

STEPS FOR NOVEL ENDPOINT DEVELOPMENT, WITH SUGGESTED APPROACHES AND CONSIDERATIONS

The steps in the following tables describe CTTI’s recommended approach to novel endpoint development. This pathway was established after convening expert teams to write four unique use cases to demonstrate the novel endpoint development process. Each use case team comprised 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, mobile device 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	Identify an <u>aspect of health</u> (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 <ol style="list-style-type: none"> 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
2	Identify the <u>scope of assessment</u>: the aspect of an individual’s clinical, biological, physical, or	This is the concept of interest (COI). ³ Clinical concepts of interests are typically simpler or narrower	Insight from patients and caregivers is critical and should inform this selection process. Careful consideration must be given	The advent of mobile technologies may allow measurement of concepts never previously considered. Consensus definitions for such	DMD Use Case, Main Success Pathway Step 3 & Step 4

[†]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.

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	<p>functional state, or experience, that the assessment is intended to capture.</p>	<p>elements of the MHA identified in Step 1 that can be more readily measured. Changes or differences in this clinical concept of interest should reflect changes and/or difference in the MHA. Example:</p> <ul style="list-style-type: none"> • MHA – ambulation-dependent activities • COI – walking capacity <p>Biomarker COIs are typically on the causative pathway of the MHA identified in Step 1. Example:</p> <ul style="list-style-type: none"> • MHA: potential for unconsciousness events • COI: hypoglycemia 	<p>to whether it is possible to measure the concept of interest.</p>	<p>concepts of interest must be established.</p> <p>It may be necessary to consider available mobile devices when determining whether concepts of interest can be measured. However, the mobile device for data capture should not be selected at this stage.</p>	<p>Diabetes Use Case, Main Success Pathway Step 1</p> <p>Parkinson's Disease (PD) Use Case, Main Success Pathway, Step 1</p>
3	<p>Select the <u>specific measurement</u> to report that is a good representation of the aspect of the patient's medical status defined by the concept of interest.</p>	<p>Select the specific measurement, also called the outcome assessment that offers the greatest incremental utility. Examples:</p> <ul style="list-style-type: none"> • 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 	<p>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.</p> <p>Explore datasets from natural history and observational studies to help determine the best measures.</p> <p>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.</p>	<p>Just because a technology-derived outcome assessment is mathematically feasible, it does not mean that it is clinically relevant and/or important to patients.</p> <p>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</p>	<p>DMD Use Case, Main Success Pathway, Step 5a</p> <p>PD Use Case, Main Success Pathway, Step 2</p>

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				technology-derived outcome assessments that do not (example: biomarkers) the burden of proof to demonstrate ecological validity is usually higher.	
4	Select <u>suitable mobile device</u> for data capture.		<p>Minimum criteria for device selection must include:</p> <ol style="list-style-type: none"> 1. Establishing tolerability and acceptability of the device by participants 2. Establishing analytic validity of the device--specifically, that the device is acceptable in terms of its sensitivity, specificity, accuracy, precision and other relevant performance characteristics <p>Recommendations and tools for device selection are forthcoming from CTTI's Use of Mobile Devices project.</p>		DMD Use Case, Main Success Pathway, Steps 5b–5e
5	Select or develop standards.	<p>Establish industry-wide standards related to:</p> <ol style="list-style-type: none"> 1. The collection and reporting of data captured by mobile devices 2. The algorithms used to convert the data into physiologically and medically useful endpoints 	Pre-competitive collaboration is required. Several examples of successful pre-competitive collaborations exist, and best practices have been proposed. ⁴⁻⁷		<p>Diabetes Use Case, Main Success Pathway, Step 2</p> <p>DMD Use Case, Main Success Pathway, Step 5h</p> <p>PD Use Case, Main Success Pathway, Step 2</p>
6	Describe the study population for whom the endpoint will be targeted.	<p>This step informs the context of use for which this outcome assessment is being developed</p> <p>This may be a time to discuss other aspects of context of use, including:</p> <ul style="list-style-type: none"> • Ensuring that the 	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	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	<p>Diabetes Use Case, Context of Use</p> <p>DMD Use Case, Context of Use Considerations</p>

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		<p>protocol/study design supports collecting the endpoint</p> <ul style="list-style-type: none"> Deciding whether the endpoint is primary or secondary Ascertaining its relationship to any other endpoints 	<p>measure differently.</p> <p>Where the use of a mobile device for data capture poses concerns for a specific patient population (example: device 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 exploratory endpoint in ongoing studies, as appropriate.</p> <p>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.</p>	<p>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 remotely.</p>	<p>DMD Use Case, Main Success Pathway, Step 6e and Step 7a</p> <p>Heart Failure (HF) Use Case, Context of Use</p> <p>PD Use Case, Context of Use</p>

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

To develop a novel endpoint for use in a regulatory trial, all of the steps in the table below should be completed, but the order of execution may vary. An iterative approach is likely necessary to complete these steps and subsequently expand the populations and settings in which the novel endpoint may be used.

	DEVELOPMENT STEP	DESCRIPTION	APPROACH	CONSIDERATIONS	LINKS TO TANGIBLE EXAMPLES
A	Determine measurement approaches.	<p>Determine the optimal sampling frequencies.</p> <p>Determine optimal device placement.</p> <p>Define the scoring algorithm.</p>	<p>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.</p>	<p>Device considerations such as battery life may influence sampling frequency decisions. In such cases, device manufacturers should be included in the multidisciplinary teams optimizing sampling frequencies.</p>	<p>DMD Use Case, Main Success Pathway, Steps 5g and 5h</p> <p>HF Use Case, Main Success Pathway, Step 5</p>

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		Determine the required training for administration of the tool.	<p>Feasibility studies should be conducted to inform optimal device placement and required training for administration of the tool. To optimize efficiency, these feasibility studies should be conducted as substudies within existing observational studies or trials where possible.</p> <p>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.</p>		PD Use Case, Context of Use Considerations , Footnote #1
B	Evaluate the extent to which the measure reflects the intended scope of assessment for the specified patient population.	This step will demonstrate content validity.	<p>Approaches should confirm content validity both in controlled environments and in the real world.</p> <p>Technologies may be particularly valuable for demonstrating content validity in real-world settings. For example, collecting wearable camera data alongside accelerometer data during daily activities.</p>	<p>In some cases, the content validity of technology-derived measures is nearly self-evident once analytical validity of the device has been established. Example: If a continuous glucose monitor has analytic validity, then it is easy to justify that this same device is correctly reporting <i>average serum glucose over 24 hours</i>.</p> <p>Floor and ceiling effects must be addressed when demonstrating content validity. All devices and measures must be able to capture data across the complete anticipated range.</p>	<p>Diabetes Use Case, Main Success Pathway, Step 3a</p> <p>DMD Use Case, Main Success Pathway, Step 5f</p> <p>HF Use Case, Main Success Pathway, Step 1</p>
C	Ensure the absence of systematic measurement error by demonstrating reliability, repeatability and reproducibility.	<p>Demonstrate that measures are highly reliable, with small measurement errors.</p> <p>Demonstrate that measures are repeatable, with minimal variation</p>	Reliability of the device should be demonstrated as part of determining analytic validity and subsequently selecting and setting standards for measures.	<p>If multiple devices are used for data capture, device equivalency should be demonstrated prior to allowing this in protocol. At this point it may be valuable to demonstrate either that:</p>	PD Use Case, Main Success Pathway, Step 2

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		<p>between measures made on the same patient under identical conditions when there is no change in the patient's clinical status.</p> <p>Demonstrate that measures are reproducible, with minimal variations made on the same patient under changing external conditions when there is no change in the patient's status.</p>	<p>Demonstrating test-retest reliability, or repeatability, of the measure is distinct from device test-retest reliability. Observational studies may be used to demonstrate that scores are stable over time when no change has occurred in the concept of interest.</p> <p>If content validity has been demonstrated in different settings, these data can be used to demonstrate reproducibility of the measure.</p>	<ol style="list-style-type: none"> 1. Compliance does not impact the reliability of the measure, or 2. There are ways to mitigate reliability issues that may be result from compliance issues 	
D	<p>Demonstrate that the assessment is measuring what it claims to be measuring.</p>	<p>This step will demonstrate construct validity.</p> <p>Provide evidence that the measure shows logical relationships with:</p> <ol style="list-style-type: none"> 1. Other measures 2. Characteristics of patients/patient groups 	<p>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 studies and trials in all phases as an exploratory endpoint and assess their relationship to the known measures.</p> <p>Regardless of whether known endpoints are well-established, respected, gold-standard endpoints 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.</p> <p>Conduct observational studies, collecting contemporaneous PRO data (and other data as appropriate) alongside the novel endpoint to assess the relationship.</p>	<p>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.</p> <p>Underscoring that novel endpoint development process is not linear, data captured from PRO measure(s) 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.</p>	<p>Diabetes Use Case, Main Success Pathway, Step 3b</p> <p>DMD Use Case, Main Success Pathway, Step 6d</p> <p>HF Use Case, Main Success Pathway, Step 2 & Step 3</p> <p>PD Use Case, Main Success Pathway, Step 5a</p>

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			<p>Inclusion of PRO measure(s), where appropriate, will increase understanding regarding the meaningfulness of the measure to the patient. It also provides support for endpoint development efforts in nontraditional research environments.</p> <p>Approaches to demonstrating construct validity may identify different functional groups of patients with respect to the measure.</p>		
E	<p>Define meaningful change that can be interpreted as treatment benefit.</p>	<p>Define the change or difference in the score or measure that can be interpreted as meaningful to patients and therefore indicates a treatment benefit.</p>	<p>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.</p> <p>Where appropriate, observational studies can measure natural changes among patients using the novel endpoint and use PROs and/or existing measures for reference.</p>	<p>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.</p>	<p>Diabetes Use Case, Main Success Pathway, Step 4</p> <p>DMD Use Case, Main Success Pathway, Step 6d</p> <p>HF Use Case, Main Success Pathway, Step 4</p> <p>PD Use Case, Main Success Pathway, Step 4</p>
F	<p>Demonstrate that the measure is effective in detecting change.</p>	<p>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.</p>	<p>Instrument should be equally sensitive:</p> <ul style="list-style-type: none"> To gains and losses in the measure Across entire range of scores expected for the trial population <p>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.</p>		<p>DMD Use Case, Main Success Pathway, Steps 6b and 6c</p> <p>HF Use Case, Main Success Pathway, Step 4</p> <p>PD Use Case, Main Success Pathway, Step 4 and Step 5a</p>

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G	Develop a user manual that is appropriate for use with the intended study population.	In this era of technology, this manual should be available as media appropriate to the intended use. This may include developing the manual as an electronic document, an interactive electronic tool, program/app, and/or video module.	This manual should include instructions for how to use the device to obtain valid measurements and should target coordinators, patients, and patients' caregivers, as appropriate. Recommendations and tools including considerations regarding device failure are forthcoming from CTTI's Use of Mobile Devices project.		

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