EFPIA Proposal for EMA: Qualification of a Novel Methodology
Briefing Book Template for Digital Measure (COA)

Scope:

This document outlines a template for information and evidence intended for submission in a request for qualification advice or opinion for a novel methodology (QoNM) – specifically measures collected by digital health technologies (DHT) that are intended as a clinical outcome assessment (COA) or digital COA. (See "Key Terms" section). The template for a biomarker collected by DHT is addressed in a separate document.

The QoNM guidance states that a submission should "provide insight into the reliability, accuracy, precision, clinical validity, generalisability, and clinical applicability of the methodology to be qualified."[1] The digital COA checklist is intended to guide companies through a structured approach to develop the necessary evidence and validation requirements in support of scientific advice with EMA as part of the QoNM process. This scientific advice is confidential.

Use of this template by companies does not require the company to seek a full qualification opinion from EMA (i.e. SV95C), which is a more public process. The template could also be used in other regulatory interactions with EMA, if desired by either the Sponsor or EMA, such as in an Innovation Task Force (ITF) meeting.

Out-of-Scope:

The following Information is out of scope for this template:
- qualification of an electronic patient-reported outcome or "eCOA" (such as a patient diary or rating scale)
- evidence necessary to obtain a CE-mark for the DHT, if it has a medical purpose (i.e screening, diagnosis, monitoring, treatment)

Acknowledgement:

We recognize the significant work on this topic originally published by Walton, et. al.[2], which served as inspiration for this aligned approach by our EFPIA working group.

[1] EMA Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products. June 2020.

[2] Walton MK, Cappelleri JC, Byrom B, Goldsack JC, Eremenco S, Harris D, Potero E, Patel N, Flood E, Daumer M. Considerations for development of an evidence dossier to support the use of mobile sensor technology for clinical outcome assessments in clinical trials. Contemp Clin Trials. 2020 Apr;91:105962. doi: 10.1016/j.cct.2020.105962. Epub 2020 Feb 20. PMID: 32087341.

Key Terminology[3]

- **Digital measure**: an obtained value using a test, tool, or instrument derived from data captured by digital health technology (DHT). A digital measure can be used to derive a variable that can be used as an endpoint in the context of a clinical trial.

- **Digital biomarker**: a defined characteristic or set of characteristics that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention and is derived from data captured by a digital health technology (DHT). A biomarker is not an assessment of how a patient feels, functions, or survives.

- **Digital clinical outcome assessment (COA):** assessments of a clinical outcome defined by how a patient feels, functions, or survives that is derived from data captured by a digital health technology (DHT).

- **Digital endpoint**: precisely defined variables intended to reflect an outcome of interest that is statistically analyzed to address a particular research question and is derived from data captured by a digital health technology (DHT).

- **Digital health technology (DHT):** systems that use computing platforms, connectivity, software, and/or sensors for healthcare and related uses. They include technologies intended for use as a medical product, or as adjunct to other medical products (devices, drugs, and biologics). They may also be used to develop or study medical products.

- **Electronic clinical outcome assessment (eCOA):** a clinical outcome assessment that has been implemented on an electronic data collection platform (e.g. smartphone or tablet). [In essence, refers to digitization of paper-based COAs, such as scales or patient diaries. It should not be considered inclusive in digital COA as defined above.]

[3] Leyens L, Northcott CA, Maloney L, McCarthy M, Dokuzova N, Pfister T; EFPIA digital endpoint joint sub-group; with contributions from Aude Clement. Why Language Matters in Digital Endpoint Development: Harmonized Terminology as a Key Prerequisite for Evidence Generation. Digit Biomark. 2024 Jan 11;8(1):1-12. doi: 10.1159/000534954. PMID: 38222479; PMCID: PMC10783888.

THE USE OF DIGITAL HEALTH TECHNOLOGY TO MEASURE XXXXXXX

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

LIST OF ABBREVIATIONS

LIST OF TABLES

LIST OF FIGURES

TABLE OF CONTENTS

Digital Measure (COA) Qualification Briefing Book

1. Executive Summary

Provide short abstract describing the novel methodology (digital COA), its context of use, and the meaningful aspect of health it intends to address. This includes a full, clear detailed description of the way the digital COA is to be used, and the medicine development related purpose of the use needs to be provided (phase of development, nature of endpoint (primary, secondary, exploratory), which parameter, which DHTs). Include brief description of the evidence to support the digital COA as well as a brief description of the DHT used to collect the data.

2. Rationale for Seeking Advice/Opinion

Objective of the request and what the applicants are trying to achieve (i.e. seeking qualification advice for a primary endpoint in XX disease).

3. Previous Regulatory Engagements

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

4. Meaningful Aspect of Health, Concept of Interest, and Context of Use

4.1 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.

4.2 Meaningful Aspect(s) of Health (MAH)

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 MAH:

"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."

4.3 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.

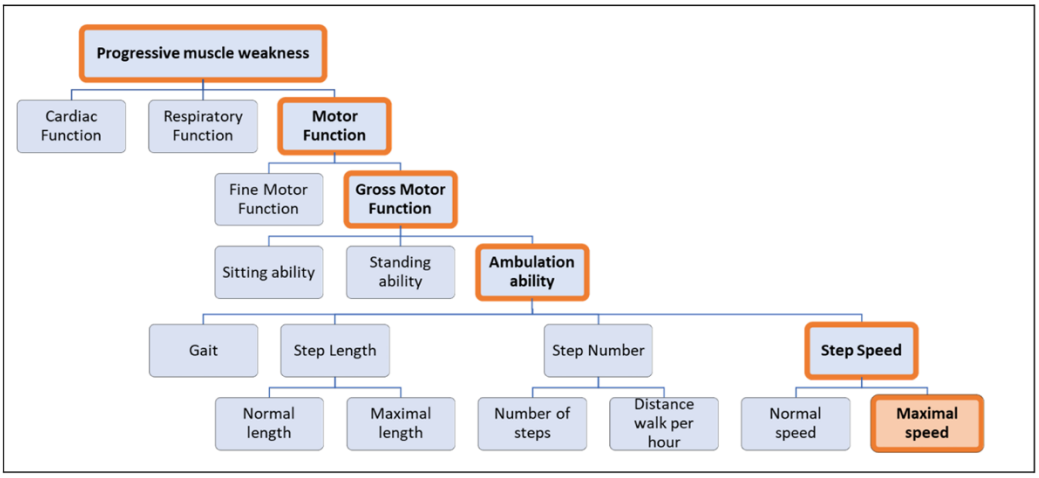
Describe which of the concepts of interest (COI) you are focusing on based on what is meaningful to patients and clinically relevant and how the digital COA relates to that concept. This section should include discussion of which COI were considered and set aside, as well as those which have been selected 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 conceptual framework from Strive Velocity 95thcentile EMA Qualification Opinion[4]

Figure 1: SV95C Conceptual Framework



4.4 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".[5] 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

[4] EMA: Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies. July 2023

[5] BEST Glossary.

- Timing of the assessment
- Digital COA implementation including how/where the DHT will be used to collect the digital COA

4.5 Endpoint Definition

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.

It is realized that with regards 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 (suggest providing a table for simplicity).

Table 1. Description of Digital Endpoints

Digital Measure	Units	Description	Concept of Interest

4.6 DHT Device

Provide the specification and technical details of the DHT device that will be used to measure the device for the proposed endpoint. Details to include sensors used, markings and certificates for the device, battery life, planned wear location and durations, how provisioned, any feedback the patient may or may not receive, etc. A data flow map should be provided detailing how data is transferred from the DHT to the sponsor database.

4.6.1 Measurement Period(s)

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

4.6.2 Missing Data

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

4.6.3 Endpoint Positioning

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

4.7 Target Label Claim

State the intended Label Claim for the endpoint.

5. Background Information on the Disease and Patient Experience

5.1. 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.

5.2. 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.

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

6.1 Currently Available Tools in Patient Care and Clinical Drug Development

Description of currently available drug therapies, measurement tools, especially other COAs, and functional tests used as endpoints for the disease of interest. 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.

6.2 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. [6]

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

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

7. Verification, Validation, Meaningful Change, and Usability/Wearability

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.

7.1 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..

7.2 Analytical Validation

Provide brief abstract.

7.2.1. 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

7.2.2. Summary of Analytical Validation Studies

7.2.3. Conclusion

7.3 Clinical Validation

Provide brief abstract.

7.3.1. Study X (can copy for additional studies)

A. Objectives and Endpoints

a. Clinical validation objectives

B. **Study Design**

a. Description of the study

b. Test subject population

c. Data capture protocol

d. Study DHT (Name, model, details)

e. Reference standard and rationale

f. Testing protocol

C. Statistical Considerations

a. Primary Effectiveness Analysis

b. Determination of Sample Size

7.3.2 Summary of Clinical Validation Studies

7.3.3 Conclusion

7.4 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.[7] 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.

7.5 Usability/Wearability

7.5.1 Summary

7.5.2 Evidence of User Experience (UX)

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 UX Research.[8]

8. Gaps in Development

Identify known gaps in development related to the measure or the DHT.

[7] 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.
.

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

9. Conclusion

REFERENCES & APPENDICES

Any types of reports, protocols, SAPs, site guides, technical verification documents