

Point-of-Care Clinical Trials:
Integrating Research and Care Delivery

Duke

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About the Duke-Margolis Center for Health Policy

The Robert J. Margolis, MD, Center for Health Policy at Duke University is directed by Mark McClellan, MD, PhD, and brings together expertise from the Washington, DC, policy community, Duke University, and Duke Health to address the most pressing issues in health policy. The mission of Duke-Margolis is to improve health, health equity, and the value of health care through practical, innovative, and evidence-based policy solutions. Duke-Margolis catalyzes Duke University's leading capabilities, including interdisciplinary academic research and capacity for education and engagement, to inform policy making and implementation for better health and health care. For more information, visit healthpolicy.duke.edu.

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Executive Summary

As the need for a more rapid and efficient means of rigorous clinical evidence generated about medical products from diverse practice settings increases, so has interest in point-of-care (POC) clinical trials. Yet, although interest in and technical capabilities to support POC trials continues to rise, actual implementation of scaled, impactful POC platforms remains limited. The Duke-Margolis Real-World Evidence (RWE) Collaborative Point-of-Care Trials Working Group outlines steps to enable point-of-care trials to achieve their potential. First, we propose a definitional framework for point-of-care clinical trials, discuss what constitutes a point-of-care clinical trial, and illustrate the applicability of our proposed approach. Then, we identify factors impacting point-of-care trial feasibility, along with possible solutions to the impediments presented by each factor. Overall, our paper provides a roadmap to improving the feasibility and scalability of point-of-care trials.

How This Paper Was Developed

This paper is informed by a landscape literature review (see [Appendix B](#)), a private workshop convened by Duke-Margolis, entitled “Point-of-Care Clinical Trials: Integrating Research and Care Delivery” (October 2021), and the expert opinion of the Duke-Margolis RWE Collaborative Point-of-Care Trials Working Group. During the workshop, stakeholders representing academic research groups, health technology organizations, patient advocacy groups, and regulators discussed a definitional framework and the fundamental components of point-of-care trials as well as obstacles and solutions.

Background

Recent multi-stakeholder interest in the use of real-world data (RWD)—“data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources”—throughout the drug development, approval, and access life cycle is well-documented in the literature. Analyzing RWD to generate RWE about the use, benefits, and risks of medical products, making RWE actionable and developed with sufficient rigor to support regulatory decision-making, is often the ultimate goal among health care decision-makers.^{2–4} Point-of-care research is a particular avenue to help accomplish this goal, although it has been pioneered and conducted only within the last decade.

Point-of-care trials are an operational approach to clinical data collection, serving the purpose of integrating clinical research into routine care delivery. Researchers from the US Department of Veterans Affairs (VA), Stanford University, and the Memorial Sloan Kettering Cancer Center pioneered point-of-care clinical trials, with VA staging the first point-of-care clinical trial in 2010.^{5–7} They recognized the lack of evidence available to support clinical decision-making, as well as inadequacies in existing trial models to decrease the overall cost of generating evidence and efficiently address outstanding evidence needs, especially for common chronic diseases (e.g., diabetes). They also helped determine and characterize key components of point-of-care research methods and identify strengths and weaknesses in point-of-care trial models.^{5,8}

The point-of-care trial concept is a direct extension of the researchers’ desire to maintain the benefits of both randomized controlled trials and observational studies by combining the scientific rigor of randomization with an

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observational style of patient follow-up that integrates well with routine care delivery (i.e., limited research-only encounters). The point-of-care model is meant to improve trial feasibility, cost, and generalizability while eliminating the need for large-scale, single-use trial infrastructure.^{5,6}

Despite the capacity for point-of-care trials to improve upon more traditional trial designs to address specific research questions, the point-of-care approach has had limited uptake to date. However, rapidly improving technologies that make point-of-care trials more feasible as well as health care delivery and payment reforms that focus on person-centered longitudinal care and better outcomes, in addition to the burden of common chronic diseases, together, motivate the need for a more robust definitional framework for point-of-care trials. The point-of-care approach has the potential to improve evidence generation, support product registration, and increase the number of patients and trial sites that are engaged in research. This potential is particularly viable in settings and disease areas in which the point-of-care approach is most feasible and applicable (see **Appendix B: Table 1**).

Stakeholders have identified best practices as solutions to increase the feasibility, viability, and scalability of point-of-care trials. These solutions may provide improvements upon the model itself, or provide solutions to the broader clinical trials enterprise that will make new approaches to administering clinical trials more sustainable. The point-of-care approach provides a path forward for better evidence generation and more widespread participation in research for patients and clinicians. As the need for better evidence continues to grow, this consolidated definitional framework and analysis of key components of the point-of-care approach can help us better understand trial conduct and move toward better, more generalizable evidence, clinical efficiency, and democratized access to research and patient care.

The point-of-care approach provides a path forward for better evidence generation and more widespread participation in research for patients and clinicians.

Proposed Definitional Framework and Fundamental Components of Point-of-Care Clinical Trials

Point-of-care trials are not well defined. Given their growing importance and emergence in practice, creating a definitional framework for point-of-care trials today is critical for understanding their applicability and advancing their implementation. Here, we provide a definitional framework for point-of-care trials based on fundamental components identified in practice and in the relevant published existing literature.

A point-of-care trial is not a type of trial design, but rather an operational approach to integrate clinical research into routine health care delivery. Our described approach focuses on enhancing key clinical trial operations, including patient screening, consent, randomization, and data collection, and their incorporation into routine care that can be applied to various trial methodologies (e.g., pragmatic, explanatory trial methods).

Point-of-care approaches have supported various research objectives, including efforts to:

- Optimize clinical trials and make them more accessible in real-world health care settings;
- Optimize the use of RWD as well as methodological designs that have provided reliable evidence for decision making;
- Enhance trial recruitment by leveraging existing patient/clinician relationships—in some cases, improving trial diversity;
- Lessen research burden on clinicians and patients by aligning clinical care and research visits;
- Optimize clinical care through alignment of research and clinical options for disease management and moving towards a learning healthcare system.

Fundamental Components of Point-of-Care Trials

Point-of-care trial components have not been discretely defined but can be extrapolated from the literature. Our landscape review (in **Appendix B**) offers an overview of the following common design features of successful point-of-care trials:

- Integration with electronic health records (EHR) for multiple aspects of trial conduct such as enrollment, randomization, and data collection;
- Completion of trial conduct in usual care conditions; and
- Integration of research and clinical care delivery workflows.^{5,6,9-11}

To operationalize these features, some point-of-care trials have eliminated research-only visits, implemented randomization at the health care encounter, centralized patient recruitment and consenting processes to data coordinating centers, reduced “number of clicks” to minimize workflow interruptions, used a centralized Institutional Review Board (IRB), and eliminated the use of site-based Principle Investigators (PIs).^{12,13} Features of some recent point-of-care trials are presented in **Appendix B1: Table 1**.

Utility and Applicability of the Point-of-Care Approach

To date, the point-of-care approach has demonstrated varying levels of utility across stakeholders and therapeutic contexts. For example, clinical trial sponsors may find point-of-care trials valuable to expand or bolster evidence around the use of therapeutics in the post-market setting, understand the safety and effectiveness of their products in real-world settings, improve the diversity of clinical trial participant populations, and/or support further product registration and labeling. Sponsors may also value the approach’s capacity to increase the diversity of clinical trial participants and to expand and improve evidence generation, continuous care improvement, and lean toward the development of a learning

health care system. Lastly, regulators may find utility in leveraging point-of-care trials to ensure therapeutic safety and efficacy, promote resource efficiency, and support product registration.

Point-of-care trials may be best suited to address specific types of research questions, care settings, trial phases, and therapeutic areas.

Point-of-care trials may be best suited to address specific types of research questions, care settings, trial phases, and therapeutic areas. Specifically, point-of-care trials may be most applicable to comparative effectiveness research for regulator-approved interventions with well-established safety and risk profiles. Point-of-care trial conduct also may be most suitable for researchable questions with objective endpoints (e.g., hospitalization or mortality) that are typically captured as a part of routine care and that do not require systematic laboratory or clinical follow-up. For example, the United States Department of Veterans Affairs (VA) conducted a point-of-care trial comparing sliding scale and weight-based insulin regimens for non-ICU in-patients with diabetes with length of stay as the primary endpoint.⁵

Point-of-care trials may address pressing evidence needs for therapeutic areas where large enough numbers of adequately characterized patients could be engaged to determine treatment effect size to denote the effects between two or more possible interventions. For instance, deploying point-of-care trials to study common chronic diseases, like cardiovascular disease, could be feasible and informative through sufficient engagement with clinical providers.

To assess the applicability of the point-of-care trial approach for supporting decision grade evidence generation, stakeholders inclusive of trial sponsors, regulators, and investigators should consider:

1. What types of interventions and therapeutic areas might be well-suited for trial conduct in routine clinical care settings?
2. What procedures might be needed beyond routine care and how can these procedures be integrated without interrupting clinician workflow?
3. Which clinical endpoints and available covariates can inform effectiveness and be reliably captured in practice (and determine if endpoint measurement would be influenced by a lack of blinding)?
4. Would safety monitoring for the product as part of clinical practice be sufficient and adequately recorded?
5. Are systems in place to extract the RWD reliably?
6. Are source records available for inspections to support data provenance?

Factors Impacting Point-of-Care Trial Feasibility: Key Considerations

Point-of-care trials can become more feasible and adoptable if trial sponsors, investigators, clinicians, patients, payers, and regulators can address internal and external factors that hinder trial implementation. Effectively engaging stakeholders would allow for the adoption of the point-of-care approach in earlier stages of research and provide evidence that, for example, could support the product registration and data collection essential for regulatory decision-making.

Technology Considerations

Point-of-care trials are typically integrated with EHR systems and thus, come with a host of technology requirements. Tools used to support routine care delivery and reimbursement may require adaptation to meet all the requirements for point-of-care trial conduct. In other cases, supplemental tools or modules may need to be deployed to support the collection of data that are not typically captured within routine care. For example, reconfiguring EHR systems for point-of-care trial conduct using add-on modules or pairing EHR data with supplementary data (e.g., sensor-generated data) may be necessary for patient randomization and robust data collection at the point of care.

Today, no single widely-adopted technology standard exists to support point-of-care trials.

Today, no single widely-adopted technology standard exists to support point-of-care trials. Adaptations to EHR systems, while feasible and necessary for improved data quality, might contribute to clinician burnout if not managed properly, even in the presence of supportive digital tools and automated data collection. Yet, such adaptations can be expensive and require many hours of training for clinicians to be used as part of routine care delivery.

Notably, as health care delivery continues to evolve and health technology improves, using EHRs as a central repository for data from multiple touchpoints may create additional work for clinicians and dilute the most relevant data. Composite data packages that leverage other data sources, including patient-generated health data from wearables or other automated data collection can be used to supplement EHR and claims data in a totality of evidence approach that is more likely

to reflect the potential for efficient data collection in the evolving health technology landscape.

Some available technology solutions may make point-of-care trial conduct more resource- and time-efficient. EHR to electronic data capture (EDC) technology is still developing, but it is currently possible to extract a minimally acceptable structured EHR data set to support research and many other applications. Leveraging interoperability standards can increase the ability to scale point-of-care trials across numerous sites and facilitate the comparison of results across trials. In addition, establishing a consensus-driven minimum set of common data elements for specific use cases (such as mCODE for oncology trials) can facilitate data capture for important endpoints as well as standardization in case reporting to support trial comparisons. Generating data suitable for both regulatory and clinical decision-making purposes is possible under the point-of-care trial approach. However, scaling the approach across multiple sites would require efforts to pre-define data elements and standards to support broad and compliant data exchange.

Trial networks can deploy data surveillance systems prior to point-of-care trial implementation to monitor data quality. In addition, dedicated members of the clinical research or care team with sufficient bandwidth and training or expertise (versus the practicing clinician) could assist with data collection. Patients also may independently provide patient experience data through patient portals or questionnaires. Lastly, highly qualified non-physician clinicians (e.g., physician assistants, nurse practitioners, doctors of nursing practice, etc.) may serve as principal investigators of point-of-care trials to oversee data collection as part of their routine clinical duties.

Care should be taken to mitigate potential time, resource, and cost burdens that point-of-care trials might introduce. Clinicians and researchers have identified impactful solutions that can help solve technology problems associated with or inherent to point-of-care trials. For example, simple technological solutions like online or phone-based processes can help screen, enroll, and consent patients before the care interaction to decrease

overall data collection burden and disruptions to clinician workflows.¹¹ However, the digital divide between patients with access to technology and those with low access may make patient completion of external online recruitment or consenting processes difficult.

Clinicians have found various ways to reduce point-of-care trial procedure burden on investigators. For example, some clinicians find that streamlining eligibility criteria and using a two-step consent process in which all patients are debriefed about participating in research, but only patients assigned to the novel intervention are consented twice.^{9,11} In some instances, these solutions have helped improve the quality of interactions between patients and clinicians while strengthening the feasibility of point-of-care trials. In any case, it is essential to ensure that consent processes adhere to regulatory requirements and standards.

Data Considerations

Beyond obtaining necessary data, optimizing data quality and utility may be a challenge for investigators and regulators seeking to leverage real-world data (see Duke-Margolis white paper, [Characterizing RWD Quality and Relevancy for Regulatory Purposes](#)). For example, many clinicians may use clinical information stored in EHRs to support high-quality care delivery, but the documentation and consistency of this clinical information may not be high quality or standardized for evidence generation. Issues with data collected as a part of routine care, such as incomplete data, may make supporting causal inferences difficult.

Recent Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance on the regulatory acceptability of RWE discusses data quality, provenance, and goodness-of-fit dimensions for decision-grade evidence based on EHR and claims data.¹⁴⁻¹⁷ Predefined evidentiary standards that align with data collection capacities across health systems and evidentiary requirements to support regulatory decision-making are critical to implement and scale point-of-care trials successfully.

Administrative and Regulatory Considerations

Point-of-care trials are presently accompanied by administrative issues that ultimately challenge trial feasibility, which may disproportionately affect the initiation of high-value, low risk point-of-care trials. For example, legal compliance requirements to consent patients, data collection during routine care visits, regulatory barriers to simplified data collection, and other factors may delay trial initiation and impact clinical workflows. Balancing data reliability, trial design integrity, and adequate human subjects protection against the ease of trial implementation also will be a challenge. In addition, added time to complete other administrative requirements, like indemnity agreements and IRB review and approval, may also impact prescribed timeframes for trial initiation and engagement. Other restrictions, such as FDA Form 1572 and rules that prohibit clinicians from cold-calling patients, may present further trial enrollment challenges.

It may be appropriate for clinicians to complete research training suited to their respective role(s) in the trial. In some cases, training allied health staff to perform research consenting and enrollment may reduce research training burden on front-line care clinicians. In some cases, it may also be necessary to reconcile certain aspects of point-of-care trials with Good Clinical Practice (GCP) standards.¹⁰

To reduce clinician burden and increase trial efficiency, legal and regulatory guidelines governing clinical research should be based on the risk inherent to the trial. Stakeholders must further discuss and align on how to approach these risk-benefit assessments, and their input should be reflected in regulatory guidance. Trials including products with well-characterized safety profiles, for example, where the point-of-care trial model is currently most applicable, may be inherently less risky than trials assessing investigational products. In trials with low levels of inherent risk or well-characterized interventions, it may be appropriate for clinicians to focus on serious adverse event reporting rather than continuous reporting of all adverse events, especially given how rare it is for new safety signals to accrue in post-market settings where point-of-care trials currently live.

While placebo-controlled point-of-care trials can become a gold-standard, most point-of-care trials conducted to date are unblinded, potentially leading to bias and decreased regulatory acceptability. Differences within and across patient populations and trial sites that are largely unaccounted for in traditional randomized controlled trials (e.g., health risk/benefit profiles), as well as the size of the trials, may impact the generalizability of trial findings. These factors may affect investigators' ability to reach broad conclusions based on finalized data and trial results.

Health System Culture and Incentive Alignment

Internal alignment of incentives within and between health system stakeholders and trial sponsors is essential for successful point-of-care trial implementation. While some health system leaders may view health research as disruptive to clinical duties or meeting tight budgets for clinical care, clinicians and patients also recognize the need for new or better evidence to inform patient care.

Most notably, clinician burden and health system pressure to prioritize fee-for-service care may interfere with point-of-care trial implementation. Overburdened clinicians and resource-constrained patients likely lack the time and ability needed to engage in point-of-care trials. Likewise, clinicians may also be concerned about possible strain to patient-provider relationships upon the admission of clinical equipoise—that is, when clinicians admit that they do not have a preference for one treatment over another during randomization, potentially making patients feel as if their provider does know what treatment is best for them or requiring additional clinician time to explain.^{18,19} Therefore, a health system culture shift toward reducing clinician burden, strengthening patient-provider engagement, and point-of-care trial integration into value-based care models is essential. Although health system culture is not easily changed, meaningful progress toward supporting point-of-care trials can result in more reliable longitudinal data on patient characteristics, health benefit/risk profiles,

treatments, and clearer outcome assessments following clinical interventions.

From a payment standpoint, point-of-care trial initiatives should offer incentives that align trial sponsors, payors, and health care providers on a single mission. There are challenges to accomplish this, including but not limited to misalignment across stakeholders in setting and aligning research agendas and priorities (i.e., developing research hypotheses and programs that are highest priority across each stakeholder). Creating incentives for intentional engagement

among key stakeholders within a given health system or clinical setting to create a steady flow of research topics of collective interest is key to establishing meaningful and lasting point-of-care trial partnerships. Financial incentives may include but not be limited to payer or trial sponsor reimbursement that would mitigate or account for administrative burdens or financial strains that health care providers might experience following point-of-care trial implementation.

Scaling Point-of-Care Trials: Next Steps

Feasibility demonstrations of point-of-care trials may lead to a greater likelihood of scaling and sustaining generalizable point-of-care trial models. Careful attention to the following is crucial to any attempt to scale point-of-care trials

Improvements in Trial Infrastructure and Payment Considerations

The widespread adoption of point-of-care trials likely will require substantial upfront investment in an adaptable and reusable clinical trial infrastructure. To support effective site activation, data collection, and the collaborative design of trials that are relevant in care delivery and return value to health systems, stakeholders must work to develop a network of engaged clinical trial sites that have sufficient time and resources, and an adequate informatics infrastructure to participate in research routinely. Trial infrastructure should be built based on the “least common denominator—that is the trial site that is least equipped for trial conduct. In addition, the use of common coordinating centers as part of this reusable trial infrastructure (such as the one used by the VA may centralize processes and reduce clinician burden as well as provide a steady flow of research questions over time. Stakeholders must keep in mind that cost savings should not be the primary driver for the implementation of point-of-care trials. Rather, stakeholders should develop business plans to assess how point-of-care trials might influence or decrease health care costs and expenditures over time following expanded access to safe and efficacious therapies. Today, health systems and clinical trial sites with longitudinal data systems,

KEY CONSIDERATIONS

- 1. applicability of the point-of-care approach**
- 2. fundamental components of point-of-care trials as described in the literature and by those in practice**
- 3. herein regarding usable trial infrastructure, payment and costs, technology, data collection, administration and regulation, and health system culture and incentives.**

aligned culture to prioritize clinical trial diversity, and supportive policies and incentives are well-suited to address point-of-care research questions.

Point-of-care trials may require a new forms of payment models and incentives to be sustainable enough to observe long-term clinical and financial outcomes. The investment needed to support point-of-care trial conduct at scale precludes the use of a single-use trial infrastructure and drives the need for a new funding model where health systems themselves invest time and money in research. Typically, sponsors will see cost savings only if an established infrastructure is reused for multiple studies. Current payment models do not typically cover costs associated with trial participation, with some exceptions (e.g., Medicare coverage for routine care costs in trials), and the cost of trial conduct that is integrated with care must not accrue to patients and clinicians going forward. Point-of-care trials will need sustained investments for trial deployment and infrastructure maintenance, including from government agencies, medical product developers, academic medical centers, or other vested entities and communities.

Setting Point-of-Care Research Priorities

A national priority disease list and a national roadmap for priority investments in the clinical trials infrastructure may help align stakeholders and identify key evidence gaps that point-of-care trial evidence may fill. Government and other major funders, medical product developers, academic medical centers, or other vested entities and communities can educate, train, support, and harmonize endpoints for point-of-care trial outcomes and metrics for point-of-care trial success for specific settings or disease focus areas. Within this process, government and other major funders, such as industry, should seek stakeholder input and consensus around leveraging existing data infrastructure that can support the point-of-care trial approach, build new point-of-care research tools; and set research priorities, missions, and goals.

Some stakeholders across the clinical trials enterprise have called for a national point-of-care clinical trials network, with one example being the

Coalition for Advancing Clinical Trials at the Point of Care (ACT@POC; www.actpoc.org).²⁰ A national network like ACT@POC could establish standards for data collection, interoperability, and creation of new tools to support point-of-care trial conduct. A national network could also focus on expanding and extending existing initiatives and networks to utilize resources across the ecosystem and reduce the number of inefficient one-off trials. To achieve this national network, existing primary care networks may provide necessary insights that can be leveraged for future trial conduct.

However, large national initiatives may prove challenging to establish, though there may be other paths forward to establish and drive point-of-care trial network efforts. For example, new or established partnerships between public funders and research collaborators would be optimal to create point-of-care trial networks that will investigate real-world outcomes following a randomized therapeutic intervention at the point of care (e.g., treatment for cancer, cardiovascular disease, and other chronic diseases).

Culture Change

A culture shift toward reducing clinician burden, strengthening patient-provider engagement, and point-of-care trial integration into value-based care models is essential to advance point-of-care trials. Health systems must view research as integral to the delivery of evidence-based medicine and continuous care improvement. Partnerships between trial sponsors, clinicians, patients, and other key health system stakeholders should be robust and ongoing to support successful point-of-care trial conduct. Clinician engagement and support are crucial for successful trial recruitment, retention, and data collection.

Point-of-care trials must be centered on researchable questions that are relevant and important to clinical practice to encourage clinician buy-in and participation. In general, there is a need to better align incentives and reimbursement in a way that supports research as standard of care and allows clinicians to carve out the time needed for trial participation. In addition, clinicians must

be provided the time and tools needed to make trial participation more feasible within routine care.

Fostering a culture of patient engagement is equally essential for successful point-of-care trial conduct. Patients should be informed every step of the way to foster their understanding around the value of point-of-care trial participation, evidence, and health care quality. Patients also should have ample and accessible opportunities to learn about the importance and value of clinical research conducted at the point of care.

Looking forward, broader point-of-care trial implementation is possible through adapting legal and regulatory frameworks governing trials, leveraging existing interoperability standards, and increasing support for patients, providers, and health systems. Payment reforms at the federal level may also improve point-of-care trial implementation and encourage their uptake. Also, as the Centers for Medicare & Medicaid Services prioritize, as a goal,

access to comprehensive care with accountability for outcomes, affordability, and equity by 2030 for all of its beneficiaries, systems built for longitudinal, point-of-care trial data collection and analysis will help accomplish this goal.

The point-of-care approach can be used to support both evidence generation for clinical decision-making and the increased use of RWD to support product registration. These changes in the environment surrounding clinical trial conduct would increase clinician participation in research, support trial generalizability across practice settings, and help the research community address pressing evidence gaps with implications for treatment availability and care delivery.

Priority Solutions for Improving and Scaling Point-of-Care Trials	
Improving the Point-of-Care Approach	Scaling the Point-of-Care Approach
Supplement EHR data with other sources (i.e., PROs, wearables).	Secure key investments in reusable trial infrastructure.
Leverage existing interoperability standards (e.g., FHIR).	Align incentives to support point-of-care trial networks that will monitor long-term patient outcomes.
Use data surveillance systems and establishing a minimum set of common data elements.	Create an engagement framework to help build capacity for future point-of-care trial research based on key stakeholder perspectives, questions, and experiences.
Align incentives both internal and external to health systems.	Create a national point-of-care trials network and hub that establishes standards for data collection, tools, and other supports.
Adopt a risk-proportionate regulatory framework.	Develop ongoing partnerships between sponsors, clinicians, patients, and other health system stakeholders.
Streamline eligibility criteria and the consenting process.	Foster a culture of patient engagement and trust.

Conclusion

Point-of-care trials have the potential to advance evidence generation, support product registration, and close important research gaps by involving more research sites and patients, but they have not been well-defined in literature or practice. This definitional framework provides a foundation for stakeholders by defining point-of-care trials as an operational approach to trial conduct that can be applied to various trial methodologies. This framework also provides key considerations for improving and scaling point-of-care trial conduct as well as solutions to overcoming obstacles associated with the point-of-care approach. As the technology and regulatory landscape continues to shift, point-of-care trials may provide meaningful improvements over traditional models of clinical research in settings where the approach is most applicable. Stakeholders must continue working through challenges associated with point-of-care trials and implement solutions moving forward for a more sustainable and equitable clinical trials enterprise.

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Appendix B: Point-of-Care Clinical Trials: A Landscape Literature Review

Introduction

Point-of-care trials are an operational approach to clinical data collection, serving the purpose of integrating clinical research into routine care delivery. As point-of-care trials have been implemented only within the last decade, they continue to be leveraged today with the intent to achieve specific clinical objectives, including but not limited to increased clinical trial efficiency, increased patient access to potentially more safe and effective treatments, and optimized care delivery.

Recognizing that point-of-care trials are not well, consistently defined, or commonly used to support product registration, we conducted a landscape literature review with the goal to capture how point-of-care trial models have been described and reported by practicing experts. Specifically, our goal was to identify and extract key details

or components of select point-of-care trials reported in peer-reviewed literature over the last 10 years. This review also describes successes and challenges that have accompanied recently reported point-of-care trials, including policy and data collection resources that may support point-of-care trial implementation in ways that directly inform regulatory decision-making.

This review was conducted as part of the Duke-Margolis Center for Health Policy's Real-World Evidence (RWE) Collaborative Workstream on Point-of-Care Clinical Trials. The Workstream is comprised of subject matter experts in RWE generation and clinical trial conduct, representing medical product developers, research groups, health technology companies, data curators, and patient advocates.

Characterizing, Defining, and Implementing Point-of-Care Trials

Initial Development and Characterization

Researchers from the US Department of Veterans Affairs (VA), Stanford University, and the Memorial Sloan Kettering Cancer Center pioneered point-of-care clinical trials, with VA staging the first point-of-care clinical trial in 2010.⁵⁻⁷ The researchers recognized the lack of evidence available to support clinical decision-making as well as the inadequacy of existing trial models for decreasing the overall cost of evidence generation and efficiently addressing outstanding evidence needs, especially in common chronic diseases (e.g., diabetes). The point-of-care trial concept is a direct extension of the researchers' desire to maintain the benefits of both randomized controlled trials and observational studies by combining the scientific rigor of randomization with an observational style of patient follow-up that integrates well with routine care delivery (i.e., limited research-only encounters). The point-of-

care model seeks to improve trial feasibility, cost, and generalizability while eliminating the need for large-scale, single-use trial infrastructure.^{5,6} These three research groups helped to determine and characterize key components of point-of-care research methods and to identify strengths and weaknesses in the design of the point-of-care model.^{5,8}

Key Definitional Components

The key components of point-of-care trials are inconsistently defined in the literature. However, two often-recognized components of point-of-care trials include 1) integration of clinical trial conduct with electronic health record (EHR) systems and 2) trial conduct in usual care conditions. In addition, other common point-of-care trial features identified in the literature include randomization at the health

care encounter, elimination of research-only visits, integration of research and care delivery workflows, and utilization of Bayesian adaptive methods. These features may be deployed differently across a range of point-of-care use cases but are generally common in the previously conducted point-of-care trials described in the literature.

Vickers and Scardino at the Memorial Sloan Kettering Cancer Center, two of the first researchers to characterize point-of-care trials, considered the most important aspect of point-of-care trial methodology to be that the clinical experience of the patient is virtually identical whether or not the patient is participating in the study.⁶

In another study, Lam et al. discussed the model's utility, describing point-of-care trials as: 1) fully randomized and leveraging an EHR to electronic data capture (EDC) platform that can be used during routine care by the clinician, and 2) reliant upon Bayesian adaptive method to limit the number of patients required to complete the study.¹²

Shih et al. described three key point-of-care trial features: 1) participants are identified and randomized at the health care encounter, such that the group of participants enrolled in the trial is as diverse as the group of patients typically seen in routine practice within the health care setting where the trial takes place; 2) once randomized, patients will continue to be treated by their providers with usual care and without research-only visits; and 3) trial data becomes integrated within EHR systems (versus manual data input by study staff).²¹

Others have defined point-of-care trials more discretely as pragmatic randomized trials conducted in usual clinical care conditions with data collection based largely on routinely collected electronic health record data. More rigid forms of data (i.e., data elements regularly collected via randomized controlled trials) are sparingly collected given that pragmatic trials are designed to test the effectiveness of available treatments in real-world versus tightly controlled settings.^{10,13,22}

Implementing Point-of-Care Trial Designs

While point-of-care trials hold promising potential to advance both continuous improvements in care delivery and evidence generation, it is possible they may only be feasible and suited to specific settings to address specific real-world problems in health care settings. There are also many considerations around product characteristics, trial objectives, and health system infrastructure that impact point-of-care trial feasibility. Thus, questions remain about the most amenable health care setting for point-of-care trials, especially given that EHR and/or EDC systems are used or adopted differently across diverse clinical care settings (e.g., community health systems, private practices, etc.).

The literature shows that point-of-care trials can be applied across several potential research scenarios. For example, Winhusen et al. noted that a point-of-care trial can be useful in the following two research scenarios: 1) to compare interventions that are clinically acceptable, and 2) in cases where there is equipoise regarding the potential effectiveness of the treatment as well as limited cost to the patient.²³ Also, Fiore et al. discussed how point-of-care trial methods are well suited for studies without any required systematic laboratory or clinical follow-up, with objective outcomes that require little or no adjudication (i.e., hospitalization or mortality).

Regulatory-approved interventions implemented in routine practice with well-characterized safety and risk profiles are ideal for point-of-care trial designs.^{8,18} Some experts have discussed which therapeutic areas are ideal for point-of-care trials, which include comparing the effectiveness of interventional treatments or techniques in sports medicine, surgery, and other areas of clinical practice. Notably, comparative effectiveness studies of "me too" drugs (i.e., drugs that are chemically related to a prototype drug that are used for the same therapeutic purpose but may differ in some respects from the prototype) and lifestyle interventions also are well suited to point-of-care trials.^{6,12,24} Yet, other therapeutic areas like neurodegenerative, cardiovascular, and rare diseases are emerging areas in which point-of-care trials might become well suited for implementation.^{6,24,25}

Exemplar Point-of-Care Trials: Lessons Learned

Exemplar Point-of-Care Trials

A small number of point-of-care trials have been thoroughly described in the literature: VA insulin study, Retropro and eLung studies, MOMs and INFANTS studies, and chlorhexidine bathing study. These studies were identified through a PubMed database search using the following key words: “point-of-care trials”; “point-of-care research clinical trials”; “point-of-care research”; “point-of-care clinical trials”; “point-of-care comparative effectiveness research clinical trials”. The aforementioned trials were selected because they have been explicitly defined by investigators and tagged in the literature as point-of-care trials and because their research methodology and results are well-characterized for analysis. These trials occurred in routine care conditions with sufficient EHR system integration. Moreover, patients were randomized at the health care encounter. Although these trials vary slightly in terms of their methodologies, they are useful examples of how variations in point-of-care trial models can exist in today’s health data infrastructure and regulatory environment. Additional studies that were selected, and thus well suited for our analysis, were based on expert working group recommendations, even though the studies were not tagged as point-of-care trials in the PubMed database. **Table 1** provides an overview and summary of each of these studies, including their research aim(s) and key design and data collection dimensions.

Insights from the Literature

The VA insulin, Retropro and eLung, MOMs and INFANTS, and chlorhexidine bath studies offer important insights for those looking to implement point-of-care trials today or in the future. Insights include clinical process improvements to help reduce clinician burden due to time-intensive patient recruitment, training, and informed consent processes and procedures, as well as balancing outcome selection with cost and technological system capabilities.

Insights from these studies also show that minimizing clinician burden is paramount to the successful implementation of point-of-care trials. For example, in the chlorhexidine bathing study, cluster randomization with waiver of consent and inclusive selection criteria improved enrollment and reduced overall clinician burden.²⁶ Thus, efficiencies needed to navigate successful patient recruitment and obtain informed consent are critical to minimize clinician burden and increase the likelihood of broad point-of-care trial implementation.

For trials with more complex eligibility criteria, there are options to consider regarding patient recruitment and informed consent. Centralized patient identification and recruitment ahead of the actual health care encounter (i.e., through telephone- or electronic-based informed consent processes with documentation waivers) are potential strategies to notify patients of their randomization and efficiently obtain their informed consent.¹¹ In addition, modified informed consent processes that appropriately balance the risks of point-of-care research against therapeutic benefits, especially for repurposed therapeutics or commonly-used interventions, are viable options reported in the literature.^{10,11}

To support point-of-care trial implementation and account for clinician time and bandwidth, lessons learned from the VA insulin study noted that practicing clinicians should be expected only to protect and treat their patients and not undergo research training and credentialing, even if the clinicians refer their patients for inclusion in a trial and sign or authorize randomly generated orders for treatment. Clinicians in this study were not required to participate in the additional research training that would have otherwise interfered with time the clinicians needed to dedicate to patient care. Overall, the authors noted that point-of-care trials are best suited for exploring commonly used interventions and comparative effectiveness among treatments with clear toxicity profiles.¹¹ They also noted that EHR systems should ideally

be configured to accommodate study-specific workflows and linkage to back-end databases.

Lessons learned from the eLung and Retropro studies show it is also important to balance the clinical relevance of study outcomes with the technological feasibility and cost of data collection. Within these studies, the participating clinicians recorded outcome measures in the EHRs, which were then aggregated for analysis and required during manual chart review. In other trials like

the VA insulin study, data collection was fully automated as the primary and secondary outcomes were ascertained from structured data elements in the VA's EHR system. Therefore, EHR systems that are not sufficiently flexible may require substantial reengineering prior to point-of-care trial conduct.^{8,10,11}

Limitations of the Model

Point-of-care trials can potentially augment or enrich traditional clinical research methodologies in some contexts but not all. Indeed, point-of-care trials are accompanied by inherent limitations. Clinician burden, limited choice in primary outcome measure selection due to what is relevant and feasible during routine care delivery, and low clinician interest in trial participation due to perceived workload are perhaps the most significant limitations that will ultimately affect broad point-of-care trial implementation.

Clinician burden was a major obstructing limiting factor in one study.¹¹ In addition, some providers noted that randomization, even to an active control, and admission of clinical equipoise may damage the clinician-patient relationship.^{5,8,18}

Risk of study bias is also a significant limitation given that treatment randomization may be unblinded. Also, the risk of low generalizability among the trial results due to inherent differences in patient populations across trial sites and health care systems also is extant.⁸ This risk is emphasized in recent FDA guidance which notes that EHR data collected during routine care may have limited generalizability because patients in different health care systems may differ in characteristics such as age, socioeconomic status, health conditions, and other confounders.¹⁴ Further, it is likely that most, if not all, point-of-care trials would have an unblinded design so that they can be conducted with limited

disruption to typical clinical care. This structure raises concern about observational bias and cross-contamination of treatments or the provision of differential treatment due to physicians' perceptions of patient needs.⁸

Further, some studies noted that EHR utilization may also limit the applicability of the model because trial treatment outcomes are limited to the data elements routinely obtained in clinical practice, thus ultimately impacting primary outcome measure selection.^{5,23,27} Some investigators propose using EHRs in combination with add-on systems or the use of simple eCRFs to increase simplicity of data collection for providers while still facilitating the collection of data on all relevant clinical outcomes.²⁸

Finally, physician interest in trial participation may be low due to the lack of proper incentives (i.e., modest payment for trial participation or access to de-identified study data).⁶ Exploring a research question important or impactful enough in the context of care delivery as well as professional development opportunities associated with involvement in research, might serve as sufficient compensation.²⁹

Review of Factors Supporting or Obstructing Point-of-Care Trial Conduct

Legal and Regulatory Challenges

Point-of-care trials are accompanied by legal and regulatory compliance requirements and challenges. The duration of research training and federal and local site approval processes were major obstacles reported in the literature. Namely, investigators felt that current regulations governing point-of-care trials were not risk-proportionate in relation to relatively low-risk nature of the trials. For example, the VA insulin study report noted that their informed consent process was the single most tangible disruption to care workflows and that variations in the traditional informed consent process could prove more efficient and appropriate where there is minimal risk to the patient.^{8,18} Further, the Retropro and eLung studies noted that training requirements and protocols were lengthy and time consuming, even when the trial was low-risk, and that clinicians had considerable experience prescribing the treatment included in the study (e.g., statins in the Retropro study).

Although point-of-care trials are intended to promote safe treatments and drive greater evidence based on data collected during clinical encounters, there are certain challenges to achieving this goal. Specifically, adherence to Good Clinical Practice guidelines, trial governance requirements, and consent procedures are major challenges. These challenges are partially due to the long legal and regulatory compliance timelines and considerable training and reporting requirements that precede and endure throughout trial conduct.¹⁰ For example, governance review and local site approval processes were a major barrier for some trials, with one study reporting that they were able to obtain site activation approvals after three years. In the Retropro and eLung studies, trial site approval was contingent upon agreeing to several conditions, including but not limited to frequent audits. Study teams also were required to immediately report side effects for commonly re-purposed drugs

(e.g., statins) into the EHR and study website, which ultimately disrupted clinical workflows and increased overall data collection burden.¹⁰

Data Collection Infrastructure Considerations

While integration between EHR and electronic trial data capture systems is a key facilitator for point-of-care trials, data infrastructure challenges persist for many. Solutions to data collection challenges described in the literature generally center around the need to modify existing EHR systems to be better fit for point-of-care trial conduct.

For example, one study discussed the idea that point-of-care trial implementation is dependent on EHR use and adoption needed to: 1) identify events in real-time; 2) intervene in clinical care workflow; and 3) track longitudinal data.⁸ Also, the MOMs and INFANTs studies on neonatal abstinence syndrome and opioid dependency in pregnancy reported struggles with standardizing EHR systems across trial sites to meet point-of-care trial needs (e.g., embedding randomization capabilities or features into EHRs), even though all three sites used the same EHR system and vendor.²³ The Retropro and eLung studies required significant investment in a costly EHR aggregation system as well as onerously converting data from clinical encounters into a useful and assessable format.

Data collection challenges at the health system level also challenge point-of-care trial implementation. For instance, EHR system integration can increase training time and place additional burden on clinicians. The Retropro and eLung studies reported that clinicians struggled with the “flagging” software that optimized the EHRs for the trials, noting that the software required considerable troubleshooting and training.¹¹ Further, the conventional EHR platform used across their health system did not satisfy GCP standards and required considerable reengineering.

The lack of harmonization between EHR and GCP standards placed a considerable burden on participating physicians, as it led to increased

paperwork and training requirements that required completion prior to patient recruitment.¹⁰

Knowledge Gaps

The impact of uncertainty around the regulatory acceptability of RWD generated from point-of-care trials remains unknown. While RWD generally holds potential to enable broader access to information collected at the point of care, indeed, there are practical and technical challenges to data and data systems that ultimately impact the regulatory acceptability and utility of the data. Future work should determine if and how point-of-care trials can produce fit-for-purpose and scientifically robust data that meet regulatory standards and needs, while taking into account existing regulatory guidance on relevant trial designs, data quality, and data standards.^{14–17,30}

Also, most of the studies reviewed lacked sufficient discussion about whether and how non-generalizable results might impact the widespread adoption of the point-of-care trials as well as the regulatory acceptability of point-of-care trial data. Although investigators set inclusion/exclusion criteria and recruitment goals in part to meet representative enrollment targets, the composition of the population in a health system where the trial is conducted may limit the generalizability of trial findings. Issues around the generalizability also

appear in instances where trials are conducted in highly-resourced academic medical centers that can quickly adapt EHR systems and provide trained research staff. Future work, therefore, also should outline standard enrollment criteria, resources to achieve optimal data standardization, and other standardizing elements that would help improve the generalizability of trial results and maximize their utility for regulators.

Finally, some of the studies recommended using financial incentives to increase the likelihood of provider participation in point-of-care trials, but a few discussed the lack of insurance coverage or reimbursement for routine care provided as part of clinical trials. Although the reimbursement landscape may change or improve over time, routine costs associated with conducting clinical trials are typically covered by the trial sponsor. Therefore, how point-of-care trials might operate within or outside of current health care reimbursement frameworks should be explored to generate potentially viable and sustainable solutions.³¹

Conclusion

Point-of-care trials hold promising potential to contribute RWD and RWE needed to support both clinical and regulatory decision-making. Although point-of-care trials are inconsistently defined, have supported varied methodological approaches, introduce real or perceived complexities to the standard-of-care, and require substantial considerations regarding EHR adoption, adaptation, and use across diverse health system settings, valuable lessons learned to date along with meaningful next steps can be ascertained through the literature and through stakeholder engagement. When approached carefully and designed with meaningful intent, point-of-care trials can become useful to meet evidentiary goals and needs across diverse contexts and stakeholders, ultimately making clinical trials more accessible and their findings more applicable to real-world settings.

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Appendix B: Table 1

Comparison of Exemplar Point-of-Care Trials						
Trial	Setting and Therapeutic Area	Study Design and Size	Randomization	Patient Identification and Consent	EHR Integration	Study Limitations
VA insulin trial ⁵	Veterans Affairs Healthcare System Common chronic disease (diabetes)	Open-label, randomized trial comparing sliding scale regular insulin to a weight-based regimen for control of hyperglycemia, using the primary outcome length of stay, in 55 non-ICU inpatients at a single site, VA Boston Healthcare System	Bayesian adaptive randomization using EHR system during health care encounter by physician at insulin-order entry screen	Clinicians indicated their approval for informed consent which was then obtained by trained study staff	VA CPRS/VISTA EHR system modification to support enrollment, randomization, and longitudinal data collection	Requirement for unblinded design which could produce cross-contamination between treatments or other biases Study may have yielded results that are locally convincing but are not easily generalized to other healthcare systems
Retropro trial and eLung trial ¹⁰	General Practitioner Practices in the United Kingdom Common chronic disease (cardiovascular disease and chronic obstructive pulmonary disease)	Open-label, randomized trials with Retropro comparing simvastatin vs. atorvastatin for CVD patients, enrolling 301 participants at 17 sites and eLung comparing immediate (prophylactic) vs. deferred or non-use of antibiotics for patients with COPD, enrolling 31 participants at 6 sites	Randomization at health care encounter by physician using trial website to record and obtain assignment	Study team used a computer program, LEPIS, for patient identification based on extracted patient information from EHR; clinicians approved patient eligibility and obtained informed consent from patients	EHR system supported enrollment and data collection; data aggregation system supported outcome assessment	Small sample size and unblinded design may introduce bias Participants worked within inner-city, under-resourced areas and patients frequently experienced language barriers, potentially impacting data collection and generalizability of results
MOMs trial and INFANTS trial ²³	Large Health System Hospital/Academic Medical Centers Neonatal abstinence syndrome (NAS) and opioid dependency during pregnancy	Open-label, randomized, intent-to-treat, two-group trials with an estimated 370 patients in MOMs comparing methadone vs. buprenorphine for opioid dependence during pregnancy, with primary outcome length of stay and secondary outcome patient retention in medication assisted treatment (MAT) through delivery, and 284 patients in INFANTS comparing methadone vs. buprenorphine for NAS in affected infants, with primary outcome length of stay and secondary outcome days of opioid treatment, at three study sites	Randomization using EHR during health care encounter by physician	Pregnant, opioid-dependent patients at one of the three study sites who were currently not enrolled in MAT and their infants were identified; clinicians obtained consent during the health care encounter and flagged participation in EHR	Existing EHR system modification to support randomization and longitudinal data collection	EHR systems required substantial modification Study sites would not typically cover cost of the clinical interventions, making this model of clinical research difficult in this setting
Chlorhexidine bathing trial ²⁶	Academic Medical Center Infection in critically ill, hospitalized patients	Pragmatic, controlled, cluster randomized design with patient blinding at one study site containing 5 ICUs with 9,340 total patients studying use of 2% chlorhexidine bathing cloths vs. nonantimicrobial cloths with a composite primary outcome comprised of central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), possible or probable ventilator-associated pneumonia (VAP), or <i>C difficile</i> infection	Cluster randomization with automatic enrollment upon ICU admission	Waiver of informed consent by clinicians at study site	EHR system supported data collection; outcomes were assessed via manual chart review	Inability to blind staff administering baths to patients

Appendix B: Table 1 *continued*

Comparison of Exemplar Point-of-Care Trials						
Trial	Setting and Therapeutic Area	Study Design and Size	Randomization	Patient Identification and Consent	EHR Integration	Study Limitations
ADAPTABLE trial ^{32,33}	PCORNet network; 40 health centers and one health plan Atherosclerotic cardiovascular disease (ASCVD)	Open-label, pragmatic design, randomization of 15,076 patients to a strategy of 81 mg or 325 mg of aspirin per day	Randomization using web portal. All study visits completed within web portal and did not require clinic visits (non-internet patients were contacted by phone)	Programming algorithms distributed, customized, and applied by participating centers to local EHR data for patient identification Direct to patient electronic informed consent, or consented by trained research staff if limited access to internet	EHR system adapted to support patient identification, consent, and data collection/endpoint ascertainment	Open-label design and enrollment of patients who previously took study drug Patient and clinician bias may have led to chance in dosing Potential limits to generalizability; trial under-enrolled women and other traditionally underrepresented groups
RECOVERY trial ^{34,35}	178 hospitals within the United Kingdom's National Health Service Repurposed therapeutics for COVID-19	Randomized, controlled, open-label, platform trial of a range of possible treatments compared with usual care in 43,268 hospitalized patients. Interventions assessed included: <i>Anti-virals</i> —lopinavir-ritonavir, hydroxychloroquine; <i>Immunomodulators</i> —corticosteroid, azithromycin, tocilizumab; <i>SARS-CoV-2</i> – convalescent plasma	Randomization using online form. Clinician then prescribes allocated treatment on usual chart	Simple 2-page information sheet & 1-page electronic consent form	No EHR to EDC integration. Simple electronic case report form to randomize, enroll, and capture patient data and adverse events (AEs) Permission to follow-up via record linkage for up to 10 years	Given the established safety profile of the repurposed drugs assessed, investigators did not collect detailed information on non-serious AE or information on physiological, laboratory, or virological parameters, which have been studied previously for RECOVERY compounds in the studied population

Appendix C: Glossary

Endpoint (Clinical endpoint): “A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, such as how multiple assessments within an individual are to be combined.”³⁶

Clinical equipoise: “The equality regarding probability of benefit that must exist between two or more groups being compared in a study. This probability of benefit is derived from existing, scientifically valid evidence of the effectiveness of the agents being tested, and not from anecdotal or ‘gut’ feelings.”¹⁹

Data provenance: Origin of the data, sometimes including a chronological record of data custodians and transformations.

Decision-grade evidence: Evidence of sufficient quality and suitability to inform regulatory and other key health stakeholder decision making.

Point-of-care trials (POC): An operational approach to conducting clinical trials that involves leveraging electronic health records, comparing treatments administered in usual care settings, integrating clinical trials into clinical care workflows.

Appendix C: References

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