Enhancing Representative Enrollment through Point-of-Care Trials

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About the Duke-Margolis Institute for Health Policy

The mission of the Robert J. Margolis, MD, Institute for Health Policy at Duke University is to improve health, health equity, and the value of health care through practical, innovative, and evidence-based policy solutions. For more information, visit healthpolicy.duke.edu and follow us on LinkedIn at www.linkedin.com/company/margoliscenter.
Introduction

Clinical trials are an important part of the drug development process and help to ensure new treatments are safe and effective. Known for their rigor, traditional randomized controlled trials have strict inclusion and exclusion criteria, multitude of required assessments, and carefully crafted outcome measures. Data collection occurs in controlled environments, often requiring patients who do not reside near trial sites to travel long distances to access innovative treatments. Data from clinical trials are then reviewed by regulatory agencies such as the U.S. Food and Drug Administration (FDA) to determine whether a medical product is safe and effective. However, despite the merits and successes of clinical trials, the current clinical trial enterprise faces structural challenges including a notable lack of representation and a fragmented post-market evidence generation system. In 2023, FDA Commissioner Dr. Robert Califf emphasized that the current post-market evidence system does not collect sufficient data after a product is approved to address the evidentiary needs of all Americans.\(^1,2\)

Clinical trial modernization is needed to create a system that eliminates barriers to efficient evidence generation and increases the representativeness of enrolled patients. Recent efforts to innovate the traditional clinical trial design include steps to reduce data collection burdens on patients and staff, support and incentivize involvement from frontline staff and patients in data collection and increase representativeness while maintaining analytical rigor.

To research these issues more in-depth, the Duke-Margolis Institute for Health Policy conducted a multiphase research study between Fall 2022 and Spring 2024 specifically on the topic of increasing representativeness in clinical trials. This research included multiple convenings, a landscape review of existent literature and published materials as well as structured stakeholder interviews with key experts across the clinical trial enterprise including patient advocacy organizations, researchers, and pharmaceutical representatives. Stakeholder interviews were conducted primarily in Spring 2023 and public workshops were hosted in July 2023 and March 2024.

This project also incorporated findings from a broader range of Institute work, including efforts with the Coalition for Advancing Clinical Trials at the Point of Care (ACT@POC) of which Duke-Margolis is a founding member.\(^3,4\)

As a result of this project, Duke-Margolis released *Fostering Collaboration to Advance Shared Goals for Representativeness in Clinical Trials*, a paper that contains recommendations for how stakeholders can collaborate in order to achieve increased representation in clinical trials, including through the use of innovative trial designs and this companion paper that endeavors to highlight the necessity for innovative clinical trial designs, such as pragmatic and point-of-care trials; to address issues of access and representation; provide an overview of the current landscape and promising models; describe an ideal state for representative point-of-care trials; and demonstrate how specific challenges to point-of-care trials can be addressed.

*For a more in-depth analysis on the overall issue of representativeness in clinical trials and recommendations for increasing representativeness while fostering collaboration among stakeholders, please refer to this paper.*

ACT@POC

Duke-Margolis is engaged in the Advancing Clinical Trials at the Point-of-Care (ACT@POC™) coalition which is a collaborative initiative that brings together health systems, community-based care organizations, health research institutions, and other partners. Its mission is to support the design and execution of adaptable and responsive clinical trials focused on enhancing patient participation, improving access, and facilitating the development of targeted therapies with significant impact on patient outcomes.
Introducing the key concepts that will be used throughout the paper will help ensure clarity and understanding. Below, we define our commonly-used terminology:

**Representativeness:** The concept that an equitable clinical research infrastructure should ideally be comprised of clinical trials and studies that accurately match the demographics of the disease burden under study. Such trials should be adequately powered to answer meaningful questions about safety and efficacy in underrepresented subpopulations. To accomplish this, it is imperative to shift evidence generation to efforts aligning with population level evidentiary needs. This shift requires acknowledging the underlying systemic factors (e.g., structural racism) influencing care disparities and representation deficits in clinical trials, including that accurate information about disease burden may not be available due to gaps in health care access and diagnosis in which case other approaches such as census-based representation can be an alternative approach. Additionally, clinical research should be a bi-directional process with patients and communities contributing to question identification and prioritization. Representativeness is a broad reaching category, not only inclusive of race, ethnicity, and gender, but also geographic location, disability, and socioeconomic status.

**Pragmatic Trials:** these types of clinical trials are “designed to inform decision-makers on the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level.” They can incorporate an innovative clinical trial approach leveraging digital health technologies which allows the trial to occur outside of research facilities. This clinical trial approach aims to enhance efficiency, flexibility, and innovation while safeguarding participants and ensuring reliable results. It achieves this through proportionate and risk-based quality management, starting from the study design phase and continuing until the trial’s final analysis.

**Point-of-Care Trials:** A type of pragmatic clinical trial in which data collection and research is integrated into routine care delivery by leveraging the electronic health record and other tools. Well-executed point-of-care trials serve to seamlessly incorporate research activities into the everyday care provided to patients by focusing on only the core data elements needed to answer a specific, straightforward research question.

**Background**

Innovative trial designs such as pragmatic trials can help to address some challenges encountered by traditional clinical trials, including patients’ difficulty accessing trial sites and the challenges of conducting postmarket trials, by moving the clinical trial away from the research facility and closer to settings where the patient typically receives care. Pragmatic trials can incorporate various methods such as telehealth visits, digital health technologies, direct distribution of products to participants, electronic informed consent, home visits to trial participants, and the use of local health care providers and facilities to streamline data collection and reduce burden on patients, providers and trial staff alike.

In the pragmatic point-of-care settings that seek to integrate clinical research fully into clinical care, data can be collected directly from the patient into the electronic health record and combined with information from sensors, trackers, and/or mobile applications which can collect more continuous data that can help identify sporadic events in a real-world environment. This approach creates new avenues for expanding the diversity of populations represented within clinical trials by making it easier to access and participate in clinical research at trusted sites.
Since point-of-care trials work with patients where they are receiving care, the patient experience is better incorporated into the trial, the clinical research team integrates workflows, and the Electronic Health Record (EHR) systems are used to improve patient enrollment, data collection, and data randomization. Within these trials, the local clinical staff follows a standard operating procedure overseen by investigators to monitor and record the trial data in real time. This process can utilize modified informed consent processes and centralize recruitment. Additionally, simplifying the trial design and streamlining endpoints by selecting outcomes that are easily derived from EHRs and typical clinical workflows can reduce costs and burdens for the local teams running the trial. The ability to include more clinicians and patients from a broader range of practices and settings, ideally at lower costs, will help reach diverse populations and increase the participation of patients who are typically underrepresented in traditional clinical trials.

The U.S. Department of Veterans Affairs system has been a pioneer in point-of-care trials. In 2010, researchers began using these trials to address existing inadequacies in trial models and decreased the cost of evidence creation while increasing the efficiency of evidence generation.

During the COVID-19 pandemic, point-of-care style trials helped identify successful steroid treatment for patients hospitalized with COVID-19 by using large numbers of patients in a shortened period. For example, in the UK, the RECOVERY Study was integrated into clinical practice and demonstrated new ways to generate evidence while delivering care. More recently the Pragmatica-Lung study had many point-of-care trial concepts incorporated into its design. Additional details on these examples can be found in Box 1.

Though point-of-care trials and other pragmatic trial approaches have shown their utility, few such designs have informed regulatory decision making and a need exists for more use cases to address barriers and show the benefits of these approaches.

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**BOX 1 | Examples of Successful Point of Care Trials and Similar Initiatives**

**Point of Care Research (POC-R) – Veterans Administration**

The Point of Care Research (POC-R) through the Veterans Administration (VA) is a new approach to clinical study design that embeds trials into routine medical care. This program is uniquely positioned to compare two or more approved treatments or diagnostic techniques that are considered to be equivalent while facilitating participant recruitment and data collection, minimizing study overhead, and streamlining the experience for patients by utilizing the EHR. Recruitment and randomization are accomplished at decision points in clinical care. Customized order-entry screens in the VA EHR allow for minimal disruption. A provider selecting between available treatments is prompted to learn more about the study. After reviewing a summary of the trial, the provider may permit the research team to approach the patient for their consent to participate. Patients who consent to be randomized are assigned to a treatment arm, and orders for the assigned treatment appear in the EHR. After this brief process, the clinical provider continues to treat the patient without deviation from usual care or interruption by research staff. Patients who do not agree to randomization may still choose to allow their clinical data to be utilized. Data collection for the study is accomplished by automatically extracting information from the EHR, and includes clinical endpoints, deviations from treatment protocols, and patient compliance. Costs are expected to be significantly reduced in comparison to a randomized controlled study, and results from these studies are expected to be available sooner to inform clinical practice.
The clinical trials highlighted in **Box 1** are instructive lessons for beginning to achieve the ideal point-of-care trial network. However, the United States does not currently have a nation-spanning system comparable to the National Health Service in the United Kingdom or the VA’s internal network to enable such approaches at scale. Given the lack of examples, confidence in such approaches is still low and skepticism of regulatory acceptance for such trials is high. However, federal agencies in the U.S. are in the midst of standing up new initiatives that seek to provide catalytic support for more initiatives to emerge.

**Federal Initiatives to Improve Clinical Trial Infrastructure and Capacity**

Initiatives spearheaded by federal agencies have set the stage for implementing changes to improve clinical trials representativeness. For example, the National Institutes for Health (NIH) is exploring the creation of a network for research in primary care settings aimed at improving access to clinical studies, particularly for underrepresented communities. The network plans to implement innovative study designs and initiatives to advance health equity by establishing infrastructure for primary care-focused clinical research. This effort pairs well with NIH’s Network for Community-Engaged Primary Care Research which was established by the NIH’s Community Engagement Alliance to use “community-engaged research in primary care settings to identify and start programs and service delivery strategies to address health inequities.” The program seeks to build trust in health care research by leveraging trusted primary care providers, with a goal of establishing “long-lasting partnerships that tackle health inequities and improve diversity and inclusion in research.” Efforts like RADx-UP, also funded by the NIH, show the potential value of intentional investment in health care capacity for underserved population.

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**RECOVERY – UK National Health Service**

The RECOVERY is an international trial which aim to study potential treatments for COVID-19, originating in the United Kingdom and now expanded out to sites in Europe, Africa, and Asia. This trial evaluated treatments on patients who are hospitalized with COVID-19 pneumonia. To date, this initiative has identified four promising treatments and demonstrated evidence of some common treatments that are not effective. The trial has been expanded from its original focus on COVID-19 pneumonia to researching influenza and community acquired pneumonia, and different treatment approaches. These large point-of-care trials were streamlined to efficiently estimate intervention effects on major outcomes which helped to encourage clinician and patient participation and expanded reach into diverse health care settings, including settings that frequently provide services to populations that have historically been underrepresented in trials. The trials use practical methods to keep costs low and researchers continually assess risks and benefits of drugs throughout their life cycles to update labels as new data emerges.

**Pragmatica-Lung – US National Cancer Institute**

Pragmatica-Lung is a clinical trial for patients with stage 4 non-small cell lung cancer. This trial is evaluating the efficacy of a combination drug treatment tested against standard-of-care chemotherapy. This clinical trial also reduces clinician and patient burden by scaling back unnecessary data collection and by not including any secondary study goals. In order to get buy-in to launch the Pragmatica-Lung trial, the Oncology Center of Excellence at FDA had to voice support for the streamlined trial design, in the face of other stakeholders wanting to add more complexity through trial approaches. Though results have not read out from this study yet, early signs have pointed to it accruing patients faster than expected.
Enhancing Representative Enrollment through Point-of-Care Trials

The Advanced Research Projects Agency for Health (ARPA-H) Advancing Clinical Trial Readiness (ACTR) initiative intends to improve the ability for researchers to conduct clinical trials more safely, quickly, and equitably. The initiative is focused on enhancing clinical trial access for people in at-risk communities with the goal of establishing a system where 90% of all eligible Americans can participate in a clinical trial within a half-hour of their home. ACTR was the first initiative launched as part of the ARPANET-H Health Innovation Network which seeks to leverage national capabilities to advance health care capabilities while emphasizing collaboration among diverse stakeholders.

While these potential federal investments and successful point-of-care trials examples are noteworthy, additional equity challenges exist in the scalability of current pragmatic approaches in under-resourced health care settings. It is important to consider the supportive resources required to implement these innovative trials, especially in the early stages of capacity building. As NIH, ARPA-H, and others explore investment in this space, providers must be included at the point-of-care in capacity building, trial design, and other aspects moving forward. Meanwhile, regulators like the FDA have been considering the role of point-of-care and other pragmatic trials designs as well as approaches to improving representativeness in trials.

Regulatory Considerations

FDA has expressed interest in point-of-care trials because of their ability to improve access, convenience, and efficiency. In 2019, FDA Commissioner Dr. Scott Gottlieb noted that point-of-care-trials “can help clinical trials become more agile and efficient by reducing administrative burdens on sponsors and those conducting trials and can allow patients to receive treatments from community providers without compromising the quality of the trial or the integrity of the data that’s being collected.” A few years later in 2023, FDA Commissioner Dr. Robert Califf noted the need to improve the integration of high quality data from EHRs, personal devices and sensors, with data from traditional clinical trials in order to improve health outcomes for all Americans, alongside “restructuring clinical research operations to support and incentivize the involvement of patients and frontline clinicians.”

The FDA also noted that tools like the Sentinel Initiative, the FDA’s electronic system for monitoring the safety of FDA-regulated medical products, will improve the efficiency of data collection and make evidence more actionable since they work at the point of care.

In service of advancing these trials, FDA has released draft guidance for decentralized clinical trials including language delineating the role of health care practitioners and associated considerations for proper documentation, task logging, and informed consent. This guidance also noted that videoconferencing and other technologies may be useful to allow investigators to oversee trial personnel performing activities described in the trial protocol at participants’ locations. The agency has more planned on these topics for release in the near future.

The FDA also released guidance on diversity plans to encourage more representative trials. The draft guidance, titled “FDA Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials,” recommends sponsors generate a diversity plan that will work to incorporate participants from underrepresented racial and ethnic populations in the United States—Black or African American, people who identify as Hispanic, Latino, or Latinx, Indigenous and Native American, Asian, Native Hawaiian and Other Pacific Islanders, and other historically marginalized populations—in clinical trials. Additionally, FDA encourages sponsors to work on the inclusion of other underrepresented patient populations in clinical trials beyond the definition of race and ethnicity, which could include demographic groups such as age, geographic location, gender identity, socioeconomic status, disability,
pregnancy status, lactation status, and co-morbidity. An update to this draft guidance incorporating legislation passed in 2022 is expected to be released soon. In the agency’s efforts to modernize clinical trials, the FDA would like to ensure that drug trials are convenient and accessible to diverse patients, including those with mobility or cognitive challenges, or rare diseases. Broadening access to clinical trials and encouraging stakeholders to collaborate ensures greater patient accessibility. Additionally, when FDA identifies higher rates of adverse events in a specific community, they may require the sponsor of the drug trial to act by conducting additional evaluations or entering a written agreement with the sponsor to conduct additional safety and efficacy research through postmarket trials on any subpopulation that lacks representative data at approval.

Internationally, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) is in the process of updating their Good Clinical Practice guidance (E6(R3)), which lays out key principles for trial design and conduct. This guidance already includes principles around representative trial conduct, and a planned Annex to this document will provide additional guidance for conducting pragmatic and point-of-care trials. In 2023 the World Health Organization released draft guidance to support well-executed, equitable trials with an eye toward global representativeness in trials. In addition to the measures detailed above, more guidance from the FDA on both diversity action plans and point-of-care trials is anticipated. In addition to the measures detailed above, more guidance from the FDA on both diversity action plans and point-of-care trials is anticipated.

These regulatory efforts are indicative of the changing landscape of clinical trials and provide an opportunity for implementing more representative clinical trials, especially innovative point-of-care trials, both within the U.S. and around the world. In order to implement and scale point-of-care trials, continued regulatory clarity is essential.

**Point of Care Trials as a Tool to Increase Representation**

As noted above, an ideal representative point-of-care trial is fully integrated with clinical workflows, and leverages primarily electronic health record systems for critical trial tasks such as patient identification, enrollment, randomization, and data collection, while enrolling a representative sample of the affected patient population. Unlike observational studies that leverage real-world data sources like EHRs for retrospective studies, point-of-care trials focus on prospective data collection and leverage a streamlined set of data elements collected at the point of care. When paired with randomization, this approach has the potential to enable broader and easier access to clinical research while still producing robust evidence to inform decision-making by regulators, payers, health systems, and providers. Ideally, there would be little difference for a patient going to their provider for a regular visit and for a visit that contributes to a point-of-care trial. This makes point-of-care trials a valuable tool for increasing representativeness in clinical trials by not requiring the patient to make a large effort to participate.

However, most community clinics and other sites cannot conduct these trials easily on their own as these organizations may lack the resources, infrastructure, and expertise needed to build capacity. A national point-of-care trial network which connects trusted local sites with organizations and institutions with experience in trial design and conduct, can enable innovative trial designs where patients and their providers can have direct access to codesign and participate in clinical research, while having access to expertise and resources which may not have otherwise been available. For an approach such as this to be successful, such a network must be built on a foundation of community engagement within the needed patient communities.
New medicines must be studied in relevant and proportional patient populations to the disease area and patients who are will be taking the drug in the real-world. Point-of-care trials offer an approach to close gaps in real-world evidence generation often left in traditional research, provide evidence on safety and effectiveness in traditionally excluded subpopulations, and could encourage a focus on more patient centered care by enabling the incorporation of social determinants of health (SDOH) and other factors that may not be captured in many trials, but could be captured in electronic health records.

Leveraging new point-of-care trials similar to the examples in Box 1 to inform a national point-of-care network in local community settings while enabling those sites to be a part of a research network, will provide clinical research access to a broader range of patients and their providers. Below, we highlight some of the challenges to building this point-of-care platform and offer recommendations and considerations for regulators, policymakers, and other stakeholders to enable a national network and platform capable of conducting point-of-care trials that reach communities across the nation and address representation in trials goals.

Recommendations—Barriers and Solutions to Implementing Representative Point-of-Care Trials

In the companion paper released alongside this one, we provided an overview of recommendations on how to foster collaboration via shared goals to increase representativeness in clinical trials. Within that white paper, we proposed the following goals for achieving a coordinated approach to addressing trial representation:

1. **Adopt and Scale Community Engagement Standards:** By prioritizing the provision of adequate financial resources, fostering genuine relationships with established community partners, and implementing measures to recognize success, stakeholders across the clinical trial enterprise can pave the way for scalable and sustainable community engagement practices.

2. **Develop and Scale Innovative Trial Infrastructure and Processes:** Implement innovative clinical trial solutions to facilitate ease of access to trials and increase the representativeness of patients enrolled utilizing a phase-based approach with a foundation of collaboration, funding promising initiatives, and developing metrics for success.

3. **Address Financial Considerations for Inclusive Practices:** Use a multi-phased approach to build a business case for increased trial representativeness. This includes funding innovative pilot initiatives, working with community experts to provide sustainable funding to successful models, and providing financial incentives for inclusive practices.

Representative point-of-care trials most closely aligns with goal number two: *develop and scale innovative trial infrastructure and processes*. However, certain solutions for implementing these point-of-care trials may also tie into the other goals mentioned above.

A few challenges to implementing point-of-care trials persist. Here, we address these challenges with an eye towards ensuring that implementation also drives improvements in access and therefore representation. Successful implementation relies on a coordinated approach among interdisciplinary stakeholders.
CHALLENGE: Lack of technical infrastructure and sufficient data standardization to support potential trial sites that serve underrepresented populations

SOLUTIONS: National investment by government and industry alongside the development of business cases for sustained investment

Anticipated Impact on Representativeness: Focusing on technical infrastructure needs for underrepresented populations may serve to increase enrollment of these patient groups once the challenge is addressed providing an opportunity for point-of-care trials to be implemented.

Challenge

Researchers need to determine if and how point-of-care trials can produce scientifically robust data that is fit-for-purpose and meets participant needs, while considering existing regulatory guidance on relevant trial designs, data quality, and data standards. Integration between EHR and electronic trial data capture systems is a key facilitator for point-of-care trials, but data infrastructure challenges persist for many. Solutions to data collection challenges generally center around the need to modify existing EHR systems to be better fit for point-of-care trial conduct. The implementation of point-of-care trials is dependent on EHR use and adoption needed to identify events in real-time, intervene in clinical care workflow, and track longitudinal data. Not all health systems are equally equipped with adequate tools and resources (e.g. to identify and consent patients or to reliably collect data) to conduct trials in a way that is robust and not burdensome to providers. EHR configurations also vary greatly across health care organizations, which often makes curating data across systems challenging. Additionally, significant infrastructure challenges to point-of-care trials exist, specifically at community sites and under-resourced sites which often serve underrepresented patient populations. Even conventional EHR platforms used across health systems may not satisfy Good Clinical Practice standards and could require considerable customization to be a better fit for point-of-care trial conduct. Once in place, a burden for systems to train staff on new or changing EHR systems may continue, and data collection requirements can disrupt clinical workflows and increase overall data collection burden.

In addition to technical infrastructure challenges, persistent gaps remain in the US data infrastructure. Though improvements have been made, lack of interoperability between data systems persists as a limiting factor in connecting different networks and supporting more research naive sites. As efforts like the NIH's primary care network mentioned above progress, work will be needed in parallel to enable standardized, interoperable approaches to sharing data.

Solution: Federal Government Investment

The concepts in development by agencies like ARPA-H and NIH to advance clinical trial readiness to drive better health outcomes are critical first steps to addressing these challenges. By utilizing ARPA-H’s health innovation network, the government is aiming to shore up the national infrastructure, increasing the access and overall representativeness of clinical trials. Alongside this initiative, NIH’s effort to create a network for research in primary care settings aimed at improving access to clinical studies, particularly for
underrepresented communities has the potential to greatly enable representative, primary care-based point-of-care trials.

Though pragmatic trial approaches could be cheaper than traditional trials once repeatable infrastructure exists, creating this infrastructure and conducting early point-of-care trials is likely to be expensive. Large investments by government agencies, if successful, can be powerful catalytic funding for the development of infrastructure that realize the vision of cost-effective clinical research that can still be leveraged for informed decision making, and can then be sustained by other stakeholders like drug developers. However, new infrastructure is unlikely to be efficiently leveraged without consideration of other challenges.

**Solution: Industry-Led National Investment and Sustainable Business Case Development**

While government support is crucial, other stakeholders can act now. The pharmaceutical industry is well placed to pilot point-of-care trials that enhance their ability to generate postmarket evidence. Learning from trials like Pragmatica-Lung can provide a jumpstart to companies interested in taking similar approaches. Beyond individual pilots, drug developers have the capacity to pool resources pre-competitively to enable trial capacity that could be repeatedly usable by those that have invested in it. Such a model could provide consistent, harmonized training to prepare participating sites for trials from multiple sponsors and provide those sites with more confidence that prioritizing research at the point of care will be a worthwhile investment.

Beyond industry, Practice-Based Research Networks (PBRNs) have been conducting primary care-based research for decades, but often struggle with sustaining grant-based funding. Incorporating PBRNs into national research networks with an eye toward enabling further point-of-care research can simultaneously increase access to research for underserved communities, leverage existing PBRN expertise, and provide a more sustainable source of funding to build capacity at PBRN sites for trials that can drive broader decision making. Other community-based health centers also can be important partners in supporting research.

For additional considerations related to funding initiatives related to increased representation, please see our accompanying paper, “Fostering Collaboration to Advance Shared Goals for Representativeness in Clinical Trials.”

**Solution: Continued Advancement of Data Standardization**

Addressing challenges around data standardization and interoperability requires continued efforts to extend current frameworks and models and ensure that even under-resourced health systems have appropriate access to health Information Technology (IT) systems supported by recommended national and international data standards to facilitate implementation and uptake of representative point-of-care trials. A few such initiatives and data standards are listed below as well as their anticipated impact.

Initiatives such as the United States Core Data Standards for Interoperability (USCDI) and USCDI+ by the Office of the National Coordinator for Health Information Technology demonstrate how common data standards must continue to be implemented as a part of health data systems. USCDI+ extends the list of common data standards to meet certain use cases, increasing both flexibility and interoperability. The Trusted Exchange Framework and Common Agreement (TEFCA) also aims to establish national interoperability and
simplify connectivity and the secure exchange of health care information, while enabling the ease of access of health care information for patients.\textsuperscript{33,34} The Trusted Exchange Framework and Common Agreement (TEFCA) also aims to establish national interoperability and simplify connectivity and the secure exchange of health care information, while enabling the ease of access of health care information for patients. TEFCA is comprised of a Trusted Exchange Framework and a Common Agreement, which was updated in 2024 to include changes required to support Health Level Seven (HL7\textsuperscript{®}) Fast Healthcare Interoperability Resources (FHIR\textsuperscript{®}) based transactions.\textsuperscript{34} The HL7 FHIR accelerator seeks to enhance the adoption and creation of high quality FHIR implementation guides to achieve a global interoperability standard, with a focus on assisting communities and collaborative groups.\textsuperscript{35,36}

With the data standardization initiatives mentioned above, lower resourced health systems and smaller health data companies must still be able to meet the requirements and have access for successful implementation and adoption within their health IT systems.

**CHALLENGE: Lack of regulatory clarity**

**SOLUTION: Updated and implemented regulatory policies for modern trials**

**Anticipated Impact on Representativeness:** Increases representativeness by facilitating the expansion of representative point-of-care trials with clear regulatory guidance

**Challenge**

Regulations governing point-of-care trials are often not proportionate with the level of risk for the trials and can add additional burden for researchers. Good Clinical Practice guidelines, trial governance requirements, and consent procedures often require long legal and regulatory compliance timelines and considerable training and reporting requirements throughout the trial.\textsuperscript{7} Sponsors and investigators are uncertain as to whether point-of-care trial generated evidence will be accepted for regulatory decision making and this uncertainty leads to risk aversion.

Regulatory concerns exist for tracking drug dispensation at less experienced sites, as drug dispensation in traditional trials involves extensive processes and paperwork that are not typically implemented in traditional clinical care.\textsuperscript{36} Regulatory concerns exist for tracking drug dispensation at less experienced sites, as drug dispensation in traditional trials involves extensive processes and paperwork that are not typically implemented in traditional clinical care.\textsuperscript{36} Regulatory concerns exist for tracking drug dispensation at less experienced sites, as drug dispensation in traditional trials involves extensive processes and paperwork that are not typically implemented in traditional clinical care.\textsuperscript{36} Regulatory concerns exist for tracking drug dispensation at less experienced sites, as drug dispensation in traditional trials involves extensive processes and paperwork that are not typically implemented in traditional clinical care.\textsuperscript{36}

As has been highlighted by other organizations, regulatory expectations for Form 1572 also increase uncertainty.\textsuperscript{37} As has been highlighted by other organizations, regulatory expectations for Form 1572 also increase uncertainty.\textsuperscript{38} This form must be filed by investigators running trials and binds investigators as responsible for following good practice. However, as trials have gotten more complex and pragmatic approaches have emerged, revisiting Form 1572 implementation can ensure that the spirit of
oversight is being maintained in a way that is conducive to point-of-care and other pragmatic trials. Although the 2023 draft decentralized trials guidance provided some guidance on the role of health care professionals (HCPs) in trial conduct, it raised additional questions about how to manage distinctions between HCPs and investigators and the proper role of Form 1572. In addition to these real barriers, additional perceived barriers to regulatory point-of-care trial acceptance exist. Assumptions that FDA will have certain expectations for what is submitted as part of an application package can lead trial sponsors to conclude that point-of-care trials are unviable. However, the FDA has clearly stated their interest in seeing more of these approaches.

Solution

Building on efforts such as ICH’s E6(R3) and the World Health Organization’s equitable clinical trial guidance, clearer policies from the FDA and other agencies defining expectations for training, reporting, and monitoring can provide critical clarity for providers seeking to contribute to research. Where possible, policies and guidelines should enable local health care providers to contribute to data collection, care visits, and other trial related tasks that fall within the usual standard of care without significant extra training or administrative burden being placed on those providers.

To address perceived barriers to point-of-care trials, clear guidance and training about acceptable evidence derived from point-of-care trials—along with examples of successful protocols and implementations—could help to provide a better landscape for the implementation of robust and representative point-of-care trials. The FDA should work alongside other stakeholders in this space to make their expectations clear and address myths or erroneous assumptions about what might be required.

Clearer regulatory expectations would support sponsors as they develop and implement diversity action plans. These diversity action plans represent the most significant impetus on drug sponsors to ensure appropriate representation in their clinical trials. Successful implementation of these plans could lead to significant improvement in overall representation in trials that inform regulatory decision-making.

Though the expectation under current FDA guidance is that premarket studies address most representativeness considerations, postmarket studies including point-of-care trials will likely be needed to fully address questions emerging from lack of representativeness in clinical research even with reasonably successful premarket diversity action plans. Real-world postmarket settings offer rich opportunities to conduct trials in broader, more representative populations. To this end, the FDA has released draft guidance on approaches to collect postmarket data on underrepresented populations. We recommend that the finalized version of this guidance include explicit suggestions for leveraging point-of-care trials in addition to the existing considerations for leveraging real-world data generally. We additionally encourage sponsors to consider, even during premarket development, how postmarket evidence generation through point-of-care trials or related approaches may further supplement the available evidence for their products.
**Challenge:** Incentives in both academic and non-academic settings are not designed to support point-of-care trials

**Solution:** Creating incentive structures that encourage integrating research into care

**Anticipated Impact on Representativeness:** Enabling providers, especially those not traditionally engaged in research, to be appropriately compensated and incentivized to support point-of-care research will encourage further participation in clinical research.

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**Challenge**

Current incentive structures do not incentivize collaborative, community engaged research. Without appropriate compensation, time, and recognition (e.g., promotions, career advancement) that encourage point-of-care research, many academic providers are likely to focus on traditional trial approaches while already burdened non-academic providers will prioritize non-research activities.

**Solution**

Point-of-care trials can be particularly well suited to enabling community engagement through increased reach into routine health care settings. It is much easier for patients to have strong engagement with a local clinic they regularly visit and providers they already know than a large medical center perhaps hours away from home that would add additional burden in terms of time off work, travel, and other associated costs. Successful point-of-care trials will pair data collection infrastructure and other tools with sustained, meaningful community engagement to design and conduct trials that provide evidence that support better care and ultimately better outcomes for currently and historically underserved communities. Our broader recommendations regarding community engagement and representative clinical trials can be found in our companion paper.

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**Challenge:** Linking community engagement to point of care evidence generation

**Solutions:** Center patients via well-resourced community engagement initiatives

**Anticipated Impact on Representativeness:** Increases representativeness through creating lasting connections and facilitating an increase in overall trial enrollment through fostering trust; could help ensure trial designs are culturally sensitive and inclusive by establishing connections between researchers and communities.

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**Challenge**

Regulations governing point-of-care trials are often not to recruit patients if lasting community engagement efforts are not already in place to build trust and identify a viable patient population for inclusion in the clinical trial.

Any plans for representative clinical trials also should have a focus on community engagement. Clinical trials structures often have limited community engagement during the recruiting phase. However, it can be difficult
Solution

Developing financial incentives for healthcare institutions and researchers to engage in point-of-care trials will increase provider buy-in. These incentives can include reimbursement models that align with standard care and compensate providers and systems for the time and resources needed to conduct these trials. Incentives that help create a stronger culture of research and learning health will enable more providers to participate in research approaches like point-of-care trials and make it easier to expand and sustain robust point-of-care trial networks. Efforts like NIH’s announced primary care network will be most successful if this need for incentive alignment is taken into consideration. Consideration should be given to tying research participation to quality improvement activities. For example, the Centers for Medicare & Medicaid Services (CMS) could example leveraging the Merit-based Incentive Payment System (MIPS) program to incentivize point-of-care research activities, given the high overlap in work required for point-of-care trials and quality improvement efforts.

LIMITATIONS: Structural Barriers in the US Healthcare System

While point-of-care trials show promising potential to increase representativeness in clinical trials, they are not a panacea. Point-of-care trials rely on the patient being able to access a care setting. Therefore, a point-of-care trial is still not likely to include patients who have reduced access to care either due to geographic considerations, socioeconomic or insurance status, or other factors. Similarly, the issues around trust and clinical trials for certain patient populations would not be completely alleviated because the structure of the clinical trial has changed. Solutions to these systematic barriers should be addressed and implemented in tandem with point-of-care trials wherever feasible. This broad-spanning challenge requires sustained work across the health care sector to remedy structural inequalities and increase access to care. While further expansion on this topic is out of scope for this particular paper, we acknowledge that implementing representative point-of-care trials within health systems is still not enough to alleviate inequality in the health care sector. Point-of-care trials would benefit from greater patient access to care to create a more inclusive health care and research ecosystem.

Conclusion

Point-of-care trials offer tremendous promise to effectively leverage electronic health records to support informed decision-making, but implementation remains limited. Research is needed to identify sustainable means to implement point-of-care trials long-term, ensure that they become an integral part of the clinical trial ecosystem, and help to increase representation in clinical trials overall. Point-of-care and other pragmatic trial approaches provide an important opportunity to design a clinical trial enterprise that better incorporates truly representative real-world populations and approaches to care. As we prepare for future pandemics and address common chronic diseases that impact millions, point-of-care trials can provide a critical means of generating practically relevant evidence in broad populations to answer critical and relevant research questions.
Appendix: Public Convening Participants

We sincerely thank the following individuals for contributing their insights and expertise to one or both of our public convenings, as noted below, during this project.

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