

Novel Endpoint Acceptance

Question Bank for Identifying Meaningful Outcome Measures

The CTTI Novel Endpoint Acceptance Recommendations advise those developing novel endpoints to collaborate and engage with a variety of stakeholders to identify meaningful clinical [outcome](#) measures and determine whether a digital health technology is the best way to capture an outcome of interest.

The following questions provide a set of considerations that sponsors and clinician investigators can use when engaging stakeholders during protocol development and study design. The goal is to identify measures that enable the development of the right endpoint for the right context.

This resource is meant to serve as an inspirational guide that should be tailored based on the target population and context of an individual study. Specifics around when and how to engage each stakeholder are not addressed in this document. Users may also want to consider qualitative best practices for stakeholder engagement—such as sample size or representative range of disease— as part of their overall approach to identifying meaningful outcome measures.

This question bank leverages the Digital Medicine Society's (DiMe) framework¹ as a foundation and expands upon it to incorporate additional stakeholder perspectives. The Core Outcomes Measures in Effectiveness Trials (COMET) Initiative is another useful resource for the development and application of agreed upon standardized sets of outcomes (i.e., core outcome sets) and is a good starting place for the development of meaningful outcome sets for a clinical trial.²

Identifying Meaningful Outcome Measures: Questions to Ask Patients/Caregivers of a Particular Disease (and/or Population of Interest)

Topic Area	Questions
Meaningful Aspect of Health	<ol style="list-style-type: none"> 1. What part of your life is most frustratingly impacted by your condition?¹ 2. How has your independence been affected by your condition? 3. What about your health do you wish you could improve? 4. Considering what you just mentioned, explain your near term goals: "In the next 3 months I'd like to (e.g. start or continue doing)..." "In the next 6 months I'd like to be able to ..." 5. Explain your longer term goals. "In the next 12-18 months I'd like to (e.g. start or continue doing)...."

Concept of Interest	<ol style="list-style-type: none"> 1. What symptoms (or things about your condition) impact your ability to do what you wish you could do?¹ Provide an example. 2. On a given day, what are the symptoms that bother you more than others? What makes these bothersome to you? 3. What do you consider to be symptom [X]? 4. How frequently do these symptoms occur? 5. Are your symptoms worse sometimes? How can you tell? 6. Is there a way that you compensate or make up for these symptoms that impact you?
Outcome to be Measured	<ol style="list-style-type: none"> 1. What could we measure to better understand if your health is improving or not getting worse? 2. Why would measuring this be a good way to track or understand your condition? 3. What has your doctor or health care provider measured to better understand your condition? Do these measures make sense to you?¹ Why/why not? 4. How useful do you think [X] measure is? Why do you feel that way? 5. What could we measure in your home environment that we aren't currently?
Method/Tool to Measure the Outcome (including acceptability)	<ol style="list-style-type: none"> 1. In your opinion, what would be the best way to capture or record [X] measure? Why do you feel this way? 2. Will capturing this measure in [X] way be a "hassle" for you? Why do you feel that way? 3. How frequently should this measure be captured? i.e. every day or periodically? Why? 4. In your opinion, is it possible to collect this measure with a digital technology (like something you wear or carry)? [define what a digital technology is and how long or how it's used] Why/why not? 5. [If a functional measure]... Would it be better to collect [X] measure by doing a specific task OR should it be collected continuously throughout the day (like wearing a watch)? Why do you feel this way? 6. If we use this approach in a clinical trial to test a new drug or therapy, what considerations should we have to support your participation in the trial? 7. If we use this approach in a clinical trial, what are the risks, if any, that we should be aware of?

Demonstrating Therapeutic Benefit	<ol style="list-style-type: none"> 1. How do you know when your condition is improving? 2. How much change would you want to see in [X] before it really starts to make a positive difference in your life?¹ 3. How would this change impact your life? 4. What would you need to see for you to feel that a treatment is beneficial? 5. Would the use of a digital technology to measure this change help? Why/why not?
-----------------------------------	--

Identifying Meaningful Outcome Measures: Questions to Ask a Clinician/Health Care Provider

Topic Area	Questions
Meaningful Aspect of Health	<ol style="list-style-type: none"> 1. What do your patients think is most important to their health and/or quality of life? 2. What do their caregivers think is most important to your patient's health and/or quality of life? 3. Are there other aspects of your patients' health that you feel are important to address? What are they and why?
Concept of Interest	<ol style="list-style-type: none"> 1. What symptoms or characteristics of the condition relate to these health concerns? How do they relate? 2. What are the underlying reasons or potential mechanisms that might be causing these symptoms? 3. What is the frequency of [X] symptom? What's the duration? 4. How do you track these symptoms or characteristics of the condition? 5. What about your patients' health or daily life can you not measure in the clinic but are important to understand? How do patients report these now? 6. What are the symptoms that increase your interaction times with patients? 7. What are symptoms that result in clinical trial drop out? Why? 8. What are the symptoms that might result in reduced data capture? Why?

Outcome to be Measured	<ol style="list-style-type: none"> 1. You mentioned [X] aspect or symptom relate to your patients' health or daily life concerns. How do you (or could you) measure that? 2. Which measures matter most in your opinion? Why? 3. How sensitive is [X] measure? How does it reflect change in health (i.e. improving vs reversing the symptom or just maintaining)? How does it reflect the severity of the condition? 4. What limitations are there for [X] measure? 5. If this is not a measure captured as part of routine care, why is that? Would you want it to be? Why/why not?
Method/Tool to Measure the Outcome	<ol style="list-style-type: none"> 1. What tool or approach is currently used to capture [X] measure? How do you feel about this approach? 2. What are the limitations for capturing the measure this way? 3. Is there another tool or method you'd like to see capture this measure? Why/why not? 4. Would you want to capture the measure remotely/outside of the clinical setting (e.g. with a wearable or sensor)? Why do you feel this way? 5. Will use of [X] tool (e.g. a remote method or digital tool) reduce staff time? How? 6. What is the level of data quality using this tool/method? 7. At what frequency should [X] be measured? Why?
Demonstrating Therapeutic Benefit	<ol style="list-style-type: none"> 1. How could [X] measure demonstrate therapeutic benefit? 2. What is the sensitivity of this measure to detect change in health from a therapeutic intervention? How sensitive does it need to be? 3. How, if at all, could the use of a digital technology or tool increase the sensitivity of traditional measures to detect change?
Identifying Meaningful Outcome Measures: Questions to Ask a Health Insurance/Payer/Health Technology Assessment (HTA) Body	
Topic Area	Questions
Outcome to be Measured	<ol style="list-style-type: none"> 1. Does this measure seem appropriate in a cost versus benefit evaluation? Why/why not? 2. What information do you need to determine that this is an appropriate measure? 3. What matters most to you when evaluating the measures that are included in novel endpoints?

Method/Tool to Measure the Outcome	<ol style="list-style-type: none"> 1. What types of digital data capture tools would you consider allowing to demonstrate clinical benefit? 2. Would the selected digitally derived endpoint be useful for quality metric reporting (considering updated requirements put in place during COVID)?
Demonstrating Therapeutic Benefit	<ol style="list-style-type: none"> 1. How do you evaluate whether a change in what is being measured will influence day to day life? 2. What information is needed to demonstrate value to align payment accordingly (from fee for service to fee for an outcome)? 3. What other information do you need to support reimbursement?
Identifying Meaningful Outcome Measures: Questions to Ask Yourself/Your Internal Sponsor Team	
Topic Area	Questions
Meaningful Aspect of Health	<ol style="list-style-type: none"> 1. What are the top 3 patient-reported meaningful aspects of health (MAH)? 2. Do the patient-reported MAHs align with clinician reported MAHs? If not, how will you address the differences? 3. What are the health aspects that prohibit participants to stay in a trial?
Concept of Interest	<ol style="list-style-type: none"> 1. What aspects of the condition matter most to patients that might be addressed by a medical therapy? (How) does this vary by subpopulation? ¹ 2. What are the top 1-3 concepts of interest (COI's) that you've selected? 3. How does worsening or improvement of this COI correlate with other symptomology? 4. What are the safety monitoring considerations for this COI?

Outcome to be Measured	<ol style="list-style-type: none"> 1. What are the possible ways or outcomes to measure the concept? 2. What core outcome sets (e.g., noted in the COMET database) exist for this concept currently? 3. What is the current accepted endpoint to date, if any? 4. Is the outcome selected meaningful to the patient? How do you know? 5. What are we addressing about the condition with this outcome? (i.e., how does the outcome reflect the COI?) 6. How does the outcome correlate with symptoms and/or disease progression? 7. Will this outcome address whether the intervention works? Or whether the intervention is safe? Why do you feel that way? 8. What are the limitations to this outcome measure? 9. Would the interpretation of this outcome be affected by intervening events? How so?
Method/Tool to Measure the Outcome	<ol style="list-style-type: none"> 1. What is the best tool to capture the outcome? Why? Can it be done remotely/outside of the clinic? 2. How will the use of the selected tool (e.g. a digital health technology) provide value beyond the traditional way of capturing this outcome? 3. How feasible is it to capture the outcome on a consistent basis? 4. If using a DHT, to what degree can we operationalize this measure into a clinical trial? (e.g., is it feasible, scalable, secure, in the country we are intending it for?) Explain. 5. What is the statistical methodology? 6. What considerations are there, if any, about data capture, privacy, and missing data? 7. How might missing data effect the quality metric reporting for a payer/health insurance company/HTA? 8. How does this approach compare to or bring added value over an existing endpoint? Over competitor approaches?

Demonstrating Therapeutic Benefit	<ol style="list-style-type: none"> 1. What is a clinically meaningful change in an endpoint from a patient perspective?¹ 2. How can we define meaningful change in a patient over time?¹ 3. What other measures may be required to get a complete picture of the treatment effect? 4. Can we infer benefit to the patient by using a digitally-derived endpoint? What makes you feel this way? 5. Will the benefit be correlative or direct? How does that influence our assessment of benefit? 6. Can the endpoint be incorporated in clinical trials in a manner that will be robust enough for regulatory decision making?¹ 7. How does the endpoint contribute to quality metric reporting for health insurers/payers/HTA's? 8. How will you address scenarios where a traditional endpoint does not meet a target in a clinical trial, but the digitally-derived endpoint does, and vice-versa?
-----------------------------------	---

REFERENCES

1. Manta C, Patrick-Lake B, Goldsack JC. Digital measures that matter to patients: a framework to guide the selection and development of digital measures of health. Digital Biomarkers. 2020; 4(3):69-77. <https://doi.org/10.1159/000509725>
2. Core Outcomes Measures in Effectiveness Trials (COMET) Initiative. <https://comet-initiative.org> .
3. BEST (Biomarkers, EndpointS, and other Tools) Resource. Food and Drug Administration. Last Update: November 29, 2021. <https://www.ncbi.nlm.nih.gov/books/NBK338448/>
4. Patient-Focused Drug Development: Methods to Identify What Is Important to Patients Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. October 2019. <https://www.fda.gov/media/131230/download>
5. Clinical Outcome Assessment (COA): Frequently Asked Questions. Food and Drug Administration. December 2020. <https://www.fda.gov/about-fda/clinical-outcome-assessment-coa-frequently-asked-questions>
6. ICH reflection paper on proposed ICH guideline work to advance patient focused drug development. European Medicines Agency. December 2020. https://admin.ich.org/sites/default/files/2020-12/ICH_ReflectionPaper_PFDD_Endorsed-ForConsultation_2020_1118.pdf
7. A Roadmap for Developing Study Endpoints in Real-World Settings. Duke Margolis Center for Health Policy. August 2020. <https://healthpolicy.duke.edu/publications/roadmap-developing-study-endpoints-real-world-settings>