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The COVID-19 pandemic and cardiovascular issues in clinical trials: Practical and regulatory issues in remote monitoring of cardiac safety

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Background

The COVID-19 public health emergency has seriously impacted the conduct of clinical trials. Challenges have arisen, ranging from quarantines, site closures, travel limitations, interruption of investigational product supply chains, and other considerations concerning potential infection of site personnel or trial participants. The FDA and sponsors have recognized the need to modify ongoing protocols to enhance public health control measures during the pandemic. Some of these modifications include phone contact between clinical trial stakeholders, virtual informed consent, virtual visits, remote monitoring, remote data capture, study drug delivery, study drug administration in the setting where the original administration is performed by a health care professional, and continued availability of clinical investigator oversight (reference: Guidance for Industry, Conduct of clinical trials of Medical Products during COVID-19 public health emergency, March 2020, updated January 27, 2021).[1] The pandemic-mediated need for remote data monitoring and data capture has accelerated innovation and altered the paradigm of clinical trial design and implementation. The implications of this paradigm shift may be far-reaching, such as the ability to recruit patients who may otherwise have been unreachable due to logistical impediments in interacting with health care professionals.[1,2] However, these innovations may lead to regulatory challenges concerning the acquisition of clinically meaningful and interpretable data sufficient enough to distinguish a drug effect from a control (placebo or active comparator) so as to facilitate a drug approval. These challenges are due to a number of potential issues, such as data quality from the digital health platform, data integration when using multiple technologies, data variability, and logistics of remote monitoring. The type of data captured is also important if required to meet the evidentiary standard for a regulatory approval. These challenges are particularly striking in the setting where ongoing clinical trials required protocol amendments to accommodate COVID-19 mediated restrictions.

Clinical outcomes – which reflect how an individual *feels, functions*, or *survives* – are often collected remotely. There are various technologies for collecting clinical outcomes data. Some collect actual clinical data remotely, such as remote laboratory testing and physiologic measurements. Laboratory data, often considered to be biomarkers, do not fall under the clinical outcome assessment umbrella.[3] Physiologic measures can be accomplished using dedicated devices provided to the patient, or in some cases, the patient's own smartphone or computer.

Examples of outcome measures include patient, clinician, and observer reported outcomes. Performance outcomes based on a standard task performed by the patient and evaluated by a trained individual may face challenges (Table I).

The Cardiac Safety Research Consortium, including regulatory, academic and industry experts, convened a webinar think tank titled, "Remote Cardiac Safety Monitoring for Clinical Trials – Pandemic and Beyond," on October 16, 2020. The Cardiac Safety Research Consortium is a public-private partnership formed in 2005 as a part of FDA's Critical Path Program and formalized in 2006 under a Memorandum of Understanding between the U.S. Food and Drug Administration (FDA) and Duke University.[2,4] The consortium's core values involve bringing together manufacturers, regulators and clinical thought-leaders; nurturing a collaborative precompetitive environment; improving knowledge, enhancing innovation and public health; and examining key cardiac safety research issues. The focus of the think tank was to address the challenges and opportunities imposed upon the drug development process as a result of the COVID-19 pandemic.

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Table I. Examples of outcome measures include

- *Patient-reported outcomes (PROs)*, based on direct reports from the patient about the status of the patient's health condition, without interpretation by a clinician or anyone else. Challenges here include the use of devices at home, training requirements, identity verification, and caregiver involvement to assist patients unable to complete assessments on their own.
- *Clinician-reported outcomes (ClinROs)*, based on reports from a trained healthcare professional after observation of a patient's health condition. For evaluation in a remote setting, these usually require video interaction. Some assessments may not be practical for remote administration, and there may be a risk to patients due to site staff not being nearby in the event of an imminent safety concern (such as a positive suicidality score).
- *Observer-reported outcomes (ObsROs)*, based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than the patient or a healthcare professional. Challenges include ensuring intra-observer variability, ability to assess behaviors remotely, and training of non-healthcare personnel.

Table II. Definition of remote data

"Remote data" are defined as data that may be electronically transmitted from the subject outside the clinical setting to a database repository, such as:

- Heart rate (eg, wearable sensors)
- Blood pressure (eg, ambulatory blood pressure monitoring)
- Heart rhythm (eg, Holter monitor)
- Patient reported outcomes (measuring how the patient feels and functions using either a provisioned or the patient's own smartphone, tablet, or computer)
- Exercise capacity (six minute walk distance [6MWD], actigraphy)
- Adverse event solicitation via a remote visit

Remote data capture and monitoring

The definition of remote data and methods of acquisition are shown in Table II. These mostly include hemodynamics (heart rate and blood pressure), cardiac rhythms, clinical outcome assessment data (eg, patient-reported outcomes), exercise capacity, and adverse event solicitation.

Digital health technologies (DHTs) and remote data capture are defined as "technologies that use computing platforms, connectivity, software, and/or sensors for health care and related uses."[5] DHTs can passively capture data (for example, through accelerometers, cardiac rhythm monitors) or capture data through patient responses (such as an electronic patient-reported outcome). Since DHTs can be operated and accessed remotely, they can reduce barriers to obtaining patient experience data by avoiding the need for travel.[6] They can enable larger, more inclusive, and more generalizable trials and evidence generation. They also have the ability to detect intermittent or rare events (including falls, seizures, and arrhythmias), and can record novel measures (such as behavior patterns in patients with depression).

Remote cardiac safety monitoring has evolved over past decades, starting with the Holter, through event monitors (looping and non-looping), to atrial fibrillation auto-trigger monitors, implantable loop recorders, and "real-time" mobile cardiac outpatient telemetry and patch technology. The COVID-19 pandemic has increased demand for decentralization of clinical trials, with solutions for preserving trial integrity being in great demand. For example, devices that are capable of recording ECGs at the patient's home can help establish the diagnosis in individuals with random episodes of palpitation. These can also provide promising tools for long-term monitoring for arrhythmia and guide development of future therapies.

Appropriate solutions depend on the medical conditions that are of interest – such as arrhythmia, prior infarction, sinus pause, ischemia, heart block or heart rate variability – and on the type of data needed. Timing is also important, including whether data are required immediately (almost real-time) or after Holter scanning (continuously and analyzed retrospectively after downloading). The data points of interest also influence choices, such as the total number of episodes, exact timing of episodes, onset of episodes related to dosing, duration of episodes (longest, shortest, average) and burden. DHTs can measure a wide variety of parameters.

Functional classes for mobile cardiac telemetry include flexible monitoring options with patch or lead wires, automatic detection (rate, rhythm, atrial fibrillation, atrial flutter, other arrhythmias, burden), real-time reporting, alert reporting, monitoring for up to 30 days, wireless transmission, round-the-clock reporting, and protocol-specific customization of the report.

Cardiac device technology has evolved to the point where devices are now able to obtain similar data without a clinic visit, and to provide alerts as soon as an event is identified. Currently available technologies offer real-time reporting, rate and rhythm auto-detection algorithms, detection and automatic transmission of asymptomatic and symptomatic events, lists of alerts customized per protocol, 2- and 6-channel ECG, 30 second

to 5 minute recording, and 24/7/365 reporting. Most recently, the development of "wearables" – including watches, bracelets and clothing – is gaining interest and holds great promise.[7] That said, there is still doubt over data integrity; the Heart Rhythm Society reports that "false positives associated with the use of wearables to detect arrhythmias can cause unwarranted concerns and screening."[8]

In addition to electrophysiologic monitoring, cardiac monitoring technologies are available that:

- Measure physiologic parameters, such as blood pressure, heart rate, and pulse oximetry
- Have potential to mimic common clinical trial endpoints, such as the six minute walk distance (6MWD)
- Provide clinical decision support tools, based on data in the electronic health record, such as medication change recommendations
- Inform novel clinical diagnostic indices/measurements or predictors based on multiple inputs from sensors.

Regulatory considerations

Novel endpoints

Regulatory considerations for DHT-derived endpoints are broadly similar to the evidentiary considerations for other types of outcome measures. These include the need to confirm that the assessment is valid, reliable and fit for purpose.

In collection of these assessments, care must be taken to consider the method of remote communication. A consistent method such as telephone or video should be used: identities of both the patient and healthcare provider should be confirmed: patient privacy must be maintained (both at the patient's location and at the clinic): and clinical trial personnel should be adequately trained on tools and methods. During the pandemic, with the need to acutely switch to another modality to minimize missing data may lead to an increase in data variability. FDA's 'Patient-Focused Drug Development discussion documents[9,10] outline a suggested pathway with upcoming FDA guidance to be issued and further detail on this guidance series can be found on the FDA website.[11] It is also anticipated that CDER will issue 2 draft guidance documents in 2021, 1 on the use of digital health technologies for remote data acquisition in clinical investigations and another on decentralized clinical trials.[12]

Methods of data capture

FDA statements on the use of innovative methods of data capture are shown in Table III, reflecting their potential to provide suitable information on physical function that can lead to a regulatory action.

Communications with regulators should cover the suitability of required assessments to be done virtually, with a focus on patient safety and privacy, and plans for training and providing necessary technology. To satisfy Institutional Review Board and privacy requirements, it is essential to obtain and update patient consent, have a suitable process to verify the identities of both parties, and have procedures to protect privacy. The informed consent procedure will need to be documented by using eConsent tools, mail or electronic document exchange, verbal consent with witness attestation, and follow-up written documentation if needed.

Safety monitoring

Cardiac safety devices may be regulated by FDA through several approaches. One option is the independent FDA approval/clearance approach (PMA, 510(k), De Novo). A second is FDA approval under an Investigational Device Exemption. A third is Medical Device Development Tool Certification,[11] which qualifies tools used to develop and evaluate medical devices for clinical uses. Finally, there are statutory exemptions for devices with clinical decision support functionality, wellness claims and medical device data systems. When selecting a device for a clinical trial, it is important to consider what needs to be measured, and what additional validation of clinical accuracy can be provided.

A final "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards" (Table II)[1] comments on some of the issues related to remote monitoring. These include the need to ensure patient safety and privacy, data quality and integrity comparable to that achieved with non-virtual data collection (eg, missing data should be minimized, and sufficient data must be collected). Clinical training is needed to adapt to changes to procedures and for proper use of virtual tools. Future FDA guidance is expected to address decentralized clinical trials, and the use of digital health technologies for remote data acquisition in clinical investigations. The European Medicines Agency released similar guidance (Table IV).

During the public health emergency when mid-study changes to remote data collection are made, it is important to document whether an assessment was conducted in-person or remotely (including type of technology used), and it may also be necessary to make adaptations to the study power and statistical analysis. Some adaptations may include including methods for handling missing data, the potential need to compare data acquired via different modalities, any impact on compliance, and ways to account for additional variability that might affect study power or require additional patients to be enrolled.

Table III. FDA is working to advance innovations, including new technologies[13]

- "Electronic capture of PRO data (ePRO) is also becoming standard, providing a rich pipeline of structured clinical data. In addition to ePRO, mobile wearable technologies can complement traditional PRO surveys by generating objective, continuous activity and physiologic data."
- "Obtaining reliable wearable device data on activity level, coupled with direct patient report on their ability to carry out important day to day activities, can provide information on physical function that is directly relevant and important to the quality of life of cancer patients."

Table IV. Regulatory guidances

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards
(March 2020, updated on September 21, 2020):[1]

- "If planned on-site monitoring visits are no longer possible, sponsors should consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites."
- An appendix Q&A includes mentions of "conducting remote (virtual) clinic visits," "remote clinical outcome assessments" and "remote site monitoring visits."
- This Guidance states that, "Sponsors should determine if in-person visits are necessary to fully assure the safety of trial participants," and, "in making the decision to continue use or administration of the investigational product, the sponsor should consider whether the safety of trial participants can be assured with the implementation of the altered monitoring approach."

European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 (coronavirus) Pandemic. Version 3 28/04/2020.[12]

"Sponsors should consider in their risk assessment whether the following measures could be the most appropriate during COVID-19. Measures should generally be agreed with investigators and could be:

- Conversion of physical visits into phone or video visits, postponement or complete cancellation of visits to ensure that only strictly necessary visits are performed at sites…"

Evidentiary standards

To be considered as supporting data for a regulatory approval, remote data would need to meet the evidentiary standard for a substantive review. This is not unique to or exacberated by COVID. First, the acquired data should be poolable. Actigraphy passively measures patients' daily activity. It is not equivalent to a 6MWD which, in contrast, is a structured task-based assessment administered according to a set of instructions. Substituting actigraphy for 6MWD in a protocol amendment as a pandemic precaution creates the potential for pooling 2 non-combinable outcomes. Second, management strategies would need to be capable of distinguishing a clinically meaningful treatment effect. This involves well-defined variability with the selected DHTT. For claims related to clinical benefit using a clinical outcome assessment, it is important to demonstrate that the endpoint score is clinically meaningful, and to assess how much within-patient change in score or variable is meaningful. Feasibility and usability are critical considerations. Finally, operational challenges may threaten pivotal trial adequacy such as subjects' possession of requisite equipment, adequate knowledge of the equipment's use, and protocol compliance (such as avoiding taking off a watch or ambulatory blood pressure monitoring device).

As the clinical trials community incorporates increasing numbers of remote visits into protocols, the questions below will need to be considered:

- How does one ascertain whether clinical measurements are candidates for remote collection?
- What are the basic requirements for remote monitoring DHTs to be considered for use in clinical trials?
- How are specific DHTs classified based on their function?
- What are reasonable components for study endpoints?
- What functionalities are available?
- How should a remote/mobile DHT be selected for a particular use?
- How much customization is required to tailor the DHT for a specific protocol design?
- Can remote DHTs adequately evaluate both safety and efficacy?
- Can patient privacy be maintained in a remote setting, both at the patient's location and at the clinic?
- What are the regulatory implications of moving assessments to a remote modality?
- What are the regulatory requirements in terms of validation of these devices?

Summary

The COVID-19 pandemic has heralded a new era in clinical trials via the digital health platform, remote data acquisition, and remote data monitoring. From a regulatory perspective, remote data capture is a viable strategy for pivotal trials with endpoints measured outside of traditional office or clinic visits, in areas including exercise capacity and patient reported outcomes. Clinical outcome assessments must also be carefully evaluated

for use in drawing conclusions about safety and efficacy, and to derived clinical trial endpoints to support labeling claims. The variability of measures should be estimated and the results should produce a clinically meaningful treatment effect. Challenges impacting the quality of evidence include undefined variability, protocol amendments resulting in measurement of non-combinable outcomes, and operational threats to assessment of trial adequacy.

Timely FDA guidance has helped those on the front lines of clinical trials to make decisions about data collection modes, what data to exclude, and where recruitment may need to be expanded. Looking ahead, more clarity is needed in defining best practices for remote data gathering, and for appropriate use of a combination of remote and traditional approaches to inform post-COVID-19 approaches.

Disclaimer

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the FDA. The FDA authors are not involved with and do not endorse any medical product or device mentioned in this manuscript.

Disclosure

Kenneth Martin Stein is an employee and shareholder of Boston Scientific. Rest of the authors declare no financial interests.

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