



## DIGITAL HEALTH TRIALS

### Developing Novel Endpoints Generated by Digital Health Technology for Use in Clinical Trials

Digital health technologies (DHTs) can capture measures as clinical trial participants go about their daily lives. These measures can be used as novel endpoints, defined as (1) new endpoints that have not previously been possible to assess or (2) existing endpoints that can be measured in new and possibly better ways. Because novel endpoints have the potential to provide high-quality data pertaining to outcomes that are meaningful to patients while enabling broader, more accessible trials with reduced barriers to participation, CTTI created the following set of recommendations (described in more detail below).

The following recommendations are an update to the 2017 Digital Health Trials Novel Endpoints Project recommendations and are based on advancements in the digital health trials space. These recommendations focus on driving novel endpoint use by sponsors and review by regulators for greater acceptance across the clinical trial enterprise.

#### RECOMMENDATIONS OVERVIEW

1. Focus on measures that are meaningful to patients and clinically relevant
2. Identify key endpoints by assessing and meeting the needs of each stakeholder
3. Select the technology after selecting an outcome
4. Engage with regulators early and often
5. Include digitally-derived endpoints in early phase clinical trials and observational cohort studies to demonstrate they are fit-for-purpose
6. Think critically about how to optimally position novel digitally-derived endpoints in interventional trials
7. Promote the sharing of knowledge and lessons learned regarding the development of digitally-derived endpoints

## Potential Benefits of Using Digitally-derived Novel Endpoints in Clinical Trials\*



### OBTAINING BETTER, MORE RELIABLE INFORMATION

- ▶ Provides a broader picture of treatment effects and how patients function
- ▶ Enables more inclusive & generalizable trials
- ▶ Supports better regulatory & subsequent reimbursement decision making



### CONDUCTING MORE PATIENT-CENTRIC RESEARCH

- ▶ Healthcare can be near or in the patient's home
- ▶ Endpoints that matter and are meaningful to patients are used in clinical trials
- ▶ Burden on the participant is reduced, which increases trial participation & retention



### MOVING AT HIGHER EFFICIENCY & SPEED

- ▶ Recruitment is faster and retention is better
- ▶ Data collection is more frequent, continuous, and/or useful
- ▶ Burden on site and staff resources is decreased

*Please note: the following recommendations for developing a novel endpoint are not necessarily in chronological order; many of these actions can be accomplished in parallel and throughout the duration of medical product development.*

## RECOMMENDATIONS

### 1. Focus on measures that are meaningful to patients and clinically relevant<sup>1</sup>

When selecting an outcome measure for development the approach should include both the patient and clinician perspectives, as a meaningful measure should show treatment benefit as well as clinical benefit.

Appropriate selection of the measure remains critically important and cannot be overlooked, especially as the field advances. When choosing measures, sponsors should consider the scientific question at hand and whether a measure addresses an unmet need for an aspect of the disease or illness that, if relieved,

\* The term "clinical trial" is used here to refer to studies done to support regulatory approval

improved, or prevented would be meaningful to patients. CTTI has developed a [Question Bank for Identifying Meaningful Outcome Measures](#) to help sponsors develop the right endpoints for the context of their trial. Sponsors may need to justify the selection of a measure, including whether a digitally-captured measure provides an added value beyond what an existing or established measure captures. To this end, sponsors, patients, clinicians, technology companies, and regulators should consider collaborating as much as possible in a pre-competitive environment to identify the digitally-derived outcome measures that provide the most value and warrant further development. The goal is to create a set of widely accepted and agreed upon measures shared across a community rather than a multitude of different, overlapping measures. CTTI strongly cautions against developing novel endpoints simply because a new digital health technology makes it technically feasible.

## **2. Identify key endpoints by assessing and meeting the needs of each stakeholder**

Developing novel, digitally-derived endpoints is a time-consuming and resource-intensive process. Collecting and addressing the needs of each stakeholder will enable the identification and development of the right endpoint for the right context. For example, regulators would like the endpoint to be fit for the purpose of evaluating a new drug or therapy, researchers want the endpoint to be suitable for implementation in a clinical trial, and patients want the endpoints to reflect a clinical outcome that is important to them. As such, sponsors, consortia, and grant-making organizations should consider taking a systematic approach to identifying key endpoints for development and use in clinical trials. CTTI has developed an [Interactive Selection Tool](#) that may be helpful when deciding among viable technology-derived novel endpoints for development. This tool could also be used by other groups, such as DHT companies, who wish to assess the potential role of a sensor or technology under development.

## **3. Select the technology after selecting an outcome**

Selecting a suitable DHT for data capture should occur only after the outcome is identified. This will ensure the evaluation of the assessment is separate from the evaluation of the technology. Recommendations and resources for technology selection are available on CTTI's [Selecting and Testing a Digital Health Technology webpage](#). However, the basic criteria for technology selection include the following considerations:

- A.** Establishing that the technology is acceptable and accessible for participants, considering potential issues of battery life, internet and wireless access, and

other aspects that could impact compliance and utilization, or increase participant burden

- B.** Verifying and validating the technology to ensure it is acceptable in terms of sensitivity, specificity, accuracy, precision and other relevant performance characteristics related to the primary data collected within the intended context of use.
  - If the technology is not validated for the context of use, sponsors may develop a plan for conducting this validation prior to using the digitally-derived endpoint in a study to support a label claim. It is also important to demonstrate that the outputs of the technology correspond to the clinical concept of interest. (For more information on DHT verification, see the CTTI recommendations on [Selecting and Testing a Digital Health Technology](#).)

#### **4. Engage with regulators early and often**

It is important for stakeholders, including technology companies, patient groups, and consortia, to engage with regulators early and often during the process of developing novel endpoints, to ensure their critical input.

There are several opportunities to interact with the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) to discuss how digitally-derived endpoints will be used within proposed clinical investigations. For drug and medical device sponsors planning to use a novel endpoint in a pivotal trial for review by the FDA, interactions will continue during the Investigational New Drug (IND) application or Investigational Device Exemption (IDE) reviews.

CTTI's [Regulatory Engagement guide](#) clarifies opportunities for interaction with the FDA and EMA and describes different pathways depending on whether advice is being sought within or outside of an individual medical product development program.

#### **5. Include digitally-derived endpoints in early phase clinical trials and observational cohort studies to demonstrate they are fit-for-purpose**

Including digitally-derived endpoints in early phase trials, as exploratory endpoints, and/or including them as a sub-study in existing clinical studies is an efficient way to understand what value they offer and how they can be further refined. Notwithstanding the need for thoughtful selection and standard approaches across measures, sponsors

and academic investigators should consider adding digitally-derived measures to existing studies and trials to identify and evaluate novel endpoints that offer incremental utility over other assessments. CTTI recommends doing this in preference to solely conducting unique pilot studies. This approach not only helps to eliminate the need for the development and execution of additional protocols, but it also allows sponsors and investigators to gather information about scientific and operational considerations related to using DHTs for data capture in a large study or trial. These considerations may include patient acceptability of the technology, identification of the appropriate sensors required to maximize the quality of the measures, and data properties, all of which inform correct protocol design and sample size. CTTI also recommends including digitally-derived endpoints as exploratory endpoints in natural history and observational studies, including those conducted by patient groups and academics.

By including digitally-derived assessments early in clinical studies, the data can contribute to the body of evidence essential to successful development for use as primary or secondary endpoints in confirmatory trials. It is critical for sponsors to remember that the general principles that apply to determining what the measure is and the basic evidence that is needed to demonstrate benefit apply to all measures, regardless of whether it is DHT-based or not. However, gathering this evidence for a digitally-derived endpoint may pose unique challenges, and certain concepts for developing an outcome assessment may not easily translate to digital measures. For example, demonstrating that the source data collected by a DHT is captured accurately and securely can be difficult due to factors such as variability in sample rates, adherence to signal processing requirements, and/or appropriate storage and time stamping. Furthermore, demonstrating that the outputs of the technology correspond to the clinical concept of interest can be particularly challenging for novel measures in which validation standards do not exist and the ground truth is not straightforward (e.g., translating accelerometry data into calories burned for the patient population of interest).

Therefore, sponsors should consider engaging early and often with regulators to ensure they appreciate the evaluation process of these assessments and are meeting regulator expectations as they translate concepts to digitally-derived clinical outcomes assessments. CTTI has created a [Flowchart of Steps](#) for general endpoint development as well as an [Evidentiary Considerations Process Map](#) to prepare a digitally-derived endpoint for primary or secondary use within an individual medical product development program. CTTI's [Detailed Steps Tool](#) also outlines possible approaches and provides recommended considerations, where appropriate.

In addition, CTTI has written four use cases to provide tangible examples of novel endpoint development. These use cases outline approaches to developing novel endpoints in trials for the following conditions:

- ▶ [Parkinson's Disease](#)
- ▶ [Heart Failure](#)
- ▶ [Diabetes](#)
- ▶ [Duchenne Muscular Dystrophy](#)

## **6. Think critically about how to optimally position novel digitally-derived endpoints in interventional trials**

There are multiple considerations that go into determining the measurement strategy and endpoint hierarchy. Where novel digitally-derived endpoints address an unmet need, they may be uniquely important as primary efficacy endpoints. However, when well-established, endpoints that effectively demonstrate clinical benefit already exist, novel endpoints may be valuable as complementary assessments, or they may be useful because they enable decentralized trials, that can reduce barriers to study participation in hard-to-reach populations (e.g., geographically disperse populations or those with mobility challenges). Digitally-derived endpoints are unique in their ability to continuously capture data about patients outside of the clinic in the context of their activities of daily living. As such, digitally-derived endpoints may offer valuable data in support of labeling claims for new therapies. Similarly, digitally-derived endpoint data may provide evidence to support the roles of other stakeholders in the healthcare ecosystem, including providers and payers who make coverage decisions related to the use of medical products. CTTI recommends that trial sponsors think critically about how to optimally position digitally-derived endpoints in pivotal trials.

Where appropriate, sponsors should include digitally-derived endpoints in phase I and phase II studies. For example, promising drugs may be terminated prematurely in phase II due to lack of evidence that they could succeed, and the use of digitally-derived endpoints may help prevent early termination by providing more sensitive data on treatment effects. By measuring concepts that previously could not be assessed, or were measured inadequately, novel digitally-derived endpoints offer the ability to improve our understanding of the safety and efficacy profile of a drug, which may in turn lead to greater success from phase I to II or phase II to phase III. As such, novel digitally-derived endpoints may be particularly impactful in phase II studies in therapeutic areas where there is significant unmet need for treatments.

## 7. Promote the sharing of knowledge and lessons learned regarding the development of digitally-derived endpoints

Stakeholders, including digital health technology companies and sponsors who may produce competing tools or develop competing therapies, should share knowledge and lessons learned regarding the development of novel endpoints. Early successes could be made public as use cases to inform future efforts and allow collaboration among stakeholders. The exchange of information may provide the scientific basis for developing or using a technology, allow investigators and technology manufactures 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.

An increase in information sharing could also lead to more attention to and discussion about developing much-needed standards for (1) terminology, (2) collection and reporting of data captured by DHTs, and (3) transparency requirements for the algorithms used to convert the data into physiologically and medically useful endpoints.

## RESOURCES

- ▶ [Flowchart: Steps For Novel Endpoint Development](#)
- ▶ [Detailed Steps for Novel Endpoint Development with Suggested Approaches & Considerations](#)
- ▶ [CTTI Novel Endpoints Interactive Selection Tool](#)
- ▶ [Regulatory Engagement Guide](#)
- ▶ [Evidentiary Considerations Process Map](#)
- ▶ [Question Bank for Identifying Meaningful Outcome Measures](#)
- ▶ [Case Study for Developing Novel Endpoints Generated Using Digital Health Technology: Duchenne Muscular Dystrophy](#)
- ▶ [Case Study: Developing Novel Endpoints Generated Using Digital Health Technology: Diabetes Mellitus](#)
- ▶ [Case Study: Developing Novel Endpoints Generated Using Digital Health Technology: Parkinson's Disease](#)
- ▶ [Case Study: Developing Novel Endpoints Generated Using Digital Health Technology: Heart Failure](#)

## REFERENCES

1. Digital Health Technologies for Remote Data Acquisition in Clinical Investigations. Draft Guidance for Industry, Investigators, and Other Stakeholders. US Food and Drug Administration. Available at: <https://www.fda.gov/media/155022/download> . Accessed December, 2021.



*These recommendations are based on results from CTTI's 2017 [Digital Health Technology Novel Endpoints Project](#) and 2021 Novel Endpoint Acceptance Project.*

*CTTI's [Executive Committee](#) approved both the initial and revised versions of these recommendations.*

*Released in 2017 and re-released in April 2022*