

## CTTI CONSIDERATIONS FOR DEVELOPING NOVEL ENDPOINTS GENERATED BY DIGITAL TECHNOLOGY FOR USE IN CLINICAL TRIALS

Currently, when data are gathered from participants in clinical trials, these assessments typically take place in healthcare settings rather than in the context of patients' daily lives. In addition, many assessments of physical function rely on relatively subjective outcome measures that are reported by participants or their healthcare providers. In addition to being limited in terms of their objectivity, these measures also may capture only brief "snapshots" of the participant's functionality and/or disease burden at a given point in time.

Digital technology offers new ways to capture objective measurements as clinical trial participants go about their daily lives by utilizing 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. These novel endpoints have the potential to provide high-quality data pertaining to outcomes that are meaningful to patients while theoretically enabling larger trials with reduced barriers to participation, thus making possible more sensitive, generalizable, and patient-centric assessments.

### Positive Impacts of Developing Novel Endpoints Generated by Digital Technology for Use in Clinical Trials\*

SPECIFIC BENEFITS			
	SHORT TERM	MEDIUM TERM	LONG TERM
Patient Centricity	Development of high-quality, patient-centric, digitally derived endpoints	Greater use of endpoints that matter to patients in clinical trials Reduced participation burden (patient and caregiver) in clinical trials Fewer barriers to trial participation Larger, more inclusive, and more generalizable trials	Increase in clinical trials that yield more complete information on how therapies affect aspects of disease most important to patients Increase in clinical trials that yield better information to inform regulatory and labeling claims as well as subsequent reimbursement decisions Increase in participation and retention of patients in clinical trials through the development and selection of measures that matter to patients
Efficacy	Inclusion of digitally derived endpoints in early-phase trials and in postmarket surveillance	Improved predictability rates for advancement from phase II to phase III trials Increased efficiency of postmarket surveillance	Increase in number of potentially successful treatments taken forward for testing in phase III trials, particularly in high-risk therapeutic areas
Efficiency	Generation of data needed by payers to make coverage determinations during clinical trials	Prevention of delays in coverage, payment, and use decisions	Prevention of delays in patient access to therapies

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

Substantial development will be required to facilitate the use of digitally derived novel endpoints to support regulatory approval and labeling claims, as the pathway for acceptance is not currently well-described. The Clinical Trials Transformation Initiative (CTTI) convened a project team to issue considerations on selecting a digitally derived novel endpoint, as well as the pathway for development for a wide range of stakeholders, many of whom may not have experience developing novel endpoints. These considerations also aim to accelerate development by encouraging collaboration among technology companies, academic investigators, patients, trial sponsors, regulators, and other stakeholders in a pre-competitive environment.

## SECTION I: CONSIDERATIONS FOR OPTIMIZING NOVEL ENDPOINT SELECTION

### 1. Focus on measures that are meaningful to patients

When selecting outcome assessments for development, the approach should be patient-centered with the patient voice included as standard in the work of clinician experts in the therapeutic area. Selection should address an unmet need for assessments that directly measure or indirectly reflect an aspect of the disease or illness that, if relieved, improved, or prevented would be meaningful to patients. The first two steps outlined in the US Food and Drug Administration's (FDA's) Roadmap to Patient-Focused Outcome Measurement in Clinical Trials,<sup>1</sup> namely 1) understanding the disease or condition and 2) conceptualizing treatment benefit, continue to apply when considering a digitally derived assessment. Subsequent selection of a novel endpoint in preference to an existing outcome assessment should only occur if the novel endpoint offers incremental utility. Specifically, the digitally derived assessment should be better than the alternative measure(s) in one or more ways: for example, the measure should be more informative or meaningful to patients. CTTI strongly cautions against developing novel endpoints simply because new digital health technology makes it technically feasible.

### 2. Select the technology *after* selecting an outcome assessment.

Selecting a suitable digital health technology for data capture should occur only after the clinical outcome assessment or biomarker is identified. This will ensure the evaluation of the assessment is separate from evaluation of the technology. Considerations and tools for technology selection are available in CTTI's [Digital Health Technologies](#) project. However, minimum criteria for technology selection should include:

1. Establishing tolerability and acceptability of the technology by participants; and
2. Verifying the technology.<sup>†</sup> Specifically, ensure that the technology is acceptable in terms of its sensitivity, specificity, accuracy, precision and other relevant performance characteristics related to the primary data collected by the technology.

### 3. Use a systematic approach to identify key novel endpoints.

Developing novel endpoints is a time-consuming and resource-intensive process. For this reason, early successes should be made public as use cases to inform future efforts. As such, sponsors, consortia and grant-making organizations should take a systematic approach to identifying key novel endpoints to be developed for use in clinical trials. CTTI has developed an [Interactive Selection Tool](#) that may be helpful when deciding between viable technology-derived novel endpoints for development. This tool could also be used by other groups, such as digital health technology companies, who wish to assess the potential role of a sensor or technology under development.

---

<sup>†</sup> For more information on digital health technology [verification](#) see the CTTI considerations on digital health technology selection and [Recommendations for Selecting & Testing Digital Health Technology](#)

## **SECTION II: CONSIDERATIONS ON PRACTICAL APPROACHES TO THE NOVEL ENDPOINT DEVELOPMENT PROCESS**

### **1. Foster collaboration among key stakeholders.**

Sponsors, patients, clinicians, technology companies, and regulators should collaborate in a pre-competitive environment to identify and advance consensus on the digitally derived outcome measures that are most valuable and warrant development.

### **2. Create technical standards for digitally derived assessments.**

Technical standards are required for the efficient development and rapid adoption of any technology. Standards promote the exchange of information derived from different studies, speed development of the scientific bases of the 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.

There are currently few standards in the field of digitally derived assessments. Consequently, digital health technologies sometimes report measures that describe the same phenomenon but use different units, and digital health technology manufactures may share the same terminology but derive assessments differently. This lack of standards has resulted in many published studies that cannot be reliably compared and has slowed the development of useful novel endpoints.

In order to promote the scientific, technical, and medical benefits of novel endpoints, shorten development time, and increase the quality and usefulness of digitally derived assessments, CTTI suggests establishing industry-wide standards related to 1) terminology, 2) the collection and reporting of data captured by digital health technologies, and 3) transparency requirements for the algorithms used to convert the data into physiologically and medically useful endpoints. CTTI suggests that stakeholders, including digital health technology companies and sponsors who may produce competing tools or develop competing therapies, collaborate in a pre-competitive space to set these standards.

### **3. Engage with regulators.**

Regulators can and should provide critical input throughout the process of developing novel endpoints. Stakeholders including technology companies, patient groups, and consortia working to develop technology-derived novel endpoints should engage regulators early in the process. For drug sponsors and therapeutic medical device sponsors planning to use a novel endpoint in a pivotal trial, interactions should continue during the Investigational New Drug (IND) application or Investigational Device Exemption (IDE) reviews. There are several opportunities to interact with FDA review staff to discuss how novel endpoints will be used within proposed clinical investigations. It is advantageous to interact with FDA staff early and frequently in order to improve the FDA's understanding of the clinical investigation, the digital health technology, and how the data collected will be analyzed and used to support subsequent applications to the FDA. CTTI has also produced a [quick reference guide](#) regarding the formal processes for interacting with the FDA around novel endpoint development.

### **4. Include novel endpoints as exploratory endpoints in existing clinical trials and observational cohort studies.**

Including novel endpoints in clinical studies as exploratory assessments is an efficient way to understand what value they offer as well as how to further refine the endpoint. Notwithstanding the need for thoughtful selection and standards across measures, sponsors and academic investigators should add digitally derived measures to existing studies and trials to determine which and

how novel endpoints offer incremental utility over other assessments. CTTI suggests including novel endpoints as exploratory endpoints in existing studies in preference to solely conducting unique pilot studies. This approach not only eliminates the need for the development and execution of additional protocols, but allows sponsors and investigators to gather information about scientific and operational considerations related to using digital health technologies for data capture in a large study or trial. These considerations may include patient compliance with, and tolerance of, the technology; identification of the appropriately sensitive sensors required to maximize signal-to-noise ratios in measurement; and data properties, all of which inform correct protocol design and sample size. CTTI also suggests including novel endpoints as exploratory endpoints in natural history and observational studies, including those conducted by patient groups and academics.

Data collected by including digitally derived assessments as exploratory endpoints in clinical studies can contribute to the body of evidence required to successfully develop them for use as primary or secondary endpoints. The process of developing novel endpoints generated by data captured using digital health technologies does not significantly differ from developing any other kind of outcome assessment. CTTI has created a [Flowchart of Steps](#) of this iterative process that includes identification of steps that would be optimized in the pre-competitive space. CTTI's [Detailed Steps Tool](#) also outlines possible approaches to completing these steps and provides recommended considerations, where appropriate.

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

- ▶ [Parkinson's disease](#)
- ▶ [Heart failure](#)
- ▶ [Diabetes](#)
- ▶ [Duchenne's muscular dystrophy](#)

## **5. Think critically about how to optimally position novel endpoints in interventional trials**

Where novel endpoints address 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 most valuable as complementary assessments. Novel endpoints are unique in their ability to objectively capture data about patients outside of the clinic in the context of their activities of daily living. As such, novel endpoints may offer valuable data in support of labeling claims for new therapies. Similarly, novel 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 suggests that trial sponsors think critically about how to optimally position novel endpoints in pivotal trials.

Where appropriate, sponsors should also include novel endpoints in phase II studies. Promising drugs may be terminated prematurely in phase II due to lack of evidence that they could succeed. By measuring concepts that previously could not be assessed, or were measured inadequately, novel 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 II to phase III. As such, novel endpoints may be particularly impactful in phase II studies in therapeutic areas where there is significant unmet need for treatments.

## SECTION III: REFERENCES

1. US Food and Drug Administration. Roadmap to patient-focused outcome measurement in clinical trials. Available at: <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm370174.pdf>. Accessed March 17, 2017.

- 
- ▶ These considerations are based on results from CTTI's [DHT Novel Endpoints Project](#).
  - ▶ CTTI's [Executive Committee](#) reviewed these considerations in June 2017.