CTTI Considerations for Advancing the Use of Digital Technologies for Data Capture & Improved Clinical Trials

For the purposes of these considerations and resources, the Digital Health Trials (DHT) Digital Technologies project team has defined ***digital technologies*** as digital applications and other wearables, ingestibles, implantables, and portable technologies containing sensors for the remote capture of outcomes data.

Introduction

Digital technology offers unique opportunities to improve the quality and efficiency of clinical trials, in part through high-quality data collection in settings outside of the health care facility or clinic, such as in the study participant's home or workplace.

A myriad of scientific and technological considerations accompany the decision to use a digital technology for data capture. These include digital technology selection; data collection, management, analysis, and interpretation; protocol design and execution; and specific issues involving the use of digital technologies to generate data supporting marketing application to FDA.[*] The Clinical Trials Transformation Initiative (CTTI) convened a multi-stakeholder project team to develop considerations and resources that address these issues with a particular focus on the scientific and technological aspects involved in the incorporation of digital technologies for data capture in clinical trials.

These considerations are characterized by three overarching themes:

- Scientific principles currently in use across the clinical trials enterprise still apply for clinical trials using ***digital technologies***.
- Data quality principles are the same for clinical trials using ***digital technologies*** for data capture and those using data collection approaches in the clinic.
- Study participant engagement is critical in the design of trials that use ***digital technologies*** for data capture.

Aligned with CTTI's Digital Health Trials (DHT) Program, these materials focus on the use of digital technologies in FDA-regulated clinical trials after the point of informed consent, concentrating on the **use of technologies intended specifically for outcomes data capture**, and not for the purposes of recruitment, retention, or as the intervention itself.

Due to the varied nature of digital technologies and the individual needs of stakeholders across the clinical trials enterprise, these materials are organized to provide the following:

[*] For considerations to support the selection, development, and inclusion of technology-derived endpoints, see CTTI's DHT Novel Endpoints considerations and Recommendations for Developing Novel Endpoints.

- A **glossary** defining critical terms that will become central to the field, but that may currently be unfamiliar to some experts. Terms defined in the glossary will appear in the considerations text in ***bold italics***,
- **Considerations** providing a common framework to optimize the inclusion of digital technologies in clinical trials,
- Accompanying **resources** supporting the implementation of these considerations, and
- **Appendices** offering additional information on a variety of technical approaches that are being successfully used at the time of publication.

Section I: Selecting Digital Technologies for Data Capture in Clinical Trials

Any test, tool, or instrument used for data collection in a clinical trial should meet acceptable feasibility and performance characteristics such as ***accuracy***, ***precision***, and ***consistency*** of measurements over time, and ***uniformity*** of measurements across digital technologies. When digital technologies are used for data capture, they should also meet relevant technical performance specifications that relate to their ability to reliably capture, process, store, and transfer the valid data to satisfy the needs of the trial. Sponsors should have access to data quantifying the ***accuracy***, ***precision***, ***consistency,*** and ***uniformity*** of the technologies. This information would reasonably be provided by the digital technology manufacturer.

This section provides considerations to guide sponsors in the selection of the most appropriate digital technology for their trial. In addition to guiding principles and a recommended digital technology selection framework, CTTI provides information to support sponsors' assessment of specific technology performance characteristics, including verification and validation.

1. Know what you want to measure† before selecting the digital technology.

Digital technology selection should occur after the identification of the aspect or experience that the assessment is intended to measure (i.e., an individual's clinical, biological, physical, or functional state.

Advances in technology have led to a proliferation of digital technologies capable of capturing objective data from trial participants. The decision to use a digital technology for data capture should be driven by:

1. Unmet patient or scientific need for a better assessment, and/or
2. The promise of more efficient, less burdensome trials through remote data capture approaches.

† For considerations to support the selection, development, and inclusion of technology-derived endpoints, see CTTI's DHT Novel Endpoints considerations and Recommendations for Developing Novel Endpoints.

Evaluating the appropriateness of any technology-derived assessment in a clinical trial should proceed independently from and prior to evaluation of the digital technology itself. To ensure this delineation is achieved, CTTI suggests that digital technology selection occur only after the identification of an ***outcome assessment*** of interest.‡ This stepwise approach ensures sponsors focus on selection of digital technologies that offer quantifiable value over existing measurement approaches, and also allows sponsors to identify the specifications they require in the digital technology prior to beginning the selection process.

2. Digital technology selection should be specification-driven and collaborative.

Collaboration is key—engage both technology manufacturers and patients as partners.

Digital technology selection should be driven by the:

1. Technical performance specifications and functional characteristics needed to measure the outcome assessment of interest,
2. Study needs (i.e., constraints and nuances of the central scientific question), and
3. Needs and preferences of study participants.

This is a multi-factorial decision that should be tailored to each trial.

Sponsors should collaborate with technology manufacturers and relevant patient groups to inform their decision for digital technology selection. A framework of specifications to consider, designed to facilitate this collaboration between sponsors and digital technology manufacturers, is available here.

3. CTTI suggests that a digital technology's regulatory status not be the sole driver in sponsors' decisions about which technology to use.

Digital technologies for data capture in clinical trials do not typically need to be approved or cleared as a ***medical device***[§]*.*

In stressing the need for a specification-driven approach to digital technology selection, CTTI strongly suggests that a technology's regulatory status not be the sole driver in the sponsors' decisions about which ***digital technology*** to use. As such, while many digital technologies are marketed and sold as ***consumer products***, they may still be useful as data collection tools in clinical investigations.

‡ For considerations to support the selection, development, and inclusion of technology-derived endpoints, see CTTI's DHT Novel Endpoints considerations. and Recommendations for Developing Novel Endpoints.

§ The FDA provides and overview of Medical Devices at https://www.fda.gov/ForIndustry/ImportProgram/ImportBasics/RegulatedProducts/ucm510630.htm

Specific suggestions to support sponsors deciding between issuing provisioned digital technologies and asking participants to "bring your own technology" (BYOT) are beyond the scope of these considerations. However, regardless of whether a digital technology is provided to the participant or if the participant brings their own, CTTI suggests considering a specification-driven approach to optimizing digital technology selection.

4. The appropriateness of the selected digital technology should be justified through verification and validation processes.

Sponsors should be able to scientifically justify their selection of a specific digital technology for a specific study.

Verification assures that the digital technology reliably measures what it claims to measure, and is usually performed by the technology manufacturer with a series of engineering bench tests. This includes documentation about the technology's accuracy, reliability over time, and safety of the digital technology and battery. ***Validation*** assures that the processed data being assessed are suitable for its intended use and patient population in a trial. If supporting data are not available in the scientific literature, ***validation*** may require clinical testing by an investigator that may or may not be performed in collaboration with the digital technology manufacturer (See Table 1).

Verification

CTTI has defined verification to include the assessment of ***accuracy*** (which may include routine ***calibration***), ***precision***, ***consistency*** across time; ***uniformity*** across digital technologies; and possibly also across different environmental conditions. The measurement standard is usually a physical measurement such as acceleration, voltage, or time. A digital technology manufacturer should provide the sponsor with documentation of these performance characteristics along with their limitations (e.g., verified within a measurement range of x_1 to x_2 if calibrated each m months and used within a temperature range of t_1 to t_2 with battery changes every d days). Sponsors are then responsible for making sure the digital technologies are used within their engineering specifications.

The raw data are often processed within the digital technology to deliver processed measures. For example, acceleration data can be reported as activity counts, and EKG voltage patterns can be reported as heart rate. The assurance that the relevant ***firmware***/software that generates the processed data is accurate, precise, consistent, and uniform should also be part of the technology manufacturer's ***verification*** process.

The responsibility for the quality of the clinical investigation lies with the sponsors. To avoid costly errors, CTTI suggests considering an automated, centralized approach to data monitoring so that discovery of irregular data, which may indicate

calibration errors, can be flagged and investigated. Sponsors should have procedures in place to document when potential calibration errors are identified and how the calibration issue was resolved. More detailed considerations on study monitoring are available here.

Validation

In this context, CTTI defines ***validation*** as the process of ensuring that the digital technology is generating objective data that accurately represents the outcome assessment it purports to be measuring. If the ultimate measure of interest is not algorithm-dependent, validation may be synonymous with verification (Table 1); however, if the ultimate measure of interest is algorithm-dependent, additional processes are required to validate the data generated by the digital technology in the context of its use in the clinical trial. For example, if acceleration measurements (verified by the digital technology manufacturer) are used to estimate sleep endpoints such as total sleep time, then a validation study would include comparison of the technology measurement to an accepted sleep standard, such as polysomnography. Similarly, heart rate variability could be compared to ECG measurements.

Validation should occur in both a controlled environment—the laboratory or clinic—and a real-world environment. ***Validation*** should occur in the participant population of interest, and it is likely that the validation process will be optimized through collaboration between digital technology manufacturers, sponsors, and other technical and clinical experts.

Ultimately, sponsors are responsible for determining whether the endpoints in question have been adequately validated for their trial; however, CTTI suggests that digital technology manufacturers support this decision-making process by being as transparent as possible. Ideally, the process by which the algorithm was developed should be published or otherwise made freely available to sponsors. Sponsors must also be assured by the digital technology manufacturer that they will be advised of any changes to the algorithm with releases of software updates. To facilitate comparisons between recent and older trials, and to protect the integrity of longitudinal trials that last several years, manufacturers are strongly encouraged to avoid algorithm changes or at least provide full transparency and backward compatibility when changes are necessary.

For more information on the validation process, see CTTI's DHT Novel Endpoints considerations.

Table 1: Verification and Validation

	VERIFICATION				VALIDATION
	Raw Data		**Processed Data**		**Outcome**
Description	*Output from physical sensor*	→	*Output from digital technology firmware*	→	*Output from analysis algorithm*
Example:	Acceleration (m/s2)	→	Activity counts (n)	→	Time spent active (min)
				→	Total sleep time (min)
Example:	Electrical potential (mv)	→	Heart rate (beats/min)	→	Heart rate variability (e.g. pNN50**)

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Case Example: Verification and Validation Processes in Practice

5. Feasibility studies conducted before full implementation in a large study reduce risk.

Feasibility studies are important assessments that may help address unanticipated potential digital technology issues when used in the context of the specific trial.

In addition to the application of a rigorous, specification-driven approach to digital technology selection, sponsors should consider conducting feasibility (or pilot) studies of their chosen technology(ies) prior to launching the trial. Such studies are helpful to assess the tolerability, acceptability, and usability in the trial population (see the Framework of Specifications to Consider during Digital Technology Selection and CTTI Recommendations for Selecting & Testing Digital Health Technology) and may

** The pNN50 statistic is a time domain measure of heart rate variability (HRV).

also identify other, unanticipated issues with their proposed use in the specific context of the trial, such as poor wear-time compliance.

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Case Example: Feasibility Testing to Promote Successful Inclusion of Digital Technologies for Data Capture

Snapshot: One Sponsor's Approach to Conducting Digital Technology Feasibility Studies

► Step 1: Run a patient focus group to conduct usability testing of candidate technologies. Use insights from the focus group to determine digital technology selection and inform study protocol design.

► Step 2: Screen participants against inclusion and exclusion criteria.

► Step 3: Deliver digital technology training to participants prior to technology assignment.

► Step 4a: Conduct study participant and investigator interviews at specified time points to gain insights into digital technology deployment and use.

► Step 4b: In parallel, implement a monitoring and communication plan to mitigate potential issues with data collection. As many digital technologies stream data to a cloud based platform in either real time or with minimal delay, frequent data monitoring which bridges periodic interviews will help to troubleshoot issues associated with user error or hardware failure sooner. This is important to minimize data loss and improve data quality.

► Step 5: Analyze data collected on digital technologies to determine quality of data captured.

► Step 6: Carry out further relevant analyses; e.g., compare equivalence of data collected on the digital technology for the intended endpoint versus the gold standard.

Section II: Data Collection, Analysis, and Interpretation

Traditionally, data collection occurs during clinical trial site visits. The use of digital technologies for data capture offers the possibility of gathering real-time information from study participants in their homes, workplaces, or other convenient settings, potentially over long periods of time, yielding a more complete picture of the investigational medical product. Simultaneously, trials using digital technologies may also be more efficient and reduce unnecessary burden on study participants. However,

the ability to realize these benefits is contingent on collecting high-quality,[1] clinically meaningful data, and conducting appropriate analyses that inform robust conclusions.

This section provides considerations for optimizing study design and data collection as well as strategies for analyzing and interpreting data captured using digital technologies. Considerations in this section are based on the assumption that biostatisticians and data scientists, as appropriate, are involved in all decisions regarding protocol design, data collection, analysis, and interpretation.

1. Collect the minimum data set necessary to address the study endpoints.

Approaches to data collection should be driven by the scientific question the clinical trial is striving to answer.

Collecting an abundance of data beyond what is required to answer the primary question(s), including crucial supportive evidence, is a common pitfall in clinical trial design and conduct. Like traditional trials, decisions about study design and data collection are critically important to clinical trials using ***digital technologies*** for data capture. Study objectives must be clear, and the study design should be constructed to address those objectives robustly yet succinctly. As such, only data that are necessary to meet the objectives of the trial should be collected.

a. **Quality by Design principles should drive decisions about the quantity of data to be collected.**

The principle of data parsimony is particularly important; the minimum data set sufficient to address the study endpoints should be what is collected. This approach is also consistent with the International Conference on Harmonization (ICH) E9 guideline "Statistical principles for clinical trials," which states that data collections should focus on the data necessary to implement the planned analysis, including the context information.[2] There will be instances where exploratory endpoints will drive the need to gather larger amounts of data without necessarily knowing in advance which will prove to be most valuable. However, when the study endpoints are well understood, CTTI warns against speculative "data fishing."

Taking a quality by design approach to data collection is particularly important when using ***digital technologies*** for data capture, as these technologies allow not only for the possibility of continuous data collection, but also the capture of myriad novel measurements from a single digital technology without adding any extra burden to trial participants. Large data sets give rise to unique computational and statistical challenges and should only be collected if they are critical to the central scientific question(s) of the clinical trial.

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Case Example: Optimizing Data Quality and Participant Privacy

b. **Sponsors should ensure that appropriate *metadata* are collected to provide sufficient contextual information to understand the outcome data captured by digital technologies while avoiding the collection of intrusive data.**

In addition to ensuring that outcome data can be readily interpreted, collecting appropriate ***metadata*** will also provide critical information on the technical origin of the data. More detailed considerations on the privacy implications of collecting metadata are available here. More detailed considerations on collecting data element identifiers, specifically when data are being gathered to support a marketing application to FDA, are available here.

THIS CONSIDERATION IN ACTION
Case Example: Optimizing Data Quality and Participant Privacy

c. **The most appropriate *epoch length* and optimal sampling frequency for a given outcome should be determined during development of the endpoint in the context of use in the trial.**

These specifications should be determined in close collaboration with clinical- and patient-driven needs that address the relevant scientific question and appropriately evaluate the performance of the investigational medical product. If data are being captured by a digital technology to inform a primary, secondary, or prespecified safety endpoint, then measurement approaches such as digital technology placement, sampling frequency, ***epoch length***, and scoring algorithms should be determined and well understood in advance of designing the trial and authoring the data collection and analysis plans. For more information on how to determine measurement approaches, see CTTI's DHT Novel Endpoints considerations.

2. Include appropriate strategies for monitoring and optimizing data quality.

Data should be collected by digital technologies in such a way as to optimize the quality of the data.

High-quality data may be defined as data strong enough to support conclusions and interpretations equivalent to those derived from error-free data.[1] digital technologies may streamline data capture while offering the ability to eliminate sources of error during collection. For example, digital technologies remove concerns over transcription errors and non-contemporaneous information when data are collected with time stamps.

However, sponsors should design trials to ensure that using digital technologies for data collection does not give rise to new data quality issues. Specifically, that the clinical trial design ensures data captured from digital technologies are accurate, complete,

and may be correctly attributed.[††] CTTI suggests considering strategies for optimizing data quality at the point of collection using a digital technology are summarized in Table 2.

3. Address *data attribution* proactively with patient input.

Data attribution *concerns should be addressed proactively with patient input, specifically at the point of digital technology selection and during protocol development.*

When data are captured using a digital technology, a member of the study team does not need to be present to observe and record the data. This offers the possibility of using digital technologies to conduct highly efficient trials that capture data in free-living conditions, providing far greater insight into participants' responses to an investigational medical product. However, the use of digital technologies also raises new challenges regarding ***data attribution***, including verifying when the data were recorded and who generated the data.

Accounting for when the data were recorded can be addressed by gathering simple ***metadata***, including date and time stamps, as part of data collection. Careful consideration should also be given to ensuring date and time synchronization across digital technologies and data collection platforms, when applicable. The effects of time zones, travel, and changes in daylight saving time also need to be taken into consideration.

A multi-pronged approach should be used to promote the likelihood of correct ***data attribution***. Strategies should focus on:

- Digital technology selection;
- Protocol design; and
- Technical approaches.

At the point of digital technology selection and during protocol development, there are a number of strategies that can increase the likelihood that data are collected only from the participant to whom the digital technology was assigned. Strategies for optimizing data quality and proactively addressing ***data attribution*** concerns through study design are outlined in Table 2, and CTTI suggests that those involved in clinical trial design and conduct emphasize these approaches, striving to implement them with patient input.[‡‡]

In addition to digital technology selection and protocol design strategies that promote the likelihood of correct data attribution, numerous technical approaches exist ranging

[††] Data quality may also be compromised after the point of collection, during transmission and storage. For suggestions to address these issues, see CTTI's considerations on data integrity and study monitoring. Specific considerations for sponsors designing trials that use digital technologies to generate data to support a marketing application to FDA, including considerations on source data and audit trails, may be found here.

[‡‡] CTTI has issued recommendations for effectively engaging patient groups in clinical trials that are intended to support sponsors' efforts to solicit this input.

from simple password prompts through biometric authentication, to trend analyses and clustering techniques. CTTI suggests using these strategies discerningly, recognizing that such approaches may impact participation if too burdensome. To ensure that decisions regarding the use of technical approaches are effective to mitigate the risk of incorrect data attribution, without introducing unintended consequences, CTTI suggests that sponsors engage participants in decisions regarding the inclusion of technical approaches to ensuring data attribution.[§§] Appendix 1 lists technical approaches currently being used to ensure correct data attribution.

4. Identify acceptable ranges and mitigate variability in endpoint values collected via digital technologies.

CTTI suggests ensuring that variability in endpoint values collected via digital technologies is well understood and appropriately minimized during trial design.

Variability in endpoint values (including variability resulting from data quality issues) is a challenge for all clinical trials and is not unique to the use of digital technologies for data capture. All trials should seek to eliminate sources of variability in data quality, for example, by reducing variability in measurements. However, the incorporation of digital technologies also introduces new potential sources of data variability, primarily due to capturing data in free-living conditions outside of the clinic.

Protocol design approaches to minimize variability in data quality are outlined in Table 2. CTTI also suggests collecting applicable ***metadata***, where appropriate, to allow statisticians and data scientists to identify data that may be irregular, inconsistent, or confounded during data cleaning prior to analysis.

5. Minimize missing data.

To gather the most complete data possible, every effort should be made to minimize missing data.

Missing data, even from participants in a randomized trial, can bias the comparison of treatment groups. Every effort should be made to minimize loss of data for any reason, as substantial data loss can impact analysis and prevent determination of representative conclusions. When using digital technologies for data capture, a multi-pronged approach to preventing missing data is optimal, with efforts focused on:

1. Optimizing trial design,
2. Ensuring technical approaches are in place to eliminate any technology- or transmission-related causes of missing data, and
3. Pilot testing to identify any unanticipated causes of missing data.

Aspects of trial design that limit the likelihood of missing data should be a critical objective in the development of all study protocols.[3, 4] Table 2 outlines strategies that

[§§] CTTI has issued recommendations for effectively engaging patient groups in clinical trials that are intended to support sponsors' efforts to solicit this input.

CTTI suggests sponsors use during trial design to limit missing data specifically when digital technologies are used for data capture.

Some wearable technologies and remote sensors transmit data to a companion application (app) prior to transmission to the centralized study data set. CTTI suggests that, if a sponsor selects a digital technology that relies on a companion app for data transfer, the sponsor should ensure that this app is capable of pairing with the wearable technology or remote sensor with minimal risk of data loss. In addition, for those technologies that connect to manufacturers' servers before providing data to the sponsor via a third-party interface, appropriate syncing strategies are critical as digital technologies may limit or lose data after periods of non-syncing (Click here for CTTI's detailed considerations on digital technology selection and here for CTTI's considerations on ensuring data integrity, including during data transfer).

THIS CONSIDERATION IN ACTION
Case Example: Optimizing Data Quality and Participant Privacy

6. Plan appropriately for the statistical analysis of data captured using digital technologies.

Statistical principles for clinical trials are well described,[2, 5] and implementing the above considerations to (1) include biostatisticians and data scientists in protocol development and (2) ensure the collection of high-quality, attributable data should support the generation of data sets suitable for meaningful analyses.

When the research question demands that digital technologies are used to collect large data sets, sponsors should ensure access to both suitable data platforms to handle these data and the necessary expertise to manipulate it at different levels of granularity.

Regardless of the anticipated size of the data set, sponsors should consider conducting small-scale feasibility studies prior to finalizing their protocol design to ensure familiarity with the nature of the data outputs from the digital technology(ies) and the correct analytical approach. Statistical analysis plans should be fit for purpose and developed prior to trial initiation. Since the use of digital technologies creates opportunities to analyze continuous time-series data as opposed to measurements collected at discrete study visits, the overarching recommendation that biostatisticians be involved in planning analyses during protocol development is particularly important. This will help ensure that these more complex analytic techniques are considered from the beginning and throughout protocol design.

7. Establish industry-wide standards to drive the successful scaling and more rapid acceptance of clinical trials using digital technologies for data capture.

Using digital technologies in clinical trials generates ***structured data*** sets. ***Structured data*** can be easily stored, queried, recalled, analyzed, and manipulated by machines. However, standards are required to promote the exchange of information derived from

different studies, speed development of the scientific bases of the technology, allow investigators and digital technology manufacturers to invest time and money with an assurance that the results will be universally useful, and increase the end user's confidence in the output of the technology.

Stakeholders, including digital technology companies and sponsors who may produce competing tools or develop competing therapies, should collaborate in a pre-competitive space to set these standards. The establishment of standards will facilitate comparison of results from studies using different digital technologies.

CTTI suggests establishing industry-wide standards related to:

1. Terminology, for example, the definition of "***raw data***" and "analysis-ready data;"
2. The collection and reporting of data captured by digital technologies, including metadata;
3. Transparency of information related to digital technology specifications, calibration, and verification bench-tests, and
4. Transparency requirements for the development of algorithms used to convert the data into physiologically and medically useful endpoints.

Section III: Data Management

The capture of clinically relevant outcomes from digital technologies necessitates the management of the integrity, security, usability, and availability of data captured by these apps, sensors, or digital products. Data management consists of several processes for which sponsors are ultimately responsible, but which may be carried out by, or in partnership with, contract research organizations or information technology (IT) service providers such as digital technology manufacturers and third-party data platforms. In this section, CTTI provides considerations for sponsors that 1) support compliance with relevant regulations and guidances and 2) highlight specific data management tasks that should be internally reviewed or discussed with potential partners prior to entering into an outsourcing agreement.

1. Ensure the authenticity, integrity, and confidentiality of data over its entire lifecycle.

Data Authenticity

Data authenticity means that the data are what the originator claims the data to be. For outcomes data captured by a digital technology to be authentic, the data should display all of the characteristics outlined in the following table.

Data Characteristic	Supporting CTTI Considerations
Precisely and accurately represent what the data claim to be measuring; e.g., heart rate (bpm) or activity (steps/day)	See considerations on digital technology selection, specifically verification and validation
Be correctly attributed to the intended participant	See considerations on data attribution
Contain metadata indicating the source of the data and a UTC time stamp	See considerations on audit trails
It should also be possible to demonstrate that the data have not been corrupted following creation	See considerations on data integrity and audit trails

Data Integrity

For data to have ***integrity***, the data cannot be modified or corrupted in an undetectable and/or unauthorized way during the generation and flow of the data. CTTI suggests addressing the integrity of data generated using digital technologies both during trial planning and conduct. This should include clarifying, at each step during the data lifecycle,

1. Who is responsible for the data, and
2. Who is accountable for data integrity.

Strategies for promoting and protecting data integrity during critical steps in the data lifecycle are outlined in Table 3. To support the assignment of responsibility for the data and accountability for data integrity, CTTI has created a data flow diagram outlining the typical passages of data from collection by a digital technology to the final analysis data set.

Confidentiality

To maintain confidentiality, study participants should be informed of and consent to the ways in which their identifiable, private information will be handled. Private information is "information about a behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not make public (e.g., a medical or education record)."[6] Care should be taken to identify all HIPAA identifiers that a digital technology collects, even if they are not the focus of the protocol. For example, a sponsor interested in analyzing steps per day should investigate whether the selected technology also collects data such as geographic location. CTTI suggests that sponsors develop strategies for maintaining the confidentiality of data collected by digital technologies in concert with developing strategies for protecting participants' privacy.

Approaches to protecting privacy and maintaining confidentiality should be proactive and preventive. Privacy and confidentiality should be considered when planning data collection approaches and should drive decisions around data access and security protocols. The collection of personally identifiable information should be minimized (see CTTI considerations on data collection), and the purpose of its collection and use should be clearly communicated to participants in the informed consent. The informed consent —and the HIPAA Research Authorization Form, where appropriate—should also clearly delineate who will have access to the participant's information and under what circumstances it may be shared (see CTTI considerations on data access). The Office of the National Coordinator for Health Information Technology (ONC) has issued an updated Model Privacy Notice (MPN) intended to help developers clearly convey information about their privacy and security policies to their users.[7] In addition to providing the structural basis of a privacy policy, this standardized framework may also be a valuable resource to inform discussions about privacy and security approaches between sponsors and digital technology manufacturers.

2. Optimize data accessibility while preventing data access from unauthorized users.

Sponsors require access to study data to monitor the conduct and progress of their clinical investigations. In order to meet their responsibilities for protecting human subjects and ensuring the integrity of the data, site investigators and their delegates should have access to data generated by trial participants (see CTTI considerations on study monitoring). Data generated from digital technologies should also be easily accessible for retrieval throughout the records retention period, including for FDA during an inspection. Regulations require that access to electronic records be limited to authorized individuals,[8, 9] and CTTI suggests that the security principles of "***need to know***" and "***least privilege***" be applied when determining access rights and privileges. These rights and privileges should also be regularly reviewed and updated to prevent risks to the integrity, privacy, and confidentiality of data generated by digital technologies.

3. Ensure that access to data meets your needs prior to contracting an electronic service vendor.

Data collected by digital technologies will often flow through the technology manufacturer's server prior to being made available to the sponsor (see data flow diagram). With regard to data access, sponsors should consider two factors before entering into an outsourcing agreement with a digital technology manufacturer:

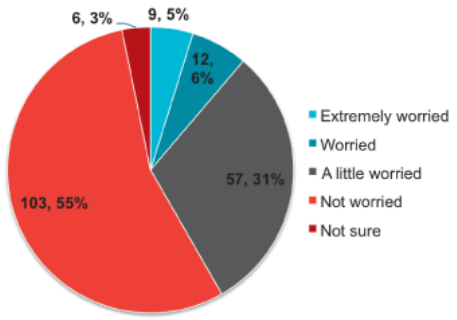
1. How the data generated by the digital technology may be accessed and used by the manufacturer, and
2. What data will be provided by the manufacturer to the sponsor.

a. Informed consent requires transparent knowledge of how all data captured may be used.

Data cannot be owned in the same way as objects or other personal property, and data may be readily commoditized. As such, sponsors should ensure that they are aware of and comfortable with the ways in which data generated by digital technologies used in their trials may be accessed and used by the technology manufacturer and any additional third parties. This information should be clearly stipulated in the outsourcing agreements, and a clear accounting of which parties will have access to each level of data should be included in the informed consent and HIPAA research authorization form. CTTI suggests that sponsors engage potential participants in these discussions regarding access to and use of data by external entities to reach a decision that ultimately meets patients' levels of comfort and expectations of privacy.

In a 2017 CTTI Survey of 193 individuals in research database:

Over half of potential participants reported not being worried that others besides the research team would be able to see their data collected by the digital technology.



In instances where sponsors prefer to prohibit external access to data generated by digital technologies, manufacturer-generated software may allow sponsors to communicate with and access data directly from the technologies used in the study, removing manufacturers from the data chain (see data flow diagram).

Sponsors may also grant electronic service providers access to data collected by digital technologies to complete processing steps such as de-duplication, filtering, and parsing. Though CTTI suggests that these steps be automated wherever possible, if data access is required, the considerations noted above for digital technology manufacturers also apply.

CTTI advises that sponsors proceed with caution and obtain participant input when determining how data generated by the digital technology may be accessed for secondary use. However, CTTI maintains that collaboration is critical to advancing the development of technology-derived novel endpoints.[10] To promote collaboration through data sharing, CTTI suggests that all stakeholders reference the Institute of

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Case Example: Using Remote, Smartphone Based Data Collection to Broadly Share Health Insights

Medicine's 2015 report, "Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk".[11]

b. Sponsors should not assume that the technology manufacturer will provide them with all of the data collected by the digital technology.

Rather, prior to selecting a digital technology for data capture (see CTTI considerations on digital technology selection,the digital technology selection framework, and Recommendations for Selecting & Testing Digital Health Technologies), sponsors should consider:

1) Whether they will have access to the raw data generated by the mobile technology,
2) To what levels of processed data (see Table 1) they will have access,
3) Whether they will have access to the algorithm(s) used to process the data, and
4) In what format the data will be provided.

There are a number of reasons that sponsors may have limited access to the data generated by digital technologies and the algorithms used to process it. First, raw, continuous data often require the transfer of huge data sets that may not, themselves, be clinically meaningful. Second, there may be intellectual property (IP) associated with the algorithms used to process the raw data to generate clinically meaningful measures. Finally, even in cases where the algorithms are not provided to protect IP, manufacturers may be concerned that the algorithms could be derived if they provide both the raw data and various levels of processed data. Regardless of the rationale for limiting access, sponsors should ensure that the level of data access granted by the digital technology manufacturer is sufficient to meet their needs for the trial. At a minimum, sponsors should be able to demonstrate the ***verification*** and ***validation*** of the digital technology. The data provided should also be sufficient to support a marketing submission or application to FDA (see CTTI's considerations on making data available to the FDA and Recommendations for Interacting with Regulators).

Digital technology manufacturers may provide data generated by the technologies in standard formats, such as HL7®. Such standard formats facilitate the exchange, integration, and sharing of data, in turn promoting interoperability. In cases where digital technology manufacturers provide data in non-standard formats, including data provided in a proprietary format, sponsors should inquire whether they will have access to decoders and interpreters to allow data use by standard software packages.

4. Apply an end-to-end, risk-based approach to data security.

*An **end-to-end**, **risk-based approach** to data security should be applied to protect participants' privacy and the **confidentiality** and **integrity** of their data.*

Using digital technologies for data capture places new demands on security solutions, as data must be secured both on the technology itself and during the transfer from the digital technology. This poses additional challenges, as the data transfer likely occurs over Wi-Fi, Bluetooth, cellular, and data networks over which neither electronic service vendors nor sponsors have any control. In addition, data generated by digital technologies may also pass through apps on associated smartphones, manufacturer servers, and through additional steps of processing not required by data captured in a traditional CRF or eCRF (see data flow diagram). As such, CTTI suggests that solutions intended to secure data captured using digital technologies be developed with the entire infrastructure in mind. While it is beyond the scope of these considerations to suggest specific security solutions, Appendix 2 lists approaches to securing data generated by digital technologies that are being successfully used at the time of publication.

There are many benefits associated with using a ***risk-based approach*** to securing data generated by digital technologies. These include increasing efficiency, promoting a proactive approach to security, and demanding comprehensive planning prior to solution implementation. This, in turn, increases the likelihood that 1) solutions are comprehensive and address the entire infrastructure and 2) sufficient resources and personnel are available to successfully implement the necessary security solutions. In addition, solutions addressing data security on the digital technology and during transfer from the technology can result in increased participant burden. Taking a ***risk-based approach*** to ensure these solutions are no more burdensome than necessary may mitigate risks of poor participant compliance with the digital technology and help optimize data collection (see CTTI considerations on data collection).

When taking a ***risk-based approach*** to data security, sponsors should expect outsourced electronic service vendors to conduct comprehensive security assessments prior to developing their risk-based security solutions. Assessments should include these six domains, which also apply to sponsors implementing their own security solutions: dependencies on outside providers, systems, procedures, people, policies, and applicable regulations. Prior to signing an outsourcing agreement with an electronic service vendor, as with any outsourced information system, the sponsor and relevant audit or compliance teams should review and evaluate the vendor's security systems.

5. Monitor the quality of data captured by digital technologies centrally through automated processes.

When digital technologies are used for data capture, existing guidance describing strategies for monitoring still applies.

FDA regulations require sponsors to monitor the conduct and progress of their clinical investigations.*** When digital technologies are used for data capture, existing guidance describing strategies for monitoring activities still applies.[12] However, the use of these technologies may help facilitate the use of centralized monitoring techniques and promote commensurate improvements in quality and efficiency.

Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians) at a location other than the clinical investigation sites.[12] CTTI suggests that when digital technologies are included in the protocol, the quality—specifically the completeness, consistency, and correctness—of the data captured is monitored centrally. To maintain data security and privacy and to promote efficiency, programming and algorithms should be the preferred techniques for verifying data quality, with programmed alerts sent when potential issues are identified.

Where appropriate, CTTI also encourages sponsors to consider a centralized approach to monitoring data collected by digital technologies to track other aspects of trial conduct and progress. Such aspects may include identifying higher risk sites in need of more intensive monitoring or training, safety monitoring, and verifying critical source data remotely.

Factors to consider when developing a monitoring plan are well described in existing guidance.[12] In addition, CTTI suggests considering more intensive monitoring early in the process to identify any unanticipated technical issues that require resolution before they compromise the study when digital technologies are used for data capture. Moreover, as monitoring should not only detect deficiencies in trial conduct but also strive to correct them, data monitoring plans should clearly state who is expected to take appropriate action in response to potential issues identified. This is particularly important when automated processes are being relied upon as part of the monitoring plan.

6. Ensure that site investigators have access to data generated by their participants.

In order to meet their responsibilities with respect to protecting human subjects and ensuring the integrity of the data from clinical investigations, site investigators, and their delegates, where appropriate, should be able to review participants' data in a human readable form. This may occur through a read-only ***Application programming interface (API)*** in order to provide a way of examining and generating reports of

*** 21 CFR 312.50 requires a sponsor to, among other things, ensure "proper monitoring of the investigation(s)" and "that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND." 21 CFR 812.40 states that sponsors are responsible for, among other things, "ensuring proper monitoring of the investigation, …" See also 21 CFR 312.53(d), 312.56(a), 812.43(d), and 812.46.

participant data without compromising data integrity. Given the volume and complexity, particularly of raw data generated by digital technologies, CTTI suggests that these read-only interfaces take the form of a dashboard, with data summarized at the appropriate levels of detail for investigators' needs.

Section IV: Protocol Design and Execution

CTTI recognizes that the decision to use digital technologies for data capture may necessitate additional protocol design and execution considerations not addressed elsewhere in these considerations. This section provides considerations for sponsors to support 1) developing protocols that leverage the benefits of digital technologies and 2) identifying the requirements for executing these protocols from a logistical standpoint.

Overarching considerations include ensuring that patients are engaged in trial design from the outset,††† and that they continue to leverage the scientific principles and resources that have informed the successful design of traditional clinical trial protocols. CTTI also suggests that the unique logistical considerations and associated SOPs pertaining to the use of digital technologies for data capture outside of the clinic be considered with a multi-stakeholder mindset, including from the perspective of the regulator, site, investigator, coordinator, and study participant, prior to launching the trial.

††† CTTI has issued recommendations for effectively engaging patient groups in clinical trials that are intended to support sponsors' efforts to solicit this input.

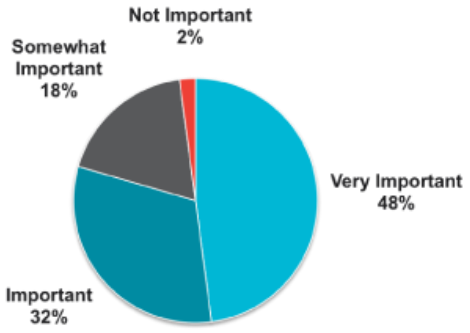
1. Data sharing decisions should be driven by safety and trial integrity.

Safety and trial integrity should be paramount when considering sharing data with study participants in real-time.

Using digital technologies for data capture raises new questions about whether data should be shared with study participants in **"*real-time*."** Displays embedded in digital technologies or in connected apps offer study participants potential access to outcomes data during the trial. Sponsors developing protocols leveraging digital technologies for data capture must weigh study participant preferences and expectations for viewing data in ***real-time*** with concerns regarding potential changes in patient behavior resulting from viewing their own outcome data, possible unblinding, and misinterpretation of data in isolation.

In a 2017 CTTI Survey of 193 individuals in research database:

Only 2% of potential clinical trial participants feel it is "not important" to see information collected by a digital technology they are asked to wear.



67% of respondents preferred to see their information at least weekly.

Conclusion: Sponsors should include some mechanism of data sharing into protocols. using digital technologies.

Study participant safety is always the priority, and this should remain a central tenet of protocol design when digital technologies are used for data capture. For both ethical and economic reasons, preservation of trial quality and integrity is also critical when considering whether to, and how to, share data with study participants in real-time.

CTTI suggests that study participants be engaged in trial design to support decision making around sharing data in real-time, and this resource can help support this shared decision. CTTI also suggests that, regardless of whether data are shared in real-time, investigators should consider sharing summarized data with each individual at the completion of their enrollment, as well as offering study participants the opportunity to learn the overall results of the trial at the end of the study.

When sharing outcomes data in ***real-time*** is not appropriate for a particular study, CTTI suggests that sponsors consider sharing other, low-risk information that may be readily available when digital technologies are used for data capture. For example, sharing compliance data such as digital technology wear-time may render a more transparent and engaging trial for study participants without compromising the integrity of the trial or sharing data that cannot be readily interpreted by all study participants.

2. Communication and transparency with participants regarding safety monitoring is critical.

Study participants should be well informed regarding the level of safety monitoring, if any, that will occur when they use/wear their digital technology. Also, the information about the level of safety monitoring must be described in the informed consent.[‡‡‡]

Using digital technologies for remote data capture offers the possibility of collecting more timely and complete safety information about an investigational medical product. In comparison to traditional trials, however, the use of digital technologies also raises two new potential issues related to safety signals that sponsors should consider:

1. Safety signals not previously observed using traditional protocol design and monitoring may be captured as a result of using digital technologies in the field.
    - For example, if a protocol requires study participants to wear an ECG/EKG monitor remotely, it may be possible to detect arrhythmias that would previously have gone undetected. A study participant wearing an actigraphy technology may fall, and these data are recorded immediately rather than being reported by the study participant at the next study visit.
2. Data collected and observed by the study participant, in the absence of context provided by clinicians, may lead to difficulty distinguishing between normal data and a possible adverse event.
    - For example, a study participant wearing a heart rate monitor in the field may record an increased heart rate, but in the absence of additional contextualizing information, it may be impossible to know whether this event is attributable to exercise or a drug-induced arrhythmia.

When a digital technology is not cleared or approved by the FDA for the labeled use of detecting the safety signal(s) or adverse event(s) of interest, the optimal strategy for addressing data of concern will likely vary with the technology, measure, resource constraints, study participant population(s), and/or study participant expectations. If a digital technology is intended to be used to detect a safety signal or adverse event, this specific measure should be valid and well understood in the context of use in the trial.

When a digital technology is relied upon to accurately detect a prespecified safety signal, measures recorded outside of acceptable limits should be directly communicated to the investigators and sponsors via automated processes and algorithms. Any actions to be taken following the detection of a safety signal or adverse event by a digital

[‡‡‡] For more information, see 21 CFR 50.25(a)(1).

technology should be prespecified in the protocol and clearly communicated to study participants.

CTTI suggests that study participants be included in decision-making on how to handle responses to safety signals and adverse events detected remotely by digital technologies. Specifically, consider to whom this information may be communicated beyond the study investigator and required safety reporting, such as the study participant, an emergency contact, and/or a healthcare provider. Also, what, if any, immediate action will be taken in response to safety events detected in real time.

CTTI suggests that sponsors look to the extensive literature on, for example, addressing incidental findings on MRI scans in clinical trials to determine how to handle ***atypical data***.[13, 14] To support sponsors seeking to optimize their approach to managing ***atypical data***, including data captured outside of the intended use of the technology, CTTI has created a framework that defines a variety of options for addressing unanticipated data and describes the implications and applications of these options.

Regardless of the level of safety monitoring that will occur when study participants use/ wear their digital technology, this information should be clearly communicated both:

1. At enrollment, and
2. Throughout the trial.

Study participants should have a clear understanding of whether and how they are being monitored for their safety during the trial and what, if any, measures may be in place to detect, communicate, and act upon any ***atypical data*** captured by their digital technology(ies)**.** This information should also be included in the informed consent.

3. Define and test processes for the implementation, operation, and maintenance of digital technologies in the field prior to launching the trial.

To optimize study participant acceptance and adherence with the trial requirements for digital technology management, CTTI suggests that study participants be engaged in technology selection and with the needs, preferences, and abilities of the study participant population in mind. (Click here for CTTI considerations on digital technology selection.)

THIS CONSIDERATION IN ACTION
Case Example: Feasibility Testing to Promote Successful Inclusion of Digital Technologies for Data Capture

FDA regulations require that all users of digital technologies for data capture, including those with digital technology management responsibilities, have the education, training,

and experience to perform their assigned tasks.[§§§] CTTI stresses the importance of developing effective approaches to prepare operators, including study coordinators and trial study participants, to correctly use the digital technology(ies) for activities including data collection, data transfer, and digital technology charging.

A sponsor's approach to prepare study participants and coordinators to use the digital technologies correctly should be both role-based and fit for purpose. Such approaches could include creating materials, including videos, with instructions and demonstrations on using the technologies; embedding instructions within companion digital apps; and taking a tiered approach to training on correct use of the digital technology.

Finally, CTTI suggests that a robust digital technology management plan be developed during the pre-trial phase, with feasibility assessments conducted where appropriate. While sponsors are ultimately responsible for digital technology management in the field, it should be clear who is assigned the task of ensuring different aspects of digital technology management. Standard operating procedures (SOPs) should be developed and in place for the operational and user issues that may arise.

Snapshot: One Sponsor's Approach to Digital Technology Training

► Step 1: Simulate participants' and coordinators' experience using the digital technology in the sponsor's innovation lab.

► Step 2: Develop role-based education and training materials incorporating lessons learned from the simulation.

► Step 3: As part of the pre-trial phase, conduct hands-on training with investigators and coordinators at two pilot sites. Ask site staff to then use the digital technologies in the presence of the trainer and identify any issues with technology use and any outstanding questions the site staff have.

► Step 4: Refine role-based education and training materials applying lessons learned from experiences at the pilot sites.

4. Have a plan in place for digital technology failure.

To minimize the burden on study participants and site staff, and to preserve the integrity of the trial, plans for monitoring and responding to technology failure should be in place before administering digital technologies to study participants.

If a digital technology stops working, is not performing as desired, or is not meeting target expectations due to defects, a replacement or fix should occur as soon as possible in order to minimize the impact of the technology failure on the study objectives. (Click here for CTTI considerations on managing missing data, including for data missing due to digital technology failure). However, CTTI suggests that

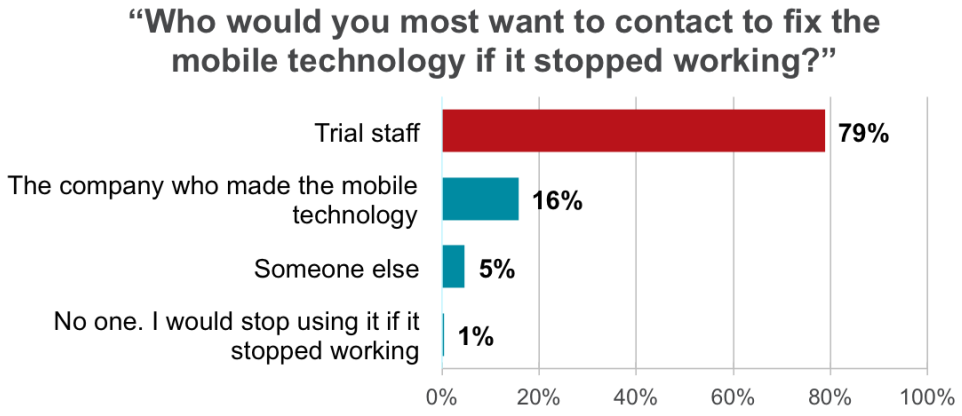
[§§§] For more information, see Code of Federal Regulations, Title 21, Chapter I, Subchapter A, Part 11, Subpart B, §11.10(i).

every effort be made to mitigate the risk of digital technology malfunction in advance of trial initiation. Specifically, digital technology selection should be informed by the failure rate of digital technologies in the field, feasibility studies should be conducted as appropriate, and technologies should be tested prior to distribution among study participants.

Designated parties assigned the various tasks associated with detecting and managing digital technology failure in the field will likely vary depending on the protocol, technology manufacturer, in-house capabilities of the sponsor, study participant population, and study sites. The roles, responsibilities, and expected actions should be clearly articulated in SOPs developed during the pre-trial phase.

In a 2017 CTTI Survey of 193 individuals in research database:

79% of potential participants would prefer to contact trial staff should the digital technology they are expected to use stop working.



While CTTI suggests engaging potential participants in a specific trial in decisions about digital technology management, when sponsors opt to establish their systems for technology management to include trial sites, they should ensure that these sites are adequately trained and resourced to provide such activities.

To effectively manage digital technology failure in the field, there should be processes in place to detect technology malfunction. CTTI suggests that this be an automated process. Examples of such processes include algorithms for detecting digital technology failure based on trends and/or utilizing predictive models that determine when batteries will likely stop working. In each of these instances, the automated process should trigger an alert when failure is imminent. Systems for providing support and solutions to participants experiencing digital technology malfunction or failure should be in place prior to the launch of the trial. Such systems could be established

either though the sites or via a centralized resource such as a participant call center. Where technologies cannot be easily fixed in the field, they should be quickly replaced. CTTI suggests that the sponsor have an inventory of extra digital technologies that can be promptly shipped directly to study participants, or that each site be provided with replacement technologies to provide to study participants, in the case of digital technology failure. This approach should extend to study participants using their own technologies if no alternate strategies to ensure continuity of data collection in the event of digital technology failure are in place. Finally, strategies for managing technology failure should include processes for determining whether it is appropriate to merge data from two different digital technologies for a single trial study participant, if needed.

5. The considerations that inform adaptive designs in a trial using digital technologies are the same as for traditional studies.

An ***adaptive design*** clinical trial is one that includes a prospectively planned opportunity for modification based on analysis of interim data from study participants in the study.[15, 16] While the use of digital technologies for data capture may provide new opportunities to generate information that can be used to trigger a design modification—or opportunities to trigger a design modification sooner or more quickly—the considerations that inform whether the trial is designed with adaptive features are the same as for traditional studies. CTTI suggests that sponsors planning to use digital technologies for data capture rely on the extensive literature and guidance on ***adaptive design*** in clinical trials if they believe that such a design may improve the quality or efficiency of the trial.

Section V: FDA Submission and Inspection

All CTTI DHT Digital Technologies considerations are intended to support the use of digital technologies in FDA-regulated clinical trials. This section addresses considerations unique to FDA submission, specifically for data collected in support of an application for the marketing approval of a medical product conducted under 21 CFR parts 312[17] and 812.[18] **Considerations in this section cascade from a critical, overarching principle that applies to all trials, not just those using digital technologies: that sponsors engage with the FDA early in the process of trial design.** The most appropriate strategy for collecting and sharing data with the FDA will likely be both trial-specific and require an open dialogue with the FDA prior to and during trial conduct. When preparing data generated by digital technologies for FDA submissions we recommend:

1. Sponsors should ensure that trials conducted using digital technologies for data capture may be readily reconstructed.

FDA inspectors review both source data and ***audit trails*** to ensure adequate protection of the rights, welfare, and safety of study subjects, as well as the quality and integrity of the trial data. As such, it is critical that sponsors create and maintain the appropriate records in such a way that FDA may access, inspect, and copy them in accordance with

the relevant regulations.[****] Several FDA guidance documents exist to support sponsors in fulfilling these obligations,[19-21] and CTTI offers suggestions herein to assist sponsors as they extend and apply these guidances to data captured by digital technologies.

Source Data

Source data include all information in original records and certified copies of original records detailing clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation. When digital technologies are used for data capture, CTTI suggests that sponsors define ***source data*** as the first level of data that is both clinically relevant to the trial and interpretable. For example, in a trial using a heart rate monitor to capture data to assess heart rate variability, sponsors may choose to define heart rate (beats/min) as the source data.

Applying this approach requires that sponsors not only select digital technologies that have been appropriately ***verified***, but that all algorithms applied to the raw data to generate the source data have been ***validated***. Documentation of the verification and validation processes should be available (see CTTI's considerations on making data available to the FDA and Recommendations for Interacting with Regulators).

Data Origins

A ***data element*** is a recorded assessment of a single observation associated with a subject in a clinical study. When digital technologies are used for data capture, CTTI suggests that the same principle for defining source data be applied to defining the ***data element***. Specifically, that the smallest interpretable unit of a clinically relevant observation captured for a subject by the technology be defined as the ***data element***.

FDA guidance states that, for the purposes of record keeping, audit trail, and inspection, each ***data element*** should be associated with an authorized data originator.[19, 21] When digital technologies are used for data capture, data elements will usually, but not always, be associated with one of the following originators:

1. The study participant. When digital technologies are used for active data collection, the study participant is the data originator; for example, when a study participant engages in an interactive app-based test.
2. The digital technology. When digital technologies are used for passive data collection, the digital technology is the data originator; for example, capturing activity, heart rate, or blood glucose data without any human intervention.

Existing guidance describing the maintenance of lists detailing authorized data originators and capturing data element identifiers continues to apply when digital technologies are used for data capture.[19, 21]

Source Documentation

[****] See 21 CFR Parts 312.57, 312.58, 312.62, 312.68, 812.140, and 812.145.

When digital technologies are used for data capture, CTTI suggests that the earliest practically retainable record of the data is defined as the ***source document***.[††††] Typically this means that the source will be the digital technology manufacturer's servers, or the server of another electronic vendor or CRO (see data flow diagram). CTTI warns against using digital technologies or their companion apps for long-term data storage in order to protect and promote data security (see CTTI considerations on data security). Only one source should be defined for any data element.

Audit Trails

Audit trails to ensure data integrity through the documentation of all changes to all pertinent data, including data generated by digital technologies during clinical trials. Audit trails in electronic systems involve computer-generated date-time stamps that capture all details pertaining to the collection of clinical trial data, such as creation, modification, or deletion of data. Sponsors should ensure that audit trails are implemented to track the data (including any modifications made to the data) from the point of creation in the digital technology to the ***durable media*** and this audit trail information should be recorded in the durable media. [‡‡‡‡]

Audit trails should include the date and time that each data element is captured/saved, as well as the originator of each data element. This information, combined with the ID of the study participant (where they are not the originator), constitutes the data element identifier. Systems should not permit edits to the data element identifier. Sponsors should maintain a list of individuals with authorized access privileges to modify trial data captured by digital technologies (see CTTI considerations on the protection of data from unauthorized users). Audit trails should also capture the date and time of any data transfer (see data flow diagram). When modifications to data captured by digital technologies are made, the audit trail[§§§§] should detail the date and time, the identification of the user making the change, the new value without obscuring the original value, and, where appropriate, the reason for the change. Audit trails should extend to pertinent ***metadata*** and all signatures.

Date and time stamps in the audit trail ensure that the trial can be reconstructed, illustrating the sequence of events and supporting the integrity of the data captured. They also act as deterrents for data falsification and tampering. To ensure date and time stamps are correct for all time zones in which digital technologies are being used for data capture, CTTI suggests using Coordinated Universal Time (UTC). This is particularly important when digital technologies are used in clinical trials, as data

[††††] This is consistent with current opinion of the EU GCP Inspectors Working Group. See Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials.

[‡‡‡‡] These individuals should be restricted to clinical investigators and delegated study personnel at the site who are authorized to make changes to the data.

[§§§§] For example, blockchain.

capture is not restricted to study sites, and study participants may travel during the study, including across time zones.

CTTI suggests that audit trails for data captured by digital technologies begin when the data first reaches ***durable media***, creating the first practically retainable record of the data; i.e., at the source. CTTI suggests that digital technologies not be considered durable media under most circumstances. Audit trails should be made available in human-readable form to FDA at the time of inspection. At a minimum, audit trail documentation must be retained for the same length of time required for the subject's electronic records, and should be available for FDA to review and copy during this period.[*****]

Given the volume of data generated by clinical trials using digital technologies for data capture, it is unlikely that spot checks of vast audit trails by inspectors will be valuable. Therefore, while sponsors should ensure that they have a complete and comprehensive audit trail as described above, CTTI suggests that sponsors consider supplementing an audit trail that documents every single transaction associated with pertinent data captured by the digital technology with summaries that may be more easily interpreted. For example, sponsors may create a dashboard that summarizes key information in the audit trail, including digests of changes to the data and summary data describing data transfers within the system.

2. Source data should be the primary data resource provided to FDA during inspection.

When documentation of ***verification*** and ***validation*** processes are available to FDA inspectors, it is not necessary to provide ***raw data*** to support the ***source data*** captured using a digital technology. However, where ***metadata*** are required to interpret the clinical meaningfulness of the source data, these ***metadata*** should also be available to inspectors. It is critical that both the source data and any supporting metadata are attributable, legible, contemporaneous, original, and accurate (ALCOA).

CTTI recognizes that sponsors may choose to archive raw data for their own purposes (i.e., for use as test data for future algorithms, etc.), CTTI suggests carefully weighing the future value of such data against the maintenance and risks of storing and securing potentially enormous data sets.

Figure 1 summarizes the data and supportive documentation CTTI suggests making available to FDA inspectors.

3. When digital technologies are used for data capture, sponsors should provide supporting material for their claims as part of their marketing application to FDA.

A wealth of resources currently exist to support the submission of study data to FDA's Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH).[22] Although

[*****] See 21 CFR 312.58, 312.68 and 812.145.

it is beyond the scope of these considerations to issue data standards, CTTI recognizes that the development of such standards is critical for more rapid acceptance and successful scaling of clinical trials using digital technologies for data capture. To this end, CTTI strongly suggests establishing industry-wide standards (see CTTI considerations on data standards).

When considering supportive documentation for submission to FDA as part of the marketing application, CTTI suggests that sponsors include robust supporting material demonstrating the digital technology verification and validation processes, as well as the clinical meaningfulness of the digital technology-derived endpoint††††† to support their claims. As with submissions for all trials, the filters used to "clean" the data set and statistical models used to interpret the data should also be included in the data analysis plan. Figure 2 summarizes the supportive documentation CTTI suggests that sponsors include in their submissions to FDA.

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