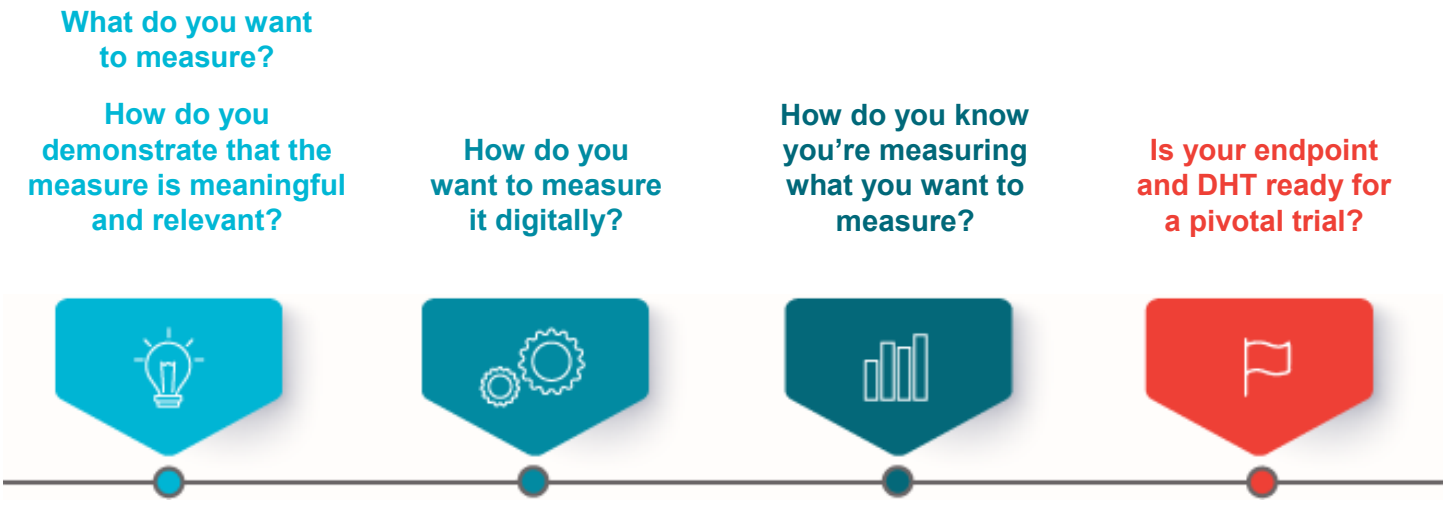
Preparing a Digitally-derived Endpoint for Key Endpoint Use

This resource provides sponsors, academics, and operational partners (e.g., technology companies) with evidentiary considerations to prepare a digitally-derived endpoint for a pivotal trial* within an individual medical product development program. This document is not meant to be prescriptive as trial needs and study contexts differ. Prior to use in a pivotal trial, sponsors should ensure that the ultimate key endpoint is aligned with the goal of the trial, is clinically relevant, that the data is adequately captured by the digital health technology (DHT), and the technology is fit-for-purpose.[1, 2] CTTI's general Flowchart: Steps For Novel Endpoint Development and Detailed Steps for Novel Endpoint Development with Suggested Approaches & Considerations serve as additional resources, recognizing that digitally derived endpoints may be developed within or outside of an individual medical product development program.

Goal To prepare a novel, digitally-derived endpoint to be used in a pivotal trial.

What steps should the trial sponsor take at each phase? There is no single one-size-fits-all answer to this question. There are, however, key steps that sponsors should be thinking about. Below is an out outline of those key steps.

Tip! Think with the end in mind. Ask your team: *What evidence do we need by the pivotal trial? To achieve this, what needs to take place during early phase trials?*



What do you want to measure?

How do you demonstrate that the measure is meaningful and relevant?

How do you want to measure it digitally?

How do you know you're measuring what you want to measure?

Is your endpoint and DHT ready for a pivotal trial?

At the beginning of a drug development program:

Describe the target population

Compile data to support the:

- Identified aspects of heath that are meaningful to the patients (MAH)
- Concept of Interest (COI) and its connection to the MAH

Provide gap assessment of existing endpoints

Start compiling rationale for the:

- Potential clinical measure(s) and endpoint(s)
- Context of Use (COU)

Compile patient and clinician input to propose a minimal clinically important difference (MCID) (i.e., to support meaningful change that can be interpreted as treatment benefit)

During your early phase trials:

Assess potential tools

Determine measurement approaches

Once tool is selected, conduct gap assessment of existing verification and validation data

Assemble, and where necessary generate data to support selection of digital tool and how it would bring value for selected measure including:

- Verification data* (relevant performance characteristics of the DHT related to sensitivity, specificity, accuracy, reliability, precision)
- Tolerability, usability and acceptability data*

Assess data privacy and Computerized System Validation considerations

During your early phase trials:

Evaluate the extent to which the measure reflects the COI

Demonstrate that the algorithm is appropriately validated against the reference standard in the target population of interest (i.e., analytical validation)*

Compile data that the assessment is measuring what it claims to be (e.g., compliance w/ technology, quality of data, relationship to known measures)

Demonstrate and obtain regulatory alignment on meaningful change that can be interpreted as a treatment benefit (i.e., MCID)

Develop statistical analysis plan, considering potential impact of a digital tool

Select and justify optimal meaningful measures for pivotal trial (a new justification may not be needed if the DHT measurement replicates an existing measurement)

Compile, and where necessary generate, clinical validation* data to support how the measure detects meaningful change during treatment (e.g., inter- and intra-patient changes, what level of change matters to patient)

Before your late phase trial, you should have:

Statistical analysis plan

All data and justification to demonstrate that the DHT is fit-for-purpose and the anticipated endpoint results can support a label claim

*See bullets below for definitions and examples.

DEFINITIONS

- The term “pivotal trial” is used here to reflect an adequate and well-controlled trial intended to demonstrate and confirm the safety and efficacy of a medical product. A “pivotal trial” is often the basis for supporting effectiveness. The term is not uniformly utilized.
- The term “key endpoint” is used here to reflect the critical endpoint in a trial intended for regulatory review of a medical product. A “key endpoint” may be either a primary or secondary endpoint. The term is not uniformly utilized.
- Verification and validation are steps for ensuring any DHT used for remote data collection in a clinical investigation is fit-for-purpose, regardless of whether the DHT meets the definition of a device under section 201(h) of the FD&C Act. Verification means confirmation by examination and provision of objective evidence that the physical parameter that the DHT measures (e.g., acceleration, temperature, pressure) is measured accurately and precisely over time. Some verification data may be leveraged from prior work done by the DHT developer or other parties.[1]
    - Examples of verification data include firmware versions, performance, resistance to shock, use life, ability to collect, store and share data, testing per consensus standards, and/or failure modes and effects analysis
- Usability studies are studies conducted to demonstrate that the DHT can be used as intended by the intended trial population, without serious errors or problems.[1]
- Validation is confirmation by examination and provision of objective evidence that the selected DHT appropriately assesses the clinical event or characteristic in the proposed participant population. Can include analytical and clinical validation. [1]
- Clinical validation is a process to establish that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest in the specified context of use. [1]

REFERENCES

1. US Food and Drug Administration. Guidance for Industry, Investigators, and Other Stakeholders. Digital Health Technologies for Remote Data Acquisition in Clinical Investigations, Draft Guidance. U.S. Department of Health and Human Services. Available at: https://www.fda.gov/media/155022/download. Accessed December 2021.
2. European Medicines Agency. Qualification of novel methodologies for drug development: guidance to applicants. October 2020. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-novel-methodologies-drug-development-guidance-applicants_en.pdf Accessed December 2021.