BIO Digital Health Technology (DHT) Evidentiary Template – Clinical Outcome Assessment (COA)

In-Scope:

This document provides a template to outline evidentiary support for the successful use of a fit-for-purpose digital health technology (DHT) that measures a clinical outcome assessment (COA) as an endpoint in a drug clinical trial. The template is intended to be used for DHTs through the IND/NDA submission mechanism.

The template for a biomarker collected by a DHT is addressed in a separate document.

Out-of-Scope:

The following Information is out of scope for this template:

- an electronic patient-reported outcome or "eCOA" (such as a patient diary or rating scale)
- drug development tools that meet the definition of a medical device
- DHTs reviewed as part of the Drug Development Tool Qualification Program
- Determining the regulatory status of the DHT
- Tools that would be considered Medical Devices.

THE USE OF DIGITAL HEALTH TECHNOLOGY

TO MEASURE XXXXXXX

Purpose: **Clinical Outcome Assessment (COA)**

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2. Introduction

Note to authors:

- Introduce the evidence dossier and Table 1 in 2-3 sentences.
- For FDA, include Table 1, "Evidence-based Rationale that the COA is a Fit-for-Purpose Instrument to Assess Concept of Interest Within Indication Clinical Studies" which is adapted from the FDA PFDD Draft Guidance 3 ([2022] Section IV; page 52). Note that component "D" and "E" have subcomponents that may pertain to the target COA(s) depending on the instrument and COA type.
- Ensure that the **digital elements** are considered and referenced as applicable for each Component below (i.e., E. method of scoring/algorithm used the COA is appropriate for the COI, algorithm objective measure of physical activity can be captured by an accelerometer).

Table 1: Evidence-based Rationale That the COA is a Fit-for-Purpose Instrument to Assess Concept of Interest Within Indication Clinical Studies

Component	Rationale and Supporting Evidence	Dossier Section
A. The concept of interest should be assessed by COA type measures.	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX
B. The COA instrument name captures all the important aspects of concept of interest.	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX
C. Participants understand instructions, of the COA instrument name as intended.	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX
D.		
D1. Task interpretations or relevance do not differ substantially according to respondents' demographic characteristics (including sex, age, and education level) or cultural/linguistic backgrounds or physical environment.	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX
D3. Participant fatigue or burden does not overly influence assessment of concept of interest [for PRO, ObsRO,	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX

ClinRO, and PerfO instruments].		
D.4 The mode of assessment does not overly influence assessment of concept of interest [for PRO, ObsRO, ClinRO, and PerfO instruments].	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX
D.5		
D.6 Practice effects do not overly influence the assessment of concept of interest [PerfO measures].	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX
E. The method of scoring COA instrument name responses is appropriate for assessing concept of interest.	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX
E.1 Responses to an individual item/task is appropriate for assessing concept of interest.	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX
E.2 Rationale for combining responses to multiple items/tasks is appropriate for assessing concept of interest.	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX
E.3 Scoring approaches based on computerized adaptive testing is appropriate for assessing concept of interest.	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX

	E.4		
F.	Scores from the COA instrument name correspond to the participants /caregivers' specific health experience(s) with concept of interest.	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX
G.	Scores are sufficiently sensitive to reflect clinically meaningful changes in concept of interest within participant/caregivers over time in concept of interest.	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX
H.	Differences in COA instrument name COA summary score(s) can be interpreted and communicated clearly in terms of the expected impact on participants'/ caregivers' experiences.	Provide 1-3 sentences summarizing the rationale/position on the component with evidence.	Section XX.XX

3. Background Information on Disease and Patient Experience

3.1 Background Information on Disease

Provide brief overview of the disease and burden of the disease in society, including natural history and address the areas of unmet need regarding treatment or measures.

3.2 Background Information on Patient Experience

Provide brief overview of the patient's experience and burden of disease, including what is important and/or meaningful to the patient. This can range from disease-defining symptoms to broader consequences in physical and psychosocial functioning that reflect the patients' experience with the disease.

4. Regulatory History

Include summary of previous HA interaction on the novel methodology development and validation plans or evidence.

5. Clinical Meaningfulness, Concept of Interest, and Context of Use

5.1 Proposed Name of the Digital COA

Include the name of the proposed digital COA measure as well as the DHT(s) that will be used to derive the measure.

5.2 Clinical Meaningfulness

Identify, clearly describe and provide scientific evidence (including patient preference studies, PFDD, etc.) as to the aspect(s) of health that are meaningful to patients with the relevant disease, condition, or disorders(s) and are clinically relevant. This can include an aspect of disease that a patient (a) does not want to become worse, (b) wants to improve, or (c) wants to prevent.

Example Clinical meaningfulness:

"Keeping up with peers is commonly reported as one of the biggest challenges in ambulatory patients with XX disease, in addition to lower mobility issues, such as running, walking, or playing sports."

5.3 Concept of Interest

The COI is the aspect of an individual's experience or clinical, biological, physical, or functional state that the assessment is intended to capture or reflect. Examples of COI could include improvement in a symptom of specific function or to prevent loss or further worsening of a symptom or specific function, such as progressive muscle weakness.

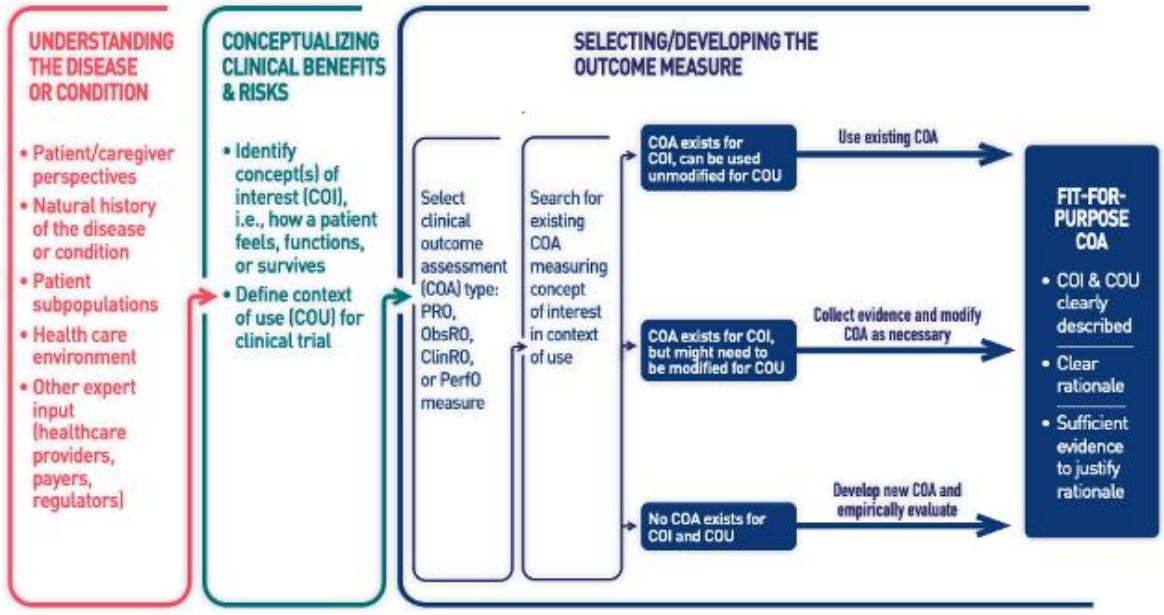
Describe which of the concepts of interest (COI) you are focusing on based on what is meaningful to patients and clinically relevant and how the digital COA relates to that concept. This section should include discussion of which COI were considered and set aside, as well as those which have been selected for

qualification advice/opinion. Depending on the disease or condition, COI may already be established and literature and any prior work should be referenced here.

Example COI and outcome to be measured:

"Lower limb function. Outcome to be measured is ambulatory speed."

Example Roadmap for Developing a Fit-For-Purpose, Patient Focused COA[1]



5.4 Context of Use (CoU)

Context of use (CoU) is defined as "a statement that fully and clearly describes the way the medical product development tool [such as a wearable sensor] is to be used and the medical product development-related purpose of the use".[2] CoU considerations can include:

- Use of the Digital COA within the clinical trial
- Target Population within the full range of the disease (e.g., the major disease related inclusion and exclusion criteria for trials)
- Study Context, including clinical trial design
- Timing of the assessment
- Digital COA implementation including how/where the DHT will be used to collect the digital COA

[1] https://www.fda.gov/media/159516/download

[2] BEST Glossary.

5.5 Endpoint Description

Describe the overarching objective for use of the measure (i.e. To evaluate the effect of compound X compared to X on the duration/intensity/amount of X in participants using a DHT device.
With regard to digitally-derived endpoints, while you are proposing to only measure 1 or 2 within the clinical trial, other measures may also be captured. Provide any discussion/description regarding what will be captured, including what the measures are, units and a layman's description of the measure (i.e. MVPA, captured in mins, and is the total time the participants spend in moderate or vigorous activity state within a day.

Describe how the endpoint will be analyzed in the clinical trial.

6. DHT Name and Description

6.1 Description of the Critical Quality Attributes (CQAs) of the DHT

6.1.1 Technical and Performance Specifications for the DHT., e.g., sensitivity, accuracy, specificity, precision over the range of expected conditions for patients within trial

6.1.1.1 Consistency across the range of patient/subject factors

6.1.2 General Hardware Considerations

Sections below are to be completed as applicable to the digital measure

6.1.2.1 Electromagnetic compatibility
6.1.2.2 Biocompatibility
6.1.2.3 Electrical safety
6.1.2.4 Liquid and dust protection
6.1.2.5 Reprocessing, including cleaning before/after use

6.1.3 Software Considerations

6.1.3.1 Cybersecurity, if involving software/mobile app, general-purpose mobile platform

6.2 Example of DHT(s) that meets the CQAs that will be used in prospective trial, including regulatory history (if applicable)

Provide a list of specific DHTs that may be used in planned trials. For each DHT listed, provide the details of sections 4.6.2.1-4.6.2.3.1

6.2.1 Capabilities to meet or exceed minimum CQAs for sensitivity, specificity, precision, accuracy

6.2.2 Hardware Considerations

6.2.2.1 Electromagnetic compatibility
6.2.2.2 Biocompatibility
6.2.2.3 Electrical safety
6.2.2.4 Liquid and dust protection
6.2.2.5 Reprocessing, including cleaning before/after use

6.2.3 Software considerations

6.2.3.1 Cybersecurity, if involving software/mobile app, general-purpose mobile platform

7. Need for and Impact of the Novel Methodology in Clinical Drug Development

7.1 Currently Available Drug Development Tools

Description of currently available measurement tools, especially other COAs, and functional tests used as endpoints for the disease of interest (traditional measures). Can also provide evidence for where medical community has indicated improved tools are needed or limitations of gold standard measurements and endpoints, ideally as described in literature via end-user qualitative research.

7.2 Identified Gaps and Needs Intended to be addressed by the Application of Digital COA in Clinical Drug Development

Description of the need for the proposed digital measure (i.e. current measurement gaps) including utility and benefits that may be realized if the digital measure is successful. [3] This may include why traditional measures or measures previously used do not serve as suitable comparators.

Supportive information for digital measure and CoU: Summary of current preclinical and clinical results supporting the digital measures proposed outcome.

[3] See CTTI Novel Endpoints Interactive Selection Tool for additional considerations.

8. Verification, Usability, Analytical Validation, Clinical Validation, and Meaningful Change

Figures and tables are key in this section. Include description for each planned study being used for evidence generation. Amount of information included will depend on phase of development.

8.1 Verification

The verification process evaluates the capture and transference of a sensor-generated signal into collected data, ensuring the sensors capture analog data accurately and the firmware generates appropriate output data. Provide description of verification evidence, e.g. bench evaluation for accuracy and precision. Furthermore, provide a rationale for the performed experiments and acceptance criteria.

8.1.1 Performance characteristics, operations manual, algorithm versioning) for the proposed DHT in the intended context of use

8.1.2 Evaluation of factors that might impact the measurement, such as placement of a wearable DHT (e.g., wrist versus hip), or physical interference with the measurement, such as participant activities that may be misinterpreted as the clinical event or characteristic of interest (e.g., a bumpy car ride misinterpreted as a tremor).

8.1.3 Evaluation of the calibration process, when applicable

8.1.4 Safety; Data Storage and Transfer Methodology

8.1.5 Ability to detect clinically relevant change in the measurement of interest

8.1.6 Interoperability

8.2 Usability

8.2.1 Summary

8.2.2 Evidence of User Experience

Describe what types of evidence were collected to ensure that the digital measure will be employed reliability and safely by the target groups **and** in the proposed Context of Use.

Methods may include observations from behavioral experiments, usability interviews, and/or usability quantitative surveys.

Describe whether an iterative process of review and adjustment was undertaken at any point to develop or modify the product as informed by user experience research.[4]

8.3 Analytical Validation

Provide brief abstract.

8.3.1 Study X (can copy for additional studies)

A. Objectives and Endpoints
- **a.** Analytical validation objectives

B. Study Design
- **a.** Description of the study
- **b.** Test subject population
- **c.** Data capture protocol
- **d.** Study DHT (Name, Model, Details (i.e. algorithm description)
- **e.** Reference standard and rationale
- **f.** Testing protocol

C. Statistical Considerations
- **a.** Primary Effectiveness Analysis
- **b.** Determination of Sample Size

8.3.2 Measurement Period(s)

Briefly describe the details regarding the proposed periods of measurement for the digital COA.

8.3.3 Missing Data

Outline the methods for resolving issues with respect to missing data.

8.3.4 Summary of Analytical Validation Studies

8.3.5 Conclusion

[4] Patient-Centric Product Development: A Summary of Select Regulatory CMC and Device Considerations - ScienceDirect

8.4 Clinical Validation

Provide brief abstract.

8.4.1 Study X (can copy for additional studies)

A. Objectives and Endpoints
- **a.** Analytical validation objectives

B. Study Design
- **a.** Description of the study
- **b.** Test subject population
- **c.** Data capture protocol
- **d.** Study DHT (Name, Model, Details (i.e. algorithm description)
- **e.** Reference standard and rationale
- **f.** Testing protocol

C. Statistical Considerations
- **a.** Primary Effectiveness Analysis
- **b.** Determination of Sample Size

8.4.2 Summary of Clinical Validation Studies

8.4.3 Conclusion

8.5 Meaningful Change

Meaningful change represents the amount of change in an endpoint measure perceived as important to patients and should be determined for each digital endpoint and given population under consideration.[5] Recommend that multiple approaches are adopted, and the derived meaningful change thresholds from different approaches to ensure greater confidence in the range of values derived. Examples include anchor-based methods, distribution-based methods, and qualitative methods.

Outline the COAs used to determine meaningful change threshold and describe the relationship to the concept of interest measured by the digital endpoint.

9. Overview of Proposed Use in Clinical Trials

9.1 Endpoint Positioning

Define the target endpoint positioning (e.g. primary, secondary).

[5] McCarthy, M., et al. From Meaningful Outcomes to Meaningful Change Thresholds: A Path to Progress for Establishing Digital Endpoints. Ther Innov Regul Sci. 2023 Jul;57(4):629-645.

9.2 Target Label Claim

State the intended Label Claim for the endpoint.

REFERENCES & APPENDICES