eCOA: COA Program Projects and Collaborations Updates

14th Annual
Patient-Reported Outcome Consortium Workshop

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CRITICAL PATH INSTITUTE

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Session Outline

- eCOA Consortium Activities and eCOA: Getting Better Together Initiative
- Turning Raw Data into Clinical Endpoint Measures: PRO Consortium's CHF Working Group
- Technical and Analytical Considerations for Wearable Digital Health Technologies
- Mobilise-D: Connecting Digital Mobility Measurement to Clinical Outcomes
- Q & A

Session Participants

Moderator:

- *Scottie Kern, BSc (Hons)* – Executive Director, Electronic Clinical Outcome Assessment Consortium, Critical Path Institute

Presenters:

- *Scottie Kern, BSc (Hons)* – Executive Director, Electronic Clinical Outcome Assessment Consortium, Critical Path Institute
- *Josephine Norquist, MS* – Executive Director, Patient-Centered Endpoints & Strategy Lead, Merck & Co., Inc.
- *Christine Guo, PhD* – Chief Scientific Officer, ActiGraph
- *Ronenn Roubenoff, MD, MHS* – Global Head, Translational Medicine Discovery & Profiling, Novartis Institutes for Biomedical Research
- *Gül Erdemli, MD, PhD* – Global Program Regulatory Director, Novartis Pharmaceuticals Corporation

Panelist:

- *David S. Reasner, PhD* – Division Director, Division of Clinical Outcome Assessment, Office of Drug Evaluation Sciences, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

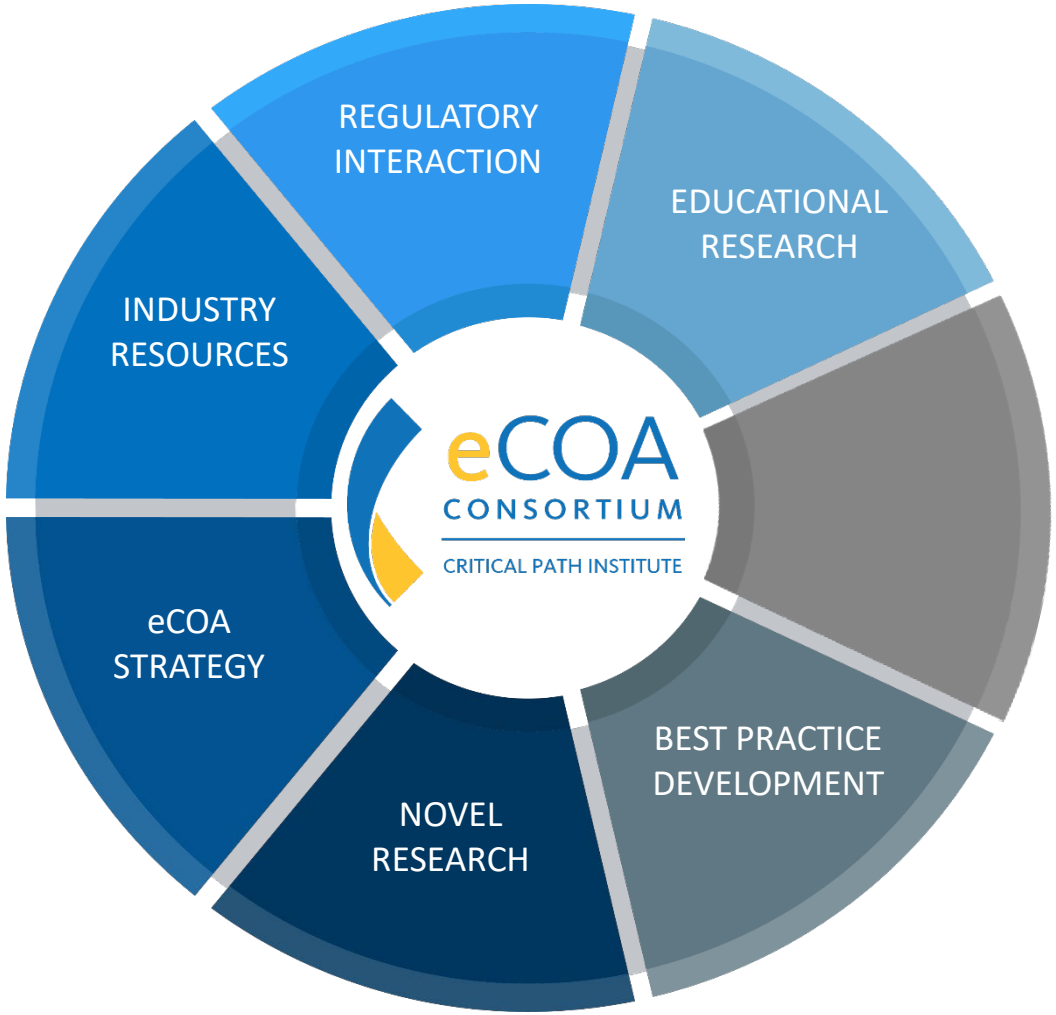
eCOA: COA Program Projects and Collaborations Update

Scottie Kern, BSc (Hons)

Executive Director, eCOA Consortium

Critical Path Institute

eCOA Consortium



Background

The eCOA Consortium was established as the *ePRO Consortium* in 2011. With C-Path as the managing member, the 21 other members of the eCOA Consortium are firms that provide electronic data collection technologies and services for capturing patient-reported outcome (PRO) and other clinical outcome assessment (COA) data electronically in clinical trials. The name was changed to the *eCOA Consortium* in January 2022 to better reflect the capabilities of the membership and the scope of the Consortium's interests and direction.

Mission

To advance the science of clinical trial endpoint assessment by collaboratively supporting and conducting research, designing and delivering educational opportunities, and developing and disseminating best practice recommendations for the electronic collection of clinical outcome data

Membership Status

eCOA CONSORTIUM
CRITICAL PATH INSTITUTE

ActiGraph™

assisTek
The eSource Company

CLARIO.

Clinical ink

ICON

IQVIA™

kayentis
Dedicated to eCOA & Patient Engagement

koneksa

Mapi™
Research Trust

Medable

MEDIDATA

medrio

parexel®

RWS

Science 37®

SIGNANT HEALTH

UVODA®

TRANSPERFECT
LIFE SCIENCES

umotif®

wcg™

yprime

eCOA Consortium Projects

Recently completed

- eCOA Systems and Conformitè Europëenne (CE) Certification
  - Examining how and when eCOA systems would be in-scope for CE certification
  - Target output: Self-published white paper

Active

- Update to Best Practices Recommendations for Paper to Electronic Migration of PRO Measures
  - Updating established best practices with new recommendations addressing newer technology capabilities as well as the creation of a single point of reference for all migration best practices.
  - Target output: Peer-reviewed manuscript; target journal identified
  - Target submission for publication: Q2 2023
- Practical Considerations for the Implementation of Wearables in Clinical Trials
  - Collection of experience-based proposals for employing wearables effectively in clinical trials
  - Target output: Peer-reviewed manuscript; target journal identified
  - Target submission for publication: Q3 2023

Planned

- Opportunities for enhancing uptake of *bring your own device* (BYOD) methods for COA data collection

Collaboration between Consortia

eCOA: Getting Better Together Initiative

Background

What it is:

A collaborative, pre-competitive initiative among C-Path, clinical trial sponsors from the PRO Consortium, eCOA providers from the eCOA Consortium, contract research organizations, and regulators (FDA)

Aims:

- Identify and address the root cause of issues with eCOA implementation in clinical trials
- Drive positive and lasting change in the eCOA ecosystem for the benefit of all stakeholders

eCOA: Getting Better Together Initiative

Wave 1		
Project title	**Deliverable**	**Status**
eCOA Lexicon	Searchable PDF document Iterative updates	• Version 3 finalized; to be posted imminently
eCOA Process/Workflow and Roles/Responsibilities	Searchable PDF document	• Version 1 posted February 2021 • Refresh ongoing; to be posted Q2 2023
Best Practice Recommendations for User Acceptance Testing	Manuscript for publication in peer-review journal	• Published with open access in *Therapeutic Innovation & Regulatory Science* on March 1, 2022. • Link: https://rdcu.be/cM2Jk
Best Practice Recommendations for ePRO Dataset Structure and Standardization	Manuscript for publication in peer-review journal	• Accepted for publication on February 19, 2023, by *Value in Health*
Best Practice Recommendations for Changing eCOA Data	Manuscript for publication in peer-review journal	• Submitted to *Journal of the Society for Clinical Data Management* on March 6, 2023

eCOA: Getting Better Together Initiative

Wave 2		
Support flexible approaches to PRO data collection	3 papers to be submitted to peer-reviewed journals	• Papers approaching completion • Target submission in Q3 2023
Bring Your Own Device (BYOD)	Podcast; manuscript for publication in peer-reviewed journal	• Podcast released May 2022 • Manuscript in development
Translations and Licensing Management	TBD	• Launched September 2022 • Sub-teams formed and active
eCOA Data Management	TBD	• Scope definition complete • Target full project launch Q2/Q3 2023
Site Readiness and Training	TBD	• Planned

Wave 3 – Planned Projects	
eCOA Request for Proposal	eCOA Design Requirements
eCOA Compliance Thresholds	Approaches to Optimizing Timelines and Efficiencies for eCOA Deployment

eCOA: Other Collaborations

Event-driven eDiaries (with PRO Consortium)

- FDA-triggered project examining best practices around use of clinical event-driven eDiaries
- Target output: TBD
- Target initiation: Q3 2023
- Scoping Committee to launch Q2 2023

Accessibility of ePRO systems (with PRO Consortium)

- Develop consideration for ensuring ePRO systems are usable and accessible to patients with physical or other disease or condition-driven limitations
- Target output: TBD
- Target initiation: Q4 2023
- Scoping Committee to launch Q2 2023

Standardization of video-based capture of clinical outcome assessments of movement-based disease status in rare disease clinical trials (with RD-COA Consortium)

- Initial scoping underway

Accessing C-Path's eCOA Resources

https://c-path.org/programs/ecoac/

https://c-path.org/programs/proc/

Home > Programs > eCOA Consortium

OVERVIEW

Introduction Resources Webinars Members eCOA Consortium Team

▸ eCOA Consortium Publications/White Papers Library

▾ eCOA: Getting Better Together Initiative

This initiative is a pre-competitive collaboration among Critical Path Institute, clinical trial sponsors from the Patient-Reported Outcome (PRO) Consortium, providers of electronic data collection technologies and services from the Electronic Clinical Outcome Assessment (eCOA) Consortium, contract research organizations, and regulators. The initiative was launched in 2019 to identify and address the root cause of challenges with the implementation of clinical outcome assessments collected electronically in clinical trials, elevate eCOA improvement efforts to the clinical trial industry level, and drive positive and lasting change in the eCOA ecosystem.

Quarterly Update

Please click here to view the most recent quarterly update, which includes the status of current and future areas of focus.

eCOA: Getting Better Together Initiative

Resources

Name	Description	Links
eCOA Lexicon	Without a common lexicon among eCOA vendors, sponsors, and regulators, the chance for miscommunication, errors, and inefficiencies increases. The objective of this team is to review the terminology and create an aligned eCOA Lexicon for use by stakeholders across the eCOA ecosystem.	eCOA Lexicon

PAST EVENTS

Oct 13, 2022 - Oct 14, 2022
DIA 2022 Digital Technology in Clinical Trials Conference

More Events >>

NEWS

Nov 3, 2022
eCOA Consortium Announces New Article for *Applied Clinical Trials*

Sep 29, 2022
eCOA Consortium Announces New Article for *Applied Clinical Trials*

Sep 27, 2022
Global Biopharmaceutical Leader to Usher C-Path in Next Phase of Growth and Innovation

Sep 8, 2022
C-Path's Kristen Swingle Named President

Turning Raw Data into Clinical Endpoint Measures: PRO Consortium's CHF Working Group

Josephine Norquist, MS

Executive Director, Patient-Centered Endpoints & Strategy Lead

Merck & Co., Inc.

Background

The Chronic Heart Failure (CHF) Working Group has been developing evidence for the qualification of 3 clinical outcome assessments (COAs) for use in CHF clinical trials:

- Two patient-reported outcome (PRO) measures
  - *Chronic Heart Failure-Symptom Scale* (*CHF-SS*)
  - *Chronic Heart Failure-Impact Scale* (*CHF-IS*)
- One activity monitor-based endpoint measure

Letters of Intent (LOIs) were submitted to FDA, and all measures were accepted into FDA's COA Qualification Program in April 2019.

- In its response to the LOIs, FDA requested a Qualification Plan (QP) for each COA.
  - QP for *CHF-SS* was submitted to FDA on March 24, 2023

Activity Monitor-based Endpoint Measure: Strategy

Main challenge: determining what variable(s) from an activity monitor will be used to derive an endpoint that would reflect a meaningful aspect of physical activity to persons with CHF.

Concept elicitation

Qualitative evidence regarding day-to-day physical activities most meaningful to patients

- Activity types
- Activity dimensions
- Narrative analysis

Literature review

Focused, non-systematic review of recent literature was performed as an informal step to guide the overall efforts

Observational study

Amgen has shared data from a parallel study using an activity monitor

- Quantitatively compare step algorithms and
- Test feasibility of proposed endpoint(s)

Advisory Panel

Provide expert feedback on the proposed metrics for an activity monitor-based endpoint measure in CHF

- 2 meetings

Concept Elicitation Study

- N=31; telephone interview - 4 US sites
  - Completed Dec 2020
- Mean age: 68
- 51.6% (n=16) female
- NYHA HF severity:
  - Class II: n=15; 48.4%
  - Class III: n=12; 38.7%
  - Class IV: n=4; 12.9%
- CHF Type:
  - Heart failure w/ preserved ejection fraction (HFpEF): n=12
  - Heart failure w/ reduced ejection fraction (HFrEF): n=19

NYHA: New York Heart Association

- Activities frequently reported involved:
  - **light to moderate physical activity** (e.g., cleaning, cooking, doing laundry, self-care, and gardening), and
  - **walking** specifically (e.g., shopping, exercise, and going to appointments).
- When asked to rate the importance of key activity dimensions for the 3 activities they found most meaningful:
  - **Fulfillment/completion of a task** was rated as most important.
  - Ratings for **duration, frequency, and intensity** were dimensions suggested for consideration as concept(s) of interest (as fulfillment of a task cannot be measured by a wearable device).
  - **Speed of activity** was rated as least important.
- Participant narratives included multiple discussions of **distance walked,** suggesting it is another important concept.

Potential Metrics to Move Forward Based on Advisory Panel Meeting Discussion

- **Two sets of related and complementary metrics proposed:**
  1. Based on **step counts** to capture physical activity related to walking/mobility
  2. Based on **activity counts** to capture general activity, which may include walking
- **Informal consultation meeting with FDA on October 6, 2022**
- **Initial findings:**
  - All advisory panel members agreed to move forward:
    - Longest duration of continuous steps
  - Additional exploratory metrics may include:
    - Number of steps in the X continuous minutes that contain the most steps per day
    - Further discussion needed regarding step count / activity count during a predefined period of time and optimal length of time
      - In addition to looking at a shorter period of time, there is an interest in looking at a longer period of time which may be more reflective of carrying out a task that takes longer (e.g., running an errand, going to an appointment)

Advisory Panel

- 2 meetings
  - December 2020
  - March 2021
- Roles of Panel Members
  - Lead of Scientific Partnerships and Communication, Actigraph
  - Director of Digital Therapeutics, Cedars-Sinai Medical Care Foundation
  - Chief Science Officer, Vivosense
  - Consultant, BTPeterson Consulting
  - Professor in Rehabilitation Sciences, Katholieke Universiteit Leuven
    - IMI PROActive initiative

Metric Type Selection

Step Count

- Estimated step count is a robust measure, has been used as the basis for endpoints in several HF trials, and is the most widely studied accelerometer output in the literature.
- Based on the concept elicitation interviews:
  - Long activity time emerged as a challenge for persons with CHF. Duration of walking was rated as an important characteristic.
    - An increase in the length of time that participants can walk without stopping to rest was noted as meaningful in the interviews.
  - The total duration of activity in a day (including walking), as well as the length of time of each episode of activity, are both important to persons with CHF.
  - Participants want to be able to walk further without needing to rest.

Activity Count

- WG elected to proceed with step-based metrics due to concept of interest being easier to clearly define than activity counts.
- All proposed metrics could be easily adapted to be activity count-based.

Current proposed metrics (1/3)

Longest duration of continuous steps [unit: seconds]

- Answers the question: What is the longest duration of time the participant walked without interruption?
- Need to define the amount of time without steps that would end the continuous period (e.g., 30 seconds, 60 seconds)
- Expected to be a shorter time frame (<1 hour)
    - Mean of the 3 longest durations of continuous steps [unit: seconds]
    - Sum of the 3 longest durations of continuous steps [unit: seconds]

Current proposed metrics (2/3)

Total number of steps within the longest duration of continuous steps [unit: counts]

- Answers the question: What is the quantity of steps during the longest duration of uninterrupted walking?
  - Mean of the total number of steps over the 3 longest durations of continuous steps [unit: counts]
  - Total number of steps within the 3 longest durations of continuous steps [unit: counts]

Current proposed metrics (3/3)

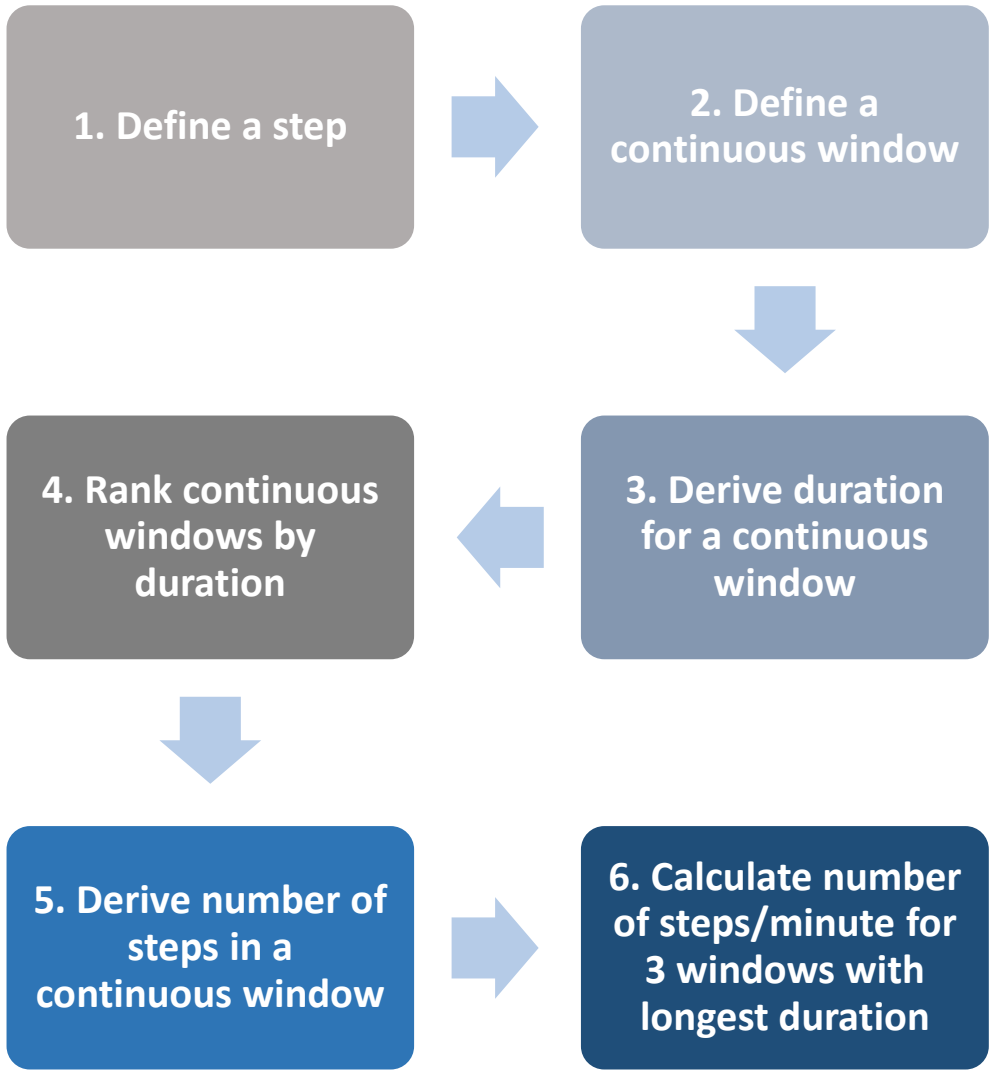
Number of steps/minute during the longest duration of continuous steps [unit: counts/second]

- Answers the question: What is the intensity of stepping during the longest duration of uninterrupted walking?
  - Mean number of steps/minute over the 3 longest durations of continuous steps [unit: counts/second]

Also exploring the following metric:

- Mean number of steps/minute for the day (denominator: wear-time) [unit: counts/second]

Derivation of Continuous Steps



1. Define a step
Select open-source step-detection algorithm and derive a programmatic approach to apply it to raw accelerometry data

2. Define a continuous window
Set up rules for what defines a continuous window (of time) including defined starting and ending criteria[1]

3. Derive duration for a continuous window
Derive a programmatic approach for calculating the duration of a given continuous[2] window

4. Rank continuous windows by duration
Derive a programmatic approach for ranking a set of continuous[2] windows by their durations[3]

→ **D** = longest duration of continuous stepping

5. Derive number of steps in a continuous window
Derive a programmatic approach for calculating the number of steps[1] in a given continuous[2] window

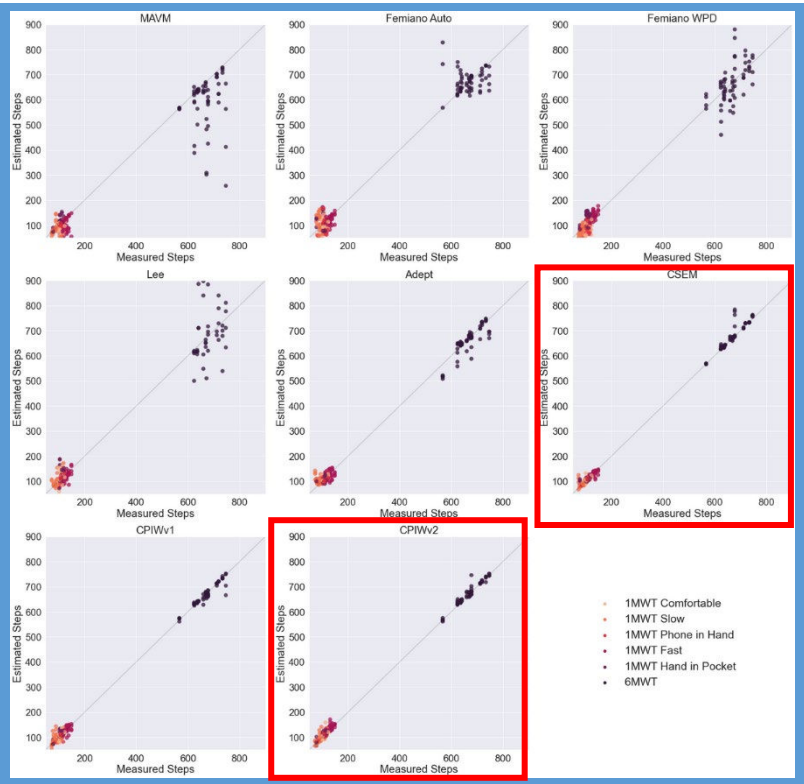
6. Calculate number of steps/minute for 3 windows with longest duration
For each of the 3 windows with longest duration[4], calculate:

- **A)** Number[5] of steps in that window
- **B)** Duration[3] of that window (seconds)
- **C)** Ratio of **A** over **B**
- **D)** Conversion from seconds to minutes

→ mean of **D** over the 3 windows with longest duration[4]

Step Algorithm Identification and Selection

- Actigraph shared a comparative analysis of open-source and commercial algorithms
  - Paper in pre-print[1]
- CHF WG evaluated potential algorithm options
- Best-performing algorithms: CentrePoint Insight Watch (CPIW) v2 and CSEM
- Work ongoing to assess the feasibility of a commercial algorithm in the context of qualification
- Algorithm test strategy in development and to be reviewed by the WG



- Vertical axis = truth steps; horizontal axis = estimated steps according to the algorithm
- Wrist-worn device
- Limitation: majority of the activity was not free-living data; mainly straight overground walking

[1] https://doi.org/10.21203/rs.3.rs-2183645/v2

Rules and Conditions

- WG is developing rules and conditions guidelines for how the activity monitor should be used and how the data should be described
  - Rationale documented
  - Supporting publications listed
- Example parameters
  - Wear time
    - Minimum wear time per day
  - Continuous walking window start/end conditions
  - Definition of “a day”
  - Rules for changing time zones, missing data, etc.

Next Steps

Goal: a transparent end-to-end process to convert raw* actigraphy data to a fit-for-purpose endpoint

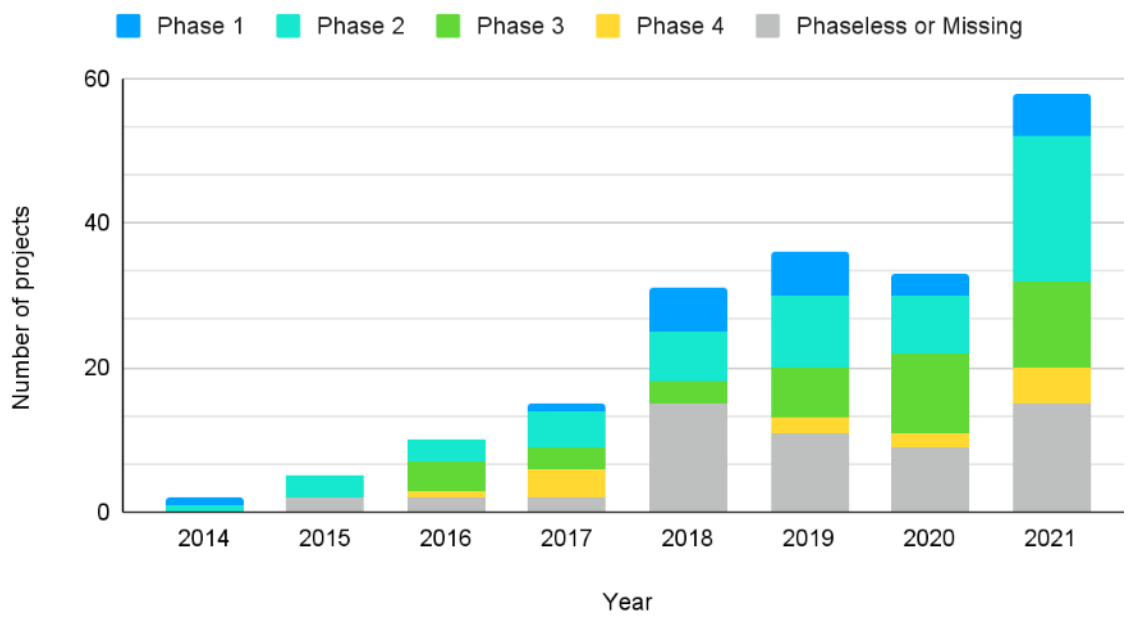
- where “raw data” format, tech specs, etc., are defined
- Algorithm selection and testing
- Endpoint identification
- Progress with QP including analysis plan preparation
- Exploring potential involvement in a validation study with ground truth component being led by ActiGraph
  - Study in patients with coronary heart disease to develop accurate disease-specific measures of activity – including Class I and II HF patients
  - In-clinic component will be video recorded and serve as the ground truth reference

Technical and Analytical Considerations for Wearable Digital Health Technologies

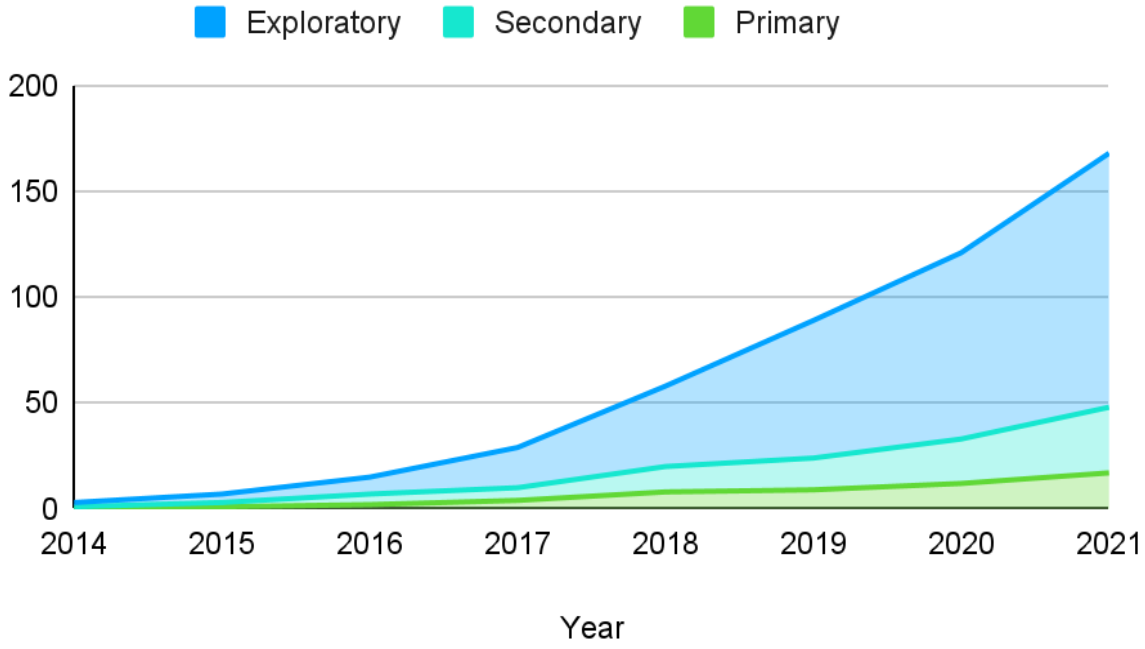
Christine Guo, PhD
Chief Scientific Officer
ActiGraph

From Data to Clinical Impact

ActiGraph internal data on the trend of wearable DHT-derived endpoints in drug development



Clinical trials by start of year and study phase



Endpoint Positioning

Validation Framework for Fit-for-purpose Wearable DHT-derived Endpoints

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Path to primary/secondary endpoints in clinical development plan

imi innovative medicines initiative | FDA | CRITICAL PATH INSTITUTE | DiMe | CLINICAL TRIALS TRANSFORMATION INITIATIVE

Start with *What to Measure -- Meaningful Aspect of Health*

Establish validity throughout from hardware, algorithm, to clinical efficacy

Fit-for-purpose in the intended clinical population

USABILITY AND OPERATIONAL EXPERTISE →

Content Validation	Technical Verification	Analytical Validation	Clinical Validation
Validate Meaningful Aspect of Health and Concept of Interest	Verify hardware and software performance	Reliability and algorithm performance in healthy and clinical conditions	Construct validity Ability to detect change Clinical meaningfulness

Validation Framework for Fit-for-purpose Wearable DHT-derived Endpoints

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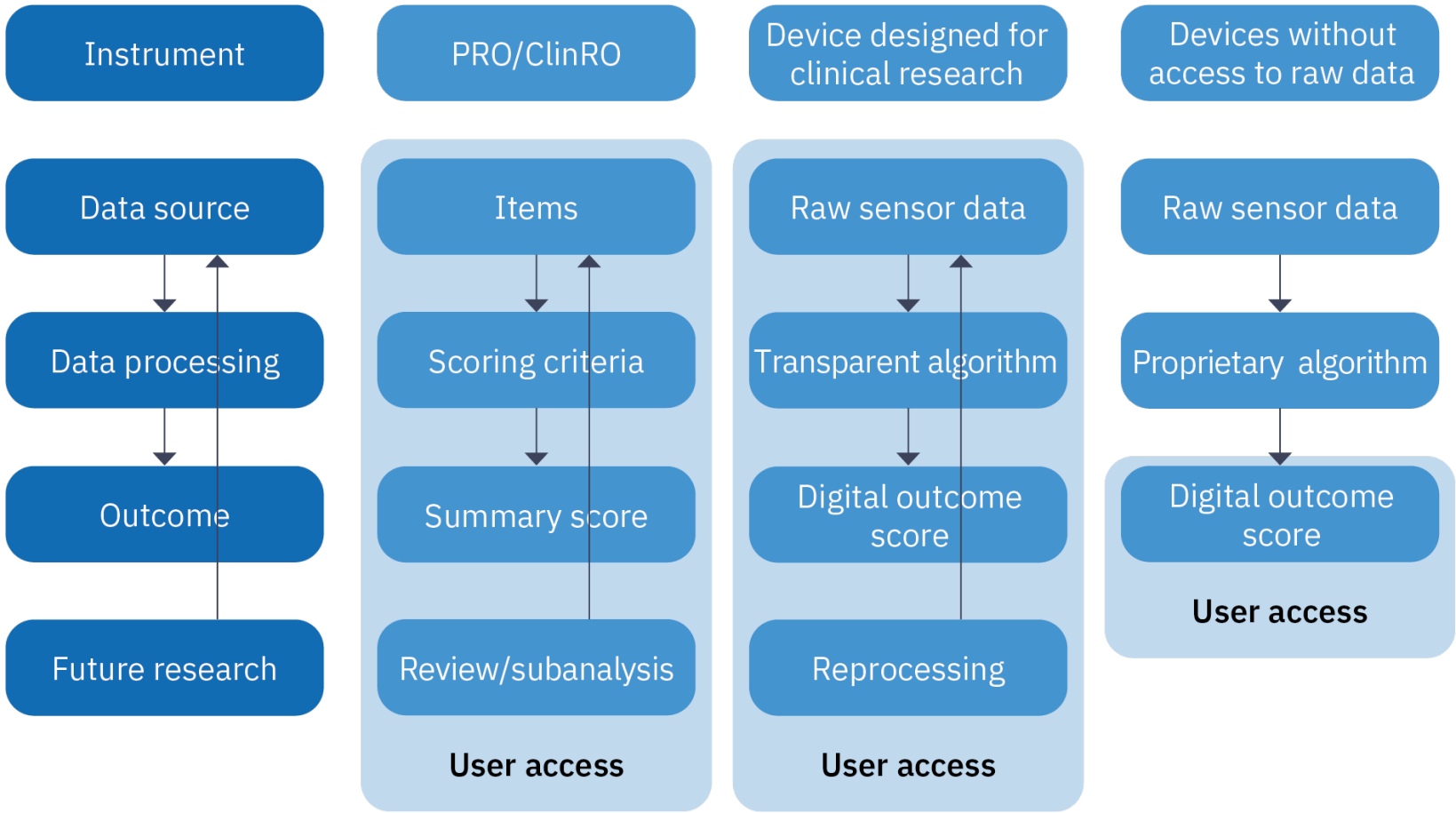
Verified raw data is the source data for wearable DHT-derived endpoints



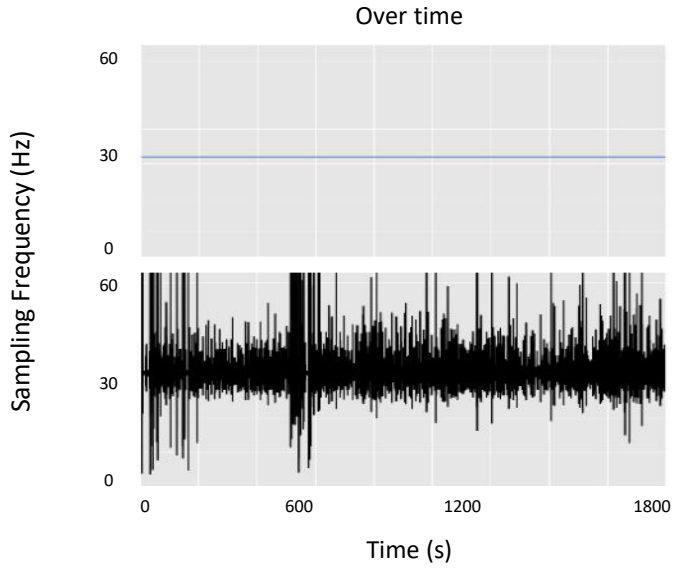
How Do We Test Raw Data: Technical Verification Approach

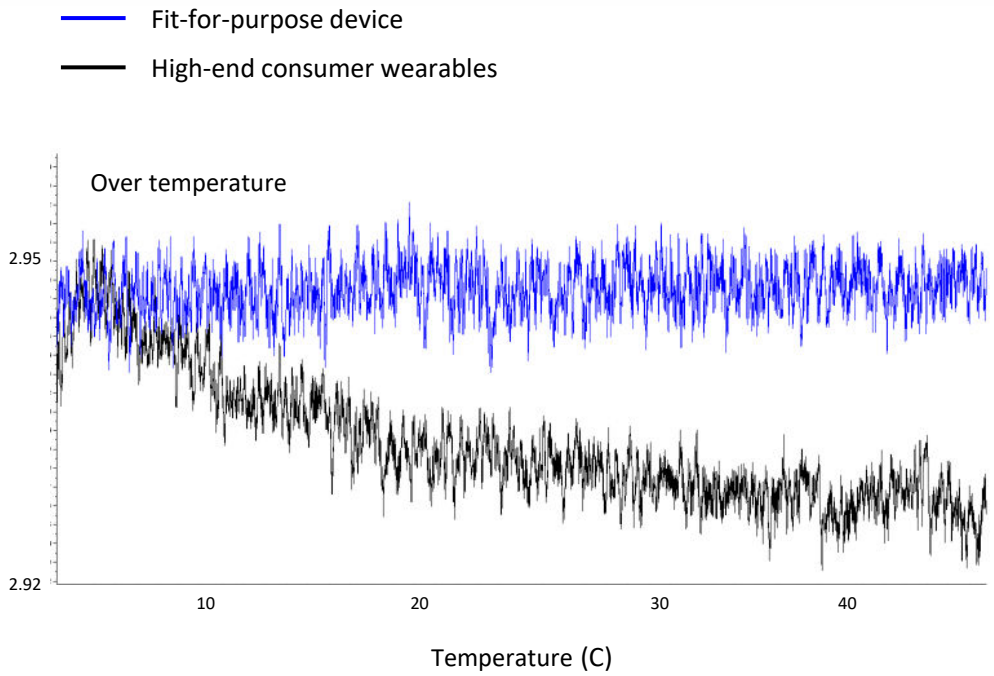
Technical Verification of Raw Data

Concept Validation | Technical Verification | Analytical Validation | Clinical Validation

DHT-derived endpoints start with high-fidelity raw sensor data

SENSOR STABILITY AND RELIABILITY





Environmental factors (e.g., temperature) that may affect the performance of DHTs in a clinical investigation should be considered.

Operational Challenges with Raw Data

Raw data collected on the device

- Transfer data cost / burden
  - Cellular / WiFi / Ethernet
- Transfer media: mobile phone or data hub.

Raw data in the cloud

- Parsing of the device data
- Hardware FIFO error, unreadable sections, duplicate data
  - Audit trail on these events occurring
- Sensor calibration
- Preprocessing / Pegging / Latching
  - Audit trail on these events

Raw data transfer

- Batch Processing and Transfers
- API will download stored daily files as requested

Raw data processing

- Industrialized algorithm implementation robust to imperfect data

Large Data Volume

Input Parameter	Value
Number of participants	100
Duration (days)	90
Sampling rate (Hz)	30

Output parameter	Value
Disk requirements for the study (GB)	466.56
RAM requirement (GB per participant)	23.328
Processing time (hours per participant)	1.5

Regulatory Requirements for Fit-for-purpose Analytical Validation

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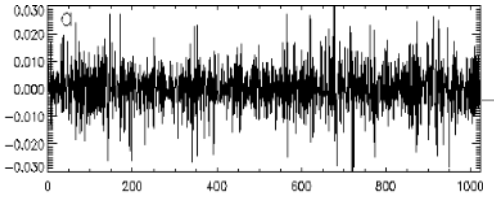
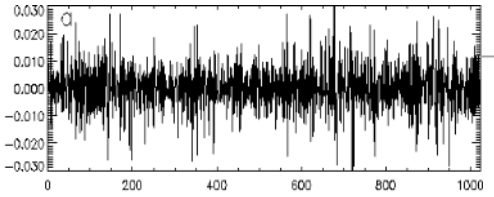
Consumer Model

Raw Accelerometer Data



Sleep Detection Algorithm → Sleep Efficiency

Fit-for-purpose Model



CLINICALLY VALIDATED OUTCOMES	
Atopic Dermatitis Sleep Detection Algorithm	Sleep Efficiency Atopic Dermatitis
Parkinson's Sleep Detection Algorithm	Sleep Efficiency Parkinson's Disease
COPD Sleep Detection Algorithm	Sleep Efficiency COPD

Challenges with Fit-for-purpose Algorithm Selections

- Need to collect ground truth reference data with DHT data
  - Require specific study design that is not common in clinical studies/trials
  - Not always feasible in clinical sites
  - Add cost and burden
- Who should do this?
  - Tech provider – Limited in resources and access to clinical populations
  - Biopharma – Some big players are investing, but most are waiting for proven solutions.
  - Academic researchers – Gap in understanding industry needs.
- Promising progress from Public-Private Partnerships
  - Can we make them more scalable?

Our Research Strategy as a Tech Provider

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Library of validated and transparent algorithms

Industrialized Implementation complied with 21 CFR Part 11

Literature Review

State of Art

Impl. and Validate *Healthy and Clinical*

R&D

Partners

- Sleep
- Activity
- Gait
- Scratch
- Tremor
- Seizure
- ...

- Atopic Dermatitis Algorithm
- Parkinson's Algorithm
- COPD Algorithm

Step Count: Algorithms

Algorithm	Method
Lee et al.	Peak detection with adaptive thresholds
Adaptive Empirical Pattern Transformation (ADEPT)	Template matching
Femiano autocorrelation (auto) and windowed peak detection (WPD)	Autocorrelation and peak detection
Centrepoint Insight Watch v1 and v2 (CPIWv1, CPIWv2)	Machine learning with autocorrelation
CSEM The Swiss Center for Electronics and Microtechnology, Neuchâtel, Switzerland	Adaptive motion frequency tracking combined with an activity classifier

Preprint: Pilkar et al. (2022). Performance analyses of step-counting algorithms using wrist accelerometry; https://doi.org/10.21203/rs.3.rs-2183645/v1

Analytical Validation: Experimental Protocol

Testing Procedures

1-Minute Walk Tests (1MWTs)

- Three 1MWTs at self-selected **comfortable, fast, and slow speeds**.
- 1MWT - **holding a phone** in one (any) hand
- 1MWT – a **hand in a pocket**.

6-Minute Walk Test (6MWT)

- Walk at comfortable speed around 2 cones placed approximately 150 meters apart on a paved walkway.

Ground Truths

Devices

CPIW

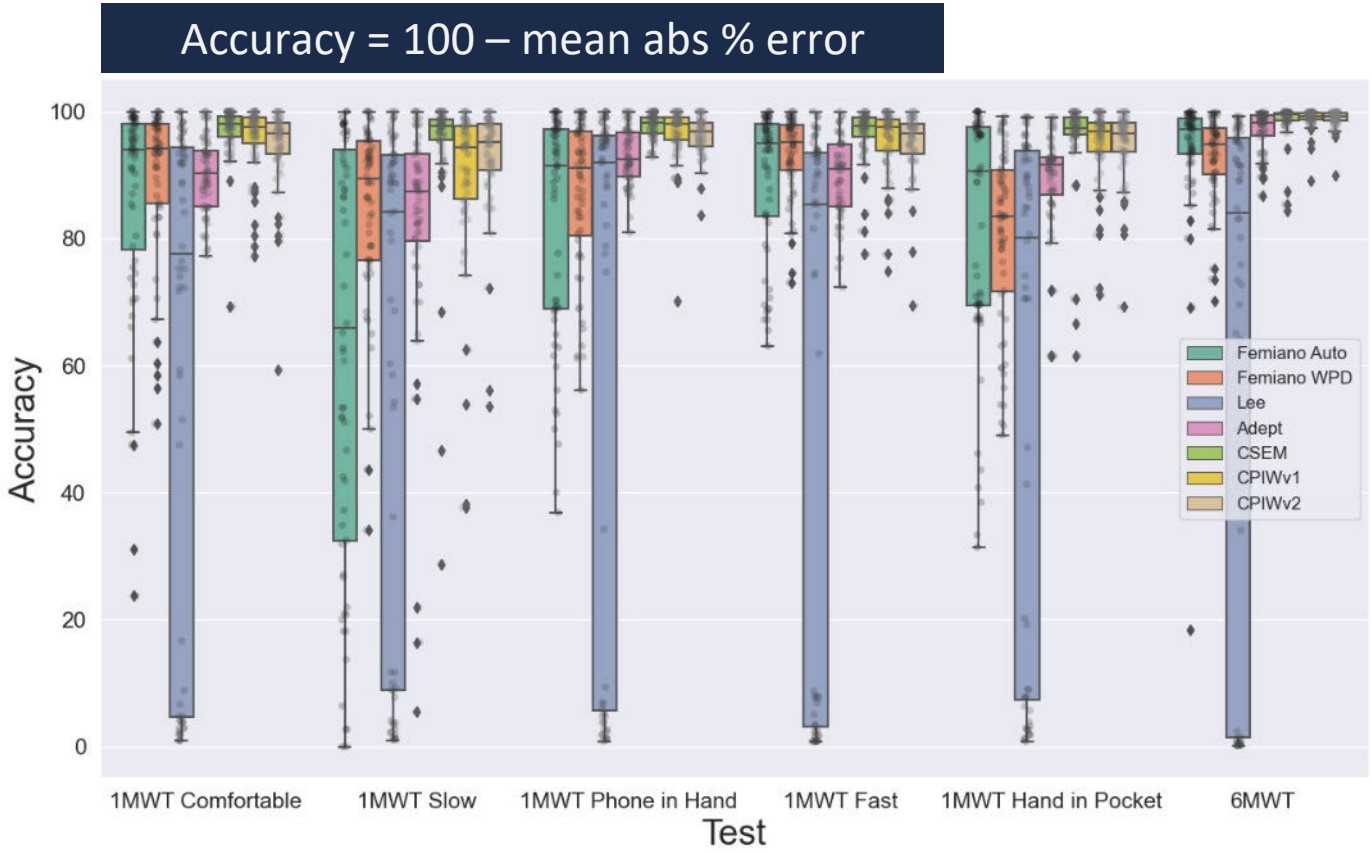
Freq = 32 Hz

GT9X - Link

Freq = 100 Hz

n=17		
Age (years)	**mean (sd):**	**38.1 (13.5)**
	Range:	19-60
Height (m)	**mean (sd):**	**1.73 (0.1)**
	Range:	1.6-1.9
Weight (kg)	**mean (sd):**	**83.26 (19)**
	Range:	56.8-118.6
Sex	10 male, 7 female	

Step Count: Analytical Validation Results



Algorithm	RMSE	CI width
Lee	155.19	572.92
Femiano A	43.04	168.86
Femiano W	31.41	123.17
Adept	17.94	68.12
CSEM	11.4	44.45
CPIWv1	10.57	41.24
CPIWv2	9.41	33.36

RMSE: Root Mean Square Error; CI: Confidence interval

Preprint: Pilkar et al. (2022). Performance analyses of step-counting algorithms using wrist accelerometry; https://doi.org/10.21203/rs.3.rs-2183645/v1

How about the real-world data?

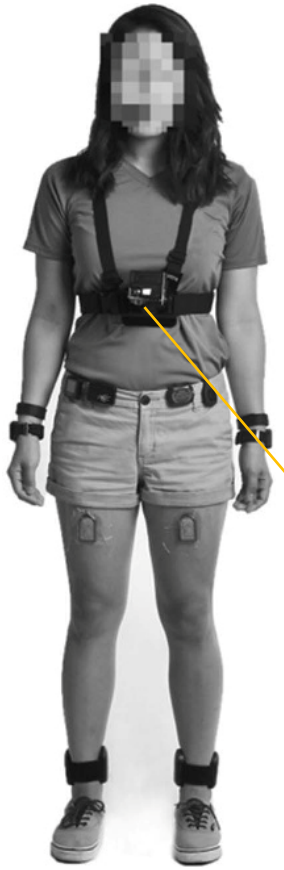


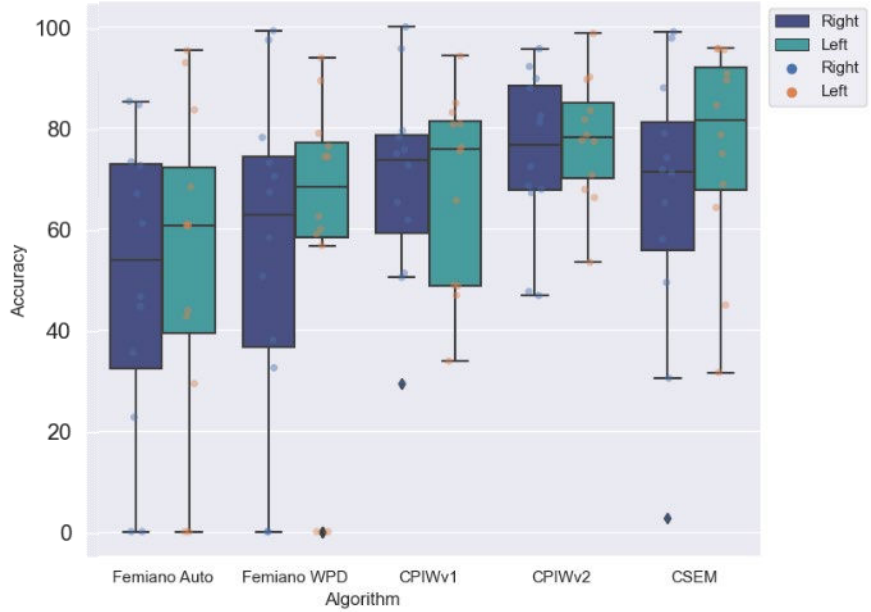
TABLE 1. Participant characteristics (mean ± SD).

	All (N = 12)	Female (n = 6)	Male (n = 6)
Age, yr	35 ± 13	35 ± 13	34 ± 14
Height, cm	170.7 ± 10.7	162.3 ± 6.4	179.1 ± 98.3
Weight, kg	72.1 ± 20.5	56.8 ± 6.7	87.5 ± 17.6
BMI, kg·m^{-2}	24.3 ± 4.4	21.5 ± 2.4	27.1 ± 4.3
Steps per day[a]	10,921 ± 5062	12,114 ± 6315	9728 ± 3617
Video recording time, min	890.3 ± 40.4	880.5 ± 39.5	900.0 ± 42.4

[a]Determined from hand-counted steps from video recordings.
BMI, body mass index.

GoPro Hero3+

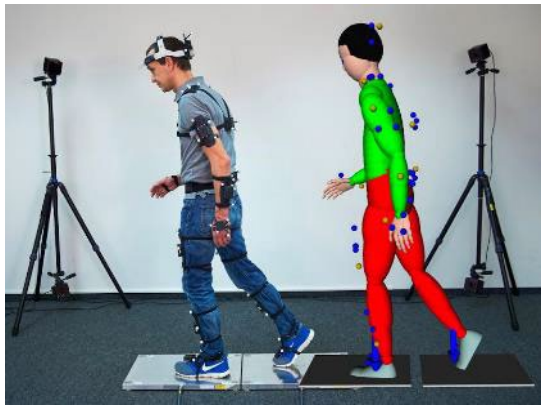
Data source: Toth et al. (2018) Video-Recorded Validation of Wearable Step Counters under Free-living Conditions, Med Sci Sports Exerc.;50(6):1315-1322



Algorithm	RMSE	CI width
Femiano A	6186.03	17375.69
Femiano W	5472.20	16765.11
CSEM	3610.34	11353.15
CPIWv1	5368.01	14502.54
CPIWv2	3153.17	12522.31

ActiGraph Digital Endpoint Accelerator Research Grant (DEAR)

- **Gap** - Lack of fit-for-purpose validation, i.e., the validation of the technologies, especially the data processing algorithms, for the intended use in the clinical populations.
- **Goal** - Support projects that aim to validate the use of DHT data as outcome measures in clinical populations where the validation from healthy populations might not apply
- **Challenge** - No consensus on the different interpretations of validation, i.e., what is the appropriate ground truth for gait, upper limb movement, sleep.

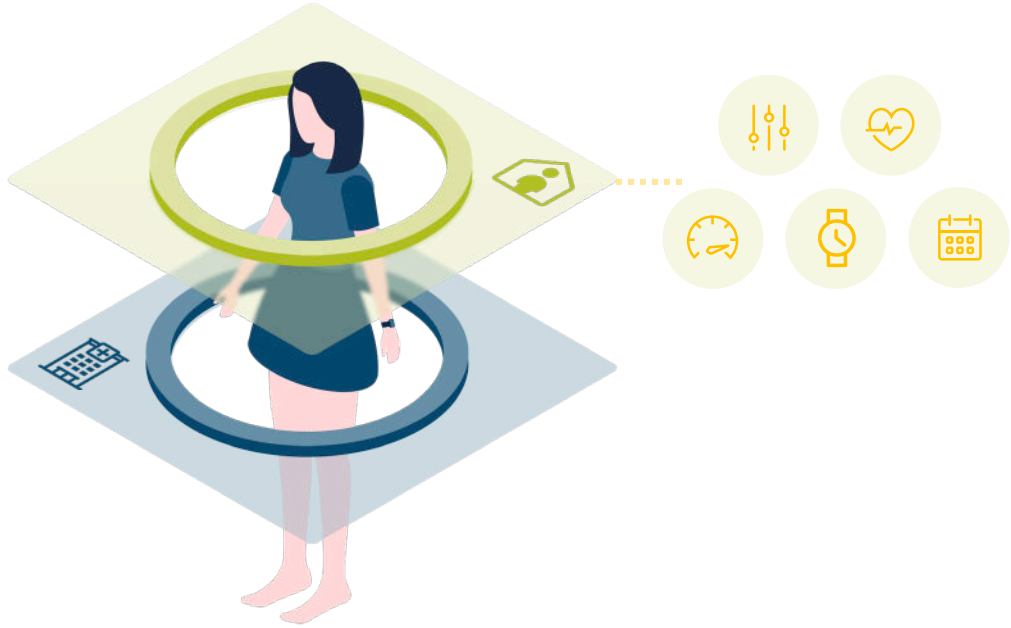


88 LOI submissions → 20 full proposal submission → 5 proposal selected

How do we move forward?

- **Alignment of regulatory guidance**
  - Technical verification – Lack of standards
  - Analytical validation
    - Generalization to similar COU
    - Algorithm transparency is desirable and can be achieved while protecting/encouraging R&D investment

- **Best practice in raw data handling**
  - Raw data is essential to maximize the value of sensor-based DHT research



- **Public-Private Partnership**
  - Tech, clinical, regulatory expertise
  - Incentivize academic research

Mobilise-D: Connecting Digital Mobility Measurement to Clinical Outcomes

Ronenn Roubenoff, MD, MHS

Gül Erdemli, MD, PhD

MOBILISE-D:
Project Background and Objectives

Ronenn Roubenoff, MD, MHS

Global Head, Translational Medicine Discovery & Profiling

Novartis Institutes for Biomedical Research

MOBILISE-D

Digital mobility outcomes as endpoints in clinical trials/care

KEY FACTS

34
PARTNERS

€49
MILLION
BUDGET

2019-2024
PROJECT
DURATION

www.mobilise-d.eu @MobiliseD @Mobilise_D Mobilise-D #MobiliseD

imi innovative medicines initiative efpia Mobilise-D

Collaboration with C-Path

The Mobilise-D consortium and the Critical Path Institute (C-Path) signed a collaboration agreement, which will be an important step forward in achieving lasting impact.

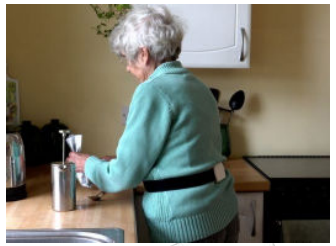
Mobilise-D and C-Path announce collaboration agreement – Mobilise-D

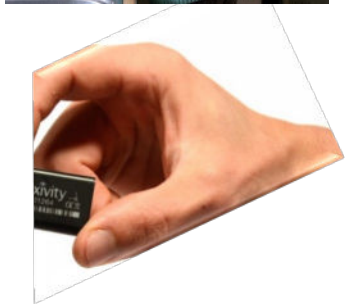
- **Mobilise-D** is developing a comprehensive **device agnostic** system to assess **real-world mobility** using **digital technology** - device worn on the body
- Focuses on conditions which affect mobility: Parkinson's disease, hip fracture recovery, chronic obstructive pulmonary disease, multiple sclerosis
- Generic and disease specific approach to mobility assessment
- **Aim for qualification of new method by regulatory authorities – <u>widespread adoption</u>**

Mobility

Ability to move freely and easily without assistance

- Perception
- Capacity





Mobility Performance

<u>mobility</u> measured in the <u>real world</u> over <u>long period</u> of time with digital device

Digital Mobility Outcomes

Speed, step count, walking bouts, etc……

What is MOBILISE-D?

Linking digital assessment of mobility to clinical endpoints to support regulatory decision making

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

Purpose:
Bring digital mobility outcomes (DMOs) to regulatory acceptance for secondary endpoint by showing validity in several indications

Scientific Background:
Gait speed predicts death, hospitalization, falls and disability in many disease settings (included: Chronic obstructive pulmonary disease (COPD), multiple sclerosis (MS), Parkinson's disease (PD), hip fracture recovery; congestive heart failure (CHF) included in technical validation study only)

Technology:
Digital mobility assessment (e.g., accelerometer) as the most advanced and widespread wearable technology

Consortium Partners and Funding:
10 EFPIA members,
2 Tech Partners,
22 public institutions,

EFPIA Lead: Novartis

Coordinator: Newcastle University

Funded by IMI - ~50mEUR budget (in-kind: 25 mEUR)

Status:
- **Runs 01 Apr '19 - Mar '24**
- Technical validation study finished
- Clinical validation study at 90+% recruitment (COPD/PD/MS 100%)

Definitions and Hierarchy of Constructs

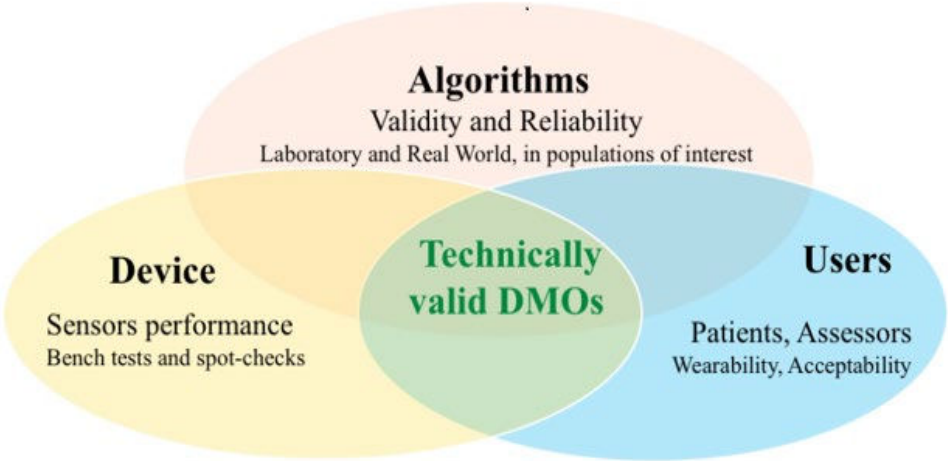
- **Mobility** – defined as “physical mobility” or “the ability to move freely and easily without assistance” and can be evaluated in term of capacity, patient’s perception, and performance
  - **Mobility capacity** – quantification through measurements of the intensity with which the patient can perform an assigned motor task
  - **Mobility perception** – quantification through questionnaires of how mobile the patients perceive themselves in their daily life
  - **Mobility performance** - quantification through measurements of the intensity or extension of mobility measured in the real world and over a sufficiently long period of time
  - **Mobility disability** – is intended as the loss of mobility performance and is marked by the loss of one or more **mobility-related Activities of Daily Living** (ADLs - activities that allow an individual to live independently in a community)

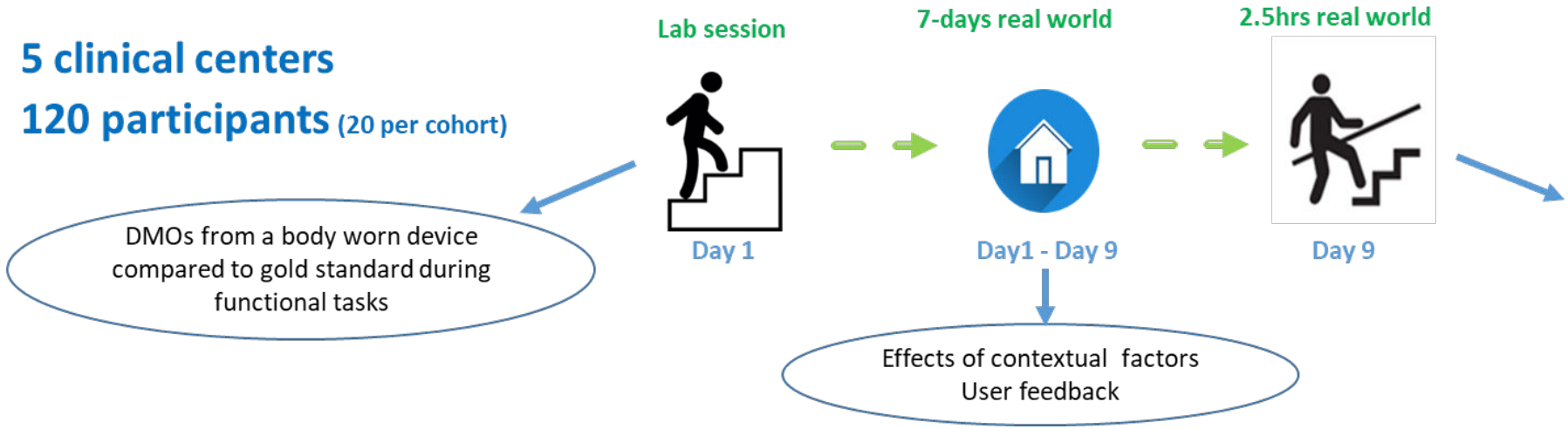
Viceconti M, et al (2022) Front. Med. 9:996903. doi:10.3389/fmed.2022.99690

Qualitative Research and Technical Validation

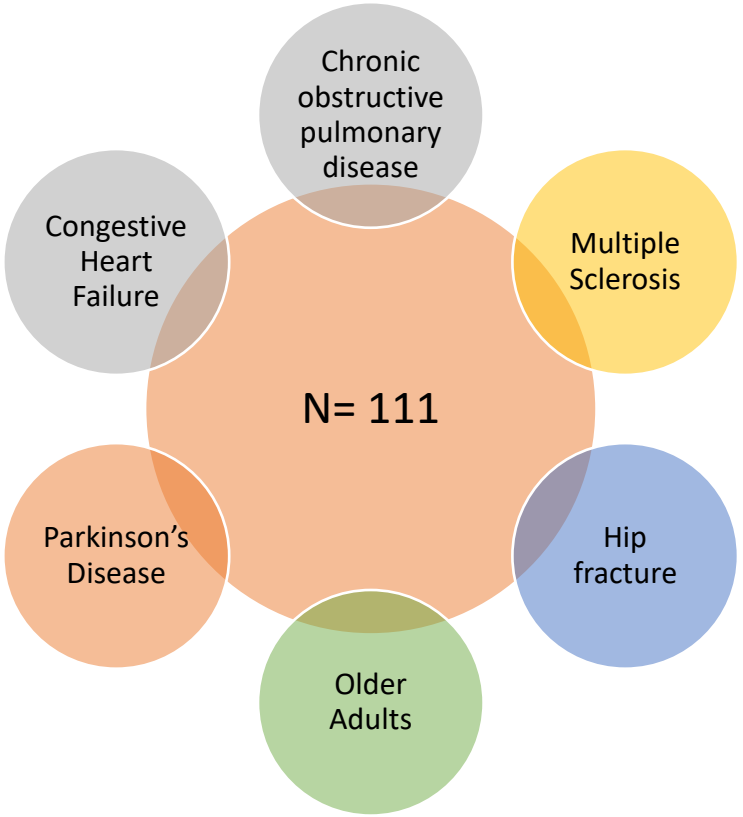
- **Qualitative research (QR)**: questionnaires to patients and medical professionals for each disease group aimed to assess the **clinical meaningfulness** of the loss of mobility performance

- **Technical validation study (TVS):** an experimental study to establish:
  - Essential **metrological requirements** for a device to be suitable to assess DMOs
  - **Accuracy** and **reliability** of the algorithms for each DMO, specifically for six cohorts of interest: **PD, COPD, MS, hip fracture, CHF and healthy adults**
  - **Users**' perception of proposed solutions



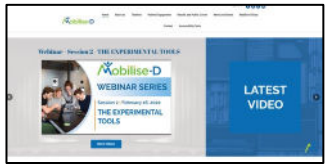


Can we accurately measure real-world mobility?



Mazza et al., BMJ Open, 2021

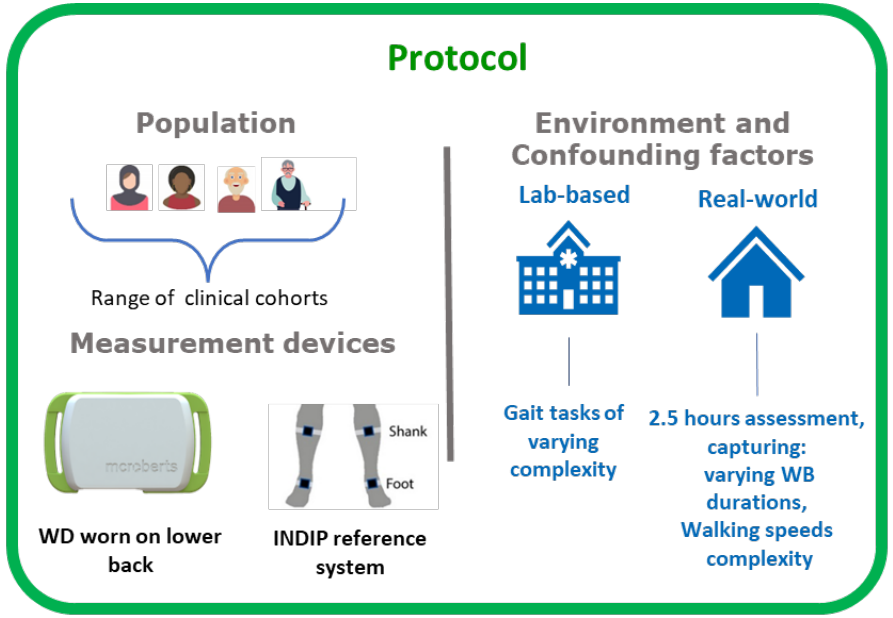
- We can accurately measure mobility in the real world for 7 days in all cohorts?
- Acceptable and excellent compliance (Keogh et al., Digital Health 2023.)
- Device agnostic – the software works on different devices (with similar technical standards)

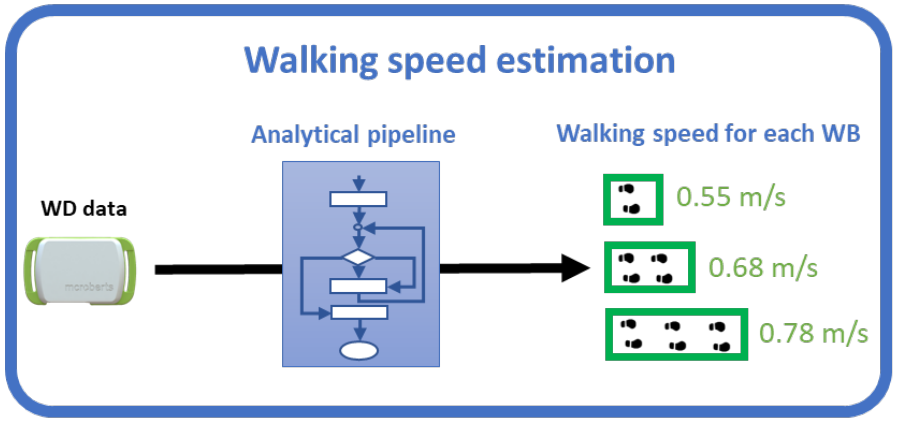


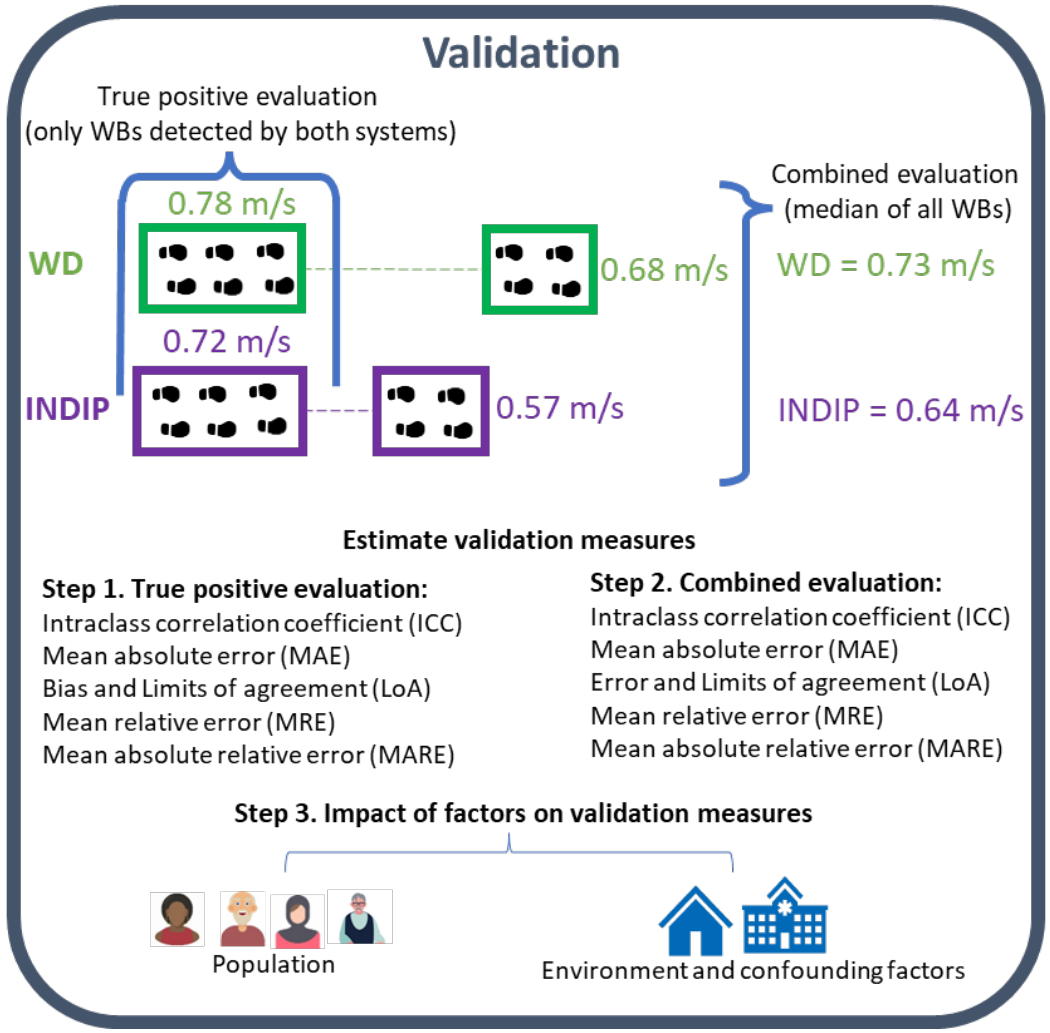
https://www.mobilise-d.eu/

Domain	DMO
Volume	**Step count**
	Number of walking bouts
Pattern	**Walking bout duration**
Pace	**Walking speed**
	Stride length
Rhythm	**Step duration**
	Stride duration
	Cadence
Turning	**Number of turns**
	Turn duration
	Turn velocity
	Max turn angle

Technical Validation Study Summary



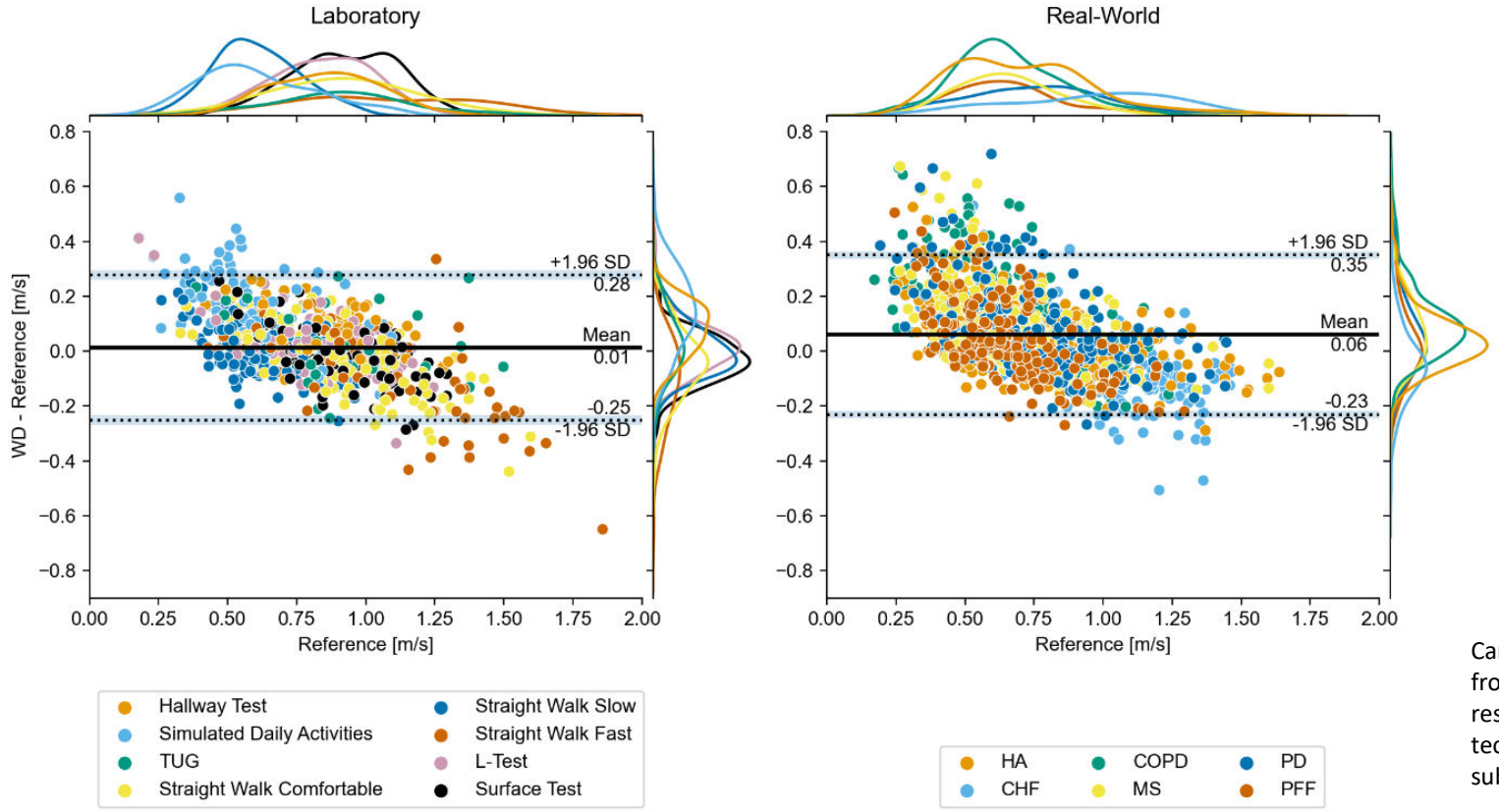




Additional work to enhance device agnostic approach:

- Effect of different sensor placement (e.g., wrist) on DMO accuracy being explored
- Effect of modification of technical standards (e.g., accelerometer only) being explored

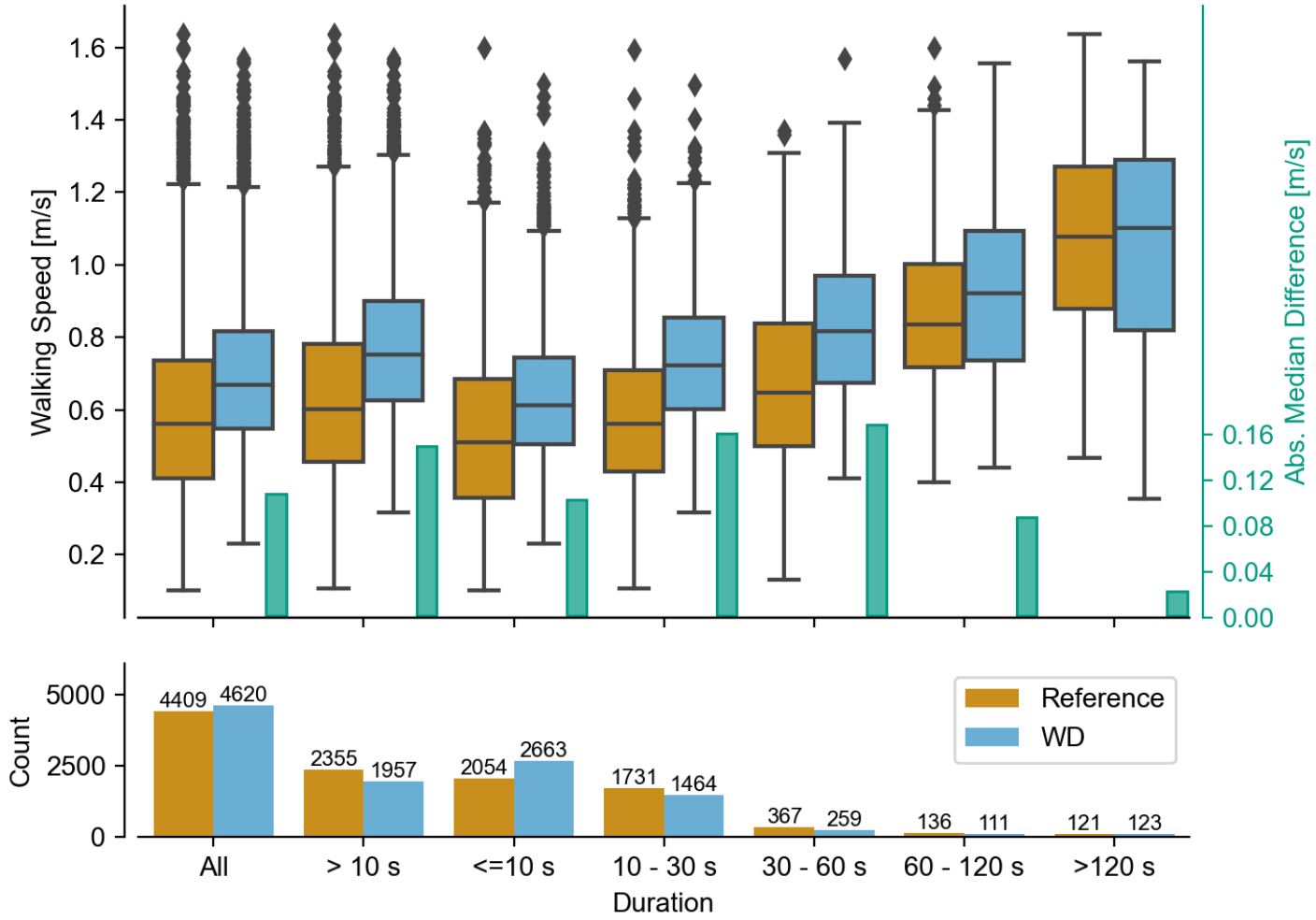
Data Overview: Walking Speed Distribution In Laboratory and Real World Settings



Cameron et al., Estimating real-world walking speed from a single wearable device: analytical pipeline, results and lessons learnt from the Mobilise-D technical validation study (in preparation for submission to NPJ-Digital Medicine

Residual plots of walking speed for WBs recorded in the laboratory (left) and during the real-world recording (right).
The margin plots represent the overall speed and error distributions. The light blue bars around the Limits of Agreement (LOA) (dashed horizontal lines) represent their bootstrapped confidence intervals.
PFF = proximal femoral fracture (hip fracture); PD = Parkinson Disease; HA = healthy adult; MS = multiple sclerosis; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease

Data Overview: Technical Validation of Worn Device (WD) by Gait Bout Length



- Walking speed (WS) estimations from the real-world recording of the reference system and the WD, from all walking bouts (WB) within the respective duration bouts. The boxplots show the distribution over all WBs.
- The bars in the upper plot show the absolute difference between the medians of the distributions (see right y-axis).
- The bottom plot shows the number of WBs in each duration bout.

Cameron et al., Estimating real-world walking speed from a single wearable device: analytical pipeline, results and lessons learnt from the Mobilise-D technical validation study (in preparation for submission to NPJ-Digital Medicine

Clinical Validation

Clinically validate the best-performing DMOs as evaluated within the technical validation study

The objectives are:

- To assess construct validity of DMOs against established clinically relevant endpoints
- To assess the ability of DMOs to detect change over time in clinically relevant endpoints
- To estimate the Minimal Important Difference (MID) of DMOs to measure change in disease state (worsened or improved)
- **Clinical validation study :**
    - a 24-month longitudinal observational cohort study conducted in 10 European countries and in Israel (ISRCTN Number: 12051706)
    - 2400 patients (600 per disease cohort – PD, MS, COPD and hip fracture)
    - 24 months, 5 assessments (baseline and 4 follow visits at 6-month intervals)
    - Wearable sensors worn for 7 days, continuously and in real-world settings

MOBILISE-D: Regulatory Interactions

Gül Erdemli, MD, PhD

Global Program Regulatory Director

Novartis Pharmaceuticals Corporation

A Staged Qualification Advice Approach

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

Stage 1:
Qualification Advice - EMA

CoU: use of DMO as monitoring biomarker of mobility performance in PD drug trials
Request submitted - **October 2019**
Advice received – **March 2020**
Letter of Support published - **November 2020**

Stage 2:
Qualification Advice - EMA

CoU: same, but extension to all four diseases
Request submitted - **June 2020**
Advice received – **December 2020**
Letter of Support published – **May 2021**

Stage 3:
FDA engagement

- Informal meeting with FDA COA Qualification Program in **October 2021**
- **LOI** in preparation and Pre-LOI meeting is planned

EMA Qualification Advice

- To discuss interim analysis results and plans for a future interventional trial (2024)

Stage 4:
Qualification Opinion

- Qualification Opinion will be pursued when responsiveness evidences are available from interventional clinical trials (post consortium)

Summary of Advice from EMA

- Technical validation plan approved
- General design of the clinical validation plan approved
- The question of meaningfulness of mobility performance for the patients remains open
- The ability to detect change cannot be proved only with an observational clinical study; to pursue the qualification demonstration of treatment effects in interventional RCTs are needed

FDA DDT COA Qualification Program

- DMO(s) are considered COAs
- An informal meeting with the FDA Drug Development Tool Clinical Outcome Assessment Qualification program in October 2021
- Objective: to better understand the qualification process requirements and to obtain the Division's feedback on:
  - Rationale and hypotheses
  - Proposed CoU
  - Draft qualification approach
- The established procedure requires a separate letter of intent (LOI) submission for each indication
  - Interrelatedness and common modules in the dossier together with indication-specific sections is recognized

FDA COA Qualification Program - *Feedback on LOI*

- The mobility should be correlated to each patient's daily activities and the information on what the participants are actually doing would be important for interpretation
- Collecting data to determine what the patients and caregivers consider important to them is essential
- The parameters measured and how they are measured including the information on sensors should be provided
- Confounding events should also be considered and discussed.
- The rationale for the selection of diseases and how the proposed DMOs would complement the existing endpoints should be explained.

Next Steps

- **FDA Drug Development Tool Clinical Outcome Assessment Qualification Program initiation**
  - Letter of Intent submission in 2023 (for one indication)
  - Pre-letter of intent meeting to get feedback on the proposed
    - Concept of interest
    - Context of use
    - Existing validation package and future plans for qualification

- **Health Authority engagement in 2024 to get feedback on**
  - Technical validation study results
  - Clinical validation study interim analysis results
  - Design of future studies to support qualification
    - To guide prospective trial designs
    - To assess treatment effect

Lessons Learned

- Concept of Interest should be relevant and clinically meaningful (with supportive evidence) to the target population
- Context of Use, a detailed description of how the outcome measure to be used, is essential for the regulatory assessment
- Utilize check-lists and publicly available feedback to cover all areas of interest. Test-retest reliability, convergent validity and ability to detect change are important properties to establish.
- Consider iterative approaches :
    - Initially qualification of novel outcome measures for secondary endpoint
    - Formulate process on how to expand to additional contexts of use, diseases
- Early interactions with Health Authorities are critical for success
    - Engagement with major Health Authorities to align requirements for global project implementation
    - Multiple advice meetings required with each Health Authority (HA) – significant resource commitment
    - Define how to coordinate various HA inputs whilst their advice processes are not easily merged
- Be aware of long lead times for the various stages

Mobilise-D Consortium Partners

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

Mobilise-D

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 820820. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.
www.imi.europa.eu

imi innovative medicines initiative

efpia

NOVARTIS

Q&A

Moderator:

- *Scottie Kern, BSc (Hons)* – Executive Director, Electronic Clinical Outcome Assessment Consortium, Critical Path Institute

Presenters:

- *Scottie Kern, BSc (Hons)* – Executive Director, Electronic Clinical Outcome Assessment Consortium, Critical Path Institute *Scottie Kern, BS*
- *Josephine Norquist, MS* – Executive Director, Patient-Centered Endpoints & Strategy Lead, Merck & Co., Inc.
- *Christine Guo, PhD* – Chief Scientific Officer, ActiGraph
- *Ronenn Roubenoff, MD, MHS* – Global Head, Translational Medicine Discovery & Profiling, Novartis Institutes for Biomedical Research
- *Gül Erdemli, MD, PhD* – Global Program Regulatory Director, Novartis Pharmaceuticals Corporation

Panelist:

- *David S. Reasner, PhD* – Division Director, Division of Clinical Outcome Assessment, Office of Drug Evaluation Sciences, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration