CLINICAL TRIALS TRANSFORMATION INITIATIVE

Steps for Novel Endpoint Development, with Suggested Approaches and Considerations

The steps in the following tables describe CTTI's recommended approach to digital health technology (DHT)-derived endpoint development. This pathway was established after convening expert teams to write four unique use cases to demonstrate the novel endpoint development process and was updated when CTTI refreshed resources in 2022. Each use case team comprised of investigators (academic and industry), engineers, patient representatives, algorithm experts, statisticians, and regulators. The use cases detail approaches for developing novel endpoints for Parkinson's disease, heart failure, diabetes, and Duchenne's muscular dystrophy. The steps outlined below represent a generalizable pathway, derived from the use case findings, that is broadly applicable across different therapeutic areas and mobile technologies. Users reviewing this table online can use the links to directly access examples of each step embedded in the use cases.

Table 1. CTTI recommended pathway for selection of outcome assessment, digital health technology, and patient population

Steps in this table should be completed sequentially; however, iterations and successive refinements may be required.

	Development step	Description	Approach	Considerations	Links to tangible examples
1	**Describe the study population for whom the endpoint will be targeted.**	This step informs the context of use for which this outcome assessment is being developed This may be a time to discuss other aspects of context of use, including: • Ensuring that the protocol/study design supports collecting the endpoint • Deciding whether the endpoint is primary or secondary • Ascertaining its relationship to any other endpoints	Use the steps outlined in Section 1 of the FDA's Roadmap to Patient-Focused Outcome Measures[2] to understand the disease or condition. Specifically, identify how different subpopulations may experience the aspect of health assessed by the measure differently. Where the use of a digital health technology for data capture poses concerns for a specific patient population (example: DHT compliance among children), these should be explored using methods including formative research with patients and caregivers, pilot studies, and the inclusion of the outcome of interest as an	Particularly during their infancy, novel endpoints may be valuable as part of a suite of measures, informed by patient and other perspectives, in order to paint a more holistic picture of disease severity, changes in severity, and therapeutic effect. This is not an exclusive consideration for technology-derived endpoints. However, sponsors must consider that strategically developing a suite of novel endpoints and electronic patient-reported outcomes (ePROs) that may be positioned together in a complete package can be a key to a paradigm shift in conducting clinical trials, allowing trials that may be conducted completely	Diabetes Use Case, Context of Use DMD Use Case, Context of Use Considerations DMD Use Case, Main Success Pathway, Step 6e and Step 7a Heart Failure (HF) Use Case, Context of Use PD Use Case, Context of Use

	Development step	Description	Approach	Considerations	Links to tangible examples
			exploratory endpoint in ongoing studies, as appropriate. It is easier to develop an endpoint within a narrow context of use. However, this limits subsequent indications for therapies developed using the endpoint. We recommend an iterative approach, seeking to first develop the endpoint for use in a clinical trial within a narrow context of use, then going on to broaden this context in future study.	remotely.	
2	**Identify an aspect of health (how a patient feels, functions, or survives) affected by the disease that 1) the patient cares about, 2) might be benefited by a treatment for, and 3) is not currently assessable or for which improvement in assessment would be valuable.**	This identifies the meaningful health aspect (MHA) to be studied. Specifically, it denotes the health aspect of the disease for which patients have a preference that it 1. Does not become worse, 2. Improves, or 3. Is prevented.[1]	Use the steps outlined in Section 1 of the FDA's Roadmap to Patient-Focused Outcome Measures[2] to understand the disease or condition. Insight from patients and caregivers is critical and should drive this selection process.[†]		Duchenne's muscular dystrophy (DMD) Use Case, Main Success Pathway Step 1 & Step 2
3	**Identify the scope of assessment: the aspect of an individual's clinical, biological, physical, or functional state, or experience, that the assessment is intended to capture.**	This is the concept of interest (COI).[3] Clinical concepts of interests are typically simpler or narrower elements of the MHA identified in Step 1 that can be more readily measured. Changes or differences in this clinical concept of interest	Insight from patients and caregivers is critical and should inform this selection process. Careful consideration must be given to whether it is possible to measure the concept of interest.	The advent of digital health technologies may allow measurement of concepts never previously considered. Consensus definitions for such concepts of interest must be established. It may be necessary to consider	DMD Use Case, Main Success Pathway Step 3 & Step 4 Diabetes Use Case, Main Success

[†]Systematically generated reports of patients' perspectives for many conditions already exist as part of the FDA's Patient-Focused Drug Development Initiative and are available at: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm.For diseases and conditions for which reports have not been generated, CTTI has issued recommendations for effectively engaging patient groups in clinical trials that may support sponsors' efforts to solicit this input.

	Development step	Description	Approach	Considerations	Links to tangible examples
		should reflect changes and/or difference in the MHA. Example: • MHA – ambulation-dependent activities • COI – walking capacity Biomarker COIs are typically on the causative pathway of the MHA identified in Step 1. Example: • MHA: potential for unconsciousness events • COI: hypoglycemia		available DHTs when determining whether concepts of interest can be measured. However, the digital health technology for data capture should not be selected at this stage.	Pathway Step 1 Parkinson's Disease (PD) Use Case, Main Success Pathway, Step 1
4a	**Select the specific measurement to report that is a good representation of the aspect of the patient's medical status defined by the concept of interest.**	Select the specific measurement, also called the outcome assessment that offers the greatest incremental utility. Examples: • COI: Walking capacity • Possible measures: duration of walking per day; number of steps walked per day • COI: hypoglycemia • Possible measures: duration of hypoglycemia; frequency of hypoglycemic events	Solicit input from patients, caregivers and disease experts to help determine whether the technology-derived measure is better, more appropriate, or additive for the target patient population, compared with an existing measure. Explore datasets from natural history and observational studies to help determine the best measures. Where possible, prioritize measures that could be/are used in healthcare delivery in order to expedite the creation of a normative database of representative patients.	Just because a digital health technology-derived outcome assessment is mathematically feasible, it does not mean that it is clinically relevant and/or important to patients. Recognize that outcome assessments vary in "ecological validity" (how closely they can be linked to real-world functioning). Consider that it is easier to go on to prove the meaningful interpretability of outcome assessments as good measures of meaningful aspects of health when they have high ecological validity and are closely linked to real-world functioning. Many technology-derived outcome assessments will closely reflect an aspect of function in the real world because they directly measure some subset of activities of daily living. For those technology-derived outcome assessments	DMD Use Case, Main Success Pathway, Step 5a PD Use Case, Main Success Pathway, Step 2

				that do not (example: biomarkers) the burden of proof to demonstrate ecological validity is usually higher.	
4b, 5, & 6	**Assess potential digital health technology for data capture, describe the context for which the measurement and technology will be used, and then select suitable digital health technology**		Minimum criteria for digital health technology selection must include: 1. Establishing tolerability and acceptability of the DHT by participants 2. Establishing analytic validity of the DHT--specifically, that the DHT is acceptable in terms of its sensitivity, specificity, accuracy, precision and other relevant performance characteristics See the steps below under Validate the Technology. Recommendations and tools for DHT selection are available at CTTI's Selecting and Testing a Digital Health Technology project.		DMD Use Case, Main Success Pathway, Steps 5b–5e

Table 2. CTTI's recommended pathway for developing a digital health–technology-derived outcome assessment into an endpoint for use in a clinical trial

To develop a novel endpoint for use in regulatory decision making, all of the steps in the table below should be completed, but the order of execution may vary. An integrated approach is likely necessary to validate the measure and validate the technology. See CTTI Flowchart of Steps for Novel Endpoint Development for additional reference.

Development step	Description	Approach	Considerations	Links to tangible examples
Validate the Measurement (in the Context of Use)				
Define meaningful change that can be interpreted as treatment benefit.	Define the change or difference in the score or measure that can be interpreted as meaningful to patients and therefore indicates a treatment benefit.	When an effective treatment exists, measure the effect of this therapy on a de novo group of patients using the novel endpoint to determine the meaningful change to patients. An alternate measure or PRO is required for reference. Where appropriate, observational studies can measure natural changes among patients using the novel endpoint and use PROs and/or existing measures for reference.	It is not necessary to determine a true "minimal meaningful change." It can be very difficult if the novel endpoint is substantially more sensitive than any other available assessment tool (including PROs). Establishing the meaningfulness of a change that is the same or smaller size than the effect size a treatment might offer is sufficient.	Diabetes Use Case, Main Success Pathway, Step 4 DMD Use Case, Main Success Pathway, Step 6d HF Use Case, Main Success Pathway, Step 4 PD Use Case, Main Success Pathway, Step 1, Step 4
Evaluate the extent to which the measure reflects the intended scope of assessment (i.e. COI) for the specified patient population.	This step will demonstrate content validity.	Approaches should confirm content validity both in controlled environments and in the real world.	In some cases, the content validity of technology-derived measures is nearly self-evident once analytical validity of the DHT has been established. Example: If a continuous glucose monitor has analytic validity, then it is easy to justify that this same DHT is correctly reporting *average serum glucose over 24 hours*. Floor and ceiling effects must be addressed when demonstrating content validity. All DHT and measures must be able to capture	Diabetes Use Case, Main Success Pathway, Step 3a DMD Use Case, Main Success Pathway, Step 5f HF Use Case, Main Success Pathway, Step 1

			data across the complete anticipated range. Underscoring that novel endpoint development process is not linear, data captured from supporting measure(s) (e.g. PRO) in observational studies may be used to support content validity by demonstrating that the outcome assessment may be generalized to real-world settings and is capable of measuring daily activities.	
Determine measurement approaches and endpoint definition.	Determine the optimal sampling frequencies. Determine optimal DHT placement. Define the scoring algorithm. Determine the required training for administration of the tool.	Statisticians, engineers and clinicians should determine optimum sampling frequencies for passively collected data. Patients and their caregivers should also be engaged in the decision when the data are more actively captured. Feasibility studies should be conducted to inform optimal DHT placement and required training for administration of the tool. To optimize efficiency, these feasibility studies should be conducted as sub-studies within existing observational studies or trials where possible. The scoring algorithm should be determined during the standardization of methods. The exception is for algorithms developed using machine learning methods. After developing these in a training dataset, they should then be tested in other datasets.	DHT considerations such as battery life may influence sampling frequency decisions. In such cases, technology manufacturers should be included in the multidisciplinary teams optimizing sampling frequencies.	DMD Use Case, Main Success Pathway, Steps 5g and 5h HF Use Case, Main Success Pathway, Step 5 PD Use Case, Context of Use Considerations, Footnote #1

Demonstrate that the measure is effective in detecting change.	Demonstrate that the outcome assessment can identify differences in scores over time in individuals and groups when the aspect of their medical status of interest has changed.	Instrument should be equally sensitive: • To gains and losses in the measure • Across entire range of scores expected for the trial population The ability of the measure to effectively detect change should be demonstrated as part of determining analytic validity and subsequently selecting and setting standards for measures.		DMD Use Case, Main Success Pathway, Steps 6b and 6c HF Use Case, Main Success Pathway, Step 4 PD Use Case, Main Success Pathway, Step 4 and Step 5a
Perform technical verification	Verify system outputs are acceptable at the bench in terms of measurement errors and other relevant performance characteristics Demonstrate that measures are highly reliable, with small measurement errors.	Benchtop studies to confirm that the system outputs meet performance specifications, such as a minimum defined accuracy and precision when compared against a ground-truth reference standard, consistently over time and temperature, and uniformly across multiple DHTs. This could also include analyses to identify potential failure modes of a DHT and their causes and effects	Using the same DHT type / model in the clinical investigation is more likely to ensure data consistency. If multiple DHTs are used for data capture, sponsors should ensure that the measurements are consistent across all protocol-specified DHTs.	
Perform technical validation	Demonstrate that the system produces measures that are accurate, reliable, reproducible, and validated against a reference standard in a representative	Where known endpoints exist for aspect of the patient's disease or condition defined by the concept of interest, add the novel endpoint under development to existing	At this point it may be valuable to demonstrate either that: 1. Compliance does not impact the reliability of the measure, or	Diabetes Use Case, Main Success Pathway, Step 3b DMD Use Case,

Development step	Description	Approach	Considerations	Links to tangible examples
	population	studies and trials in all phases as an exploratory endpoint and assess their relationship to the known measures. **Regardless of whether known endpoints are well-established, respected, existing or "legacy measures" that modern science judges to be suboptimal, the novel endpoint should still be compared with them. However, novel endpoints should not be expected to correlate as closely to legacy measures as they do to true gold-standard endpoints.** Approaches to demonstrating construct validity may identify different functional groups of patients with respect to the measure.	2. There are ways to mitigate reliability issues that may be result from compliance issues Because novel endpoint development is not a linear process, much of the work to demonstrate construct validity may have been done early in the process. In such cases, this may allow the novel endpoint to be included in existing studies and trials as a secondary endpoint rather than an exploratory endpoint at this stage.	Main Success Pathway, Step 6d HF Use Case, Main Success Pathway, Step 2 & Step 3 PD Use Case, Main Success Pathway, Step 2, Step 5a

REFERENCES

1. Walton MK, Powers JH 3rd, Hobart J, et al. Clinical Outcome Assessments: Conceptual Foundation-Report of the ISPOR Clinical Outcomes Assessment - Emerging Good Practices for Outcomes Research Task Force. *Value Health.* 2015;18(6):741-52. doi: 10.1016/j.jval.2015.08.006. PMID: 26409600 PMCID: PMC4610138

2. 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.

3. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Available at: https://www.ncbi.nlm.nih.gov/books/NBK326791/. Accessed March 17, 2017. PMID: 27010052

4. [No authors]. US drug development consortia. Focus issue. Nat Rev Drug Discov 2014;13(781). Available at: http://www.nature.com/nrd/focus/consortia/index.html. Accessed March 17, 2017.

5. Gastriend E, Lee B. Pre-competitive collaboration in pharma. An overview study. [White paper]. Available at: https://futureoflife.org/data/documents/PreCompetitiveCollaborationInPharmaIndustry.pdf. Accessed March 17, 2017.

6. Stephenson D, Hu MT, Romero K, et al. Precompetitive data sharing as a catalyst to address unmet needs in Parkinson's disease. *J Parkinsons Dis.* 2015;5(3):581-94. doi: 10.3233/JPD-150570. PMID: 26406139 PMCID: PMC4887129

7. Weninger S, Carrillo MC, Dunn B, et al. Collaboration for Alzheimer's Prevention: Principles to guide data and sample sharing in preclinical Alzheimer's disease trials. *Alzheimers Dement.* 2016;12(5):631-2. doi: 10.1016/j.jalz.2016.04.001. PMID: 27157073 PMCID: PMC5111162