RESEARCH PRACTITIONER

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25 Years

DCT fatigue: Research sites, patient face challenges, financial burden while sponsors reap greater rewards

by Elizabeth Tilley Hinkle

Principal investigators, study coordinators and other members of research teams are learning that sponsors are reaping the biggest benefits of decentralized and hybrid trials, such as lower long-term costs. Meanwhile, sites are bearing the burden of up-front costs and increased demands on staff. And evidence that the model has a positive impact on patients is mixed. That's led some in the research community to wonder: Is the model all it's cracked up to be?

Decentralized clinical trials (DCT) have gained popularity in recent years, often touted as the answer to some of the trickiest aspects of clinical research, including recruitment and retention, participant diversity, equity and inclusion, patient experience and satisfaction, and greater access to real-world data. The DCT model boomed during the COVID-19 pandemic, driven by a mandate for effective and safe remote care. But now research teams are facing challenges implementing

Learner Outcomes:

1. Summarize the likely causes of DCT fatigue or disillusionment and its impact on clinical research.
2. Explain the current thinking on the pros and cons of decentralized and hybrid clinical trials.
3. Compare and contrast the benefits to sponsors vs. research teams and sites.
4. Outline the benefits and burdens of patients who would like to take part in DCTs.

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New regulatory requirements push diversity to the forefront of clinical trial planning

by Elizabeth Tilley Hinkle

Inclusion of appropriately diverse trial participants has been a concern for well over two decades. But in recent years, diversity among clinical trial participants has become a growing concern for sponsors, regulators and researchers alike.

Regulatory guidance, research organization policies and even sponsors' company principles have begun to feature practices aimed at improving diversity in clinical trial participants. And there's a move to standardize these emerging practices as stakeholders gain familiarity with available tools and methods, WCG notes in a recent white paper.[1]

Recent changes in requirements for clinical research under the Food and Drug Omnibus Reform Act (FDORA) highlight these common practices, mandating that clinical trial protocols include DEI plans and report to the FDA on progress toward meeting study-specific targets in underserved age, gender, race, ethnicity and other groups.

"There is a growing recognition that the clinical research enterprise has a diversity problem, given that

Learner Outcomes:

1. Describe how the focus on diversity, equity and inclusion affects clinical research.
2. Discuss new and existing DEI regulatory requirements in the U.S. and abroad.
3. Explain how investigators and coordinators can support DEI efforts in clinical trials.
4. Outline how to create a patient-centric approach to DEI efforts and programs.

many clinical trials recruit historically marginalized individuals or patients

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- Conduct clinical trials to comply with U.S. and global regulations.

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Regulatory Update

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FDA Expands Guidance on Gathering Race, Ethnicity Data to Observational Trials

The FDA has expanded its existing guidance on collecting race and ethnicity data in clinical research to include noninterventional, or observational, studies as well as clinical trials.

In the new draft guidance, "Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products," the agency notes that the ways race and ethnicity data are collected in clinical practice can vary considerably and thus affect the demographic data available for analysis in noninterventional studies. To account for this, "sponsors seeking to conduct noninterventional studies to support regulatory decision-making should discuss the availability of race and ethnicity data with the relevant review division," the guidance advises.

It also includes updated references and agency contact information and editorial changes intended to provide greater clarity.

Compared to the current 16-page final guidance, which came out in October 2016, the newly issued draft guidance is considerably more concise, standing at eight pages, and makes recommendations in five areas:

- The two-question format for requesting race/ethnicity information
- Self-reporting by participants
- Ethnicity
- Race
- The use of more detailed racial/ethnic categories in certain situations, such as trials being run outside of the U.S.

Comments on the draft guidance are due by April 29.

Read the draft guidance here.

Draft Guidance Says Asymptomatic People Should Be Included in Alzheimer's Trials

Drugs for cognitively and functionally normal people who have the pathophysiologic changes of Alzheimer's disease (AD) could be approved on a single biomarker outcome, according to the FDA's new draft guidance on drug development for early AD.

These people, defined in the draft as patients with Stage 1 disease, are an important population for Alzheimer's clinical trials because early intervention might alter disease progression, the draft says.

"Because it is highly desirable to intervene as early as possible in AD, it follows that patients with characteristic pathophysiologic changes of AD but no subjective complaint, functional impairment, or detectable abnormalities on sensitive neuropsychological measures" (Stage 1 AD patients) are an important target population for enrollment in clinical trials, the guidance says.

But the guidance also notes that it's impossible to measure neuropsychiatric symptoms in an asymptomatic group, so it codifies for the first time that biomarker changes alone can be enough to support an accelerated approval for an Alzheimer's drug — including one for people with no clinical symptoms.

"Because there is no clinical impairment to assess," the guidance also explains that a clinically meaningful benefit cannot be measured in these patients. "In Stage 1 patients, an effect on the characteristic pathophysiologic changes of AD, as demonstrated by an effect on various biomarkers, may be measured. Such an effect, analyzed as a primary efficacy measure, may, in principle, serve as the basis for an accelerated approval."

The guidance suggests a future in which Alzheimer's is defined by biomarkers rather than clinical symptoms, according to Lon Schneider, director of the State of California Alzheimer's Disease Center at the University of California, Los Angeles, a perspective that comes on the heels of a similar push for a biological definition from the Alzheimer's Association.

"This continues the 2018 FDA draft guidelines and the recent Alzheimer's Association Criteria by saying Alzheimer's disease equals a positive amyloid-PET scan," said Schneider. "Effectively, it means that if a treatment changes the amyloid or tau biomarkers toward normal, that the treatment will be approved. Symptoms and function really don't matter."

Comments on the draft will be accepted until May 3.

Read the draft guidance here.

FDA Gives Direction on Using RWD in Noninterventional Studies

In a nod to the increasing potential of demonstrating drug/biologic safety and/or effectiveness through noninterventional studies, the FDA has pub-

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lished long-awaited draft guidance on designing and analyzing such studies with real-world data (RWD) in mind.

The eight-page guidance, which defines noninterventional studies as those in which patients are given the investigational product during routine medical practice, stresses the importance of using appropriate RWD sources. It also emphasizes identifying and addressing sources of bias that could lead to incorrect inferences, including such confounding factors as noncomparable treatment groups.

"The reliability and relevance of RWD used in a noninterventional study are critical for making appropriate causal inferences and are essential to establishing the data's fitness for use in generating real-world evidence to support a labeling change or address a safety concern," the guidance reads. "Reliability includes accuracy, completeness, and traceability; relevance includes the availability of data for key study variables (exposures, outcomes, covariates) and sufficient numbers of representative patients for the study."

The guidance directs sponsors to demonstrate that their proposed data sources are appropriate and carefully consider their limitations, as data sources will frequently have been generated initially for nonresearch purposes. Each protocol or accompanying documents should provide detailed descriptions of the following:

- Proposed data source(s), including how the data were originally gathered
- Rationale for selection
- Relevance of the data to the drug-outcome association of interest
- Appropriateness of the information to relevant confounding factors
- Available information on data reliability, including how it was accrued from source data
- Common data models used to provide a standard structure for sharing data from various sources and the rationale behind selecting the model
- Available information on the timing of assessments for key data elements and key data element completeness
- How the proposed coding is appropriate based on operational definitions of key variables
- Appropriateness of the data for the target patient population
- Quality assurance activities that will be carried out on extracted original source data
- Existing or potential links to other data sources as applicable, such as merging data from EHRs and claims databases
- Plans for additional data collection, if applicable

Comments are due by June 18.

Read the full draft guidance here.

Reminder to Sponsors: One Year Left to Transfer Trial Data to EU's CTIS

Sponsors have one more year to transfer records on any ongoing trials in Europe to the EU Clinical Trials Information System (CTIS) database.

The three-year transition period established in the EU's new Clinical Trials Regulation will end on Jan. 31, 2025.

Sponsors of trials that are expected to run past Jan. 30, 2025, should consider the time it will take EU member states to complete trial authorizations. Although CTIS will use an accelerated transition process whenever possible, the authorization process can take up to three months, according to the European Medicines Agency (EMA).

Ongoing trials do not need to be paused or closed out while they're transitioned to the CTIS.

The EMA is providing training courses to help sponsors with the transition.

Access the EMA's CTIS training materials here.

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and managing these studies and navigating the burden on researchers and support staff.

The pandemic established some unrealistic expectations around DCTs, Catherine Gregor, chief clinical trial officer at Florence Healthcare, says in an Association of Clinical Researchers (ACRP) post, leading to some disillusionment and a slight drop in the number of decentralized and hybrid trials.[1] This could be the reason behind DCT fatigue, as sponsors look more critically at decentralized elements in new trials.

The number of DCTs conducted saw a significant bump after decentralized elements were introduced to existing clinical trials to allow them to keep going forward during the COVID-19 pandemic. The number of clinical trials that included at least one DCT or virtual element rose 50 percent from 2020 to 2021 and 28 percent from 2021 to 2022, according to the Tufts Center for the Study of Drug Development (CSDD).[2]

The overall pace of study decentralization slowed in 2022, down 9 percent compared to 2021, according to data from *Clinical Trials Arena*'s DCT Tracker, which uses an exclusive taxonomic approach to identify decentralization methods across thousands of drug trial public records. Nonetheless, the DCT model in 2022 was more prevalent than in 2020 and the organization predicts that decentralization will continue to trend upward.[3]

According to the DCT Tracker, digital data collection was the fastest growing DCT component, rising 54 percent in 2021 compared to 2020. Although it fell 16 percent in 2021, it was expected to recover by 13 percent in 2023. Use of electronic patient reported outcomes (ePRO), clinical outcome assessments and consent forms and procedures also slowed by 31 percent in 2022 but were expected to recover and reach similar activity levels by the end of 2023.

Meanwhile, remote monitoring using sensors, devices and trackers continues to be a popular DCT component, decreasing just 5 percent between 2020 and 2021. It's expected to increase by 10 percent in 2023, according to the tracker.

Decentralized trials — or at least elements of the model — are likely here to stay, Pamela Nelson, founder and CEO of research manager Bracane Company, tells ACRP.

That leaves researchers and sites looking for ways to improve efficiency and reduce the costs of decentralized and hybrid model trials.

Sponsors reap cost, data benefits

In the plus column, DCTs appear to offer a financial benefit to sponsors. While they do need more spending on the front end of a clinical trial, sponsors earn returns on their investments faster than for traditional studies, according to a 2023 CSDD analysis.[4]

Screen failure rates account for 11 percent of trial costs, according to CSDD data. The average screen failure rate for trials without DCT elements is more than 31 percent for phase 2 and about 30 percent for phase 3. When DCT elements are added, screen failure rates fall by 23.5 percent for phase 2 and 32.8 percent for phase 3, resulting in a 2.58 percent and 3.61 percent reduction, respectively, in trial costs.

A substantial protocol amendment costs an average of $141,000 in phase 2 and $535,000 in phase 3. The 2023 CSDD data show that phase 2 trials see an average of 3.3 amendments, while phase 3 trials have an average of 3.4. These numbers are reduced to 2.4 and 3.2, respectively, when DCT elements are added. This results in savings of $507,600 in phase 2 and $321,000 in phase 3 due to fewer protocol amendments.

Another assumptive benefit to the model is that remote technology can improve participant access and diversity. DCTs offer a chance to get more of a "real-world" look at how investigative treatments work. Technology's ability to gather information during participants' normal daily activities also offers valuable real-world insight into how a treatment performs, according to Leonard Sacks, associate director for clinical methodology at the FDA's Center for Drug Evaluation and Research Office of Medical Policy.[5]

In theory, it's more convenient for participants and allows research teams to collect data more often than they can with scheduled trial visits, Sacks writes.

Investments and returns

That said, sites do not always reap the same benefits as sponsors, which could be behind signs of the "DCT fatigue" that some industry experts, including Adam Samson, head of clinical delivery operations and real-world evidence clinical trials at Walgreens, have seen as DCTs mature, according to ACRP.

For example, individual sites bear the burden of upfront investments in the software and technology that enable DCT elements in clinical trials, Florence Healthcare notes, although long-term savings could eventually offset that expense.

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The massive volume and variety of data collected during a DCT also comes at a cost to sites. Collecting, managing and using this data adds to personnel costs and time. Software that can automate data collection and organize data can help with this challenge, Florence Healthcare notes, although such software also costs money.

Meanwhile, all new technology requires time and money for staff training. Choosing user-friendly software can reduce the learning curve, but even the most intuitive programs will require an implementation process, training and ongoing support.

Sites must consider hiring specialists to handle the data demand associated with DCTs, too. Electronic data engineers, data scientists and informaticists integrate, harmonize and validate data from multiple sources, including devices that send patient-reported outcomes, Jamie Dwyer, associate dean of clinical research and director of the Utah Data Coordinating Center, says in a 2023 ACRP post.[6] Cybersecurity experts help mitigate threats from cyberattacks and malware.

And for smaller sites in underserved geographic areas, staffing in general may be a challenge, according to Nadege Gunn, medical director and senior scientific advisor at Velocity Clinical Research. High turnover and loss of staff to other locations with more competitive salaries is still a concern, she says in a January 2024 ACRP blog post.[7] A potential solution could be for sponsors and CROs to fund long-term presence for sites within diverse communities, possibly as part of broader diversity, equity and inclusion (DEI) plans.

And yet, site approaches to budgeting have remained unchanged for many years and primarily reflect the tasks associated with conducting traditional studies that center around brick-and-mortar sites, ACRP notes. Budgets often fail to account for the time and cost related to learning and implementing new systems and technologies, for example.

Sites must be appropriately compensated for these extra efforts, ACRP maintains in a December 2023 white paper, saying, "Decentralized elements add activities and responsibilities to study implementation, a cost in terms of both time and effort that is being absorbed by sites and not accounted for in their budgets."[8]

These can include:

- Onboarding and managing third-party vendors
- Training and managing multiple technology platforms
- Providing digital health devices to participants when required by the protocol
- Serving as technology training and support for participants in bring-your-own-device studies
- Managing payments to participants, either directly or through a patient concierge vendor
- Coordinating direct-to-patient shipments of treatments

ACRP has created a resource — the DCT Budget Buddy — to help sites navigate budget challenges, the white paper notes. Rather than showing specific monetary values, this tool helps sites determine specific needs for a given clinical trial. It's intended for use during the planning stages to ensure that sites examine important questions to help set them up for accurate and complete budgeting.

The DCT budget tool also helps sites evaluate their roles in managing and monitoring software and technology to ensure that all associated time and effort, including training time, is represented in the budget.

Technology and workloads

Much of the tech-related time and effort results from multiplying technologies, with each sponsor having preferred systems and technologies for each trial, which rarely overlap. Each one requires separate training, along with separate passwords and logins, adding to the burden of entering data for each clinical trial, Gregor says.

Technologies come with changed workflows that also primarily burden sites, she adds. Change management should be the responsibility of sponsors and CROs, which should work together to coordinate the demands they make on sites, Gregor says, adding that such tools as shared sponsor portals could ease site burden.

Integrating technologies is challenging not only for sites but also for participants, James Streeter, global vice president of life sciences product strategy at Oracle Health Sciences, says in an Oracle white paper.[9] Dealing with multiple systems can create a fragmented and possibly frustrating patient experience. It also makes it hard for sites to get a full picture of patient experience. Integrating different systems and platforms makes them seamless for sponsors, sites and patients alike.

These technologies often are developed with sponsor or CRO convenience in mind, rather than looking first at user needs at the site level, she notes.

Nancy Sacco, head of clinical/site development operations at SiteBridge Research, agrees in the ACRP's post that

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sponsors are likely to press for studies to be done as quickly as possible using the most experienced sites, within a certain budget. That results in technology overload at sites.

"Moving forward, we need a clinical trial ecosystem that does not disproportionately burden one set of stakeholders — in this case the sites," Gregor advises in the same post.

"Having more say in technology choice would be more in line with the fact that sites are accountable for carrying out the study, including the PI's obligations to protect patient safety," Sacco says. "Responsibility also needs to be allocated to an individual group to ensure that sites are well-trained and can use the required technology."

Data generation and management

Related to technology is the management of the large amounts and varied sources of data generated during a DCT, another challenge for research sites.

Adding decentralized elements to a trial could use study data faster and more effectively, CSDD found in its 2023 analysis. The volume, frequency and variety of data collected from eCRFs, patient health records, wearables and diagnostics may let researchers draw insights from the data sooner and increase its statistical power while reducing the number of patients needed to reach conclusions about a new product.

But handling and using that data can be burdensome with the variety of virtual collection methods available, Streeter says. It can be tough to manage and track DCT-generated data using EDC systems. Since these are based on paper forms and paper-based processes, they aren't designed to collect large volumes of data or to handle various data in one place.

New tools could efficiently integrate data collection and management, while also supporting data collection from new sources and nonconventional formats, he suggests.

The FDA also acknowledges data challenges around DCTs. These include secure electronic data storage, safe treatment transport and patient-initiative adverse event reporting. Further, collecting data from multiple remote sources requires strong data management platforms and skilled personnel, he adds.

All of these efforts must be focused on ensuring the reliability and quality of data generated during a DCT and protecting participants' private health information. With new remote sensors and wearables that collect data continually evolving, questions remain about which methods are most reliable and how to compare data collected in different ways, Streeter says.

In DCTs, the same info may be gathered both virtually and in a face-to-face encounter within the same study, even for a single patient. Regulators may demand proof that data collected in different ways is comparable and won't compromise the trial outcome.

The flexibility DCTs offer also means that a patient's health data may vary based on environment, Florence Healthcare notes in its blog post. For example, blood pressure could fluctuate due to stress from work and temperature due to changes in weather.

Authentication of data is a related issue. For example, if data is collected through a wearable sensor, it's critical to know that the patient is actually wearing the device, Streeter points out.

Trials must be designed with these types of challenges in mind, he says. For example, during a virtual visit, a healthcare professional can observe and guide patients in taking their vitals to enable more control and increase data reliability. And technologies such as facial recognition could be used to ensure that data from a wearable comes from a specific study participant.

Equally important to data quality is ensuring the privacy of study participants' confidential health information. Data privacy has been a longstanding concern when it comes to DCTs and their reliance on remote data collection, notes Florence Healthcare. Sponsors and research sites must take care to use validated information-sharing technology that meets FDA and international privacy policies.

Ensuring compliance, especially with privacy laws, is complex, Streeter agrees. Requirements vary among countries and can be handled differently across clinical sites. Integrating diverse data collection into a trial, especially moving it out of the clinic and into patients' homes, introduces more considerations, including data ownership. The technology vendor, the sponsor or the trial site could all have claims on the data under different laws, he notes.

Concerns around data management and privacy also exist among regulators. EU regulators surveyed by Amos De Jong and colleagues at the University of Utrecht in the Netherlands agree that protecting participants' personally identifiable data is paramount, including preventing this information from becoming available to the sponsor during a DCT.[10] One recommended option to avoid this is to ensure

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that any activity that includes sharing of personal data is performed under the responsibility of the PI. In addition, data transfer and storage methods must be clearly described and secure.

Risks and rewards

While technology is often the first thing that comes to mind when considering DCTs, the evolution of the modern clinical trial includes other options for making study participation realistic for more people. For example, DCTs also may use dispersed local clinics and healthcare providers, including home health services, to decentralize some or all the data collected in a trial, THREAD Research's Noah Goodson et al. suggest in *npj Digital Medicine*.[11]

Locations can include local pharmacies, such as CVS and Walmart, as has been seen with vaccines and other services in the post-COVID period. Nurses could be employed directly by these locations to perform clinical trial services, clinical research nurses Elizabeth Johnson and Lisa Marsh suggest in *Clinical Researcher*.[12]

These nontraditional sites can be used for various clinical trial procedures, such as specimen collection, physical assessments of participants or dispensing of the investigational product, Johnson and Marsh note.

But this brings an added burden to research staff, particularly principal investigators. And some PIs are still wary of DCTs, concerned that "remote patients won't receive the same high standard of care at home as they do at a site," Michele Richardson and Jasmine Stacey of Medical Research Network write in *Clinical Leader*. "However, the most effective DCTs provide in-person care at the patient's home or community. The difference between these DCTs and traditional trials is merely location, not quality of care."[13]

Coordinating trial activities across multiple nontraditional clinical sites is a complex undertaking, Deepak Behera, CEO and CMO of Adaptive Research, cautions in a LinkedIn article.[14] Proper training and oversight, along with proactive risk assessment and management are all necessary. Additionally, as Goodson et al. note, certain lab tests or surgical procedures are simply not amenable to remote measurements.

Regulators surveyed by De Jong et al. also expressed concerns about investigator oversight and participant safety when physical examinations and face-to-face contact are limited.

One concern is ensuring proper adverse event reporting when nontraditional sites or home health services are used in a DCT. For example, Johnson and Marsh write, clinical trials might experience a side effect or critical symptom that requires medical attention. Making sure that local hospitals and clinics are aware of a patient's participation in a clinical trial, including any special considerations, is also important.

"Having a clinical nurse attuned to assessing for trial participation in a nonhospital setting benefits the patient to ensure safe care congruent to the protocol restrictions," the authors write. "The clinical nurse may then also contact the CRN of the research study for more information related to adaptations to nursing assessments and explanations of signs or symptoms attributable to the study drug or commonly seen on the trial."

DCTs also have a higher risk of protocol deviations compared to traditional clinical trials, Florence Healthcare notes, whether participants perform measurements at home with the aid of home healthcare providers or if local pharmacies or clinics assess trial participants.

Risks may increase if participants receive their treatments directly at their homes. Delivery of investigational drugs via mail, for example, is a more complex endeavor than dispensing through a hospital pharmacy, Goodson et al. write.

Communication and roles

With so many moving parts outside a central research site, the risk of protocol deviations can also go up, Johnson and Marsh note in *Clinical Researcher*. Having research sites provide thorough training and ongoing support to staff at local facilities in the study protocol — including the use of apps and wearables by participants — may help with this concern, according to Florence Healthcare. Some organizations may even invest in devices that record data and send it straight to a research site where staff are fully trained in receiving and handling such data to avoid participant mistakes.

One solution could be to use site management teams to liaise among many stakeholders — including sponsors, research sites, local facilities and technology vendors — to help support clear communication among all partners, Richardson and Stacey suggest. For example, such teams can help evaluate such processes as data collection and training to ensure that sites' needs are met. Other elements include supporting and improving communication with sites, patients and other players.

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Similarly, vendors must do more to make their services and products interoperable, Gregor says in the ACRP white paper. This would help up the benefits of digitizing data and workflows for all players. Lessons can be learned from other industries, such as banking: Financial data can be transferred across multiple systems and institutions in a way that is seamless for the user.

Finally, many sites have concerns about lack of clarity about DCT responsibilities. Despite decentralization growing in recent years, DCT stakeholder responsibilities, especially those of PIs, are still unclear. "While decentralized study elements bring benefits for patients and enrollment diversity, they can be burdensome for sites," ACRP notes.

The FDA issued draft guidance in 2023 on DCTs, but that document lacks sufficient clarity about who among sponsors, investigators and vendors handles various aspects of DCTs, ACRP maintains. This particularly involves PI oversight of participant safety, protocols and data-handling.

The FDA must clarify PI responsibilities, especially when the sponsor chooses home healthcare companies and tech products to support a DCT or hybrid study, Sacco agrees.

Patient pros and cons

Increased patient diversity achieved by expanding means by which people can take part in clinical trials despite geographic, socioeconomic and other barriers is one of the most common arguments made in factor of DCTs.

And patients overall seem to welcome these efforts. In a 2021 survey, consulting firm McKinsey & Company found that 98 percent of patients were satisfied with telemedicine calls and 72 percent of physicians reported that patients seemed engaged by remote medicine.[15]

But patient feedback can vary depending on many factors, including their medical condition, according to a Florence Healthcare post. For example, a 2018 trial involving back pain showed that 78 percent of participants preferred a DCT to a traditional study. Furthermore, 89 percent of patients who chose a decentralized approach completed the trial, compared to 60 percent of those who selected the site-based approach.

Meanwhile, a 2020 survey of patients living with chronic diseases showed a slight preference for hybrid trials over completely virtual or in-person studies, according to Florence Healthcare.

Diversity and inclusivity

It's unclear if DCTs truly have an overall positive impact on inclusivity in clinical trials, however. The basic idea is that adding decentralized elements or even conducting an entirely remote study would reduce the burden on trial participants, thus appealing to a broader range of patients. Common sense, along with early evidence generated in the wake of the COVID pandemic, seems to dictate that it would be beneficial to let participants take part at or near their homes, Goodson et al. say.

DEI concerns traditionally focus on improving representation of patients from racial and ethnic minority groups, but DCTs can open access to individuals who are underserved for other reasons, as well.

For example, older individuals and people with disabilities may find it tiring to travel even a shorter distance to a clinical trial site or may not be able to drive themselves, Sacks notes in the article on the FDA website, while people with family obligations may also find it difficult to meet prescribed times for clinical site visits.

But "it remains to be seen if DCT approaches will yield significant improvements in participant inclusivity," Goodson et al. note. For example, some DCTs looking to be more inclusive on a single element, such as race, had unintended consequences in other areas, such as education or gender.

In some cases, focus on DCTs to improve diversity and inclusion seems to be "largely virtue-signaling by entities with an interest in providing services," Paul Evans, president and CEO of Velocity Clinical Research, says in the ACRP post. "Whether these views are backed by data may be another story."

DCTs are also unlikely to have much effect on enrollment in drugs targeting limited patient populations, Goodson et al. write. They note that numbers of trials for orphan drugs with a limited patient base to start with and cancer treatment studies with restrictive inclusion/exclusion criteria have doubled over the past 10 years.

The real impact DCTs have on inclusivity cannot truly be known without clear evidence gathered via randomized controlled trials comparing DCTs head-to-head with traditional studies, according to Jennifer Dahne, researcher at the Hollings Cancer Center of the Medical University of South Carolina and co-director of the remote and virtual trials program at the South Carolina Clinical & Translational Research Institute, in a *Clinical Research News* article.[16]

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Dahne speculates, based on her experience with DCTs and technology-enabled interventions, that DCTs likely outperform traditional studies in some but not all areas. A hybrid approach using some decentralized elements likewise comes with tradeoffs.

"We need to [examine] the impact of decentralized methods vs. traditional methods on each step of the [clinical trial] pipeline," Dahne tells *Clinical Research News*. This includes recruitment, screening activities, treatment delivery, data collection and dissemination of results to participants.

Decentralized trials may enroll a more diverse participant group, "but you lose something in data quality because it is all done remotely," she adds.

A research agenda should systematically apply tools, such as studies within a trial or the INCLUDE ethnicity and socioeconomic disadvantage frameworks, Goodson et al. suggest. Without these types of specific efforts, research teams that conduct DCTs may "miss the opportunity to share outcomes and lessons learned in broadening participant inclusion," they write, including when improvement in one dimension has unintended consequences in others.

Travel time and distance

Participation in a clinical trial comes with several burdens for patients. These are largely viewed to be associated with the time and financial costs associated with travel to a central research site for assessments and procedures, which DCTs are intended to relieve.

Clinical trial participants must bear some financial burden when enrolled in a study. But the financial and economic burden of the 2008 fiscal crisis, climate change and COVID-19 also affect the ability of some people to take part in clinical trials, Goodson et al. note.

Even the FDA notes the importance of travel requirements. Sacks says specifically that recruiting and enrolling study participants can be easier without the added burden of travel.

"Many potential participants, even those with conditions serious enough to ensure continued research engagement, are unwilling to travel for many hours for a traditional study and may withdraw from a trial if subjected to long waits at trial sites," Goodson et al. write.

Both travel time and distance are factors. Certain groups are more affected by geographic constraints, Goodson et al. point out. For example, women often bear the responsibility for child and family care, face payment gaps that reduce their economic power and feel less able to take time off work for trial visits compared to men.

But that is not the whole picture. For example, the number of procedures that participants must undergo during trials has been climbing steadily since 2000, Goodson et al. note, which can increase the perceived burden to potential participants regardless of whether a trial is decentralized.

Tufts CSDD figures bear this out: A January 2021 report shows the mean number of distinct phase 2 and phase 3 protocol procedures had increased 44 percent since 2009.[17] This increases the perceived burden of a trial, regardless of whether site visits or remote treatments are offered, Goodson et al. write. Some patients may not be willing to undergo that many visits or procedures, no matter where they occur.

Geographic and digital divide

Another issue is DCTs' focus to date on using technology, such as telemedicine visits, ePROs or diaries and wearables that record physical information directly from patients.

In fact, advances in these and other types of technologies, such as a needle-free, remote control blood collection device that replaces portable phlebotomy stations, have allowed DCTs to take off, Jeri Burr, executive director of the Utah Trial Innovation Center, points out in the 2023 ACRP post.

But many of these technologies require reliable wireless internet or access to a cell phone, which is not available to all patients. Wearables, for example, rely on consistent internet access and troubleshooting support, Nelson says. It is easy to assume that everyone has these things, but this is not the case. Even in large cities, there are residential pockets without access, she notes.

"While DCTs can improve patient access to clinical trials, they require tools to support this access, which in turn are associated with costs," she says.

And some patients may not understand or be comfortable with using the necessary technologies and so may end up shut out of fully remote trials, cautions Florence Healthcare.

The McKinsey & Company survey bears this out, showing that some patients are hesitant about using unfamiliar technology for clinical trials. For example, many people have never worked with electronic data capture (EDC), ePRO or similar programs. The experience of learning a new technology while also learning about the protocols of a clinical trial can overwhelm some participants, McKinsey says.

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"The most significant barrier to DCT adoption may well be the 'digital divide,'" Goodson et al. write, noting that about 20 percent of the U.S. population lacks any access to broadband internet or a smartphone — the type of technology necessary for participation in many DCTs. Patients who are older, less educated, less wealthy, living in rural areas or part of a minority ethnic group are disproportionately affected by lack of technology access.

Additionally, some impediments to clinical trial participation affect DCTs as much as traditional, site-based trials. For example, technology use is unlikely to overcome barriers related to structural racism vs. simple inconvenience, Goodson et al. say.

Some solutions to the technology divide exist. For example, a fully or partially decentralized trial can also offer patients the choice of using little or no technology, Florence Healthcare notes.

Or when patients can't use technology necessary for fully remote trials due to lack of wireless technology or cell service, a local healthcare provider can bring devices to the patients, record the necessary information and share it with the site once back in wireless or cell range, Richardson and Stacey suggest. The provider can also educate patients on how to use technology to improve participation and compliance.

Relationships and engagement

And some patients just prefer to have in-person interactions with investigators and other research staff over telehealth calls or remote collection of impersonal data, Florence Healthcare points out in the April 2023 post. This may be harder to cultivate when those staff see patients less often. Hybrid trials can address these concerns.

Some of these patients may need support from on-site research staff, Florence Healthcare notes. Others may prefer to have their data collected at familiar community pharmacies, doctors' offices or community centers. Hybrid trials that offer options outside of apps or wearable devices can offer more options to suit a wider range of patients.

Keeping patients engaged without site visits can be harder, agrees Streeter in a white paper. DCTs offer an opportunity to engage with underserved patient groups who may struggle to access brick-and-mortar sites. But a one-size-fits all solution may still alienate certain groups. It will likely take a variety of approaches to best meet all patient populations' needs.

For example, Scott Gray, CEO of patient logistics services firm Clincierge, notes in a October 2023 *Clinical Research News* article that attempts to move visits to participants' homes for an Alzheimer's study were unpopular. The participants enjoyed the trip to the research site "because for many of them, it was one of the few social interactions that they had left in their lives," he says.

Some regulators may agree with this assessment. While the limited in-person interaction of a DCT would seem to be more convenient for participants, regulators surveyed by De Jong et al. consider it a challenge. In-person visits help engage study participants and build rapport with research staff.

Services and support

To address these concerns, some in the clinical research industry are highlighting patient concierge — sometimes called "white glove" — services as alternatives to address problems or concerns that may lead some people to avoid clinical trial participation. Paul Bledenbach, vice president of operations and medical communications at PPD, the clinical research arm of Thermo Fisher Scientific, suggests that these types of personal, targeted support programs can increase participant engagement and boost recruitment and retention.[18]

Relying solely on technology as a solution rather than a means of support is short-sighted, Gray writes. Concierge services can help add a personal touch that many patients may find attractive.

Challenges faced by patients and caregivers in clinical trials often revolve around financial strain, logistical difficulties and emotional stress. Concierge services can help mitigate many of these. And these are the sorts of challenges that a concierge service is well-designed to address. Having a foundational mentality of hospitality is important. Equally important is including funding in research budgets to pay for hotels, transportation and meals for participants, for example.

The basic idea behind a concierge service is that trial participants or their caregivers can get reassurance, support or help with a specific issue from a single phone call.

For example, concierge services can feature travel help, Bledenbach suggests. One success story at PPD, for example, involves a patient in a rare disease trial with concerns about being able to travel to appointments due to sharing a car with

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a spouse. The concierge scheduled a car service and recommended a rental car service to the sponsor to overcome this ongoing barrier to participation in the trial.

Services can range from something as simple as getting participants a taxi or Uber to take them to a site visit to as complex as visa support for relocation to another country, along with long-term lodging and cultural assistance, John Fontenault, executive vice president of operations at Scout Clinical, says in an October 2023 *Clinical Research News* article.

They can specifically help with DCT elements in remote or hybrid trials. For example, they could help address issues with adverse event notification. Bledenbach points to a patient in a PPD trial who experienced severe nausea while on the study drug and told the concierge he would have to leave the trial. The concierge connected the participant with the study site for care and reporting. The patient's treatment was adjusted and he remained in the study.

Concierges can also help with such tasks as using an electronic diary app for patient reports. This could include troubleshooting technology glitches, more training and guidance in using the app or simple reminders of when entries are due.

A concierge service may also be useful to support protocol adherence through reminders, guidance in technology use or even helping with unusual occurrences, such as ensuring an app will be accessible to a patient during international travel.

Concierge services can also provide financial and emotional support. For example, financial aid can ensure that study participants' loved ones can provide support without undue burden. And help with travel plans lets participants concentrate on their treatment without the added worry of handling those arrangements, Sarabeth Velazquez, associate director of project management at Precision for Medicine, a global biomarker-driven clinical research organization, writes.[19]

Scout Clinical, for example, offers reimbursement services to cover expenses associated with trial participation and any per diem or stipends offered to participants.

"The integration of patient and caregiver concierge services is a game-changer in clinical trial execution," Velazquez writes. "By addressing the financial, logistical and emotional challenges of trial participation, we optimize trial efficiency and outcomes for sponsors while improving the experience for patients and caregivers."

Flexibility and customization

All this means is that DCTs are not the sole component for modernizing clinical research, Samson writes. While continued progress to modernize clinical trials to better meet the needs of both patients and research teams, this progress must include carefully "evaluating appropriate use of technology and the potential of nontraditional sites, such as retail pharmacies, as well as offering at-home services to study participants."

In short, organizations shouldn't try to implement DCTs across the board, Hassan Kadhim, global head of clinical trial business capabilities at Bristol-Myers Squibb, cautions on a recent podcast.[20] Sites and patients are at different levels of readiness to do so. Flexibility and customization are critical to accommodate different types of sites and different patient preferences.

One goal should be to see a "less disjointed use of service providers and more consistent control over operational aspects of DCTs," Nelson says. "This is especially important in patient care, including home health visits, lab services and the increasing use of wearables."

This likely will mean focusing on providing what Samson calls a "high-quality end-to-end patient experience." That means sponsors and researchers must identify the real needs and preferences of different target populations and develop practical solutions to address them. For example, lack of study awareness and access among some underserved communities may be the key issue, with travel demands being a major factor for others.

Shifting from a site-based to a patient-centric clinical trial model should be context-adapted, agree Eric Nebie et al. from the University of Basel in Switzerland, who assessed opportunities and challenges of study decentralization in sub-Saharan Africa from the perspective of different stakeholders, including researchers, patients, sponsors and community members.[21] They found that major challenges fall into four broad categories:

1. The usability and practicability of technology used
2. Trial data quality
3. Ethical and regulatory hurdles
4. Contextual factors, such as site-specific research environments and sociocultural aspects

Gregor even recommends moving away from the term "DCT," which is polarizing, to focus discussion on modern-

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izing clinical trials using a mix of technology, physical sites, new processes and people.

Samson recommends journey mapping to understand how the patient will experience the workflows under a protocol. This path can become more complex with the introduction of decentralized elements such as direct-to-patient distribution of study drugs, use of mobile lab services or remote monitoring of safety events. Journey mapping helps identify any gaps and risks so they can be addressed, he says.

These types of efforts should then yield effective clinical trial approaches that are adaptive to various environments and participant pools, without overburdening research sites with new technologies or demands.

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reflective of real-world data at a rate that is far below the inci-dence and prevalence of the disease for which the investigational therapy or device is targeting," Genentech's Ubong Peters et al. write in *Therapeutic Innovation & Regulatory Science*. "This lack of diversity in clinical research participation can obscure the safety and efficacy of drug therapies and limits our collective ability to develop effective treatments for all patients, leading to even wider health disparities."[2]

While 2020 census data shows that minority populations account for about 41 percent of the U.S. population, only 25 percent of U.S. clinical trial participants are drawn from minority groups, Ohio State University's Demi L. MacLennan et al. report in *Clinical Pharmacology & Therapeutics*.[3]

The FDA itself reported in November 2020 that participants enrolled in clinical trials during the 2015-2019 period skewed strongly White and under 65, although sex/gender distribution was more evenly matched, with 51 percent of trial participants identifying as female and 49 percent as male. Figure 1, on page 15, provides details of the agency's analysis of clinical trial demographics.[4]

Diversity crucial to clinical research data

There are many reasons to emphasize diversity within clinical trial populations; chief among those is ensuring new products are safe and effective in the entirety of the real-world population they are likely to treat. And with innovative drugs becoming more complex, clinical trials must be able to demonstrate outcomes relevant to the patients most likely to receive those drugs, according to Stuart D. Faulkner and a group of European researchers in *Pharmaceutical Medicine*.[5]

"Lack of diversity in clinical trials can impair quality, increase costs and put patient safety at risk," WCG says in its white paper. "Many therapies work differently, depending on a person's gender, race and ethnicity, so without diverse participants, scientists and clinicians have only a limited understanding of the effectiveness and suitability of treatments for underrepresented populations."

The impact of such differences often presents only after a new product has been approved for sale and enters broad use in the more diverse public population, according to WCG.

Broader healthcare disparities may limit ethnic minorities' interaction with healthcare providers, Cerevel Therapeutics' Stacey Versavel et al. note in *Contemporary Clinical Trials*.[6]

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This can hinder consistent care and reduce opportunities for these patients to learn about clinical trials that could help them.

And underrepresented minority groups, including Black, Hispanic, Asian/Pacific Islander and Native American people, can experience higher rates of illness across several diseases, including diabetes, heart disease and cancer. Different racial and ethnic groups can see different outcomes for environmental, genetic and other reasons, they add.

For example, some beta blocker responses are much lower in Black and African American patients compared to White patients, while some Asian patients are twice as sensitive as White patients to some beta blockers, MacLennan et al. note.

All of this means nonrepresentative research populations can limit the generalizability of study results, which may lead to questions about safety and efficacy in certain subgroups of patients, Genentech's Shalini V. Mohan and Jamie Freedman explain in *Clinical Pharmacology & Therapeutics*.[7] And this can challenge regulators, healthcare providers and patients alike in efforts to "adequately consider the benefits and risks of a therapeutic treatment across all populations," they add.

New regulatory demands drive DEI change

Recognition of the importance of testing new medical products in a diverse population is not new. Federal efforts to enhance diversity and inclusion in clinical research can be seen as early as 2001, when the National Institutes of Health (NIH) issued guidelines on including women and minorities in clinical research.[8] More recently, the FDA published a guidance document on enhancing diversity in clinical trial populations.[9] The agency also released a draft guidance in 2022 on diversity plans for clinical trial participants.[10]

What is new is the growing agreement among clinical research stakeholders on the importance of diversity and the new requirements under FDORA.[11] The act requires investigational drug and device applicants to report clinical trial enrollment targets by demographic subgroup, including age, gender, race and ethnicity. They also must provide a rationale for those targets and submit a diversity action plan detailing how the sponsor intends to reach those targets. These provisions apply to phase 3 drug studies and most device studies, explain David Peloquin, Mark Barnes and Carmen Lam of regulatory law firm Ropes & Gray in a blog post.[12]

The plan may be waived in certain conditions, such as situations in which the patient population targeted is so

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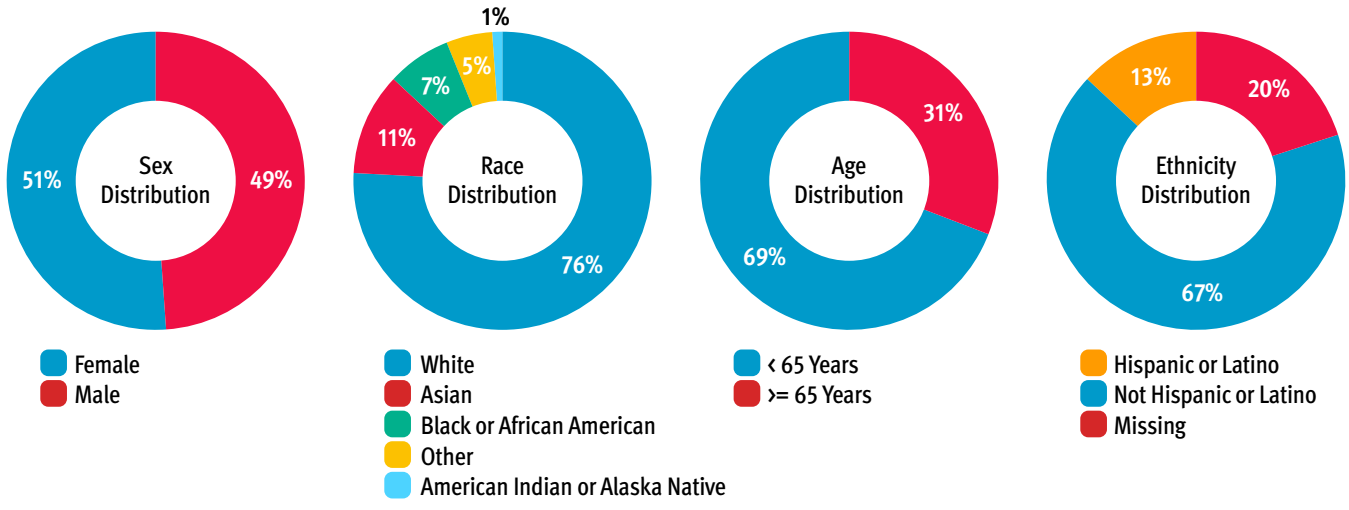
Demographics of Trial Participation

Demographic Categories

Clinical trial participation is broken down into four categories: sex, race, age and ethnicity.



Source: FDA

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small and/or homogenous that enrolling a diverse population is not possible, the Ropes & Gray post notes. It may also be waived if implementing a diversity action plan is otherwise impracticable or if the waiver is necessary to protect public health during a public health emergency.

The law also gives the FDA authority to mandate postmarket studies if sponsors don't meet their diversity enrollment targets without sufficient justification.

Clearly defined terms help build DEI plan

Meeting the requirement for a DEI plan means that clinical research stakeholders — from sponsors to sites — must fully understand how to incorporate DEI into the development and execution of clinical trials.

Diversity, equity and inclusion are equally important parts of any plan to increase the diversity of clinical trial participants. The terms stand for three linked values. Diversity refers to who is represented in the workplace or other population, such as clinical trial enrollees, according to global management consulting firm McKinsey & Company.[13] It can refer to many characteristics, including sex/gender, age, race/ethnicity, physical disability and neurodiversity.

But having a diverse population in place is only the first step. Equity refers to fair treatment of all people, regardless of which categories they may fall into. Researchers must create policies to ensure that identity is not predictive of opportunities in clinical research, according to McKinsey & Company.

Specific to clinical trials, the Multi-Regional Clinical Trials (MRCT) Center of Brigham and Women's Hospital and Harvard proposes a broad definition of diversity in a guidance it developed for research sites.[14] The definition includes demographic factors, such as race, ethnicity, sex, age and genetics, and other factors, such as social determinants of health, comorbidities, organ dysfunction, concurrent medications, environmental factors, nutrition and patient compliance, which may change over time. Any of these dimensions may contribute directly or indirectly to trial outcome measures, the guidance says.

Equity is another important aspect. McKinsey & Company emphasize that it differs from equality in a subtle yet important way. "While equality assumes that all people should be treated the same, equity takes into consideration a person's unique circumstances, adjusting treatment accordingly so that the result is equal."

To illustrate the difference between equality and equity, they offer the example of a company that hires unpaid interns. While this is equal treatment across all interns that land a spot, it limits the pool of interns to only those who can afford to work without pay for an entire summer.

These concepts apply equally to healthcare in general and to clinical research specifically. The principle of health equity is to eliminate or at least reduce unfair and avoidable differences in healthcare linked to economic, social or environmental disadvantage experienced by certain groups.

"Clinical trials are an important part of the continuum of healthcare," they add, noting they "offer valid treatment options for many patients during the course of their care, essentially providing them with access to emerging therapies."

Finally, inclusion refers to how the population experiences the workplace or other environment. The degree to which the organization embraces all employees and makes them welcome and comfortable.

"Companies that are intent on recruiting a diverse workforce must also strive to develop a sufficiently inclusive culture, such that all employees feel their voices will be heard — critical if organizations want to retain their talent and unlock the power of their diverse workforce," McKinsey & Company says.

With a clear idea of what is needed to incorporate all parts of a DEI program, research organizations can move forward to follow the new requirements.

DEI plan should permeate trial lifecycle

The FDORA requirements also discuss information that may be included depending on how it pertains to the sponsor's rationale for a study's enrollment goals, Olga Balderas, WCG IRB chair/vice chair (regulatory), writes in an undated WCG white paper:

- The prevalence in the U.S. of the disease or condition the investigational product aims to treat, including breakdowns by race, age, gender and other pertinent factors
- What is known about that disease or condition
- Relevant pharmacokinetic or pharmacogenetic data
- An explanation of how a sponsor intends to meet diversity goals
- Information about what is known about the patient population for the target disease or condition.[15]

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This suggests that diversity must be included in the earliest stages of protocol development. The content recommendations in the FDA's 2022 draft guidance on DEI plans suggest the same. That document recommends that a DEI plan include:

- Defined enrollment goals for underrepresented racial and ethnic participants based on protocol goals
- A description of how race and ethnicity will be assessed, along with other covariates, such as those with known potential to affect drug pharmacokinetics and pharmacodynamics, with known potential to affect the safety and efficacy of the investigational product
- A plan to collect data to explore potential differences in safety and efficacy with race and ethnicity throughout drug development
- A description of study design features to support analysis when data exist indicating that the product may perform differently across the population based on factors associated with race or ethnicity
- Other data sources, such as published literature and real-world data, that will be used If limited data exist about the incidence/prevalence of the disease across diverse populations
- Clinical pediatric studies planned for inclusion as part of pediatric development of the product

That said, it's not enough to focus solely on the DEI plan required under FDORA, Versavel et al. write. To be effective, DEI plans should be incorporated throughout a clinical trial lifecycle, they advise. At the trial planning and protocol development stage, this effort should focus on developing a participant-centric protocol, confirming the demographic distribution of the target population and broadening trial eligibility criteria where possible. This is the point at which input from advocacy and community groups can be useful. Endpoints should be based on input from health outcomes/real-world evidence and medical affairs teams, as well.

Preparation for trial startup also includes many opportunities to take steps to increase diversity. For example, sponsors should select sites with access to patient pools that align with demographic diversity goals and ensure that all staff at these sites receive effective DEI training. This must include ongoing collaboration with advocacy organizations and careful consideration of cultural differences within the target communities. Finally, a demographic target tracking mechanism can provide feedback on how well DEI goals are being met as enrollment begins.

The third stage is trial maintenance. At this stage, Versavel et al. recommend that researchers continue the diversity strategies previously established, maintaining relationships with advocacy organizations to keep engagement going. They should also continue monitoring demographic goals and study retention, as well as offering refresher DEI training to address staff turnover.

At the close of a trial, sponsors and sites should evaluate how well the trial met its demographic goals. This should include feedback from community partners and from sites and CROs regarding training and recruitment strategies. Sponsors and sites should foster relationships with community organizations even after the study ends.

Existing guidelines still apply

As of mid-February, the FDA was several weeks past the FDORA deadline of December 2023 for issuing the mandated guidance on what must be included in a DEI plan, according to a recent Regulatory Affairs Professionals Society (RAPS) report.[16] Lola Fashoyin-Aje of the FDA Center for Biologics Evaluation and Research says in that report that the agency is working to wrap up a draft guidance on diversity action plans, although she cannot provide any details.

But clinical researchers don't need to wait for new guidance to begin working toward compliant DEI plans. While FDORA marks the first time DEI plans are encoded in law, the FDA has been vocal in encouraging more diversity in clinical trials. This has been the focus of several guidelines in recent years; clinical trial sites and sponsors can still look to these documents, as well as the older NIH guidelines, for strategies to include in their DEI plans.

For example, the 2001 NIH guidelines state explicitly that "women and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research."

The guidelines further instruct that inclusion of women and minority groups must be addressed as part of the research design, which should describe the composition of the target study population in terms of sex/gender and racial/

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ethnic group. It should also provide a rationale for participant selection, along with a description of proposed outreach program for recruiting women and minority participants.

Sponsors and sites can also continue referring to the FDA's November 2020 guidance on enhancing diversity in clinical trial populations. The document is intended to "promote enrollment practices that would lead to clinical trials that better reflect the population most likely to use the drug" after approval, the agency says.

In particular, the guidance recommends that protocols should specify target participant populations that accurately reflect the demographics and other characteristics of the patient population likely to use the new product after approval.

Recommendations in the guidance include broadening enrollment eligibility criteria to increase diversity in enrollment. It urges sponsors to work to ensure that eligibility criteria serve the goal of having a representative sample of the population that will use the drug in the real world, rather than to exclude all higher-risk patients. Exclusion criteria should be examined closely to decide if they are truly needed to assure participant safety or achieve study goals, the guidance says.

The 2020 guidance also recommends close review of very restrictive exclusion criteria from phase 2 studies to decide if they can be eliminated or changed for phase 3 trials, which have a different aim than phase 2 studies. This can help to avoid unnecessary limits on the study population.

And the agency in April 2022 issued a draft guidance — "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials" — that initiates the notion of a diversity plan of the FDORA requirements. The 2022 draft is intended as an expansion on the agency's 2016 guidance "Collection of Racial and Ethnicity Data in Clinical Trials," which explains how the FDA expects researchers to collect and present race and ethnicity data. That document also recommends development of a plan to include clinically relevant populations.

The guidance recommends submission of a diversity plan to the relevant IND application as early as possible during drug development. The plan must be provided no later than when a sponsor is seeking feedback regarding pivotal trials for the drug. For devices, sponsors should include the plan in the IDE application.

Practices aimed at making trials more patient-centric and boosting participant engagement should include specific focus on diversity, Faulkner et al. suggest. They point to a 2020 FDA guidance entitled "Patient-focused Drug Development: Collecting Comprehensive and Representative Input," which recommends focusing on patient perspectives about both current treatments and the investigative product.[17]

Key factors include:

- Burden of living with or managing the disease
- Burden of treatment
- Burden of study participation
- Expectation of benefits
- Tolerance for harm or risks

These can vary among different subpopulations in clinical trials.

Exclusion criteria can challenge diversity

Scientifically, there is broad agreement throughout the clinical research industry that diversity in patient populations is important to develop and market the most widely effective new products possible. There are still challenges when ensuring that key stakeholders invest in moving DEI initiatives for clinical trials forward effectively, according to WCG.

"The barriers to diversity have been well-documented, but despite significant progress, the industry still struggles to overcome them," WCG notes.

One such challenge is that inclusion/exclusion criteria and other study design factors can inadvertently exclude members of underrepresented demographics. Peters et al. suggest exclusion criteria around comorbidities common in underserved communities, even if they have nothing to do with the safety, efficacy and outcomes of the study, can lead to decreased diversity among study participants.

To address this challenge, "during clinical protocol development, study teams should use data analytics tools to carefully assess the impact each eligibility criterion will have on the inclusion and exclusion of underserved populations and make accommodations as needed, Peters et al. suggest. This also includes expanding the network of clinical sites beyond the usual large, established organizations.

The FDA has acknowledged that past guidance may have led sponsors to focus on tightly limited inclusion/exclusion criteria, Steve Smith, president of patient advocacy at WCG, notes in a recent post.[18] But the agency is now urging more open and flexible approaches to increase diversity.

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For example, the agency's 2020 guidance on diversity similarly promotes broader enrollment criteria, recommending that these types of exclusion criteria be considered carefully in terms of how they may affect targeted inclusion of certain populations that will be likely to receive the investigational product after approval.

"For example, patients with varying degrees of kidney or liver impairment are often excluded early in drug development programs because adequate information is not available on how to adjust doses of the investigational drug for such patients or whether such patients could be more vulnerable to certain risks," the 2020 guidance says. "Pregnant or lactating women are also frequently excluded when there is inadequate information to assess the risk to the fetus or infant."

Tyler Bye, WCG director of site solutions and product strategy, said on a recent podcast that there are three main areas of focus that can help recruit trial participants from underserved populations: protocol development, site selection and recruitment outreach efforts.[19]

"You really have to look at each of those individually to understand," Bye said. "They all build off each other, but when you need to bring research to the real-world population, starting with the protocol development and how it's written to identify and recruit individuals is a key piece. We all know that in clinical research, the protocol defines who we can recruit, who we can bring into the study."

In other words, the study must have parameters stating how its population will represent a real-world population.

Lack of data challenges enrollment goals

Setting and meeting enrollment goals can pose another challenge to increasing diversity in a clinical trial population.

One challenge facing the research industry is a lack of race and ethnicity data. Currently, no universal definitions exist for race and ethnicity. The terms represent distinct concepts but are often used interchangeably and inconsistently. In the U.S., for example, race categories are defined under the Office of Management and Budget's classifications. Outside the U.S., the concept of race has largely been replaced by national ancestry, with some movement toward replacing race with genetic ancestry, Mohan and Freedman note.

The Friends of Cancer Research organization agrees that there are several data-related challenges to setting enrollment goals for underrepresented patient groups. For example, no standardized data source exists for patient demographics; the various disparate sources that do exist can be incomplete and hard to combine. Also, current biomarker data by demographic group are insufficient, social determinants of health variables are not routinely collected, definitions of race and ethnicity are inconsistent and data on populations outside the U.S. is not robust. The group proposes two strategies to address these challenges:

- Create a central repository of biomarker data in the U.S. and Canada that includes race and ethnicity data
- Bring groups together to combine and harmonize curated data sources

Similarly, the FDA's 2020 guidance on diversity recommends that sponsors focus on trial designs and methodologies that facilitate enrollment of a broader population, including identification of drug metabolism differences among underrepresented patient groups and use of adaptive trial designs to allow prespecified changes as data become available.

Diversity efforts should not focus solely on race, however, Peters et al. caution. A common misconception about health DEI is that it only pertains to persons of color, Peters et al. note. But many historically underrepresented communities around the world fall outside those classifications and would benefit from clinical trial participation. These include rural populations, people with low socioeconomic status, the elderly, children and adolescents, women and disabled people.

Access starts with awareness

Even with all those considerations, if research sites lack access to underrepresented populations, meeting DEI enrollment goals will be a challenge.

Implicit bias can be exaggerated by site selection, logistical and financial patient burden, and patient distrust of clinical research, Mohan and Freedman note.

"For patients considering participation in a clinical trial, clinician recommendations have a key role," Mohan and Freedman write. "This can hinder patient participation in clinical research because engagement of healthcare providers for clinical studies is often limited to research and academic institutions. Industry sponsors often use the same

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large sites and well-known investigators due to concerns about meeting recruitment goals and timelines."

But these sites are seldom among those that provide care to underserved, diverse communities. So, community providers may not be aware of current trials, nor may they have the training or resources needed to take part in research themselves.

Achieving trial population diversity must start with awareness of and access to the clinical trial before recruitment can even be considered, MRCT emphasizes. That means making connections and building relationships with diverse communities and their healthcare providers on an ongoing basis before a clinical trial begins. Only then can recruitment and screening be conducted.

At that point, research sites need to assure that patient-facing staff are culturally competent and able to meet any special needs of the target minority communities.

Jamie Harper, WCG VP of site solutions and engagement, suggests in the 2023 WCG podcast that including voices that represent the target patient communities should be part of protocol development, as well. Every population will have unique recruitment pathways, levels of trust, etc. Having a participant voice helps shape the protocol from the start will help boost diversity.

"The barriers to diversity have been well-documented, but despite significant progress, the industry still struggles to overcome them."

– WCG Clinical Trial Trends & Insights 2024

Site outreach is central to building trust

Community outreach and involvement can also help overcome another challenge: the mistrust of the healthcare system that is prevalent in some underrepresented groups or communities.

Seeking to enroll more diverse populations can be supported by making contact and engaging with a target community before enrollment in a study is an issue, Balderas suggests. Community-centered organizations such as churches can be helpful in outreach.

Mohan and Freedman emphasize the importance of cultural competency in recruitment efforts. All participant-facing materials should be specifically designed to increase potential enrollees' understanding of the study's design and goals and should stress the importance of representative trial populations to help build trust between the patient and the research communities.

"Cultural competency allows researchers to decrease the gap between participant concerns and openness to participate in clinical trials by providing the tools needed to communicate and deliver services that are respectful and responsive to the beliefs and cultural and linguistic needs of racially and ethnically diverse participants," they write.

Broadening the investigator base to include clinicians and researchers to serve people of color can help because patients often feel more comfortable interacting with someone who shares and/or appreciates their cultural experience.

The diversity of the clinical trial workforce at the site staff can play a critical role in outreach to underserved patient communities and building trust with those groups, Peters et al. agree. Sites should commit to recruiting personnel — particularly investigators, coordinators, nurses and other participant-facing staff — from diverse backgrounds, they recommend. This lets participants "see themselves in the healthcare workforce" and ensures that at least some site staff are familiar with the targeted communities and their needs.

"The front lines of medical research need to be filled with individuals from diverse backgrounds to serve as a mirror of those we want to be enrolled in clinical trials," Balderas agrees in the WCG blog post, adding that research teams should also include more minorities and marketing materials should be representative of target populations.

DEI initiatives should address real patient needs

Clinical researchers have tried a variety of approaches to increase diversity among study participants. And one lesson learned from that experimentation has been that the needs and preferences of each underrepresented group or community must be considered when developing DEI strategies.

Some efforts to expand access to clinical trials to more diverse populations, for example, have included features

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associated with decentralized clinical trials (DCT), such as home study or telemedicine visits, use of electronic or digital data collection devices and cell phone apps, and econsent options, due to the increased flexibility they offer. The 2020 FDA guidance on diversity even suggests DCT elements to make it easier for underrepresented demographics and communities to take part in clinical trials.

However, according to MacLennan et al., when sites were surveyed about the success of a variety of current diversity practices, the DCT elements were not among the top performers in terms of impact, at least from the point of view of surveyed research staff.

Rather, staff report that measures to cross language barriers and reduce costs to participants had the most impact on diversity. For example, having informed consent and other patient-facing trial documents professionally translated into languages other than English — rather than translated quickly only upon demand — was a top incentive for certain participant groups.

Similarly, having at least one bilingual staff member at the research site and having translators readily available improved participation among patients who do not speak English as their native language.

Compensation for study participants and free or subsidized transportation to site visits were also ranked highly as measures that helped increase diversity, MacLennan et al. report. Out-of-pocket expenses associated with study participation can be a top barrier to enrollment, Peters et al. agree.

Reducing the burden on participants is critical to improving access to underrepresented populations, according to the WCG post. This can include incorporating DCT elements, such as remote technology and management.

"It is critical that we do not lose sight of the fact that many patients are unable to participate in a clinical trial because they cannot afford to take time off work, cannot afford childcare or live in a rural area that is far from the clinical site and cannot afford transportation," Peters et al. write. "This is a broad socioeconomic issue that patients face which invariably affects their ability to participate in a clinical trial." Solution: Ensure that patients do not have to bear any costs associated with participating.

And for communities in which potential enrollees might have trouble taking time off work to attend visits, the availability of weekend or evening timeslots is also a strong incentive, MacLennan et al. say.

Tools available for site DEI assessment

Before embarking on any DEI measures, however, research sites need to have a clear view on how they currently stand in terms of their ability to recruit and enroll study participants from diverse demographic groups.

Several groups within the industry have developed tools intended to help research sites assess their own DEI performance. For example, the Society for Clinical Research Sites (SCRS) has developed a diversity assessment tool, a survey that guides research sites through self-assessment of their ability to recruit and meet the needs of clinical trial participants from diverse groups.[20]

It is important to understand that some elements of diversity, such as age and gender, represent biological differences, while others, like race and ethnicity, represent social constructs, MRCT emphasizes in its 2020 guidance. However, such characteristics as race and ethnicity may serve, to a degree, as surrogates for factors like genetic allelic frequencies, environmental factors and social conditions. Thus, analysis of study populations using those categories can "identify underrepresentation about which we as a society should be deeply concerned."

The MRCT guidance promotes basic principles that sites should apply to patient recruitment efforts. For example:

- Efforts to ensure diversity and inclusion in clinical trials should promote fairness in the distribution of the benefits and risks of the research
- Race, ethnicity, sex, gender, age and geographic ancestry do not define genetic or biological groups, but these, along with social, cultural and economic factors, can be associated with differences in disease susceptibility and manifestation, treatment response and rates of inclusion in clinical research
- Enhancing diversity and inclusion in clinical research may help reduce health disparities and can advance biomedical science

In addition to its diversity guidance, MRCT developed a tool kit to help research sites and sponsors improve their diversity performance. It includes a data variables tool, suggestions on key performance indicators in diversity for the study design, an eligibility and enrollment log, screen failure tracking log and suggested key performance indicators to guide site selection.

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Purdue University's Maya N. Birhiray and Ruemu E. Birhiray of the American Oncology Network also present a strategy for helping ensure diversity targets are met. Although the paper focuses on cancer research, the concepts are applicable across most clinical research areas.[21] The approach is dubbed DRIVE, an acronym that includes the five components of an effective DEI strategy:

- Diversity officer for clinical research studies
- Ranking of clinical studies for diversity
- Individual DEI plan
- Verification of study diversity
- Elevation and enhancement of training for minority research team members

Most trials include a statement on diversity with targets that often are missed, the two Birhirays note. Having an official tasked with ensuring goals are monitored and modified if needed to reach a suitable target can help with that. Major corporations have chief diversity officers who act as strategists to promote DEI efforts; this concept can be applied to research.

And ranking studies for diversity (DRIVE rank) based on representation of minority participants relative to disease epidemiology can provide an accessible measurement of how well clinical data applies to all patient subgroups that might ultimately be prescribed a new treatment.

Individual DEI plans can help ensure that all research staff understand and address unconscious bias and develop strategies to overcome those issues, the Birhirays recommend. A cultural competency plan and removal of any communication barriers is equally important.

Verification can begin with self-reporting by the clinical research team, they say. But robust strategies for auditing data should be developed as well so that IRBs and regulators, as well as internal research organization leadership, can continually evaluate DEI performance.

And finally, they note that diversity in research teams has been shown to improve the likelihood of achieving diversity goals in clinical research. Scholarships, grants and funding mechanisms to train minority/diverse investigators and non-minorities practicing in minority communities can help meet that goal. Include physicians, advanced providers, nurses, social workers, pharmacists, medical assistants, students and other members of the clinical and research team.

FDORA places a new regulatory demand on clinical researchers by mandating that all clinical trials include a DEI plan for regulatory review. But the clinical research industry has been promoting increased diversity in study populations for the past two decades, and during that time has had the opportunity to evaluate a host of different approaches to boosting participant diversity.

And many of the most successful of those efforts have been codified in existing FDA guidances, as well as various industry guidelines and tools to help research sites assess their readiness to recruit and enroll appropriately diverse study participants. Even absent new, FDORA-specific guidance from the FDA, research institutions can make use of the available tools and information to help ensure they develop DEI plans that are both compliant with FDORA requirements and effective in diversifying clinical trial participants.

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DCT fatigue

1. **Which of the following is one cause of wariness about decentralized and hybrid trials for researchers and research organizations?**
   a. Unrealistic expectations set during the pandemic.
   b. Lack of technological advancement.
   c. Decreased interest from sponsors.
   d. Increased regulatory hurdles.

2. **Which group primarily bears the financial burden of upfront investments in decentralized and hybrid clinical trials?**
   a. Sponsors.
   b. Research sites.
   c. Patients.
   d. Regulatory agencies.

3. **What is a benefit of decentralized and hybrid trials for sponsors?**
   a. Increased burden of upfront costs.
   b. Faster return on investments.
   c. Limited access to diverse patient populations.
   d. Low personnel costs.

4. **According to the text, what is a concern about remote data collection in decentralized clinical trials?**
   a. Insufficient data collection.
   b. Lack of participant engagement.
   c. Privacy and security.
   d. Low statistical power.

5. **Which of the following is a benefit to patients enrolled in fully decentralized or hybrid trials?**
   a. Greater interest in clinical research.
   b. Shorter travel and wait times.
   c. Improvement in the severity of health conditions.
   d. Lower barriers to withdrawing from a study.

6. **Which of the following is a drawback for patients who might participate in a DCT with remote elements?**
   a. Lack of technological advancement.
   b. Regulatory barriers.
   c. Lack of in-person interactions.
   d. Decreased travel time and costs.

7. **What of the following tactics could increase patient engagement in decentralized trials?**
   a. Additional site visits.
   b. More monitoring technologies.
   c. More clinic support staff.
   d. Personalized concierge services.

8. **Which of the following best describes a barrier to patient participation in decentralized trials?**
   a. Lack of access to smartphones.
   b. Lack of focus on traditional methods.
   c. Decreased data quality.
   d. Decreased clinical quality.

9. **Which of the following is an example of a solution to protocol deviations in decentralized trials?**
   a. Increasing the number of site visits.
   b. Increasing training and support at local facilities.
   c. Decreasing the complexity of study protocols.
   d. Eliminating the use of technology.

10. **Which of the following describes the best way to accommodate different types of sites and patient preferences in decentralized trials?**
    a. Standardization of study protocols.
    b. Fewer study procedures.
    c. Flexibility and customization.
    d. Reduction of patient burden.

Diversity

11. What is one major reason diversity, equity and inclusion (DEI) in clinical trials is crucial?
a. To increase research funding in order to support population health.
b. To ensure new products are safe and effective in the target population.
c. To reduce the number of clinical trials.
d. To decrease the complexity of clinical trials.

12. Which of the following must be reported in investigational drug and device applications under FDORA to improve diversity?
a. The number of clinical trials conducted in underserved areas.
b. Trial enrollment targets by demographic subgroup.
c. The duration of clinical trials.
d. The geographic locations of clinical trials.

13. How does the lack of diversity in clinical trials affect the generalizability of study results?
a. It has no impact on the generalizability of clinical trial results.
b. It may lead to questions about safety and efficacy in certain subgroups.
c. It decreases opportunities for peer-reviewed publication.
d. It decreases the need for postmarket studies and marketing.

14. Which of the following is an example of how to enhance diversity and inclusion in clinical trials?
a. Narrowing enrollment eligibility.
b. Excluding higher-risk patients.
c. Broadening enrollment criteria.
d. Publicizing diversity goals.

15. True or false: Sponsors and sites can evaluate how well a trial met its demographic goals by getting feedback from community partners.
a. True.
b. False.

16. What can be a barrier for sites to enrolling minority populations?
a. Lack of financial support from minority donors.
b. Lack of access to underrepresented populations.
c. Lack of awareness of DEI enrollment goals.
d. Lack of financial incentives for DEI enrollment.

17. How can research sites address the challenge of exclusion criteria inadvertently excluding members of underrepresented demographics?
a. By creating a second trial exclusive to diverse and underrepresented demographic groups.
b. By using data analytics to assess the impact of eligibility criteria on diverse populations.
c. By asking community groups.
d. By hiring bilingual researchers.

18. What is one of the top incentives when recruiting diverse trial participants?
a. Providing informed consent documents in multiple languages.
b. Providing translation services quickly upon patient demand.
c. Providing participants with advanced technology devices.
d. Providing community groups with access to study results.

19. What principle does the MRCT guidance promote regarding diversity and inclusion in clinical research?
a. Fair distribution of the benefits and risks of the research.
b. Fair distribution of financial incentives to participants.
c. Extra financial incentives for underserved populations.
d. Narrowing eligibility criteria to improve study results.

20. Which of the following is among the five components of an effective DEI strategy?
a. Appointing a diversity officer for clinical research studies.
b. Ranking clinical studies for diversity.
c. Creating an individual DEI plan.
d. All of the above.