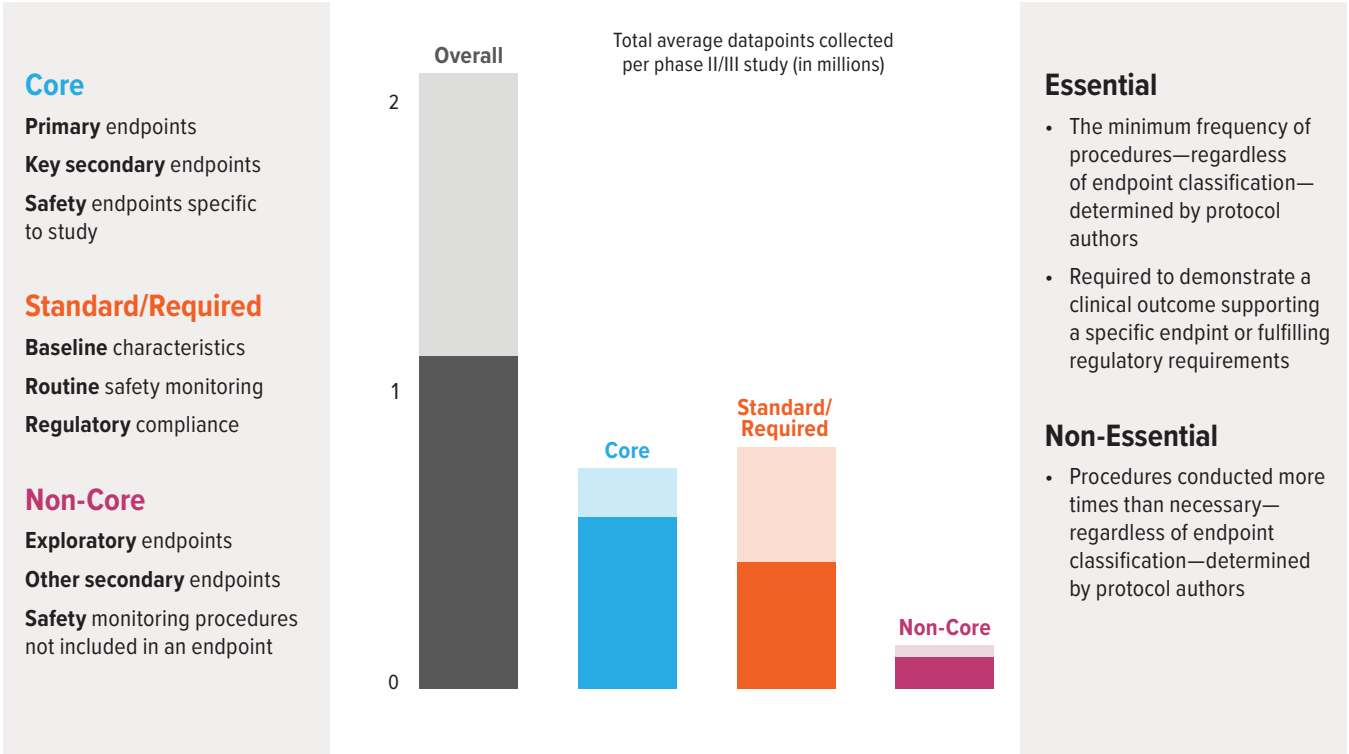
Increasing Efficiency and Effectiveness of MRCT Oncology Clinical Trials is a Global Health Imperative

There has been significant progress in treating cancer, however, the global burden remains high. A 2025 WHO publication estimates there will be 35 million new oncology cases in 2050, a 77% increase from the 20 million cases recorded in 2022.[1] Currently, global oncology trials represent a significant portion of all clinical trials (41% of new trial starts in 2024) and engage a significant number of sites (45,000 global oncology trial sites in 2024).[2,3] The total number of subjects enrolling across all global oncology trials in 2024 was 306,000, a 10% increase from 2023 and up 15% from 2019.[3] The U.S. alone has 6,710 cancer treatment Phase I-III trials open to enrollment across 1,836 clinical trial sites in 2022.[4]

In addition to the sheer scale of global oncology clinical trials, these trials are being conducted in an environment where the return on research and development investment has been declining over the past two decades (3–5% in 2020s vs. 12–15% in 2000s), as presented in Where Are We Now? A Look at the Data (Getz). Clinical trial success rates have remained steady over the past three decades (Years 2014-2021: Phase I–II = 63%; Phase II–III = 31%; Phase III – Submission – 58%) but trials have become significantly more complex, generating significantly more data. In fact, data volume (total number of data points collected) for Phase III pivotal trials has increased from 1.8 million data points in 2015 to ~4.9 million in 2025. Costs for investigative sites, CROs, tech vendor services, and internal staff and infrastructure have all increased over the past two decades. Costs for CRO and tech vendor services have more than doubled since 2010 ($43.1B to $95.6B). These points illustrate a key concern; more R&D money is being spent ($94.2B in 2000s; $188.1B in 2020s) but the ecosystem is less efficient, underscoring the importance of advancing efforts to optimize the clinical trial ecosystem.[5]

Oncology clinical trials are especially in need of reform as they continue to have the lowest overall probability of success (5.1% compared to 19.1% for infectious diseases and 15.1% for GI diseases) and are more complex and take longer to conduct.[b] For example, when comparing oncology mean days for Phase II/III protocols to non-oncology protocols, the total duration is longer (1,598.7 vs. 1,080.9) and enrollment duration is significantly longer (1,327.2 vs. 852.1).[5] A 2022 Tufts study found that for Phase II and III trials oncology protocols had a mean number of 15.3 endpoints and 315 procedures.[6] A 2025 update to this study found that approximately one-third of procedures and associated data in clinical trials did not directly support primary objectives or secondary endpoints (i.e., non-core procedures/non-essential).[7] The study also found that as much as 30% of participant and site burden were associated with non-core/non-essential procedures (Figure 1).[7] Additionally, a majority of oncology trials are focused on rare cancers (74% of trial starts in 2024) which adds complexity.[3] The need to advance reforms is clear.

FIGURE 1. PROCEDURES GENERATING PROTOCOL DATA BY ENDPOINT CATEGORY



Note. From Insights Informing Strategies for Optimizing the Collection of Clinical Trial Data.[7]

b This Roundtable did not explore why oncology clinical trials have the lowest overall probability of success; rather, the discussion addressed how to improve oncology clinical trial operations and execution.

TOPIC ONE:
Improving Oncology Site Activation, Enrollment & Study Start-Up Timelines Is Imperative – Especially in the U.S.

Discussion Overview

Roundtable participants discussed challenges and opportunities to improve multi-regional oncology clinical trial site activation, enrollment, and start up timelines, and address complexities unique to the U.S. In general, there was agreement that improving efficiencies and generating standard site activation and study-start-up processes would be broadly beneficial. The participants prioritized recommendations to: 1) Unlock the potential of network approaches; 2) Improve enrollment and study start up timelines by advancing more patient-centric, rather than trial-centric, approaches; 3) Explore common budget and contract processes for U.S. trial sites; 4) Ensure utilization and deployment of technology yield benefits; and 5) Align on training needs and minimize duplicative activities.

While these recommendations are the focus of this report, participants discussed a few other topics, such as aligning timelines for the submission of final protocols and lab manuals. The need for best practices that streamline certain site requests (e.g., limiting the number of requested tables, listings, and graphs) was discussed as a potential way to reduce clinical site burdens. Participants also agreed that removing redundant confidentiality, feasibility, and training requirements would streamline site activation and study start-up timelines. Lastly, participants discussed the merits of sponsors, sites, and regulators identifying what processes should be deemed redundant and outmoded and redeveloped using modern technology (e.g., hand-signing CVs, capability, and resource documentation).

A common theme throughout these discussions was the need for stakeholders to collaborate and generate specific steps to implement reforms. It was noted that many efforts have been underway for years, but execution has generally been inconsistent and not occurring at a system level. For example, the American Society of Clinical Oncology (ASCO) has been doing important work to streamline oncology clinical trials through improved contract negotiations and streamlined feasibility and workload assessments for several years.[4] The Association of American Cancer Institutes (AACI) is in the process of publishing a paper with recommendations to enable more rapid activation of clinical trial sites. The paper is expected to include several recommendations such as defining “operationally ready” oncology clinical trial documents to drive faster alignment on study start up timelines. These are additional opportunities for sponsors of trials and clinical trial sites to coordinate responses and determine what recommendations should be implemented and, importantly, how Roundtable participants hope that this document will help catalyze such actions and generate system-level improvements.

Below are detailed descriptions of the prioritized challenges, solutions, and recommendations discussed during the meeting.

Challenges Facing Patients and Families

Access to Oncology Care and Trial Sites

The number of practicing oncologists in the U.S. is not keeping pace with the demand for cancer treatments. This is especially true for cancer patients living in rural areas, as a recent ASCO survey revealed that 90% of oncologists practice in non-rural areas.[8,9] Access to oncology clinical trial sites is similarly limited: U.S. high-prevalence remote counties (top quarter of disease prevalence) and counties with lower incomes are generally >60 miles from a clinical trial site. U.S. affluent suburbs, towns and urban cores are usually <60 miles from trial sites.[10] These dynamics create socioeconomic and geographical barriers to clinical trials.[4] The need to find more efficient approaches to conduct oncology clinical trials across a broader array of sites is crucial to building a sustainable clinical trial ecosystem in the U.S. Finally, there is a clear need to improve how patients and their families are made aware of clinical trial opportunities and how they are screened and qualified for trials.

Clinical Trial Financial Burdens

In addition to distance, individual patient financial concerns can be a factor in low trial participation rates. A 2018–2020 survey examined U.S. economic burdens and financial toxicity for cancer patients (n=213) enrolled in Phase II clinical trials for more than 1 month. Half of patients lived more than 300 miles away from the clinic, and 27% of patients lived 101–300 miles. Thirty-seven percent traveled by airplane, 62% traveled by car only, and 1% traveled by bus. Almost half of the patients (48%) had monthly total out-of- pocket costs of at least $1,000 and 14% had at least $2,500. A significant portion of these costs were non-medical (ranging from $600 to at least $1,500 a month) to cover travel and hotel-related expenses and only 29% reported receiving partial or full reimbursement for these costs. Forty percent of the surveyed patients reported a ‘significant’ to ‘catastrophic’ financial burden.[11]

Recommendation #1: Unlock the potential of network approaches

Lee et al. performed an analysis of U.S. cancer trial sites and proposed that existing clinical trial centers build collaborative efforts with nearby hospitals closer to underrepresented populations, or set up community centers to support new collaborative networks to improve geographical clinical trial access equity.[12]

Hub-and-spoke clinical trial models are one mechanism that allows more patients to access clinical trials. These models could also help usher in more consistent practices between clinical sites and sponsors across the U.S. An effective “hub” manages key functions of a clinical trial such as data management systems, regulatory compliance, and distribution of investigational products. The “spokes” manage patient-focused activities such as recruitment, administering investigational medicines, and collecting clinical data.[13] Ideally, a clinical trial could launch simultaneously across the hub and all its spokes in a timely manner. In practice, however, clinical trial sites, trial sponsors, and regulators must agree on the expectations and responsibilities for hubs, and their spokes for such an approach to work.

The efficiency of a hub-and-spoke model is optimized when the hub centralizes processes, such as budgeting and contracts. Further, it is important to have an empowered lead principal at the hub that manages processes, such as the utilization of a single Institutional Review Board (sIRB) and how investigational products are provided to the hub and its spoke sites. Importantly, Roundtable participants pointed out that the definition of the hub and spoke approach as a network—and empowering that efficiency—requires additional clarity from regulators (confirming any necessary parameters for such an approach), from sites and CROs (alignment with such parameters), and commitment from biopharmaceutical companies to use the network approach. Regulators

should clarify any restrictions on what processes can be centralized. For example, FDA should clarify how regulatory compliance requirements apply to trial networks, specifically, whether and when one site (i.e., the hub) can manage compliance for other related/connected sites *(*i.e., the spokes). The ability to centralize core aspects of clinical trial management is foundational to extracting maximum efficiencies from a hub and spoke model. Additionally, efforts should be made to align these approaches to international standards (e.g., risk-based approaches discussed in ICH E6 (R3)).[14]

Recommendation #1: Unlock the Potential of Network Approaches
Solution
Collectively define specifics of operational and regulatory compliance processes for network approaches, ideally harmonized with international standards

Recommendation #2: Improve enrollment and study start up timelines by advancing more patient-centric, rather than trial-centric, approaches

The current clinical trial ecosystem, particularly for oncology trials, tends to be more trial-centric than patient-centric. Site locations, screening and validation processes, and overall administrative burdens challenge patient enrollment and slow research. Enrollment timelines increased for all phases and therapeutic areas between 2019–2023. Phase I trial enrollment times increased by 39%, taking an average of 5 months longer in 2023 than 2019, Phase II increased by 23% by adding six months and Phase III increased by 16% taking three months longer to enroll patients. Oncology enrollment timelines are *double* those seen in other therapeutic areas. These increased timelines have been attributed to increases in trial enrollment requests and requirements, complexity related to therapeutic mechanisms (e.g., cell and gene therapies and multi-specific antibodies) and narrower inclusion/exclusion criteria.[15,16] (Concurrent with these increasing enrollment durations, the average number of countries represented in trials declined 20% and sites per trial declined by 15%. The trend of decreases in country utilization per trial may be driven by strategies to reduce costs by sponsors but may also be contributing to longer enrollment times by creating saturated geographies.[16]

Sponsors, sites, as well as patient and research organizations have been working to improve enrollment by improving the ability of patients to locate, assess, and participate in clinical trials. For example, the industry collaborative TransCelerate has several initiatives underway designed to advance stronger patient engagement strategies, to promote interoperable systems that allow for seamless data sharing across platforms and geographies, and to build sustained cross-industry collaborations that bring clinical research closer to the patient.[17]

Below are recommendations to advance more patient-centric, rather than trial-centric, approaches in oncology trials and improve enrollment timelines.

Improve Screening and Referral Processes

Roundtable participants discussed the potential of systematic, pre-competitive platform approaches to assessing oncology clinical trial eligibility that could pivot toward a more patient-centric approach. Rather than screening individual patients against criteria for an individual trial, a structure that catalogued patient information and then screened the patient for a broad array of available trials has the potential to improve enrollments for patients and sponsors. Finding trials for patients, rather than patients for trials, would require collaboration among sponsors for the trial criteria compilation, and among sites, where referral to another site—with the appropriate trial—would better serve the patient.

Other approaches and options with the potential to improve patient-centricity included efforts to minimize delays in obtaining molecular screening results, sharing (or creating) a common repository for such results, and shortening qualification processes. Pragmatic clinical trials and how inclusion and exclusion criteria impact clinical trial recruitment and enrollment efforts was discussed but it was noted that these approaches can add heterogeneity complexities and risks to oncology clinical trials.[18,19] TransCelerate developed a resource guide that curates existing pragmatic trial resources to help advance understandings about design, implementation, interpretation and regulatory considerations that may be helpful to continued discussions about the potential benefits and pitfalls of these approaches in oncology.[19]

Build More Opportunities to Enroll in Oncology Clinical Trials[c]

Michaeli et al. examined clinical trial patient accrual rates for 170 FDA-approved drugs in 455 anti-cancer indications from 2000 to 2022. Disease incidence and disease burden along with the number of study sites and participating countries were identified as the main drivers of patient enrollment, not trial design features. For example, first-line treatments had faster enrollment than advance-line treatments, likely due to a larger eligible patient population. Patient enrollment per month was positively associated with the total number of study sites and participating countries as well as industry sponsorship. Additionally, successful trial completions were driven by the funding and existing administrative structure to conduct clinical trials.[20]

Sponsors have been working to broaden the number of clinical trial sites in areas that have been historically underserved and under-resourced. These efforts require deploying operational and regulatory flexibility to address the needs of new sites to meet training, technical validations, or documentation protocol requirements. Sponsors should share or publish examples of what has and has not been successful when working with inexperienced sites to establish manageable schedules of assessment and data collection requirements so that others can learn from those experiences.[18] Continued collection and publishing of lessons learned about how to build new site capacities are important to ensuring these efforts are successful and sustainable.

The use of technology, decentralized trials, remote monitoring, telemedicine, and integration of real-world evidence (RWE) to improve enrollment and representation in trials have been gaining attention as a way to breakdown geographic barriers and reduce patient burdens since the COVID pandemic.[4,21,22] A recent survey of sites found that 73% were approached by sponsors or CROs to conduct hybrid decentralized trials.[23] There is evidence that these approaches improve enrollment by reducing time and cost burdens.[17] There are also examples of the use of electronic consent making onboarding and check-ins easier for patients.[17] Over the past several years, RWE has been utilized to effectively support decentralized models and to inform protocol designs across different disease areas. However, policies that enable the effective and appropriate use of these tools and approaches need to be solidified to ensure their potential is optimized and realized.

Lastly, in addition to creating more sites and improved coordination across sites, sponsors should share best practices to support sustainable long-term community engagement and educational models that enable patients and families to better locate and evaluate clinical trial opportunities.[18]

Reduce Patient and Family Financial Burdens

As discussed previously, financial burdens can be a deterrent to enrollment and retention in clinical trials. Historically, payments to trial participants raised ethical concerns, however, the FDA has clarified that covering these costs does not equate to undue influence. States such as Texas and California are developing policies to

c While the approach was not specifically explored in this discussion, adaptive platform trials provide a mechanism to enroll patients across a wider range of agents and minimize control requirements.

encourage reimbursement for certain of these expenses.[11,24] Stakeholders (e.g., biopharmaceutical companies, CROs, patient organizations, clinical trial systems and organizations) should promote policies that reduce financial burdens on patients and advocate for the removal of statutes that prohibit or limit ability to reduce patient burdens.

Recommendation #2: Improve Enrollment and Study Start Up Timelines by Advancing More Patient-Centric, Rather Than Trial-Centric, Approaches
Solution: *Improve Referral and Screening Processes*
Develop pre-competitive platform approaches to enable patients to be screened for a broad array of trials and referred to the trial(s) that best fit their needs
Solutions: *Build More Opportunities to Enroll in Oncology Clinical Trials*
Develop and promote policies and best practices that enable sites with little to no experience to build clinical trial capacity
Clarify regulatory policies and remove barriers to the effective deployment of tools that support decentralized approaches such as remote monitoring and in-home data collection
Explore pre-competitive approaches to support sustainable long-term community engagement and educational models that enable patients and families to better locate and evaluate clinical trial opportunities
Solution: *Reduce Patient and Family Financial Burdens*
Promote policies that reduce financial burdens on patients and advocate for the removal of statutes that prohibit or limit trial sponsors' ability to reduce patient burdens

Challenges Facing Clinical Trial Sites and Sponsors

In a 2024 WCG (a clinical research consulting firm) study, 70% of global investigative staff reported that trials have become more difficult to manage in the last five years. They identified the complexity of clinical trials, participant recruitment and retention, study start-up times, and site staffing as main factors driving these challenges.[15] Clinical trial site saturation, difficulties in expanding the number and location of clinical trial sites, and enrollment and study start-up timelines have been identified by biopharmaceutical companies as factors delaying oncology clinical development programs. Study start-up (final protocol to first subject first visit) times for oncology trials in 2024 were estimated to be 4 months, an increase of 0.6 months from 2019.[3] Enrollment timelines for oncology trials (from first subject first visit to last subject first visit) are double those seen in other therapeutic areas.[2]

There are differences in what factors site investigative staff viewed as most challenging depending on type of site. For example, larger sites including academic medical centers and community hospitals report study start-up as a top challenge more often than small independent sites due to differing levels of bureaucracy. Smaller sites report more difficulty with recruitment and retention and working with sponsor-provided technology, due to limited resources and staff.[15] Staffing resources are a top issue across all sites. Financial pressures and funding needed to support staff have been identified as a driving factor of sites deciding not to initiate a clinical trial.[25]

There were also reported differences between U.S. and ex-U.S. sites. U.S. sites ranked complexity of clinical trials and study start-up as top challenges while ex-U.S. sites ranked recruitment and retention as their top challenges followed by complexity of trials.[8] Globally, 47% of sites have stated that because of these challenges

they are agreeing to engage in fewer studies. Fifty percent of U.S. sites reported a reduction in the number of studies they agreed to conduct. In 2024, 31% of site survey respondents reported having fewer physicians available or interested in conducting trials.[15] In the U.S., 20% of new investigators exit the clinical trial ecosystem after one trial.[26] There is also a growing trend of sites reporting challenges working with increased use of technology in clinical trials.

The U.S. clinical trial ecosystem is complex and has specific challenges. Each U.S. oncology clinical trial site is unique and often requires varying approaches to site activation and study start initiations. By contrast, ex-U.S. countries, with more centralized health care systems, are often able to more efficiently activate sites and initiate studies. In all cases, conducting oncology clinical trials remains a complex and difficult undertaking.

Recommendation #3: Explore common budget and contract processes for U.S. Trial sites[d]

In addition to the improvement opportunities that have been put forward from organizations such as AACI and ASCO, Roundtable participants called for more ambitious efforts to streamline approaches to budget and contracting processes, especially in the U.S. The 2024 WCG survey found that budgets and contracts were leading drivers of delayed study start-up timelines across all clinical research sites.[15] Disparate budget and contracting systems require staff at clinical sites to review documents and meet myriad, sometimes conflicting, requirements, and many sites are not sufficiently staffed. As previously stated, funding for staff to carry out these tasks can be difficult for sites facing financial pressure and may lead to decisions to not initiate a clinical trial.[25] From the trial sponsor perspective, companies acknowledge that imposing unique requirements on sites for budget reporting and contracting increases complexity and slows progress. Roundtable participants also acknowledged that negotiations between sites and sponsors of trials often begin with a wide divide on budget estimates as a leading factor for prolonged site activation and study start up timelines.

Developing universal base-line budget and contracting processes for U.S. clinical trials and establishing an iterative process for publishing case studies and capturing data about how best to manage site budget and contract variabilities could increase the study start up and activation efficiency and begin to address the nation's gap in global competitiveness. New budget and contract paradigms should challenge sponsors and sites to move beyond incremental improvement to existing requirements but also to re-think if there are better approaches that should be adopted. For example, processes that combine the accuracy and benefits of budgets negotiated by procedure with the desire to reduce administrative burdens by paying by the visit; processes for patient reimbursements that are less burdensome to sponsors and faster for patients; and pay-for-performance options.[15,25] These base-line approaches should also address known challenges, such as cash flow for sites. A Society for Clinical Research Sites (SCRS) survey found that 80% of sites had six or fewer months of operating cash. They cited prolonged payment terms and delayed payments as key factors in creating cashflow issues.[25] Developing and consistently implementing streamlined site payment processes, such as reducing the lines of payment and automating validation of payment activities, should be a priority.[25]

The current process for establishing per-patient costs and site-specific funding needs is opaque. Roundtable participants recommended stronger alignment on budget costs that is data-driven and developed via a collaborative effort of clinical trial sites, CROs, and biopharmaceutical companies. This process should include developing consistent approaches for cost analysis of activities such as protocol reviews, protocol amendments, enhanced recruitment needs to meet representativeness expectations and setting up and utilizing new trial

d While this recommendation may be considered a simple process to develop templates or best practices, the effort is likely to be substantial and require extensive engagement. Some aspects of the work may require clarification regarding allowed activity under antitrust rules. The potential benefits of such resources are similarly substantial and extensive.

technologies.[25] Artificial Intelligence and platform technologies can yield information to support alignment on budget costs. Platforms can analyze global benchmarking cost data and supplement pricing factors like site location, procedures, and disease prevalence in a manner that provides information about past payments and performances. Use of these types of tools could help advance stakeholder wide efforts to align on clinical trial costs and streamline individual sponsor and site budget negotiations, as well as sponsor multi-site budget management.[27] Developing and aligning data about actual time and money spent on a clinical trial task would speed up budget negotiations.

Alignment on budget costs should also consider compensation or reimbursement for activities, such as patient enrollment. Appropriate compensation for physicians that refer or participate in clinical trials could significantly improve patient access to clinical trials by helping to compensate busy physicians for their unbillable time. Some oncology care health systems have created professional service agreements in their networks to better align compensation of time for outpatient setting physicians to participate. These agreements could serve as a model for similar compensation for clinical trial physician referrals and work.[28]

The participants also called for the development of universal base-line templates for budgets and contracts. These templates can be applied across all or most sites and build case examples for how to best address site variabilities. Examination of approaches utilized by NCI's cooperative groups for budgeting and contracts (e.g., Cooperative R&D agreements or CRADAS) could be helpful to informing template development. It will be imperative for companies to align among themselves and with clinical trial sites and organizations to achieve system-wide adoption and utilization of these templates.

In addition to process alignment and template development, stakeholders should develop actionable steps for building collective resources and funding for site budget and contract needs, including outsourcing certain functions. These efforts could address resource constraints, enabling sites to more efficiently manage start up and activation processes and expedite negotiation timelines.

Legal teams should be included in these endeavors to help identify what policies may be needed to facilitate appropriate state to state variances under Medicare and Medicaid regulations and manage antitrust issues important to the advancement of universal budget and contract processes and templates.

Recommendation #3: Explore Common Budget and Contract Processes for U.S. Trial Sites
Solutions
Develop base-line budget and contracting processes for U.S. clinical trials and establish an iterative process for publishing case studies and capturing data about how best to manage site budget and contract variabilities
Develop data-driven processes for clinical trial costs and how to structure budgets
Develop and implement streamlined payment processes
Develop a framework that promotes best practices and enables widespread adoption of AI and platform approaches to streamline clinical trial budget and contract processes
Develop common compensation for physician referrals and physician participation in clinical trials (e.g., reimbursement for time spent and execution of specific tasks)
Develop multi-sponsor and site budget and contract templates
Develop actionable recommendations for building collective resources and funding for site budget and contract needs, including outsourcing certain functions

Recommendation #4: Ensure utilization and deployment of technology yield benefits

The use of technology has been touted as foundational to realizing the decades-long goal of implementing more effective and efficient clinical trials. There is significant optimism that AI/ML, advances in medical technology, and improved ability to capture and analyze complex data sets will make that goal a reality. These tools have the potential to streamline operations (e.g., optimize trial designs, enhance participant recruitment, and improve site performance timelines) and enable improved predictive and data analytics.[7,18] However, to date, these innovations have often become *additive* to clinical trial protocols rather than ushering in significant efficiencies. The increased use of technology in trials is also creating additional pressures on clinical trial sites. Clinical sites report being overwhelmed by technological demands with 60% of sites using more than 20 different systems on a daily basis.[29] Site investigators have requested that the biopharmaceutical industry improve sponsor-CRO alignment, standardize and simplify technology solutions, and consider site-preferred technology options.[15]

Sponsors and clinical trial sites should work together to ensure the utilization of technology improves clinical trial performance and minimizes duplicative processes such as data entry on trial sites. A collaborative effort should articulate when and why sites should select or use their own vendors/technology resources or when and why they need to deploy a specifically requested technology, with a goal of enabling more aligned, integrated, and consistent approaches to site technology demands among sponsors of trials and trial sites.[29] It is also imperative that sponsors and sites incorporate a data-driven approach to appropriately budget compensation for these technology demands. The importance of addressing financial burden is underscored by a SCRS survey which found that the most significant hurdle for tech-enabled trials is financial cost, not technical expertise.[29]

Recommendation #4: Ensure Utilization and Deployment of Technology Yield Benefits
Solution
Develop a framework describing best practices for determining when sites should be able to select or use their own vendors/technology resources or when they need to deploy a specifically requested technology that works to promote a more integrated and consistent approach to site technology demands

Recommendation #5: Align on training needs and minimize duplicative activities

Strategically aligning training requirements is an opportunity to streamline site activation and study start up timelines. A 2025 WCG survey found that 72% of sponsors believe that enhanced training would improve site performances.[30] Sites, however, have noted that excessive training requirements for every individual trial can be overwhelming, costly, and create drags on timelines.[21] The 2023 SCRS site landscape survey found that sites face financial pressures from numerous unpaid training requirements (e.g., 40% spending 5–15 hours per month on training for trials with remote technology).[29] Sponsors of trials (biopharmaceutical companies and CROs) and clinical trial sites (clinical trial sites and organizations) should align on how best to balance training requirements with minimizing duplicative activities.

Recommendation #5. Align on Training Needs and Minimize Duplicative Activities
Solution
Construct collective, or at least aligned, training requirements to minimize duplicative clinical trial site activities

Regulatory Policies Key to Improving Site Activation and Study Start Up Timelines

The FDA issued two Notices of Proposed Rulemaking, one on the single Institutional Review Board and one on the Protection of Human Subjects and IRBs (the Common Rule).[31,32] These proposed regulations are intended to harmonize FDA regulations with the Common Rule and streamline informed consent processes. The final single IRB regulations are expected to be published in 2025.[33] This information should provide clarity on how to utilize a single IRB across multiple clinical trial sites including with hub-and-spoke models that will enable faster study start up timelines.

The ICH Good Clinical Practice E6 (R3) Annex 1 that went into effect in July 2025 includes recognition of increased use of decentralized trials, greater emphasis on Quality Management Systems (QMSs) to ensure clinical trial quality, and expanded guidance on use of digital health tools and use of technologies to inform trial participants and obtain consent.[14] The document encourages fit-for-purpose data collection and reductions in unnecessary trial complexity. These steps are pivotal to advancing alignment on what is necessary to demonstrate safety and effectiveness and how that evidence can be generated in the most effective and efficient manner.[14]

The FDA published guidance in 2016 which allowed for informed consent to be collected electronically. In 2023, the FDA published *Informed Consent a final guidance for IRBs, clinical investigators and sponsors* that "encourages researchers to use innovative methods and technologies in informed consent to aid in communicating and educating research subjects."[34,35]

TOPIC TWO:
Importance of Global Harmonization of Science-Based Approaches to Clinical Trial Representativeness Targets and Generalizability Analyses

Discussion Overview

Roundtable participants discussed the importance of global harmonization of science-based approaches to clinical trial representativeness targets and generalizability analyses. Discussions underscored complexities that are particularly challenging in the U.S., due to variable standards of care across the country as the pace of adoption of new therapies differs across clinics and the general phenomenon of faster-evolving standards of care compared to other countries (a side effect of bringing new treatments to the U.S. market before others). In general, Roundtable participants concluded that stakeholders (including regulators) should collaborate and develop additional, contextualized guidance on how to address representativeness and generalizability expectations and manage evolving and varying standards of care across different regions. To advance research and serve patients, guidance should be both reflective of patients' needs and operationally feasible. Participants further called for continuing to develop context for such requirements, such as iterative publication of case studies to provide insights on how to address different trial scenarios and disease-specific factors. Specifically, the participants recommend:

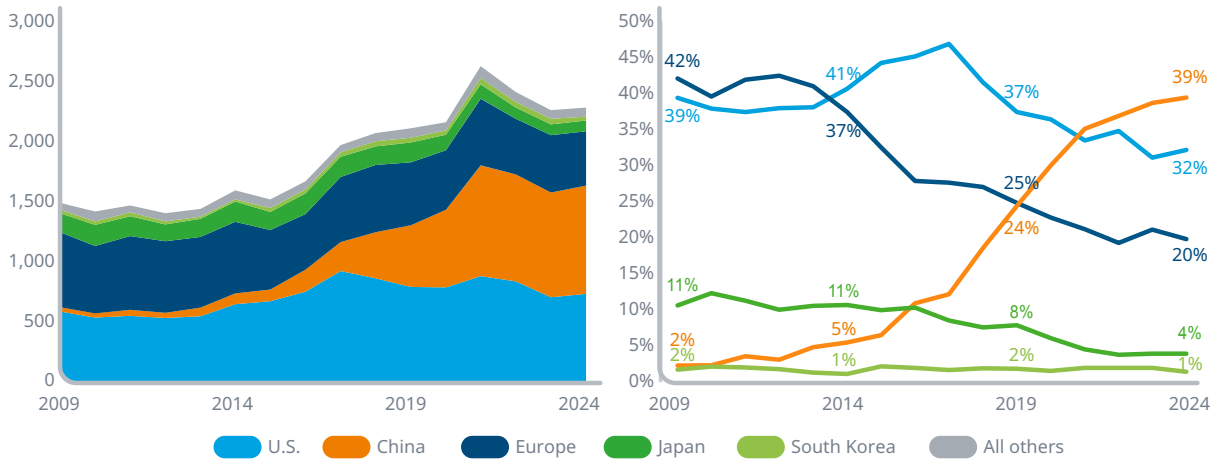
A) Develop scientific principles for representativeness targets and adapt for disease-specific application; and,

B) Manage heterogeneous and continuously evolving standard of care by articulating contextualized regulator/researcher understandings for discrete cancer areas.

MRCT Geographic Clinical Trial Trends

In 2024, MRCTs represented 20% of clinical trial starts, down 17% from 2015 largely due to an increase in China single-country studies. U.S. single-country starts increased from 497 to 542 over ten years but the global share of trial decreased from 36% to 27% in 2024.[3] U.S. headquartered companies accounted for 32% of oncology clinical trial starts in 2024 (down 5% from 2019). Oncology trials from China-headquartered companies accounted for 39% of total starts (84% of Chinese trials were conducted domestically). The share of European headquartered companies' oncology trials was 20%, down 5% from 2019. Japan's share decreased from 8% to 4% over this same time. These trends are often reactions to factors impacting cost and time burdens as well as the country's regulatory environment (Figure 2).[3]

FIGURE 2. NUMBER AND SHARE OF ONCOLOGY TRIAL STARTS BY COMPANY HEADQUARTERS LOCATION, 2009–2024.



Source: Citeline Trialtrove, Jan 2025; IQVIA Institute, Apr 2025.

Note. Global Oncology Trends 2025. Adopting New Therapies and Modalities Shift and Expenditures Rise (p.7). IQVIA Institute for Human Data Science.[3]

Science-Based Principles, not Quotas, Should Drive Globally Harmonized Approaches to Representativeness Targets and Generalizability Analyses

Discussions about how to approach defining and setting region representativeness targets are not new. The International Council for Harmonisation E5 document, published in 1998, provided a framework for assessing acceptability and generalizability of clinical data gathered outside a region by evaluating variables in genetics and physiology, medical practices, available therapies (including supportive care medications and subsequent oncological treatments), as well as social and cultural determinants such as diet and concomitant herbal medications.[36] Japan's Pharmaceutical and Medical Devices Agency (PMDA) published guidance in 2007 about how to take into consideration ethnic factors in their review of applications.[37,38] The European Medicines Agency (EMA) published a reflection paper in 2009 on the impact of factors such as medical practice, disease definition, and study population and how they could complicate the evaluation of data from a European perspective.[39] In 2013, the FDA published a paper discussing the need for improved MRCT design and sample size estimations which could be addressed by identifying differences in diagnosis and treatment practice (concomitant treatments and standard of care) that may lead to differences in treatment effect between U.S. and non U.S. countries, and then quantifying the extent to which these differences might affect the sample size needed from each region in addition to the total sample size.[40] ICH published E17 in 2017 which states that MRCTs foster more efficient drug development, avoid duplication, allow earlier access to innovation, enhance infrastructure development, and establish new standards of care. E17 discusses how these regional variables and factors should be addressed in exploratory phases before the MRCT.[41]

In the U.S., an application based solely on foreign clinical data can only be approved if the foreign data is applicable to the U.S. population and medical practice, the studies have been performed by clinical investigators of recognized competence, and if the data may be considered valid without the need for an on-site inspection by FDA or if FDA considered an inspection necessary, they are able to validate the data through on-site inspection or other appropriate means (21 CFR 314.106 (b)).[42,43]

The FDA published a paper in 2022 raising concerns about the increasing number of oncology development programs based solely or predominantly on clinical trial data from China. The authors stated these applications may have less ethnic and racial representation relevant to the U.S. population. The authors discuss how the degree of regulatory flexibility in establishing the acceptability of data from a single country and its generalizability to a new population needs to be balanced against the drug's innovation. The degree of previous regulatory interaction between the U.S. and a foreign country was cited as a possible factor in the evaluation of submissions from that country, as the extent of past participation in MRCTs may provide added confidence in trial conduct and data integrity. The authors discussed how clinical site inspections cannot fully capture the heterogeneity of data quality and study conduct across many clinical sites. Previous participation in MRCTs and previously reported data integrity challenges were also cited as factors in whether the FDA will request additional information on trials. The authors emphasized the importance of sponsors with these types of applications to engage with the FDA during key milestone meetings.[44]

Two recent situations underscored these challenges. In May 2025, the FDA held an Oncology Drugs Advisory Committee (ODAC) meeting to discuss the differential results observed in the Asian and Non-Asian regions impact on the overall interpretation of the STARGLO trial results (a post-approval confirmatory trial for glofitamab for treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy) and the generalizability to a U.S. patient population. The ODAC voted 8–1 that the

population and trial results were not applicable to the proposed U.S. patient population. This trial met its primary endpoint with a 40% reduction in death but concerns were raised about significant differences between U.S. and non-U.S. regions and low U.S. sample size (n=25). The ODAC cited a lack of regional stratification in study design and potential imbalances in patient characteristics.[45] FDA subsequently issued a Complete Response Letter for this application due to concerns that the patient population studied was not applicable to the U.S.[46]

An ODAC meeting in July 2025 examined the results of the DREAMM-7 and DREAMM-8 trial for belatamab mafodotin in two different combinations to treat patients with multiple myeloma in the second line. Both combination regimens met their primary endpoint of progression-free survival, with one demonstrating a significant improvement in overall survival. The FDA raised concerns about the low percentage of U.S. patients (less than 5%) and that older adults and Black/African American patients were underrepresented. The FDA further raised concerns about the safety profile; the ODAC voted no on the question of whether appropriate dosages had been identified for the proposed patient population.[47] FDA subsequently approved this application.[48]

There is concern among sponsors that country-specific representation regulatory requirements are not always informed by operational practicalities or by scientific principles that define disease, disease prevalence, and incidence by region(s). Specifically, the previously discussed ODAC meetings and the 2024 FDA Guidance Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Program appear to go beyond scientific principle and have raised concerns that the expectations of U.S. representativeness may exacerbate current challenges relating to clinical research staff shortages and limited patient pools.[49] Roundtable participants pointed out that this becomes even more daunting as more countries are calling for specific domestic representation requirements—which raise an inherent risk of competing enrollment targets and potential for redundant trial exposures. Some countries also have additional domestic enrollment requirements (e.g., FDA 2024 Guidance Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Trials).[50] However, there is little understanding about the underlying scientific principles driving these domestic representation expectations, and ICH E17 discourages arbitrary quotas. Further, Roundtable participants called for regulators and trial sponsors to better align on what should be required for trials well-underway, in contrast with how best to approach representativeness in future clinical trials.

Recommendation A: Develop scientific principles for representativeness requirements and adapt for disease-specific application

The Roundtable participants discussed the vital need for ICH, FDA, sponsors, clinical trial sites, and patients to collaborate and align on what scientific principles should drive representative targets and what statistical and data quality principles should drive analyses of the generalizability of safety and effectiveness in trials with patients from different regions. For example, representativeness targets that map to key intrinsic and extrinsic factor distributions relevant to the intended global use population likely better meet the needs of patients than local enrollment quotas. They further pointed out that these principles should be further developed to account for disease-specific factors. For example, what principles should drive representation for rare diseases where a global approach is required to recruit enough patients to enable statistical analysis of data? For diseases with larger patient populations, where there is no significant difference in safety profiles in patients from different countries and no known differences in how diseases are presented, when might post-approval studies using RWE be a more effective way to evaluate any potential differences in clinical outcomes? The frameworks should include information about what should be applied to recently-completed or nearly-completed trials and how more efficient and effective approaches could be deployed for future MRCTs. Enrollment target

frameworks should consider and weigh several factors such as disease prevalence and incidence, target population demographics, the quality and access of care in the country/region, safety and/or toxicity profile of the treatment, eligibility criteria, rare/orphan disease status, availability and effectiveness of other treatments, and the probability of achieving enrollment. Collaboration with TransCelerate on their work developing global data standards to reduce friction and inefficiencies across trial sites could be beneficial to these efforts.[51] The outcome of these collaborative endeavors should be the publication of frameworks that include case examples for different scenarios. Additionally, inspection activity to assure the integrity of clinical research must align with these principles and be conducted in a timely and consistent manner.

Recommendation A: Develop Scientific Principles for Representativeness Requirements and Adapt for Disease-Specific Application
Solutions
Define scientific principles for representative requirements and statistical and data quality principles to drive analyses of safety and effectiveness in trials with patients from different countries and different racial and ethnic groups that include activities to provide context for specific diseases
Develop processes that enable timely inspections aligned with other clinical research requirements

Recommendation B: Manage heterogeneous and continuously evolving standard of care by articulating contextualized regulator/researcher understandings for discrete cancer areas

Managing evolving standards of care is an issue that raises complications in MRCTs and requires immediate attention. These are especially difficult issues for U.S.-based clinical trial sites, where patients often have access to novel treatments sooner that patients in other regions, and in global sites where standard of care may be strikingly different than in the US. Even within the U.S., there are variations of access to the latest standard of care as innovative and novel treatments may not uniformly be adopted at the same rate across all oncology treatment facilities.

In 2015, Tanaka et al. proposed an analytical approach to considering genetic physiological variables (e.g., polymorphisms, organ dysfunction differences in causes, histologically and molecularly defined disease subtypes) and regional factors (e.g., medical practice and available therapies, including supportive care medications as well as subsequent oncological treatments). They proposed creating a check list of these factors, running a *k*-means cluster algorithm and examining the different *k*'s to decide *k*, defining region based on these results, estimating regional sample size as part of overall sample size estimation and controlling region for primary efficacy analysis and predefined consistency assessment. This publication acknowledged that until harmonized guidance is created, trialists will have to defend their results against potentially misleading regional findings.[52]

Roundtable participants explored the tension between the length of time it takes to conduct a clinical trial (3–5 years), the quick evolution of standards of care, and regulators' requirements for evidence that demonstrates the treatment will be safe and effective in the current landscape of care in their regions of oversight. MRCTs nearly always involve different standards of care for different regions, even within an individual country. In the U.S., the standard of care for oncology can vary from site to site. U.S. site principal investigators and trial sponsors often face difficulties retaining patients in trials when the standard of care changes mid-trial. There are often multiple clinical trials being conducted simultaneously to treat the same disease, which can create *competing* standards of care. Both sponsors and principal investigators at clinical trial sites have stated that there is not sufficient regulatory clarity about how best to manage evolving and

varying standards of care across sites and regions. Additionally, changing control arms mid-trial is often not feasible in countries where proposed control-arm interventions are not yet approved in those countries. Continuously chasing an evolving standard of care can yield a sense of trials pursuing a moving target within, and between, regions.

Important insights may be learned from how PD-1/PD-L1 development programs have managed evolving and varying standards of care.[53] For example, the use of PD-1/PD-L1 blockade for the treatment of melanoma has significantly improved survival rates for these patients and shifted the standard of care. There have been more than 20 FDA approvals of anti-PD-L1s for more than 20 different cancers and more are expected.[53,54,55] Additionally, use of real-world effectiveness and post market surveillance of these treatments has been effectively deployed to gain additional insights on safety and clinical outcomes.[53]

Rather than pursuing a broad approach to this challenge, Roundtable participants recommended that patients, sites, sponsors, and regulators work together to address evolving and varying standards of care at the *specific cancer disease level* to yield 'contextualized regulator/researcher understandings'. The engagement needed to develop these contextualized documents should involve shared learning among the various stakeholders. Focusing on specific cancer areas enables alignment on key intrinsic and extrinsic factors to evaluate, and how to approach development of treatments that are ethical, operationally feasible, and consider patients' needs. The outcome of these collaborative endeavors should be the publication of guidance from the FDA and ICH that includes examples that help guide sponsors in managing different scenarios and unique aspects of specific diseases.

Recommendation B: Manage Heterogeneous and Continuously Evolving Standard of Care by Articulating Contextualized Regulator/Researcher Understandings for Discrete Cancer Areas
Solution
Develop and advance regulatory understandings about how to address evolving and varying standards of care for oncology patients in MRCTs that consider clinical context/discrete disease area, patients' needs, and operational feasibility

Conclusion

Multi-Regional Clinical Trials are a cornerstone of developing innovative treatments for cancer. However, the clinical research ecosystem is facing several strains and challenges. The Roundtable discussions brought to light the significant amount of work being done by both sponsors of trials and clinical trial sites to improve clinical trial enrollments, site activation, and start up times via internal reforms, especially in the United States (U.S.). The group developed recommendations to:

- Unlock the potential of network approaches;
- Improve enrollment and study start up timelines by advancing more patient-centric, rather than trial-centric, approaches;
- Explore common budget and contract processes for U.S. trial sites;
- Ensure utilization and deployment of technology to yield benefits;
- Align on training needs and minimize duplicative activities;
- Develop scientific principles for representativeness targets and adapt for disease-specific application; and,
- Manage heterogeneous and continuously evolving standard of care by articulating contextualized regulator/researcher understandings for discrete cancer areas.

Participants discussed the importance of ensuring recommendation implementation advances meaningful change by streamlining clinical trials, not adding unnecessary complexities. Further, the next phase of advancing these recommendations requires task-oriented cross-stakeholder collaborations, with the right expertise, to implement solutions. Lastly, they observed the need to distinguish between what short-term solutions can be applied to clinical trials that are underway and long-term solutions to improve the clinical trial ecosystem.

FDA Initiatives: Projects Orbis, Optimus and Site Selector

The FDA has launched three initiatives that are also affecting oncology clinical trials, submission, and review processes. The FDA's Oncology Center of Excellence (OCE) launched Project Orbis in 2019. The purpose of Project Orbis is to provide a framework for concurrent submission and review of oncology products by global regulators. Current participants include Canada, Australia, Singapore, Switzerland, Brazil, the U.K., and Israel and has included 633 applications for 79 products. The OCE also has a project called Project Site Selector designed to invest more time with sponsors discussing clinical trial site locations. This approach was developed because regulators have traditionally not thoroughly queried companies prior to trial initiation on methods to select sites and the generalizability of the data collected from these sites to the U.S. population and medical practice.[56] Additionally, the OCE launched Project Optimus in 2023 to reform dose optimization and dose selection approaches. Many of the principles have been part of early clinical trial design for years (e.g., simulations, Bayesian designs etc.) but these new requirements may introduce additional complexities and affect speed and costs of these trials. It will also require more collaborative engagement between sponsors and regulators.[57]

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Appendix A

Improving Oncology Site Activation, Enrollment & Study Start Up Timelines Is Imperative – Especially in the U.S.							
Solutions	Collaborators						Time
	Regulators	Clinical Trial Sponsors	Clinical Trial Sites & Organiza-tions	Clinical Research Groups	Patient Groups	Medical Research Groups	Short,- Mid-, or Long-Term Endeavor
Recommendation #1: Unlock the Potential of Network Approaches							
Collectively define specifics of operational and regulatory compliance processes for network approaches, ideally harmonized with international standards	✓ (FDA, ICH)	✓	✓	✓			
Recommendation #2: Improve Enrollment and Study Start Up Timelines by Advancing More Patient-Centric, Rather Than Trial-Centric, Approaches							
Improve Referral and Screening Processes							
Develop pre-competitive platform approaches to enable patients to be screened for a broad array of trials and referred to the trial(s) that best fit their needs		✓	✓	✓	✓	✓	
Build More Opportunities to Enroll in Oncology Clinical Trials							
Develop and promote policies and best practices that enable sites with little to no experience to build clinical trial capacity	✓ (FDA)	✓	✓	✓			
Clarify regulatory policies and remove barriers to the effective deployment of tools that support decentralized approaches such as remote monitoring and in-home data collection	✓ (FDA , ICH)	✓	✓	✓	✓		
Explore pre-competitive approaches to support sustainable long-term community engagement and educational models that enable patients and families to better locate and evaluate clinical trial opportunities		✓	✓	✓	✓	✓	

Time Endeavors: Short-Term Mid-Term Long-Term

Improving Oncology Site Activation, Enrollment & Study Start Up Timelines Is Imperative – Especially in the U.S.

Solutions	Collaborators						Time
	Regulators	Clinical Trial Sponsors	Clinical Trial Sites & Organiza-tions	Clinical Research Groups	Patient Groups	Medical Research Groups	Short,- Mid-, or Long-Term Endeavor
Reduce Patient and Family Financial Burdens							
Promote policies that reduce financial burdens on patients and advocate for the removal of statutes that prohibit or limit trial sponsors' ability to reduce patient burdens	✓ *Federal and state policy leaders (some solutions may require statutory changes)	✓	✓	✓	✓	✓	
Recommendation #3: Explore Common Budget and Contract Processes for U.S. Trial Sites							
Develop base-line budget and contracting processes for U.S. clinical trials and establish an iterative process for publishing case studies and capturing data about how best to manage site budget and contract variabilities		✓	✓	✓			
Develop data-driven processes for clinical trial costs and how to structure budgets		✓	✓	✓			
Develop and implement streamlined payment processes		✓	✓	✓			
Develop a framework that promotes best practices and enables widespread adoption of AI and platform approaches to streamline clinical trial budget and contract processes		✓	✓	✓			
Develop common compensation for physician referrals and physician participation in clinical trials (*e.g.*, reimbursement for time spent and execution of specific tasks)		✓	✓	✓			
Develop multi-sponsor and site budget and contract templates		✓	✓	✓			
Develop actionable recommendations for building collective resources and funding for site budget and contract needs, including outsourcing certain functions		✓	✓	✓			

Improving Oncology Site Activation, Enrollment & Study Start Up Timelines Is Imperative – Especially in the U.S.							
Solutions	Collaborators						Time
	Regulators	Clinical Trial Sponsors	Clinical Trial Sites & Organiza-tions	Clinical Research Groups	Patient Groups	Medical Research Groups	Short,- Mid-, or Long-Term Endeavor
Recommendation #4: Ensure Utilization and Deployment of Technology Yield Benefits							
Develop an industry-wide approach to site technology demands, such as a framework for determining when sites may select/use their own vendors/technology resources or when deploying a specifically requested technology is required		✓	✓	✓			
Recommendation #5: Align on Training Needs and Minimize Duplicative Activities							
Construct collective, or at least aligned, training requirements to minimize duplicative clinical trial site activities		✓	✓	✓			

Appendix B

Importance of Global Harmonization of Science-Based Approaches to Clinical Trial Representativeness Targets and Generalizability Analyses							
Solutions	Collaborators						Time
	Regulators	Clinical Trial Sponsors	Clinical Trial Sites & Organiza-tions	Clinical Research Groups	Patient Groups	Medical Research Groups	Short,- Mid-, or Long-Term Endeavor
Recommendation A: Develop Scientific Principles for Representativeness Requirements and Adapt for Disease-Specific Application							
Define scientific principles for representative requirements and statistical and data quality principles to drive analyses of safety and effectiveness in trials with patients from different countries and different racial and ethnic groups that include activities to provide context for specific diseases	✓ (FDA , ICH)	✓			✓	✓	(Active Clinical Trials) Mid-term (Future Clinical Trials
Develop processes that enable timely inspections aligned with other clinical research requirements	✓ (FDA)	✓	✓				(Active Clinical Trials) Mid-term (Future Clinical Trials)
Recommendation B: Manage Heterogenous and Continuously Evolving Standard of Care by Articulating Contextualized Regulator/Researcher Understandings for Discrete Cancer Areas							
Develop and advance regulatory understandings about how to address evolving and varying standards of care for oncology patients in MRCTs that consider clinical context/discrete disease area, patients' needs, and operational feasibility	✓	✓			✓	✓	(Active Clinical Trials) Mid-term (Future Clinical Trials)

Time Endeavors: Short-Term Mid-Term Long-Term

Appendix C

Improving Oncology Multi-Regional Clinical Trials

A Roundtable Discussion hosted by the Reagan-Udall Foundation for the FDA

1333 NEW HAMPSHIRE AVE NW, ROOFTOP CONFERENCE CENTER, WASHINGTON, DC

SEPTEMBER 4, 2025

MEETING PURPOSE

Multi-regional clinical trials (MRCTs) are a cornerstone of oncology drug development and are critical for building the evidence base for product safety and efficacy as well as expanding patient access to new therapies. However, prolonged timelines for trial site activation and patient enrollment, regional variability in time to diagnosis and other dimensions, inconsistent or non-representative control arm selection, and lack of therapy availability pose significant challenges, undermining the comparability of efficacy and safety outcomes across regions. Misalignment in standards of care, such as time to diagnosis and then access to treatments, in different U.S. regions, as well as globally, further complicate data interpretation. Moreover, limited infrastructure outside major hospital systems constrains the number of clinical centers currently offering clinical trials, and those systems are facing additional financial strain. The U.S. and other countries are exploring decentralized clinical trials and digital tools, among other approaches, that have potential to increase patient access and compress timelines for conducting studies. This meeting will explore what approaches and revisions are needed to significantly improve oncology clinical trial efficiencies. This convening will explore actionable ways to improve trial clarity, consistency, and efficiency with a focus on what the private sector, FDA, and global regulators might realistically address.

FUNDERS

BeOne Medicines, Jazz Pharmaceuticals, Lilly, and Merck provided funding for this meeting.

Agenda

10:00 AM	**Welcome and Introductions (~60 seconds per participant)**
	• Name, title, organization • Pose the one question that, if addressed, would have the greatest impact on improving multi-regional clinical trials of oncology products
10:25 AM	**Session 1: Illustrate barriers that delay oncology MRCTs**
	• Discuss timely site activation, patient enrollment, and study start up, including processes that are working well and what creates delays **Discussion Questions** (Addressing only site activation, patient enrollment and study start up in this section) 1. How would you define optimal site activation, patient enrollment, and study start up processes and conditions? What are the main factors needed to normalize these practices? 2. What are the main challenges in expanding, validating, and starting up clinical trial sites and studies in the U.S.? ex-U.S.? 3. What can be done to address these challenges/barriers (e.g. regulatory reform, statutory changes, best practice frameworks) and who is responsible for implementing these changes?
11:25 AM	**Break**
11:35 AM	**Session 2: Explore population enrollment questions in oncology trial design and execution**
	• What does the "right" enrollment population amassed from multiple regional trial sites look like? **Discussion Questions** 1. What considerations should drive country/region enrollment targets? – Is there alignment on these considerations? 2. What are the main concerns with current FDA enrollment requirements? What are the main concerns in other countries' requirements? 3. Do current guidance and published methodologies enable science driven approaches to identifying U.S. and ex-U.S. enrollment targets? If not, what is needed to improve?
12:35 PM	**Lunch**
1:15 PM	**Session 3: Explore questions outside of the individual trial participant (e.g., standard of care, data fidelity, data generalization etc.) in oncology trial design and execution**

	• How should trial sponsors evaluate the different environments of trial sites when constructing clinical trials, specifically standard of care, data fidelity, and data generalization? • How should trial sponsors evaluate the different environments of trial sites when constructing clinical trials, specifically standard of care, data fidelity, and data generalization? **Discussion Questions** 1. What are the biggest challenges for sponsors to implement predominantly, or exclusively, U.S. participant trials? 2. Does current guidance from the FDA provide sufficient information about how to address regional differences in standard of care? And if not, what are the three key issues? 3. What might advance alignment of requirements for acceptance of foreign data by the FDA? 4. How can sponsors and FDA and other global regulatory entities better engage on MRCTs to enable early issue identification and resolution?
2:15 PM	**Session 4: Illustrate approaches to address regulatory and operational barriers that delay oncology MRCTs**
	• Consider how regulatory and operational barriers that delay oncology MRCTs might be addressed through technology and clinical trial modernization. • Discuss the environment that would support the implementation of these approaches: private sector and regulator actions **Discussion Questions** 1. Consider the challenges identified in Sessions 1, 2, and 3. Which challenges are most urgent and/or impactful to address? 2. How might those priority challenges be addressed? (e.g., additional regulatory guidance, enhancement of trial capability, expanded use of digital technologies and technology-enabled platforms for regulator communication, incentives, infrastructure investment, etc.) 3. Do current guidance and published methodologies enable efficient and effective selection of country and sites? If not, what is needed to improve these processes?
3:30 PM	**Meeting Wrap-Up**
	• From the discussion, what three items might be realistically addressed by the FDA, global regulators, and the private sector to improve trial clarity, consistency, and efficiency?
4:00 PM	**Adjourn**

Appendix D

Roundtable Contributors

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Moderator: Susan C. Winckler

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