BIOMARKERS CONSORTIUM
IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

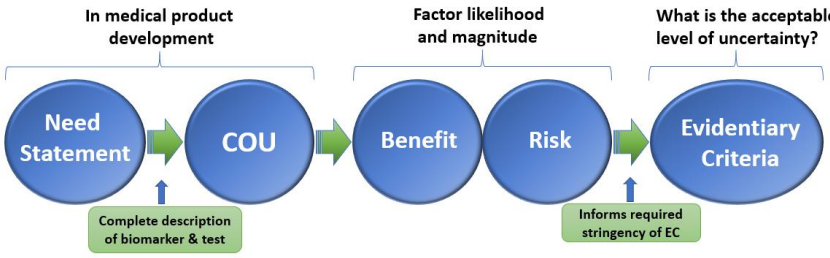
FNIH
Foundation for the National Institutes of Health

Remote Digital Monitoring for Medical Product Development Workshop

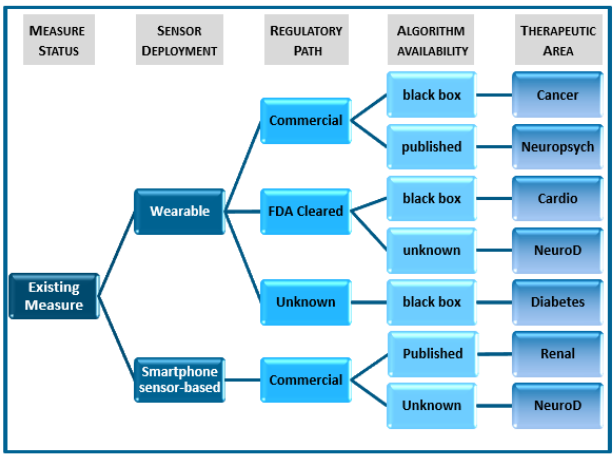
The use of digital health technologies has gained interest from consumers, providers, and researchers as a new way to improve research and development (R&D) of new therapeutics. This Workshop will provide a venue to address challenges and opportunities in the use of remote sensing technologies for improving the probability of success of drug development trials. Important characteristics of tool development in this growing digital landscape will be addressed in a series of case studies that will be described by presentation and discussed in open panel sessions.

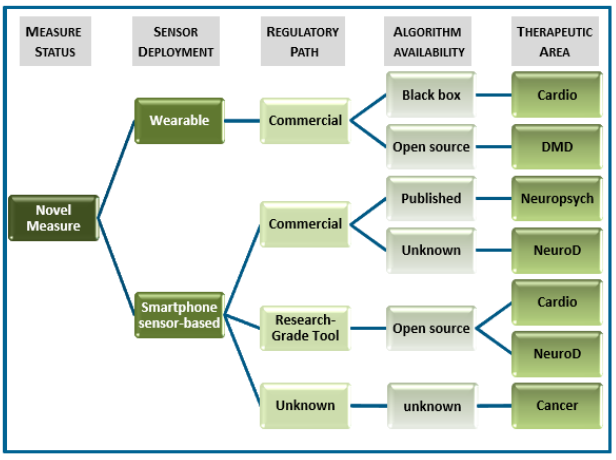
Workshop Goals:

- Bring together diverse stakeholders in the field to reach consensus on the use of a single vocabulary that will be understood consistently in the regulatory context
- Identify areas of high medical need that could be addressed using digital system technologies
- Ensure stakeholder alignment and application of an evidence-based framework for the use of digital health technologies for therapeutic research and development



The individual drug development use case studies will provide an important backdrop for obtaining a decision-making perspective and will lead to deeper discussion on specific steps of the Drug Development Tool (DDT) process. The planning committee took a data driven approach to choosing the case studies based on identifiable criteria (e.g. type of sensor and its regulatory path and algorithm availability). A broad range of potential DDTs were identified, and ultimately selected, based on different parameters (e.g. novel or existing measures; commercial or FDA-cleared devices; if the algorithm is open source or black box; and multimodal or single modality). These criteria were chosen to present different challenges in evidence collection and enrich the discussion during the Workshop.





In addition to these selection criteria, the planning team wanted to choose case studies across several therapeutic areas and covered both multimodal or single modality measures. Using this thought process, the team has identified 5 case studies that they felt would provide a good basis for identifying the types of evidence needed to develop a confident decision-making tool. Two case studies were selected in neurologic disorders as progress and development of mobile monitoring technologies to measure disease status and deliver care are likely to significantly enable this therapeutic area soon.

Case Studies for the Workshop are described briefly below. All the case study team members have been asked to follow a template set of slides so that the studies can be more easily compared. In addition, the teams have been asked to focus on the drug development tool, rather than the disease or specific measurement device. Additional reference materials and links to online resources related to each of the case studies is provided below.

Case Studies:

The first case study discussion will address the development of a monitoring biomarker in Parkinson's disease using data and design from the Mobile Parkinson's Observatory for Worldwide, Evidence-Based Research (mPower) study. These monitoring markers are novel, smartphone apps to measure tremor/activity/movements. The mPower dataset is extensive and should provide a wealth of data and information for comparative analysis.

Monitoring of vital signs (e.g. heart rate (HR)) in early drug development trials is central to early safety studies. The second case study explores the use of wearable technology to monitor HR and tachycardia and uses data from FDA-cleared devices. Thus, while the measurement approach is new, the existing measure is very well established (HR and tachycardia) for cardiovascular monitoring.

The next case study will address the relationship between blood glucose level, Hemoglobin A1c (HbA1c) and continuous blood glucose monitoring in a drug development setting. This discussion will address the challenge of running a remote trial, and the addition of new, continuous monitoring data, when a backup measure (HbA1c) is available. The VERKKO trial, a fully remote online Phase IV clinical trial for diabetes, will provide a background to this discussion but the case study will allow discussion of how results from a non-wearable device trial can aid in generating evidence from a novel wearable device in a drug development context.

Measurement of movement in Duchenne Muscular Dystrophy (DMD) is a fundamental part of the drug development paradigm of this disease. Recently, the EMA has approved a 95th percentile stride velocity DDT for use in DMD trials. This case study will describe a successful path for a novel, commercial wearable device. Lessons learned from stride velocity will be helpful for the development of approaches that are in earlier stages of DDT development.

Finally, the objective measurement for diagnosis and monitoring of Major Depressive Disorder (MDD) has been a significant roadblock to the development of new treatments for this disease. The Remote Assessment of Disease and Relapse in Major Depressive Disorder (RADAR-MDD) study has been setup to develop novel methods and infrastructure for monitoring MDD (and epilepsy and MS) using either wearable devices or smartphone apps that either collect data passively from existing smartphone sensors, or can deliver questionnaires, cognitive tasks, and speech assessments. While the development

of a biomarker or Clinical Outcome Assessment (COA) from this work is in the early stages, the data generated is being used to identify a multimodal measure for objective diagnosis and monitoring.

Several presentations outside the case study framework will help guide discussions and set the stage for effective information sharing. Keynote Speaker Jennifer Goldsack, Executive Director of the Digital Medicine Society, will provide a scientific landscape in digital health. Given her role at the Digital Medicine Society, Jennifer can provide a unique and broad overview of the opportunities and challenges in the area.

Dr Jill Heemskerk, Deputy Director, National Institute of Bioimaging and Bioengineering (NIBIB), will provide a plenary talk on the NIH Pipeline in Digital Technologies and describe the current areas of interest for NIBIB and NIH. Finally, the regulatory interest in this area will be evident from two plenary talks by FDA representatives (Dr. Christopher Leptak, Director of the Biomarker Qualification Program, CDER, and Dr. Bakul Patel, Director, Division of Digital Health, CDRH) who will discuss the FDA perspective addressing evidentiary principles for drug development tools, and digital health technology development.

Meeting Deliverables:

The planning team will incorporate the insights and proceedings of the Workshop into a white paper and related manuscript that can be used to develop operational and regulatory guidance. This meeting will suggest a set of steps (framework) that can guide the process of remote monitoring measure development for confident decision making. The team will also seek to propose a prioritized list of high-impact endpoints or measures that could be addressed through mobile sensing. This 2-day meeting will provide a forum for open discussion on multiparametric mobile monitoring approaches and a framework for analytical and clinical validation needs for drug developers and regulators.

Recommended Pre-Read Resources:

Guidance Documents
Draft Guidance Document - Biomarker Qualification: Evidentiary Framework
Draft Guidance Document - Qualification Process for Drug Development Tools

Scientific Publications
What evidence do we need for biomarker qualification? C. Leptak, J. P. Menetski, J. A. Wagner, J. Aubrecht, L. Brady, M. Brumfield, W. W. Chin, S. Hoffmann, G. Kelloff, G. Lavezzari, R. Ranganathan, J.-M. Sauer, F. D. Sistare, T. Zabka, D. Wholley, Sci Transl Med. 2017 Nov 22;9(417). pii: eaal4599. doi: 10.1126/scitranslmed.aal4599.

Traditional and Digital Biomarkers: Two Worlds Apart? L. Babrak, J. Menetski, M. Rebhan, G. Nisato, M. Zinggeler, N. Brasier, K. Baerenfaller, T. Brenzikofer, L. Baltzer, C. Vogler, L. Gschwind, C. Schneider, F. Streiff, P. Groenen, E. Miho, Digit Biomark 2019;3:92–102, DOI: 10.1159/000502000

Digital Medicine: A Primer on Measurement. A. Coravos, J. Goldsack, D.R. Karlin, C. Nebeker, E. Perakslis, N. Zimmerman, M.K. Erb, Digit Biomark 2019;3:31–71,DOI: 10.1159/000500413

CTTI Recommendations: Developing Novel Endpoints Generated by Mobile Technology for Use in Clinical Trials

BEST Resource Taxonomy

Case Study Resources:

Safety Cardiac Monitoring

Izmailova ES, McLean IL, Bhatia G, et al. Evaluation of Wearable Digital Devices in a Phase I Clinical Trial. *Clin Transl Sci*. 2019;12(3):247–256. doi:10.1111/cts.12602

Izmailova ES, McLean IL, Hather G, et al. Continuous Monitoring Using a Wearable Device Detects Activity-Induced Heart Rate Changes After Administration of Amphetamine. *Clin Transl Sci*. 2019;12(6):677–686. doi:10.1111/cts.12673

mPower – Parkinson's Disease

Bot BM, Suver C, Neto EC, et al. The mPower study, Parkinson disease mobile data collected using ResearchKit. *Sci Data*. 2016;3:160011. Published 2016 Mar 3. doi:10.1038/sdata.2016.11

Lipsmeier F, Taylor KI, Kilchenmann T, et al. Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial. *Mov Disord*. 2018;33(8):1287–1297. doi:10.1002/mds.27376

Continuous Glucose Monitoring

Russell C, Ammour N, Wells T, et al. A Pilot Study to Assess the Feasibility of Collecting and Transmitting Clinical Trial Data with Mobile Technologies. Digit Biomark 2018;2:126–138

Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. *Diabetes Care*. 2019;42(8):1593–1603. doi:10.2337/dci19-0028

RADAR – Major Depressive Disorder

Matcham F, Barattieri di San Pietro C, Bulgari V, et al. Remote assessment of disease and relapse in major depressive disorder (RADAR-MDD): a multi-centre prospective cohort study protocol. *BMC Psychiatry*. 2019;19(1):72. Published 2019 Feb 18. doi:10.1186/s12888-019-2049-z

Simblett S, Matcham F, Siddi S, et al. Barriers to and Facilitators of Engagement With mHealth Technology for Remote Measurement and Management of Depression: Qualitative Analysis. *JMIR Mhealth Uhealth*. 2019;7(1):e11325. Published 2019 Jan 30. doi:10.2196/11325

Stride Velocity 95th centile in Duchenne Muscular Dystrophy

Haberkamp M, Moseley J, Athanasiou D, et al. European regulators' views on a wearable-derived performance measurement of ambulation for Duchenne muscular dystrophy regulatory trials. *Neuromuscul Disord*. 2019;29(7):514–516. doi:10.1016/j.nmd.2019.06.003

EMA Qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device. 26 April 2019 EMA/CHMP/SAWP/178058/2019 Committee for Medicinal Products for Human Use (CHMP)

FDA Letter of Intent (LOI) submission for DDT COA #000103 ActiMyo®

Miscellaneous Drug Development Resources:

EMA Guidance on qualification of novel methodologies
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-novel-methodologies-drug-development-guidance-applicants_en.pdf

EMA eSource Qualification opinion
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-esource-direct-data-capture-ddc_en.pdf