Digital Health Technology (DHT) Evidentiary Framework- Biomarker

This document provides a framework to outline evidentiary support for the successful use of a fit-for-purpose digital health technology (DHT) that measures a biomarker as an endpoint in a drug clinical trial. The framework is intended to be used for DHTs through the IND/NDA submission mechanism (not the DDT qualification program) that are considered digital tools for use in drug development and are not considered Medical Devices.

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1. Executive Summary

1.1 Background

1.1.1 Regulatory History

1.2 Biomarker Name, Type, and Description

1.3 Context of Use (COU) Statement

Summary of measurement gaps in the current measurement tools in the functional domain that the digital biomarker aims to assess and what value it has for patients. Include targeted patient population.

1.4 Example DHT name and description

1.5 Overview of Verification

Summary of benchtop lab tests results available from the manufacturer.

1.6 Overview of Analytical Validation

Summary of measurement process including such details as lab process specifications; how ground truth was assessed; populations which have been a part of validation trials; algorithms used to convert raw signals into digital measures; algorithm characteristics such as sensitivity, specificity, etc.; summary of validation trials performed.

1.7 Overview of Clinical Validation in support of the proposed biomarker's COU

Summary of the clinical validation evidence: trials, populations, list of conventional outcomes considered when developing the digitally-assessed biomarker.

1.8 Overview of Proposed use in prospective Clinical Studies

2. Biomarker Name, Type, Description, COU

Refer to the BEST Glossary https://www.ncbi.nlm.nih.gov/books/NBK338448/ for more information on terminology

2.1 Proposed biomarker name and type (e.g., imaging, actigraphic)

2.2 COU Statement

2.3 Description of the target disease population (severity of disease and any unmet need)

2.4 Biomarker category

2.5 Proposed use: outcome of interest, purpose of use, stage of development, clinical trial population or model

3. DHT name and description

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

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

3.1.1.1 Consistency across the range of patient/subject factors

3.1.2 General Hardware considerations

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

3.1.2.1 Electromagnetic compatibility

3.1.2.2 Biocompatibility

3.1.2.3 Electrical safety

3.1.2.4 Liquid and dust protection

3.1.2.5 Reprocessing, including cleaning before/after use

3.1.3 Software considerations

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

3.2 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 3.2.1-3.2.3.1

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

3.2.2 Hardware considerations

3.2.2.1 Electromagnetic compatibility

3.2.2.2 Biocompatibility

3.2.2.3 Electrical safety

3.2.2.4 Liquid and dust protection

3.2.2.5 Reprocessing, including cleaning before/after use

3.2.3 Software considerations

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

4. Verification for DHT to be used in prospective trial

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

4.2 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).

4.3 Evaluation of the calibration process, when applicable.

4.4 Safety; Data Storage and Transfer Methodology

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

4.6 Interoperability

5. Usability validation

This section is to explain usability studies performed or will be performed

5.1. Evaluation of whether the DHT can be used to achieve specified goals with ease, efficiency and user satisfaction (including different metrics: Satisfaction, Usefulness, Ease of use, Learnability, Efficiency, Readability, Actionability…)

Include relevant users: patients, clinicians, etc. Use compliance and other human factors information.

5.2. Usability of the DHT to effectively capture the biomarker in the population of interest, including patient diversity (e.g. PPG sensors and skin tones).

6. Analytical Validation for DHT to be used in prospective trial

6.1. Summary of analytical data

6.1.1. DHT's measured performance characteristics (Accuracy, precision, consistency across time, across different environment conditions (e.g., fatigue testing or reproducibility); Reliability assessments including intra- and inter-unit reliability assessments

> Briefly describe population of the trial (e.g., healthy volunteers and patient population). Provide a summary of the methodology behind true labels collection. Cite the algorithms used to transform the raw signal into digital measures including temporal resolution. Provide performance characteristics of developed algorithms: sensitivity, specificity, predictive values, AUC etc., reliability including summary of noise characteristics.

6.1.2. If DHT will be used remotely: Evaluation and justification of potential differences between measurements obtained from participants remotely compared to measurements obtained from participants in a clinic setting using the same DHT.

> Summary of evidence looking specifically at situations when the same DHT is used remotely compared to in-clinic. Processes employed, methodology of assessment, the summary of results.

6.2. Comparisons of measurements made by the DHT with reference measurements of the clinical event or characteristic (e.g., step count by actigraphy versus step count by observation)

> Describe device comparability generated evidence: gold standard versus DHT-derived. Both processes should be described and evaluated, sources of explained variance as well as summary of unexplained variation should be provided. Methodology behind process comparisons should be provided along with the results of these comparisons. It is advised to have both observational data and treatment effect assessment data as measured by the both processes/devices.

6.3. Impact of missing data on interpretation of the biomarker and mitigation steps

7. Clinical Validation for the biomarker

7.1. Summary of clinical validation evidence for the proposed biomarker, as measured by the DHT, in the intended context of use

> Include summary of any prior validation of the biomarker and/or the DHT (e.g., prior investigations, qualification as a drug development tool, biomarker, or other similar regulatory construct) where applicable

7.1.1. Estimation of meaningful change (Threshold of change: magnitude, timing of change, and reasoning for selection)

7.1.2. Ability to detect clinically relevant change in the measurement of interest

> May be addressed in other sections as appropriate. Should include description of validation method if applicable. Should address clinical relevance of biomarker in context of use/targeted population.

7.1.3. Consistency of biomarker in diverse subgroups of targeted population

> If variability exists in biomarkers across subgroups, then should include plan for addressing variability across populations, where appropriate.

8. Overview of proposed use in prospective Clinical Studies

8.1. Applicability of COU to proposed study

Explain the fitness of purpose of digital biomarker for proposed study.

8.2. Study description

8.2.1. High-level description of the use of the DHT in the planned study

8.2.2. High-level description of analysis plan for evaluation of endpoint