OPINION

Decentralized Trials in the Age of Real-World Evidence and Inclusivity in Clinical Investigations

Sean Khozin[1,*] and Andrea Coravos[1,2]

Decentralized clinical trials (DCTs) facilitate conducting studies outside the physical boundaries of traditional clinical research facilities. They can extend the reach of clinical investigations to historically underserved populations while enabling incorporation of tools, such as digital health and telemedicine, for high-frequency remote monitoring of patients in real-world settings. DCTs require special attention to cybersecurity and data privacy protection laws and can be an efficient means of supporting a more patient-centered and inclusive clinical research enterprise.

BACKGROUND

Clinical trials are the cornerstone of evidence generation for making causal inference and assessment of the safety and efficacy of medical interventions and therapies. However, conventional clinical trials can be inefficient, producing results with limited external validity that may compromise extrapolation to personalization of treatment decisions at the point of routine care. Several factors can contribute to external validity deficits. Traditional clinical trials often centralize operations at specialized centers far from where most patients live. In a recent global survey of over 2,000 clinical trial participants, study location was viewed by patients as one of the most disliked features of participating in clinical research, coming only second to the possibility of receiving placebo.[1] Further reducing external validity is that most traditional clinical trials exclude many patients due to narrow eligibility criteria and are conducted according to strict protocol-based procedures that can deviate from treatment standards in routine care. In recent years, efforts by clinical researchers, regulators, industry, and patient advocates have been paving the way for modernizing clinical evidence generation by shifting focus to collection of data from the real world (i.e., the point of routine care in addition to locations outside brick and mortar boundaries of the healthcare system). The ubiquity of electronic health records in community-based medical practices coupled with advances in mobile technologies, telemedicine, and machine learning algorithms are making these modernization efforts possible today.

In December 2016, the 21st Century Cures Act (Cures Act), designed to accelerate the discovery, development, and delivery of new cures and treatments in the United States, was signed into law. Among the key objectives of the Cures Act were directives to the US Food and Drug Administration (FDA) to create a framework for evaluating the potential use of real-world evidence in support of regulatory decisions for product approvals. In response, the FDA has launched a series of demonstration projects, internal working groups, and workshops, recently publishing a framework that outlines the general contours of the Agency's strategy for the use of real-world evidence to inform regulatory decisions.[2] In the framework, traditional clinical trials are characterized as studies with restrictive eligibility criteria conducted at specialized facilities that are typically separate from routine clinical practice. Although the bulk of today's dialogue on the use of real-world evidence focuses on retrospective examination of data collected as part of routine delivery of care, pragmatic and DCTs are prospective investigations that can be conducted not only at specialized centers but also in the real world. Whereas pragmatic clinical trials are exclusively anchored at the point of routine care, decentralized studies can be designed to extend the reach of highly controlled clinical investigations to where patients live and work, including the comfort of their homes.

DEFINITION

There are several definitions for DCTs and, when examined closely, most clinical studies today have decentralized components. In general, *locality* and *methods* for data collection as part of clinical investigations are ideal metrics for defining the degree of decentralization in a study (**Figure 1**). Using

[1]US Food and Drug Administration, Silver Spring, Maryland, USA; [2]Harvard-MIT Center for Regulatory Science, Boston, Massachusetts, USA.
*Correspondence: Sean Khozin (sean.khozin@fda.hhs.gov)

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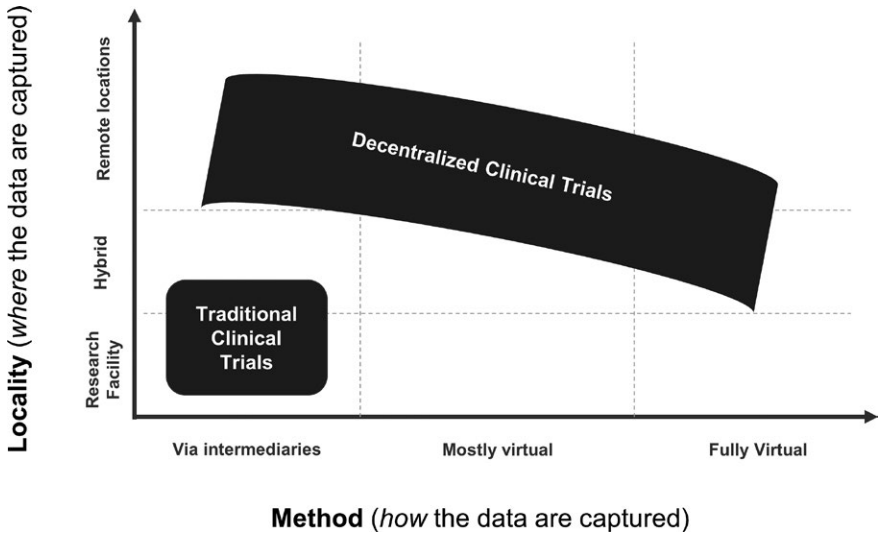

Figure 1 Comparative characterization of traditional vs. decentralized clinical trials. Decentralized clinical trials are characterized by decreased reliance on specialized research facilities and intermediaries for data collection. Many traditional clinical trials today use a hybrid locality approach, collecting data outside of central research facilities (e.g., plasma and tissue samples sent to off-site locations for testing). Traditional clinical trials also routinely incorporate semi-virtual data collection methods, acquiring protocol-specified information via email, facsimile, and telephone. Decentralized clinical trials can distribute data collection to remote locations, leveraging modern virtual methods, such as telemedicine and sensor-based technologies, to accommodate data collection needs close to where patients live and in real-world settings.

this definition, the magnitude of clinical trial decentralization is inversely correlated with the degree of the study's operational dependency on specific sites, such as specialized research facilities or reliance on intermediaries for data collection. DCTs can accommodate both traditional and pragmatic real-world study designs, including those using randomization, given that decentralization refers to attributes related to the methods and procedures governing the conduct of clinical investigations and not study design features or statistical analysis plans. DCTs can be conducted according to protocol-specified procedures in compliance with regulatory standards and accepted best practices that ensure data quality and integrity.

METHODS FOR DATA COLLECTION IN DCTS

The majority of clinical trial data today are collected via *intermediaries*, typically, trained individuals on a study team who record protocol-specified information from a variety of sources into a case report form, defined by the International Conference on Harmonization Guidelines for Good Clinical Practice as a printed, optical, or electronic document designed to record all of the protocol required information on trial participants.

The term *virtual* generally refers to the use of digital technologies for remote and passive collection of data. We define *fully virtual* as a method for collecting data without an intermediary. Virtual collection of data *passively* further obviates the need for clinical trial participants to actively engage with a data collection tool or an intermediary. For example, telemedicine platforms and mobile applications tracking dietary calorie intake are semi-virtual technologies, which require an intermediary or *active* patient engagement for collecting information. In contrast, a wearable gyroscopic accelerometer can be a fully virtual tool that passively collects data without the need for active patient or intermediary engagement. Regulatory innovations, such as the FDA's Information Exchange and Data Transformation (INFORMED) program and the Center for Devices and Radiological Health's Pre-Certification Pilot are enabling new opportunities for the use of fully virtual digital health tools in support of product development and patient management.

LOCALITY OF DATA COLLECTION IN DCTS

Historically, drugs, biologics, medical devices, and surgical interventions are tested on human participants at specialized sites designed to support clinical research. The rapid evolution in mobile and telemedicine technologies has enabled novel means of collecting data from a participant's home and natural environment to improve operations. A blended approach that combines the expertise and coordinating functions of traditional research facilities with new capabilities enabled by remote virtual data collection can increase patient convenience and compliance while facilitating the capture of new pipelines of data using digital health tools.

BENEFITS AND LIMITATIONS OF DCTS

The goals of decentralization are centered on improving the logistics of conducting clinical trials and creating new ways of capturing the individual experience of patients in real-world settings by incorporating technical solutions into data collection workflows. As clinical trial designs become more complex, there is a growing demand for larger and more diverse pools of study participants. Given the convenience of remote and virtual data collection, DCTs have the potential to improve patient recruitment, retention, and engagement, allowing for continuous data capture in real-world settings.

As stakeholders continue to place greater emphasis on expansion of eligibility criteria in clinical trials, DCTs are ideal means of accommodating patients traditionally excluded from clinical research. DCTs reduce the burden of participation by facilitating in-home and remote monitoring, particularly important for patients with comorbidities for whom clinical trial participation can be particularly challenging.[3] The convenience of remote monitoring can also facilitate enrollment of patients with poor performance status and those especially vulnerable to the financial toxicities of clinical trial participation, such as the elderly and those with low socioeconomic status.

When utilized as end points, validated remote collection of digital biomarkers can potentially reduce trial sample size by enabling the development of individualized

thresholds for measuring treatment effects derived from continuous or high-frequency data.[4] Furthermore, digital biomarkers can serve as objective metrics for traditionally subjective end points. For example, the FDA's INFORMED program is conducting foundational research for the development of objective methods of measuring pain, quality of life, functional status, and cognitive function using biometric sensors, computer vision, and voice recognition technologies.[5] The Cures Act has created new pathways for qualification of digital biomarkers and algorithms derived from such efforts as *drug development tools*. When incorporated into decentralized study designs, these tools can create new means of understanding individual responses to treatment, the burden of disease, and treatment-emergent toxicities from a uniquely patient-centered vantage point.

Despite the benefits, fully decentralized trials may not be appropriate for all types of clinical research today. For example, translational and dose-finding studies that require frequent interventions, such as dose modifications and serial tissue biopsies, are best suited for traditional settings with centralized resources, staffing capabilities, and subject matter expertise.

DCTs that rely on virtual collection of large volumes of data from digitally connected tools may face other unique challenges. Many connected devices, including sensors and wearables, remain in early development and require extensive analytical and clinical validation, especially for use cases intended to support regulatory decisions. Issues such as device battery life, availability of technical support, and practicality of continuous monitoring with in-home devices and wearable sensors, are factors that necessitate advanced technical, organizational, and human capital capabilities not yet widely present in standard clinical development programs.

The benefits of virtual data collection in DCTs across distributed networks of connected technologies must be coupled with efforts to ensure patient privacy. Protecting the privacy of personally identifiable health information stored on connected devices and distributed channels calls for establishing strict guidelines governing the collection and use of the data. Furthermore, because most traditional clinical trials rely on firewalled local systems or centrally managed cloud-based infrastructure for data storage, developing advanced cybersecurity capabilities for ensuring data security is an important requirement for the optimal design and execution of DCTs.

CONCLUSION

DCTs take advantage of modern technological solutions to extend the reach of clinical research to where patients live, facilitating remote collection of data reflective of the individual experience of patients in real-world settings. By developing new capabilities to meet the technical and organizational needs of DCTs, we can help usher in a new era of high-performance clinical research, one that is more inclusive and highly tuned to the diversity and unique needs of individual patients.

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CONFLICT OF INTEREST
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DISCLAIMER
The views described in this work are those of the authors and do not necessarily represent the position of the US Food and Drug Administration or the US government.

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