Pre-Meeting Materials

Obtaining Novel Endpoint Reliability and Acceptance

CTTI Expert Meeting – July 27 – 28, 2021

OVERVIEW

In preparation for the virtual CTTI Expert Meeting on July 27-28, we ask that you review the material in this document.

Below, you will find information about existing frameworks related to novel endpoint development that use digital health technologies (DHTs) for data capture in clinical trials for medical product purposes. As part of CTTI's Novel Endpoint Acceptance work, we will be building off of CTTI's 2017 Novel Endpoint recommendations, Flowchart of Steps for Novel Endpoint Development, and other resources. Since the launch of those materials, the landscape has greatly evolved and other tools have been developed as well. It is important that we are aware of all these existing tools in our toolbox, identify any gaps that these resources do not address, and consider how to build on and enhance them as needed. Please review each framework in advance of the Expert Meeting.

Please also re-familiarize yourself with the meeting scope and review the list of terms that will be used throughout the meeting. Thank you and we look forward to a robust and interactive set of sessions to help advance the adoption of DHT-derived endpoints!

EXAMPLES OF EXISTING FRAMEWORKS

- CTTI Flowchart of Steps For Novel Endpoint Development
  A step-by-step guide to developing a novel endpoint. It is recommended that the initial steps occur in a precompetitive space to ensure novel and useful endpoints are identified and adopted efficiently.

- DiMe V3 | Verification, Analytical Validation, and Clinical Validation (V3)
  A three-component framework that combines well established practices from software and clinical development to establish the shared foundation for evaluating whether digital clinical measures are fit-for-purpose. (Related material: *The Playbook*)

- FDA Roadmap to Patient-Focused Outcome Measurement in Clinical Trials
  A three-step roadmap to 1) understanding a disease/condition, 2) conceptualizing treatment benefit, and 3) selecting/developing the outcome measure.

MEETING SCOPE

This meeting will center on endpoints related to functional measures and/or other clinical outcome assessments (COAs) that use DHTs for data capture.

IN SCOPE	OUT OF SCOPE

• Clinical Outcome Assessments (COAs)*
  • *Functional outcomes*
  • *Passive and active monitoring*
  • *Technology intended for use in clinical trials*
	• Surveys (ePROs)
	• Digital therapeutics
	• Biomarkers

DEFINITIONS

Term	Definition	Source
Algorithm	A clearly specified mathematical process for computation; a set of rules that, if followed, will give a prescribed result.	NIST/CSRC Glossary
Biomarker	A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Biomarkers may include molecular, histologic, radiographic, or physiologic characteristics. A biomarker is not a measure of how an individual feels, functions, or survives.	FDA/NIH BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource
Clinical Outcome Assessment (COA)	Assessment of a clinical outcome that can be made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment. There are four types of COAs. • clinician-reported outcome • observer-reported outcome • patient-reported outcome • performance outcome	FDA/NIH BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource
Clinical Trial	A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.	NIH Clinical Research Trials and You Glossary of Common Terms
Clinical Utility	The conclusion that a given use of a medical product will lead to a net improvement in health outcome or provide useful information about diagnosis, treatment, management, or prevention of a disease. Clinical utility includes the range of possible benefits or risks to individuals and populations.	FDA/NIH BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource
Concept/ Concept of interest (COI)	In a regulatory context, the concept is the aspect of an individual's clinical, biological, physical, or functional state, or experience that the assessment is intended to capture (or reflect).	FDA/NIH BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource
Context of Use (COU)	A statement that fully and clearly describes the way the medical product development tool is to be used and the regulated product development and review-related purpose of the use.	FDA/NIH BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource
Digital health technology	A system that uses computing platforms, connectivity, software, and sensors for healthcare and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a medical product, in a medical product, or as an adjunct to other medical products (devices, drugs, and	FDA/NIH BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource

	biologics). They may also be used to develop or study medical products.	
Drug Development Tool	The term 'drug development tool' includes— "(A) a biomarker; "(B) a clinical outcome assessment; and "(C) any other method, material, or measure that has the potential to facilitate drug development	Adapted from Section 507 of 21st Century Cures Act
Fit-for-Purpose	A conclusion that the level of validation associated with a biomarker or COA is sufficient to support its proposed use.	FDA/NIH BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource
Endpoint	A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.	FDA/NIH BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource
Firmware	Permanent software programmed into the mobile technology that serves as its operating system.	CTTI's Digital Health Technologies Glossary
Medical Device	Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease. Medical devices are regulated and subject to FDA's laws and regulations.	CTTI's Digital Health Technologies Glossary
Medical Device Development Tool	A method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device	Qualification of Medical Device Development Tools: Guidance for Industry, Tool Developers, and Food and Drug Administration Staff
Novel Endpoint	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.	CTTI 2017 Novel Endpoint Recommendations
Patient	Any individual with or at risk of a specific health condition, whether or not he or she currently receives any therapy to prevent or treat that condition. Patients are the individuals who directly experience the benefits and harms associated with medical products.	FDA's Patient Focused Drug Development Glossary
Patient Advocate	An individual or group of individuals, who may or may not be part of the target population and who has a role in promoting an interest or cause to influence policy with respect to patients' health or healthcare	FDA's Patient Focused Drug Development Glossary
Patient Reported Outcome (PRO)	A type of clinical outcome assessment. A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient can only be measured	FDA/NIH BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource

	by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others.	
Processed Data	Output from mobile technology firmware; raw data that has been mathematically processed	CTTI's Digital Health Technologies Glossary
Raw Data	Output from physical sensor. If the sensor data is not accessible because it is processed by the firmware before being recorded, then the output of the firmware is often considered "raw" data.	CTTI's Digital Health Technologies Glossary
Reliability	The ability of an instrument to yield consistent, reproducible estimates of true treatment effect.	Adapted from FDA's Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Guidance for Industry
Software	Computer programs (which are stored in and executed by computer hardware) and associated data (which also is stored in the hardware) that may be dynamically written or modified during execution.	NIST/CSRC Glossary
Sensor	A sensor is a transducer that converts a physical, biological or chemical parameter into an electrical signal, for example: temperature, pressure, flow, or vibration sensor. Sensors also measure some physical parameter and return digital data representing that parameter to a processor.	Adapted from NIST/Intelligence System Division Definitions
Software as a Medical Device (SaMD)	Software intended for one or more medical uses that may run on different operating systems or in virtual environments. Software run on a hardware medical device is a SaMD when not part of the intended use of the hardware medical device. Software is not SaMD if it drives or controls the hardware medical device	FDA's Digital Center of Excellence's Digital Health Criteria
Validation	A process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose.	FDA/NIH BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource
Analytical Validation	A process to establish that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include specimen collection, handling and storage procedures). This is validation of the test's, tool's, or instrument's technical performance, but is not validation of the item's usefulness.	FDA/NIH BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource
Clinical Validation	A process to establish that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest.	FDA/NIH BEST(**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource
Verification	The assessment of accuracy (which may include routine calibration), precision, consistency across time, uniformity across mobile technologies, and possibly also across different environment conditions. Verification also provides	CTTI's Digital Health Technologies Glossary

	assurance that the relevant firmware/software that generates processed data is accurate, precise, consistent, and uniform	