Case Study #1: Connecting Digital Mobility Assessments to Clinical Outcomes – Mobilise-D Consortium

Daniel Rooks, PhD; Alison Keogh, PhD; Arne Mueller, PhD; Gül Erdemli, MD, PhD; and Nicholas Wong MS

FDA/FNIH - Digital Measures Workshop, June 24-25, 2024

Agenda

- Introduction to Mobilise-D
- Patient and Public Involvement
- Technical Validation Study
- Regulatory Interactions and Advice
- Clinical Validation Study
- Summary and next steps

Development of Real-World Digital Mobility Outcomes in Multiple Conditions: Mobilise-D Consortium

Daniel Rooks, PhD
Translational Medicine, Novartis
Mobilise-D Industry Lead

Mobility is an important indicator of health, modifiable risk factor, and viable target to measure, monitor and target therapeutically


Ageing Research Reviews 81 (2022) 101704

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Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Association of clinical outcome assessments of mobility capacity and incident disability in community-dwelling older adults - a systematic review and meta-analysis

Tobias Braun [a,b,c,*,1], Christian Thiel [a,d,2], Raphael Simon Peter [e,3], Carolin Bahns [f,4], Gisela Büchele [e,5], Kilian Rapp [b,6], Clemens Becker [b,g,7], Christian Grüneberg [a,8]

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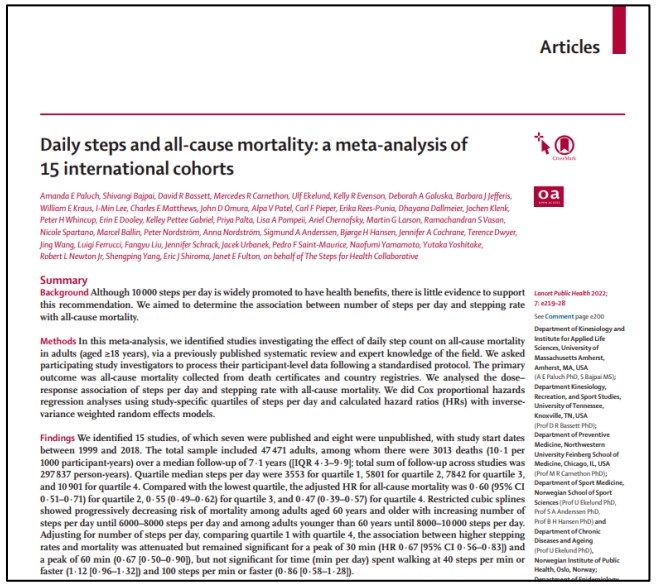
Association between mobility capacity (at baseline) and future disability in non-disabled older adults – community dwelling


Articles

Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts

Amanda E Paluch, Shivangi Bajpai, David R Bassett, Mercedes R Carnethon, Ulf Ekelund, Kelly R Evenson, Deborah A Galuska, Barbara J Jefferis, William E Kraus, I-Min Lee, Charles E Matthews, John D Omura, Alpa V Patel, Carl F Pieper, Erika Rees-Punia, Dhayana Dallmeier, Jochen Klenk, Peter H Whincup, Erin E Dooley, Kelley Pettee Gabriel, Priya Palta, Lisa A Pompeii, Ariel Chernofsky, Martin G Larson, Ramachandran S Vasan, Nicole Spartano, Marcel Ballin, Peter Nordström, Anna Nordström, Sigmund A Anderssen, Bjørge H Hansen, Jennifer A Cochrane, Terence Dwyer, Jing Wang, Luigi Ferrucci, Fangyu Liu, Jennifer Schrack, Jacek Urbanek, Pedro F Saint-Maurice, Naofumi Yamamoto, Yutaka Yoshitake, Robert L Newton Jr, Shengping Yang, Eric J Shiroma, Janet E Fulton, on behalf of The Steps for Health Collaborative

Summary

Background Although 10 000 steps per day is widely promoted to have health benefits, there is little evidence to support this recommendation. We aimed to determine the association between number of steps per day and stepping rate with all-cause mortality.

Methods In this meta-analysis, we identified studies investigating the effect of daily step count on all-cause mortality in adults (aged ≥18 years), via a previously published systematic review and expert knowledge of the field. We asked participating study investigators to process their participant-level data following a standardised protocol. The primary outcome was all-cause mortality collected from death certificates and country registries. We analysed the dose–response association of steps per day and stepping rate with all-cause mortality. We did Cox proportional hazards regression analyses using study-specific quartiles of steps per day and calculated hazard ratios (HRs) with inverse-variance weighted random effects models.

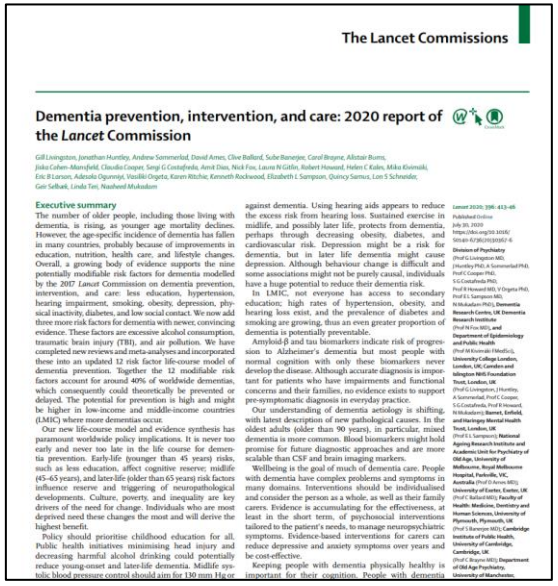
Findings We identified 15 studies, of which seven were published and eight were unpublished, with study start dates between 1999 and 2018. The total sample included 47 471 adults, among whom there were 3013 deaths (10·1 per 1000 participant-years) over a median follow-up of 7·1 years ([IQR 4·3–9·9]; total sum of follow-up across studies was 297 837 person-years). Quartile median steps per day were 3553 for quartile 1, 5801 for quartile 2, 7842 for quartile 3, and 10 901 for quartile 4. Compared with the lowest quartile, the adjusted HR for all-cause mortality was 0·60 (95% CI 0·51–0·71) for quartile 2, 0·55 (0·49–0·62) for quartile 3, and 0·47 (0·39–0·57) for quartile 4. Restricted cubic splines showed progressively decreasing risk of mortality among adults aged 60 years and older with increasing number of steps per day until 6000–8000 steps per day and among adults younger than 60 years until 8000–10 000 steps per day. Adjusting for number of steps per day, comparing quartile 1 with quartile 4, the association between higher stepping rates and mortality was attenuated but remained significant for a peak of 30 min (HR 0·67 [95% CI 0·56–0·83]) and a peak of 60 min (0·67 [0·50–0·90]), but not significant for time (min per day) spent walking at 40 steps per min or faster (1·12 [0·96–1·32]) and 100 steps per min or faster (0·86 [0·58–1·28]).

Lancet Public Health 2022; 7: e219–28

See Comment page e200

Department of Kinesiology and Institute for Applied Life Sciences, University of Massachusetts Amherst, Amherst, MA, USA (A E Paluch PhD, S Bajpai MS); Department Kinesiology, Recreation, and Sport Studies, University of Tennessee, Knoxville, TN, USA (Prof D R Bassett PhD); Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (Prof M R Carnethon PhD); Department of Sport Medicine, Norwegian School of Sport Sciences (Prof U Ekelund PhD, Prof S A Anderssen PhD, Prof B H Hansen PhD) and Department of Chronic Diseases and Ageing (Prof U Ekelund PhD), Norwegian Institute of Public Health, Oslo, Norway;

Taking more steps associated with lower risk of all-cause mortality


The Lancet Commissions

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costafreda, Amit Dias, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

Lancet 2020; 396: 413–46

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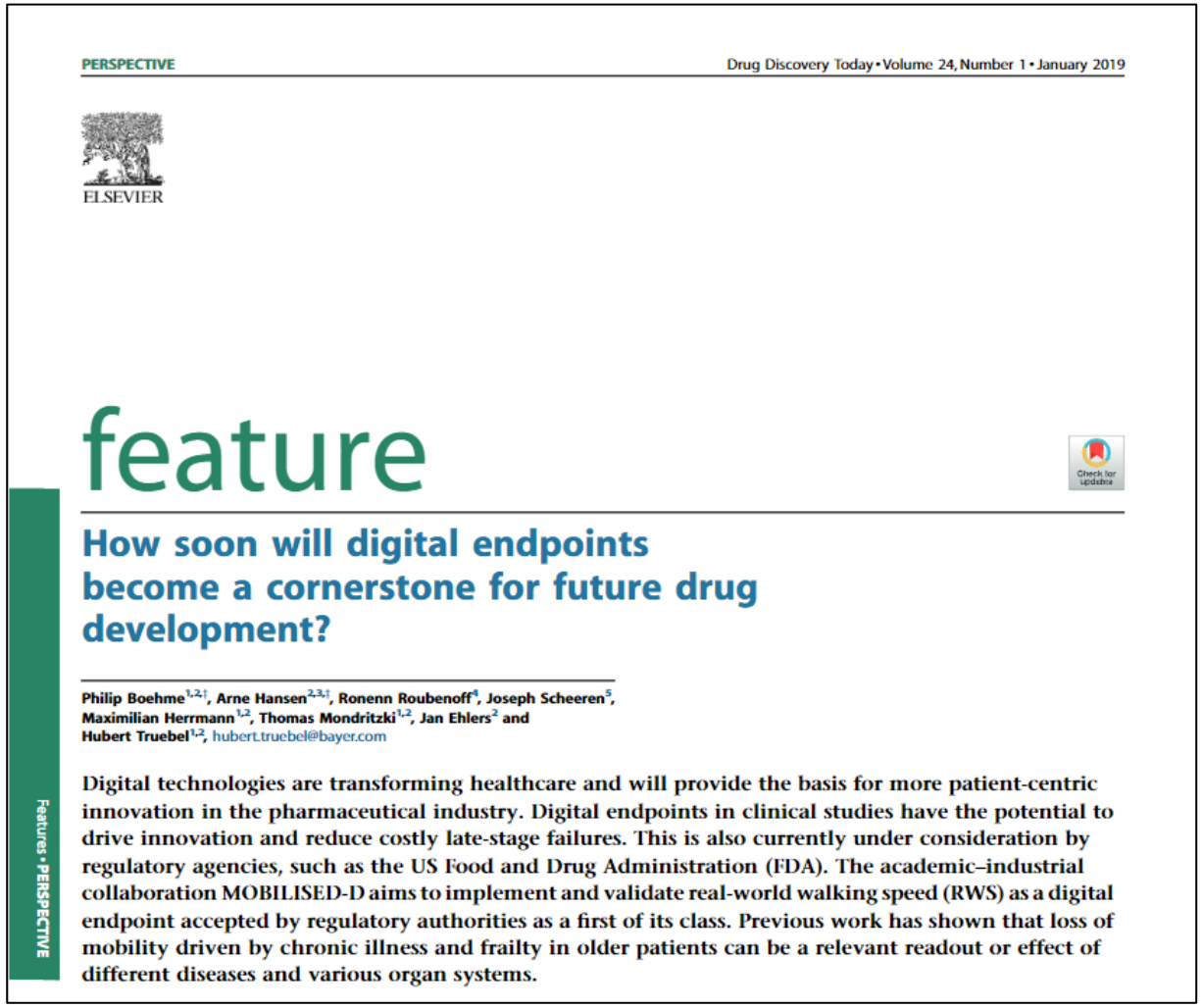
Division of Psychiatry (Prof G Livingston MD, J Huntley PhD, A Sommerlad PhD, Prof C Cooper PhD, S G Costafreda PhD, Prof B Howard MD, V Orgeta PhD, Prof E L Sampson MD, N Mukadam PhD), Dementia Research Centre, UK Dementia Research Institute (Prof M N Fox MD), and Department of Epidemiology and Public Health (Prof M Kivimäki PhD), University College London, London, UK; Camden and Islington NHS Foundation Trust, London, UK (Prof G Livingston, J Huntley, A Sommerlad, Prof C Cooper, S G Costafreda, Prof B Howard, N Mukadam); Barnet, Enfield, and Haringey Mental Health Trust, London, UK (Prof S L Sampson); National Ageing Research Institute and Academic Unit for Psychiatry of Old Age, University of Melbourne, Royal Melbourne Hospital, Parkville, VIC, Australia (Prof D J Ames MD); University of Exeter, Exeter, UK (Prof C Ballard MD); Faculty of Health: Medicine, Dentistry and Human Sciences, University of Plymouth, Plymouth, UK (Prof S Banerjee MD); Cambridge Institute of Public Health, University of Cambridge, Cambridge, UK (Prof C Brayne MD); Department of Old Age Psychiatry, University of Manchester,

Being more active modifiable risk factor for dementia

Braun et al., 2022



PERSPECTIVE Drug Discovery Today • Volume 24, Number 1 • January 2019

ELSEVIER

feature

How soon will digital endpoints become a cornerstone for future drug development?

Philip Boehme[1,2,†], Arne Hansen[2,3,†], Ronenn Roubenoff[4], Joseph Scheeren[5], Maximilian Herrmann[1,2], Thomas Mondritzki[1,2], Jan Ehlers[2] and Hubert Truebel[1,2], hubert.truebel@bayer.com

Digital technologies are transforming healthcare and will provide the basis for more patient-centric innovation in the pharmaceutical industry. Digital endpoints in clinical studies have the potential to drive innovation and reduce costly late-stage failures. This is also currently under consideration by regulatory agencies, such as the US Food and Drug Administration (FDA). The academic–industrial collaboration MOBILISED-D aims to implement and validate real-world walking speed (RWS) as a digital endpoint accepted by regulatory authorities as a first of its class. Previous work has shown that loss of mobility driven by chronic illness and frailty in older patients can be a relevant readout or effect of different diseases and various organ systems.

Features • PERSPECTIVE

- Pharma industry needs to **innovate** clinical trials – reliable **novel endpoints**, show an efficacy signal with predictive value
- **Multiple** indications
- Device **agnostic**
- **Patient-centric** innovation
- **Real-world** data
- **Broad application** in research and clinical
- Digital technology + Mobility = **opportunity** for novel digital endpoints
- Reliable, valid digital endpoints have potential to **transform** drug development trials and clinical research and care

Connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement

Mobilise-D

imi innovative medicines initiative

efpia

>300 experts

12+ countries

34

Universities, Pharma / Tech Companies & CROs

Patients & Public

€ 50 m

2019-2024

Newcastle University · The University Of Sheffield. · Tel-Aviv Sourasky Medical Center · CAU Christian-Albrechts-Universität zu Kiel · KU LEUVEN · EPFL · FAU · UCD Dublin · NTNU Norwegian University of Science and Technology · Robert Bosch Krankenhaus · uniss

ISGlobal Barcelona Institute for Global Health · Northumbria University Newcastle · Imperial College London · University of Zurich · ixscient · mcroberts · Universitätsklinikum Erlangen · pri · CHU

AMGEN · AstraZeneca · BAYER · CLARIO. · GRÜNENTHAL · ICON · MERCK · NOVARTIS · Pfizer · sanofi · Takeda · teva

Mobilise-D

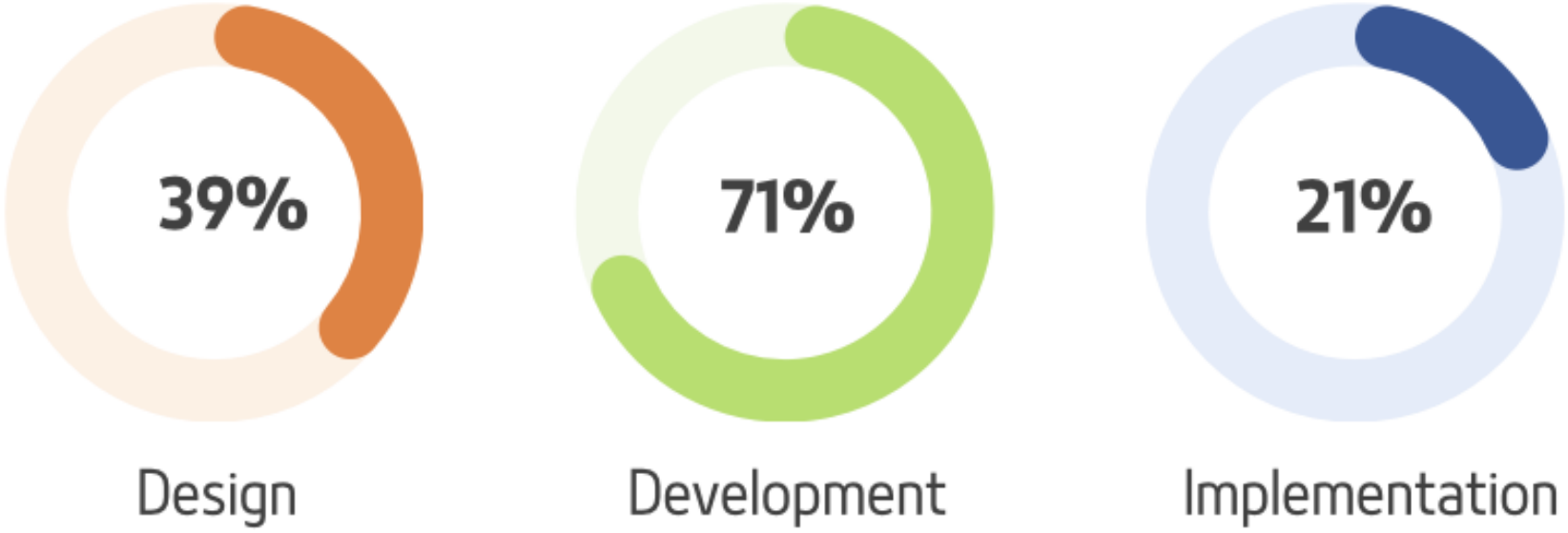
*Deliver a **valid** solution for **real-world** digital mobility assessment in **multiple conditions** that affect **mobility** & provide a roadmap to bring **digital mobility outcomes** from concept to widespread **adoption***

The use pf patient and public involvement activities within Mobilise-D to support digital mobility [illegible] development

Alison Keogh
alison.keogh@insight-centre.org

How can patients shape digital medicine?

PPIE is conducted sporadically across the research cycle, with little consistency in PPIE approaches. Contributors to date are mainly involved in development, and seldom involved in implementation with little reporting regarding impact of PPIE on research.



An investigation into the role of Patient and Public Involvement and Engagement (PPIE) in the development of digital health technologies – Hanrahan et al., under review

Within Mobilise-D, it was not a question of if we would have patient involvement in our project, but ***how*** we would.

4 Patient cohorts

5 Consortium objectives

12 Countries

17 International sites

34 + Research partners

Mobilise-D

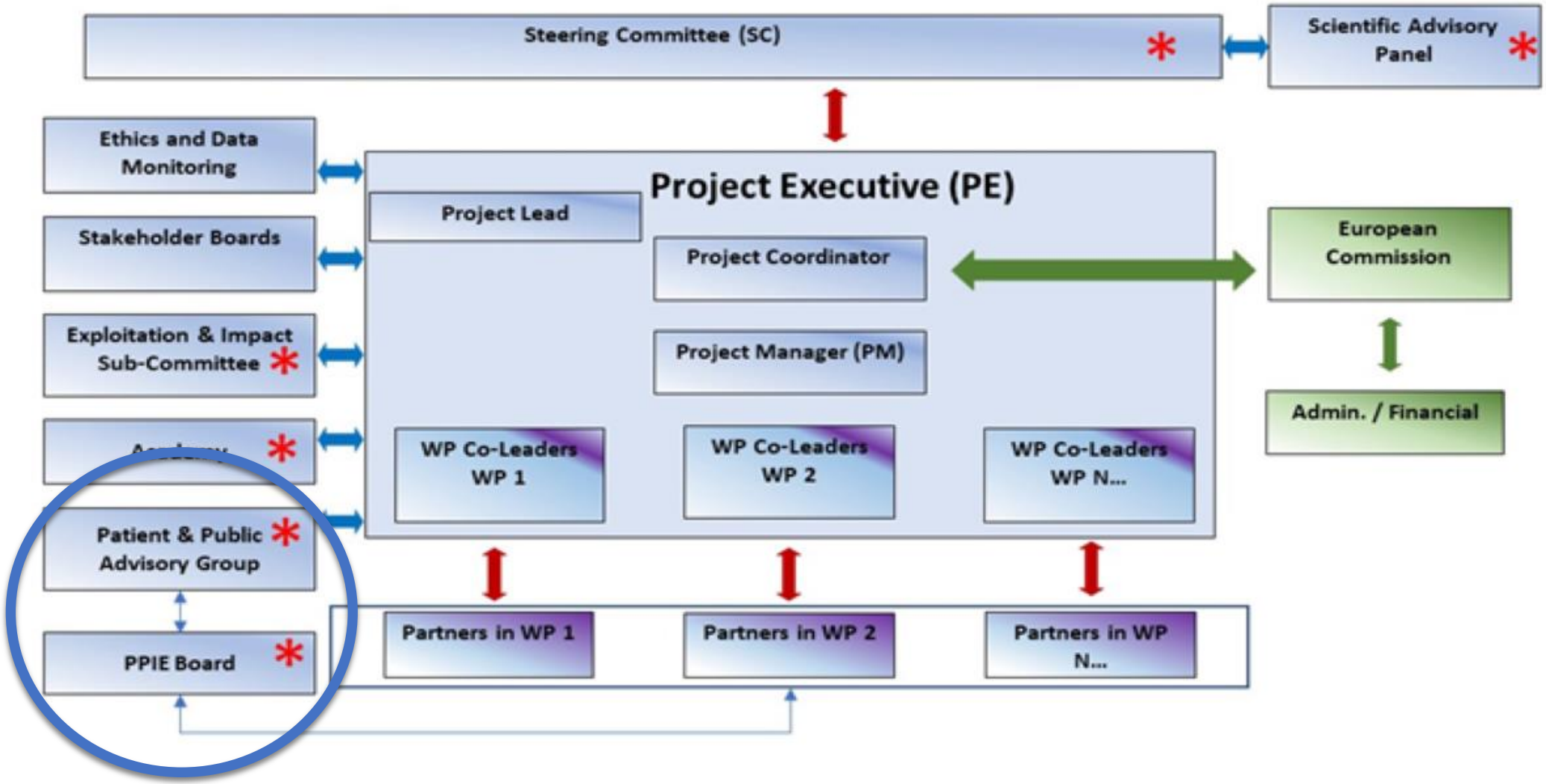
JOURNAL OF MEDICAL INTERNET RESEARCH

Tutorial

Mobilizing Patient and Public Involvement in the Development of Real-World Digital Technology Solutions: Tutorial

Alison Keogh[1,2], BSc, MSc, PhD; Ríona Mc Ardle[3], PhD; Mara Gabriela Diaconu[4], MSc; Nadir Ammour[5], PhD; Valdo Arnera[6], MD; Federica Balzani[7], MSc; Gavin Brittain[8,9], MD; Ellen Buckley[10,11], PhD; Sara Buttery[12], BSc; Alma Cantu[13], PhD; Solange Corriol-Rohou[14], PhD; Laura Delgado-Ortiz[15,16,17], MSc; Jacques Duysens[7], PhD; Tom Forman-Hardy[7], BA; Tova Gur-Arieh[7], BA; Dominique Hamerlijnck[7], MBA; John Linnell[7], BA; Letizia Leocani[18], MD, PhD; Tom McQuillan[7]; Isabel Neatrour[3], MSc; Ashley Polhemus[19], PhD; Werner Remmele[7], DipHE; Isabel Saraiva[7], BA; Kirsty Scott[10,11], PhD; Norman Sutton[7]; Koen van den Brande[7], BSc; Beatrix Vereijken[4], PhD; Martin Wohlrab[20,21], MSc; Lynn Rochester[3,22], PhD; Mobilise-D consortium[23]

Project Management Structure



* = PPIE representative

All Members:





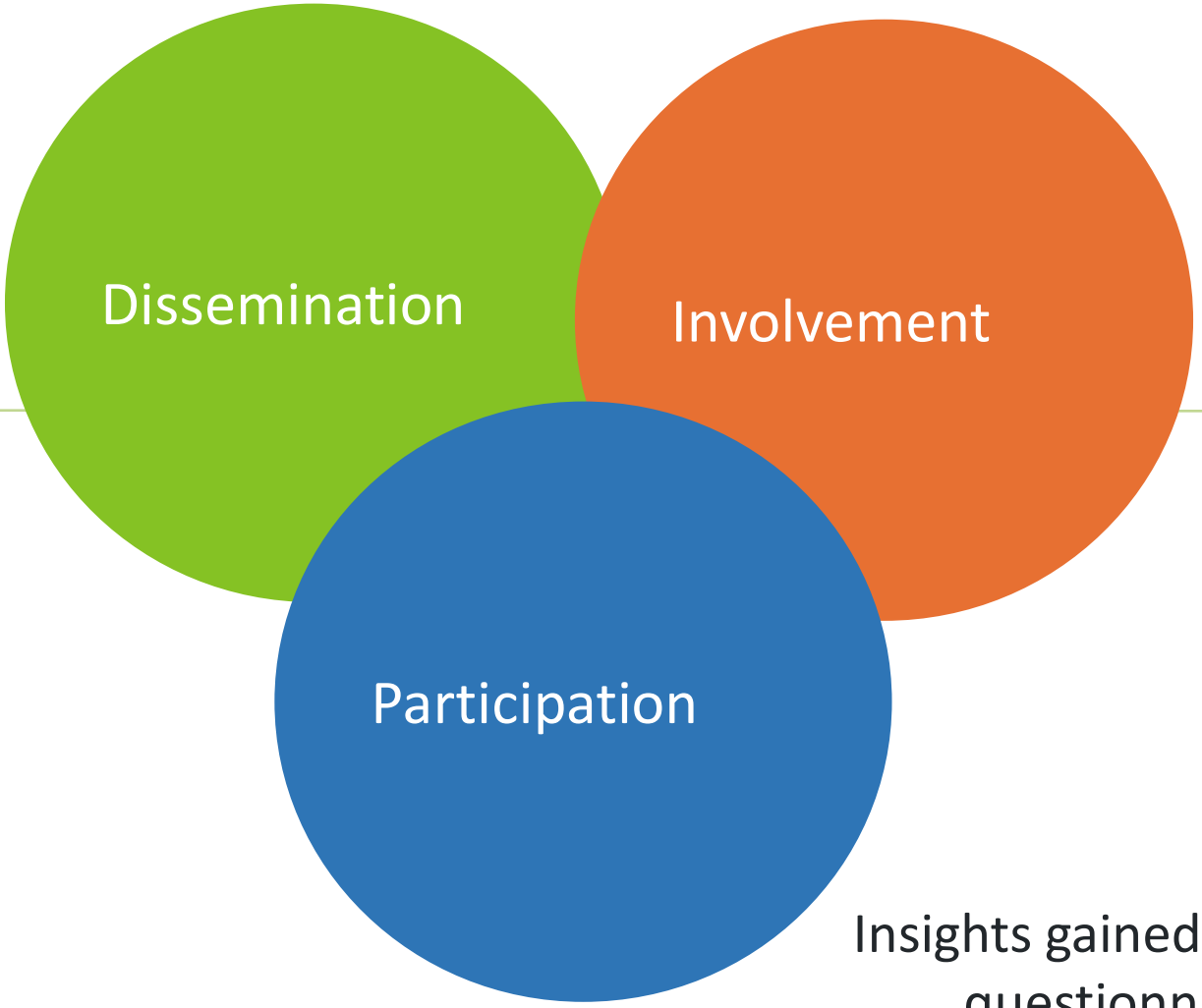






Where and how did our PPIE occur?

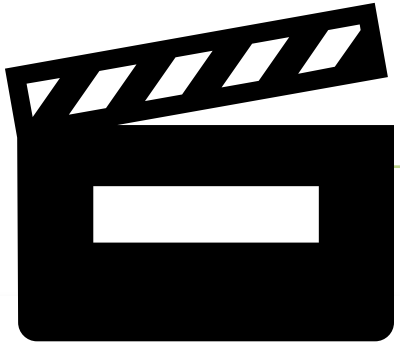
Advice and support to increase project visibility & impact

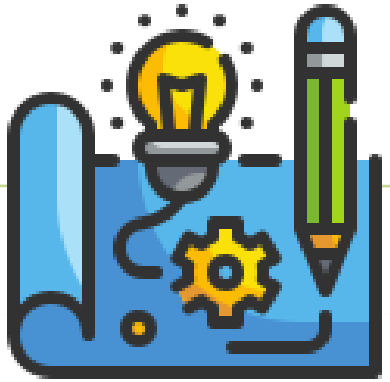


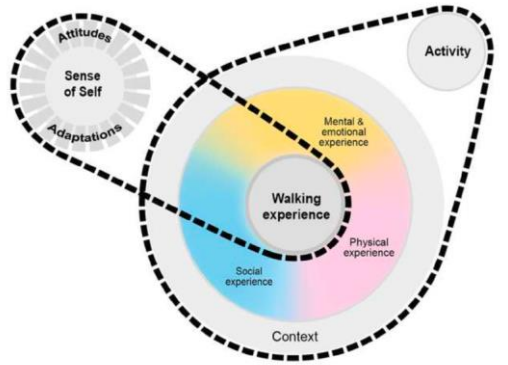
Co-design, interpretation & co-authorship of research

Insights gained through participation, questionnaires & interviews

What changed because of our PPIE?





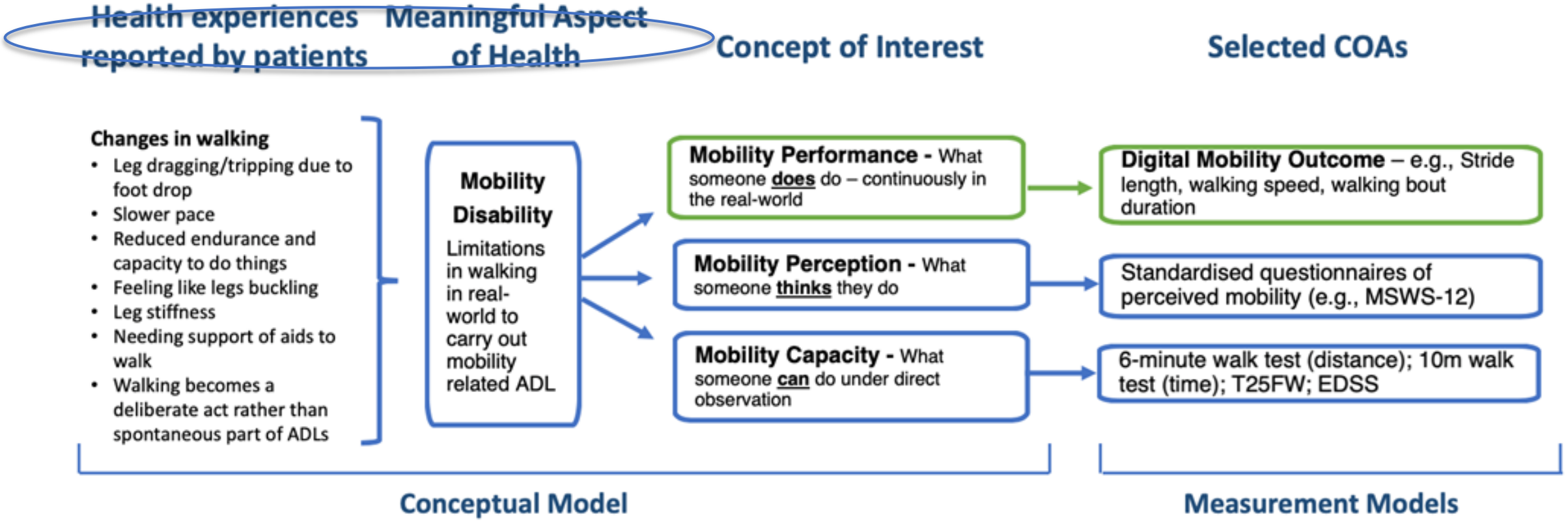


Novel & engaging approaches to inform patients and the public

Improved study design for now and in the future

Clearer understanding on the importance of mobility

Development of conceptual model – for example MS



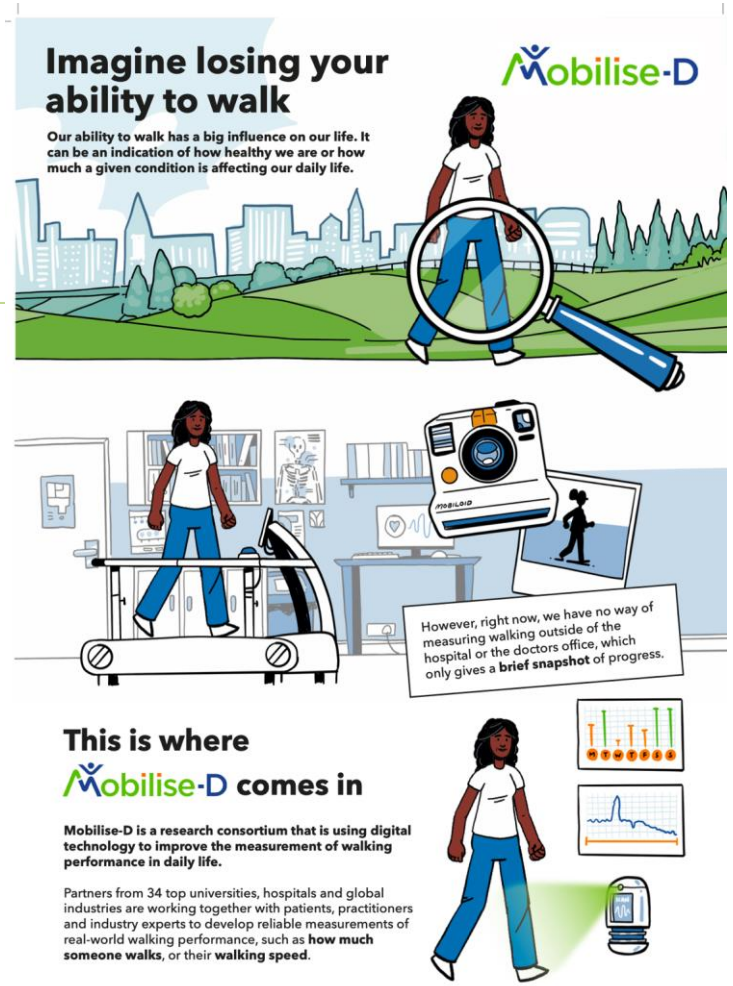
Novel and engaging ways to inform the public

PPIE promoted the work of the consortium in a way that is suitable for the public.

Emphasising the importance of mobility in daily life using multiple methods.

Co-designing the following:

- Webinars on PPIE and walking importance
- Public information sheet on the study and why it is happening
- 3 x Public videos promoting the study, how data is shared and the impact of patient involvement in it.



Real-world walking as a meaningful aspect of health

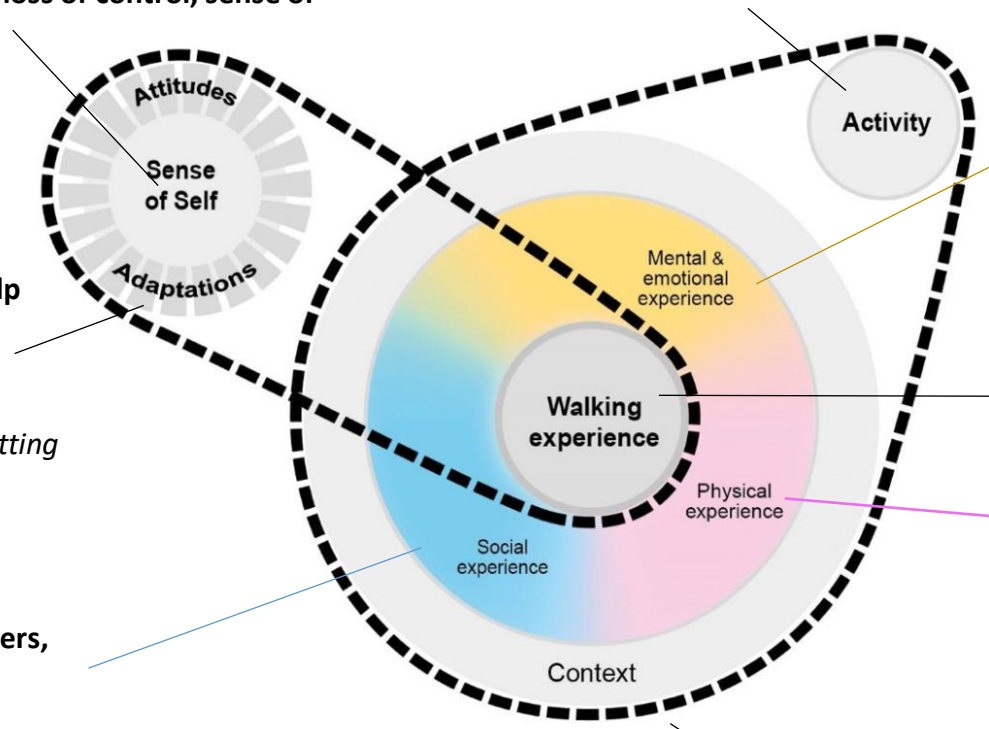
Maintaining independence, loss of identity, loss of control, sense of normality

Walking aids, planning, stopping activities, continuing even with risk, pacing, taking help etc.

"*The fact that my mobility is really hard now. Really difficult. And, you know, just sort of getting a cup of coffee sometimes, I think "Do I want one? Do I really need one?"*

Needing help from others, judgement of others, feeling 'disabled', loss of social roles, lack of understanding by others etc.

"I look pretty goofy when my foot drops really bad. Like my leg will drag. And friends know that. Family know that. And it's like, "This is just how I am."



Any task they wish to complete – dressing, grocery shopping, work, walking to a venue etc.

Home, health clinics, holiday venues, supermarkets, work etc.

"So, I'm always aware of distance, of how far I have to walk. And I'm always aware of the temperature."

Grief, emotional fatigue, stress, mood disturbance, fear, frustration, embarrassment, loss of esteem etc.

"I just have to concentrate a lot more, you know? The amount of - it's difficult to explain the amount of concentration that's put into these things, particularly when you're tired, particularly when you're fatigued or if you're doing something else at the same time"

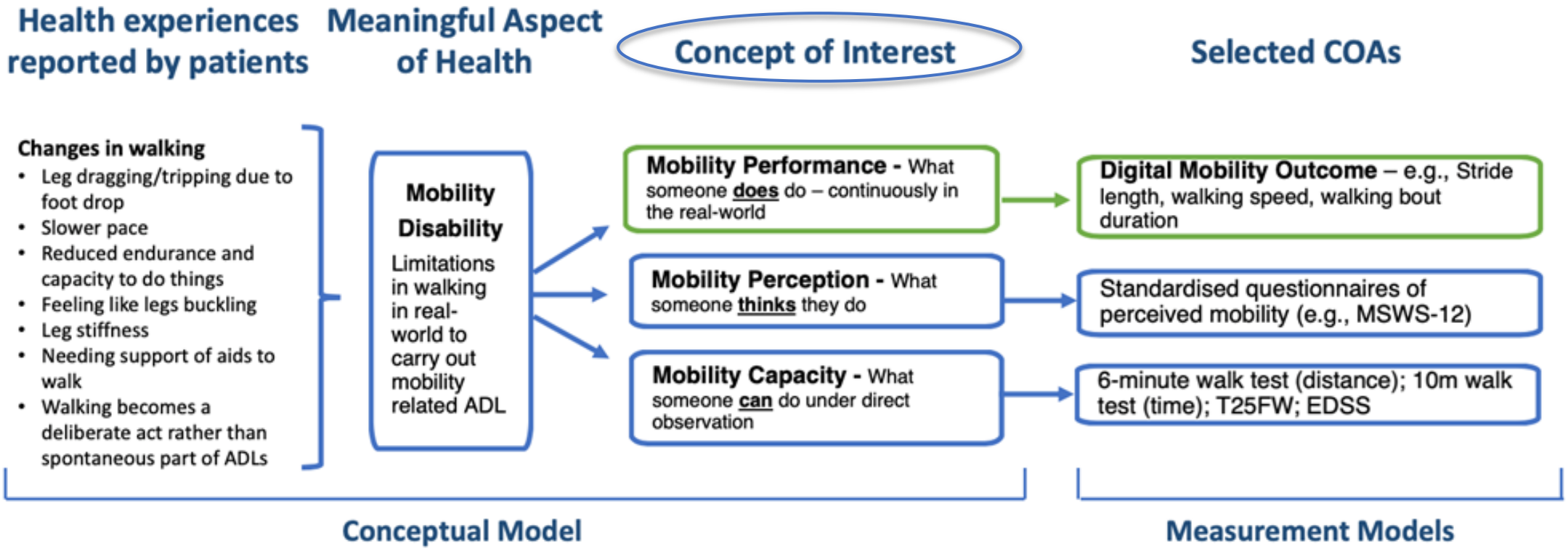
Performance of walking related activities of daily living

Reduced balance, fatiguability, feet dragging, legs buckling, reduced energy, sensory disturbances, weakness, pain, temperature sensitivity, blurred vision etc.

"I just find it harder to lift my legs. You know, it's that general sense of strength that you start to lose"

Taken from Delgado-Ortiz L, et al. doi: 10.1093/ageing/afac233.

Development of conceptual model

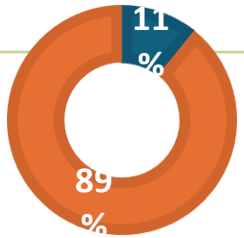


Concept of interest exploration, including acceptability of remote monitoring & opinions of under-served groups

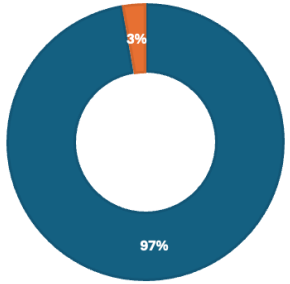
Activities have sought to ensure that we asked questions that are important, that results are interpreted from the perspective of patients and that the lived experience of monitoring mobility performance was acceptable.

Co-designing the following:

- Experience questionnaire of the CVS.
- Development of minimal important difference questions for the CVS.
- Exploring the acceptability of remote monitoring in TVS participants.
- How to include those from under-served groups.



89% said the device did not interfere with daily activities



97% would be willing to use this in clinical care

86%

Said the device was comfortable

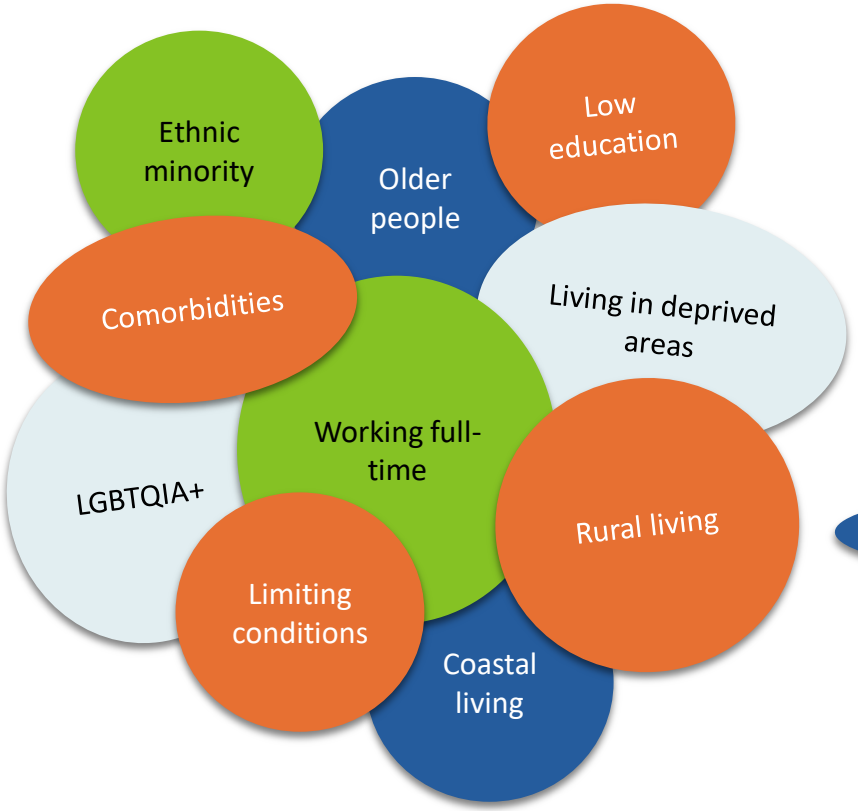
71%

Would like information during the study not at the end

97%

Found remote monitoring acceptable

Concept of interest exploration, including acceptability of remote monitoring & opinions of under-served groups



We focused on how best to access underserved groups and support them into research.

A range of professionals and researchers took part, including researchers, neurologists, and physiotherapists.

value within research reinforced from the beginning to the end of

Communications should be both informal and sensitive to the populations

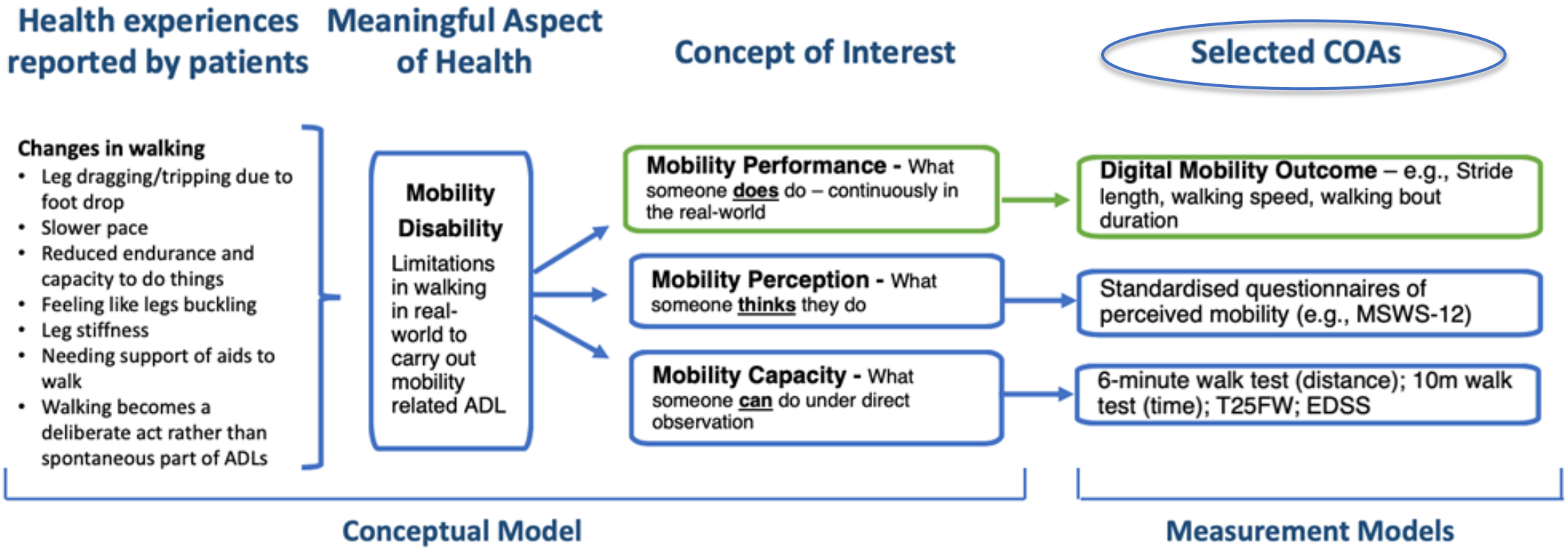
represent the communities intended to be targeted

Important to understand the priorities of the population

Provide online and in person options where possible

Underserved groups provide meaningful insights into the accommodations that can be made in designing and marketing of digital health technologies. Recruitment should be more than advertisement but rather a means of engaging and uplifting communities. The workshops allowed us to expand our recruitment network.

Development of conceptual model

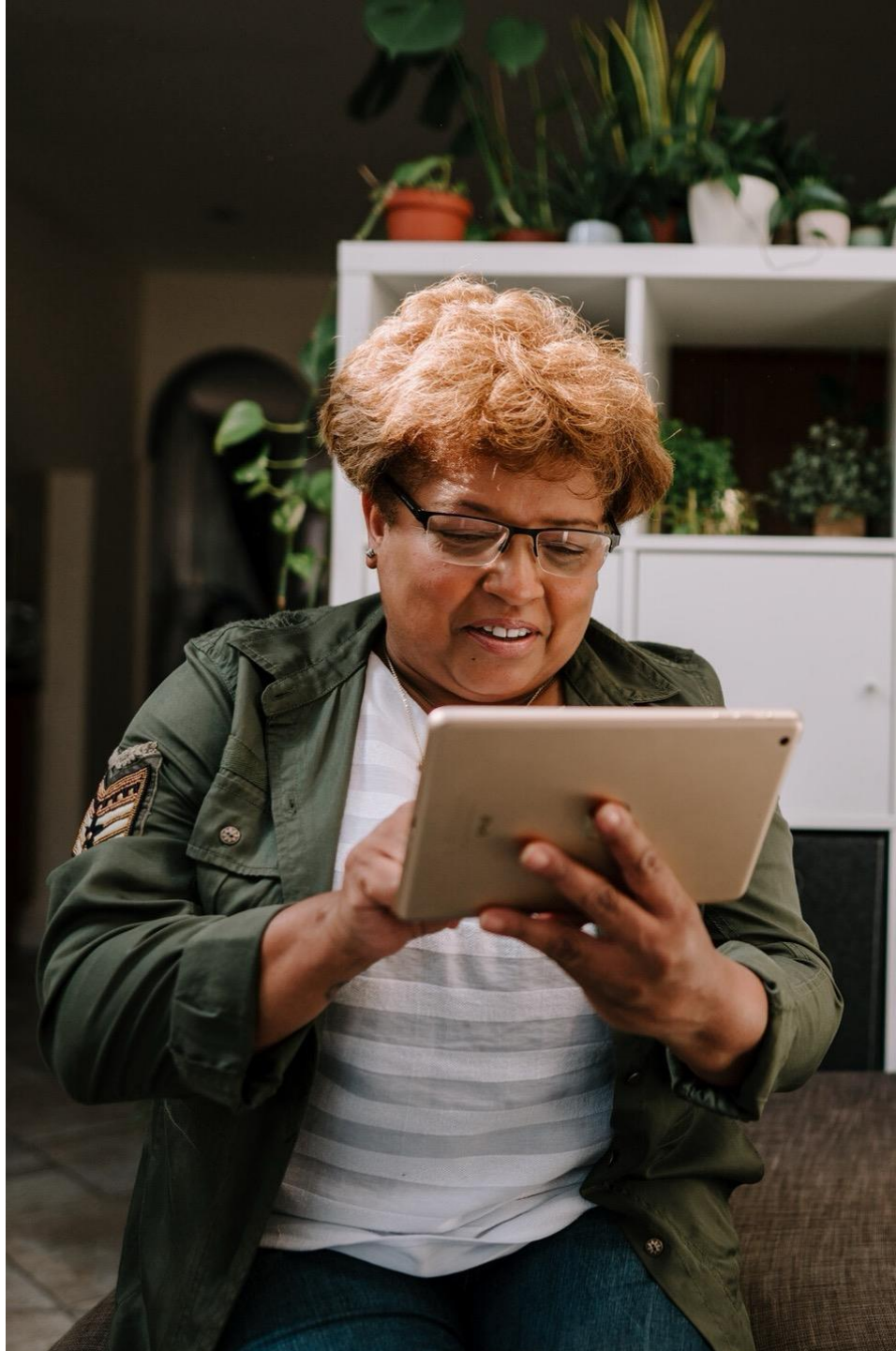


Mapping mobility experiences to DMOs

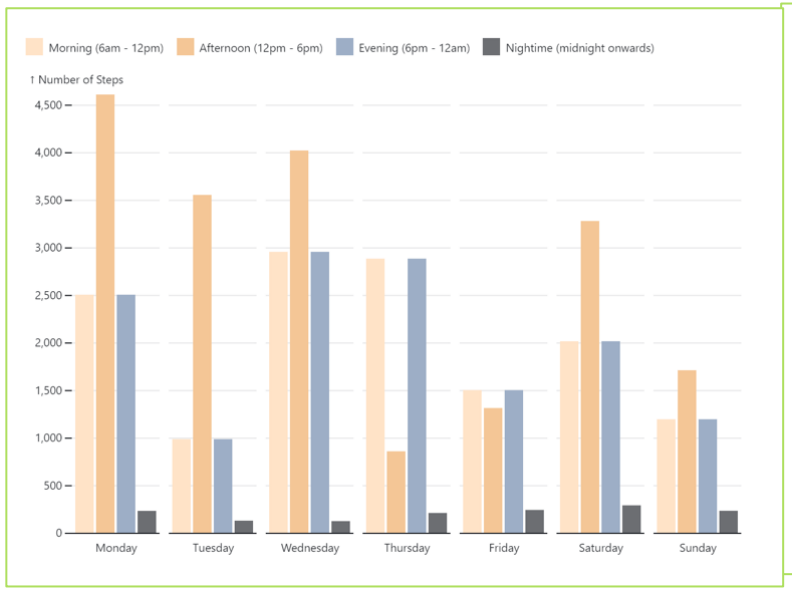
Our conceptual framework links the experiences of walking to daily tasks.

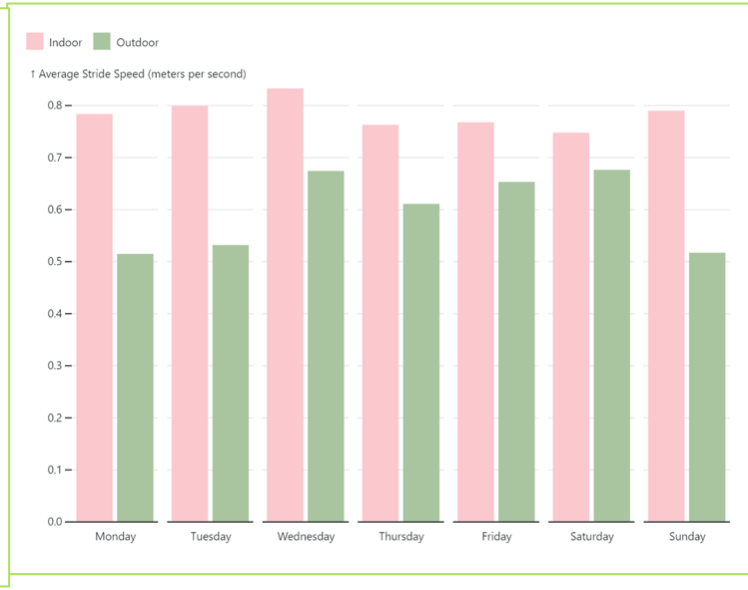
For example: "So, I’m always aware of distance, of how far I have to walk" is a contextual experience, that links to a patients' mobility related symptoms of MS and can be mapped to a digital mobility outcome such as duration of walking bout.

We are currently interviewing people with PD to map these experiences explicitly to the Mobilise-D DMOs. Additionally, we iteratively exploring how walking experiences and DMOs might be visualised to people with chronic conditions to understand how they want their data over time shown to them.



Mapping mobility experiences to DMOs





Patients wanted to see superimposed graphs to get a better grasp of the data

The data presented needs to be relevant to their experiences

Emphasis on accessibility – bigger font and brighter colours

Most participants found the graphs easy to understand

Key takeaways

PPIE has improved the outputs of Mobilise-D, guided us on what is important, and challenged our thoughts about key concepts.

PPIE has demonstrated that real-world walking is meaningful to patients and that they find remote monitoring to be acceptable.

Patients have a clear desire for more information about their mobility. Remote trials have the potential to be impactful and change future healthcare assessments.

Technical Validation: Challenges and solutions for the estimation of technically valid real-world Digital Mobility Outcomes

Mobilise-D Technical Validation Study Leads:

Andrea Cereatti, Silvia Del Din, Arne Mueller, Claudia Mazzà and the WP2 team

Dr. Claudia Mazzà
Univ. Sheffield/Biogen

Dr. Silvia Del Din
Univ. Newcastle

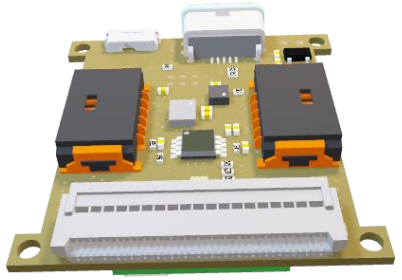
Prof. Andrea Cereatti
Politecnico di Torino

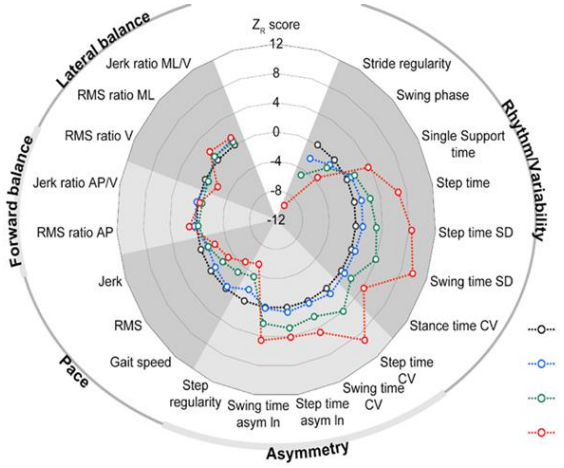
Dr. Arne Mueller
Novartis

The goal of the technical validation study

To provide **valid**, **robust** and **feasible** digital **tools** to describe **digital mobility** in **Real World** conditions

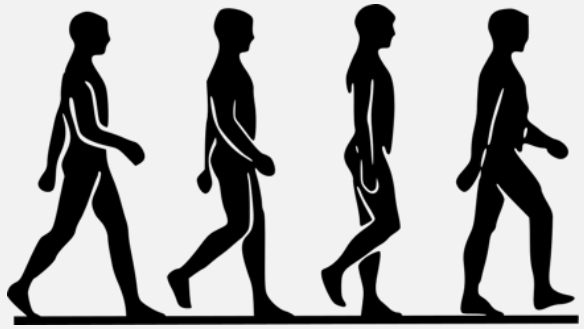
Digital device





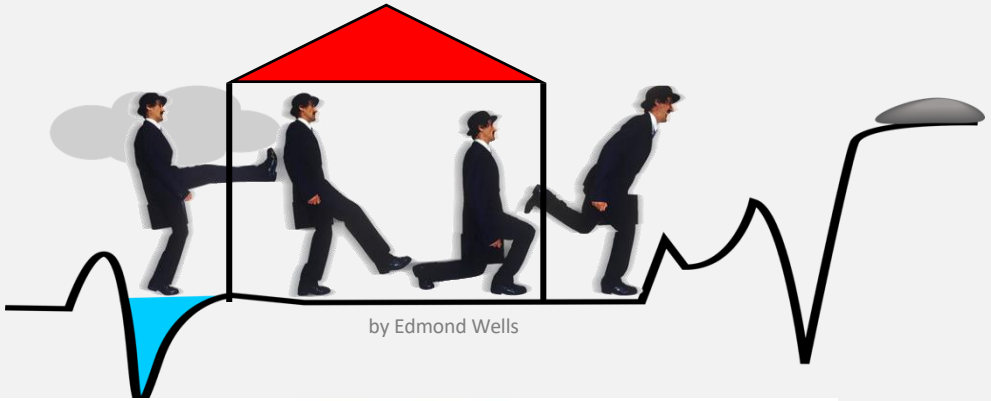
From the laboratory to the real world

What we are used to in the **lab**

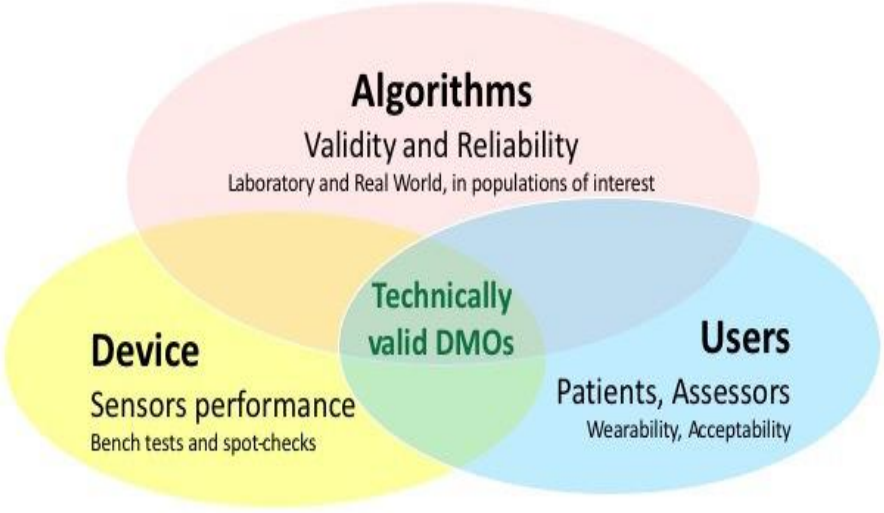


Challenges

What happens in the **real world**



1. Definitions
2. Choosing a device
3. Quantifying real-world walking (algorithms)
4. Establishing a technical validation framework
5. Data analysis to quantify and show validity



Mazza et al., 2021, doi: 10.1136/bmjopen-2021-050785.

Challenge 1: Defining a common language for real-world walking

Felix Kluge

Real world

- Free-living, unsupervised, uncontrolled, and non-standardised
- Distinct from laboratory-based, supervised, and semi-controlled tests

Output

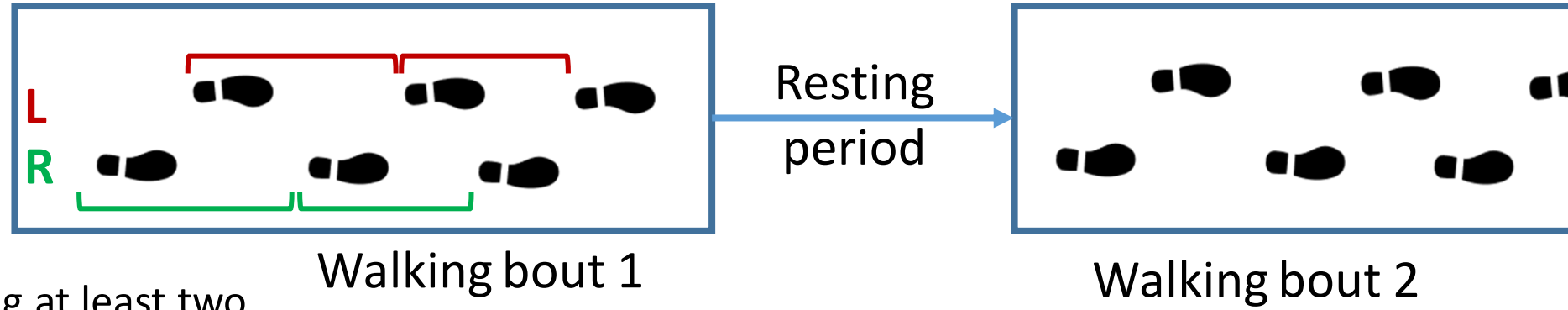
Consensus based framework for digital mobility monitoring, Kluge et al., PlosOne, 2021

Walking

- Method of locomotion using both legs to displace the center of mass in an intended direction
- Includes walking aids
- Includes turning

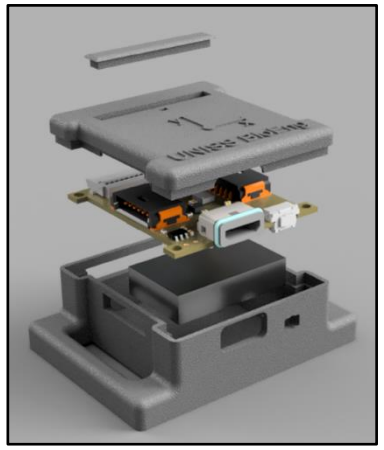
Walking bout

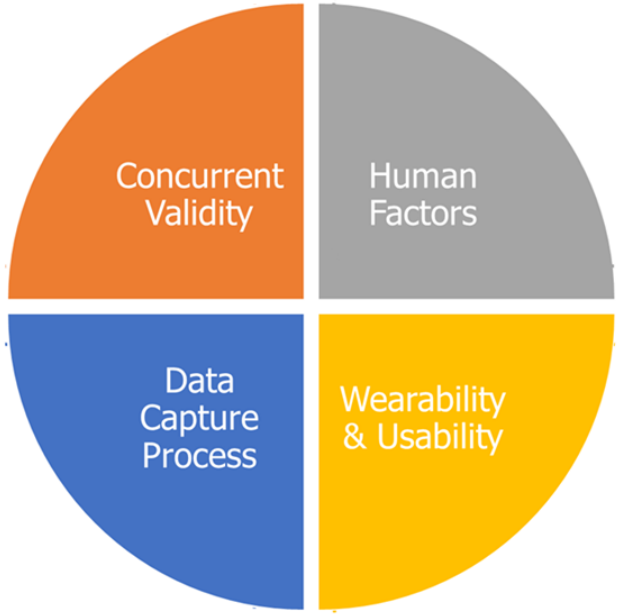
Walking sequence containing at least two consecutive strides of both feet

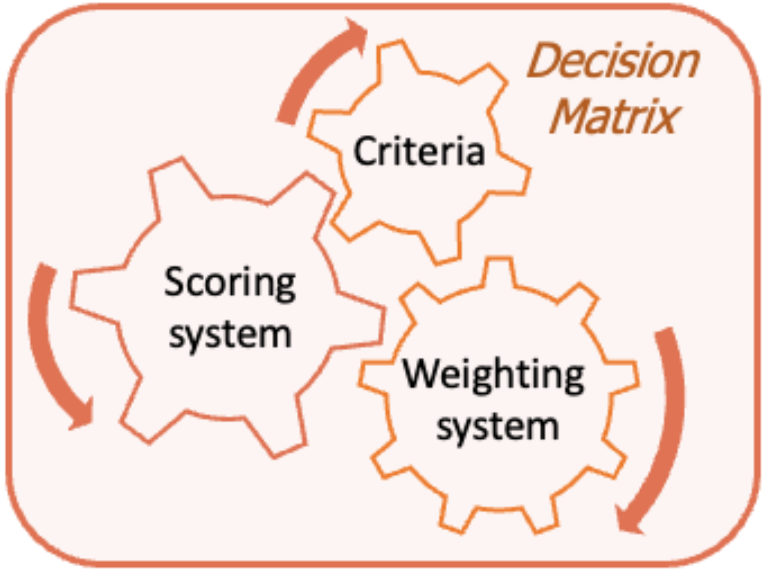


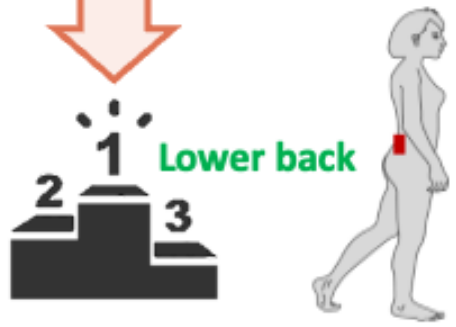
Challenge 2: Deciding on a solution

A single Inertial Measurement Unit (IMU) including
- 3 accelerometers (linear accelerations)
- 3 gyroscopes (angular velocities)
- 7-days continuous recording at 100Hz









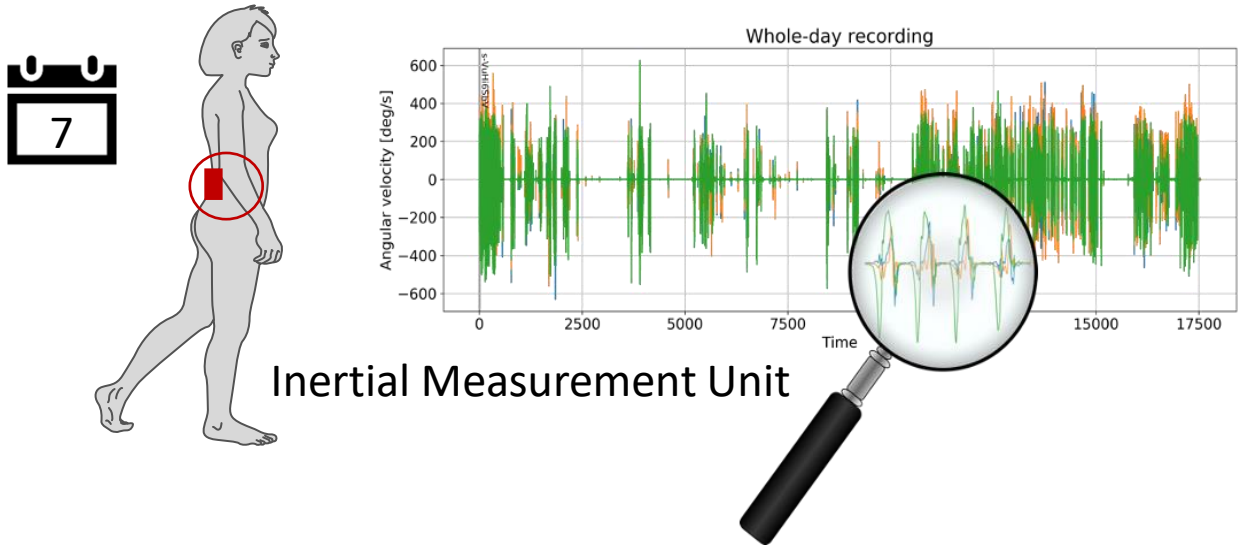
An objective methodology for the selection of a device for continuous mobility assessment. Bonci et al., Sensors 2020

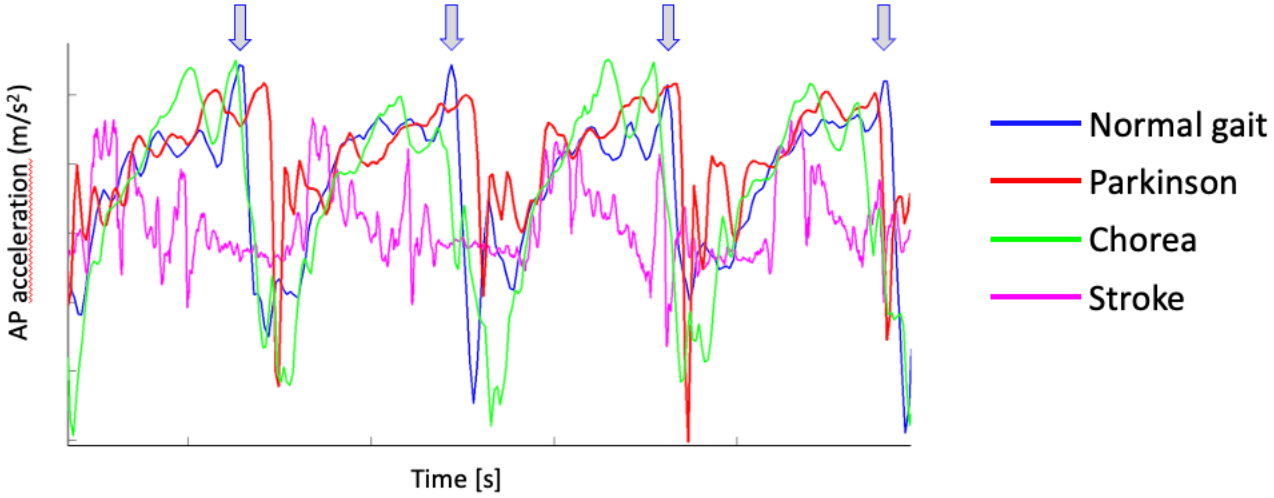
Tecla Bonci

The University Of Sheffield.

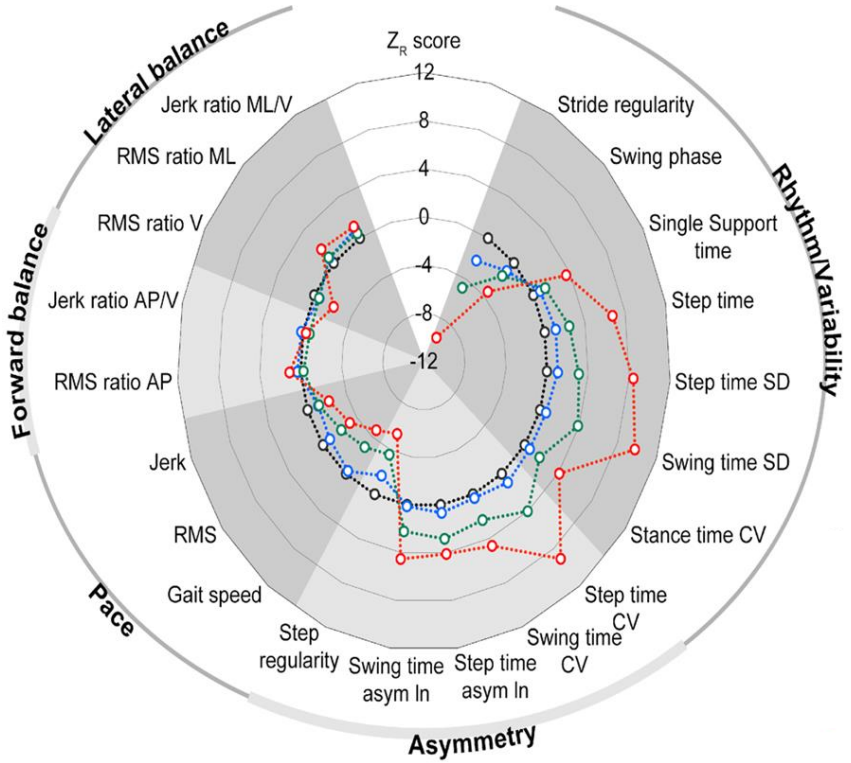
Challenge 3: quantifying real-world walking

In the real world





Digital Mobility Outcomes (DMOs)



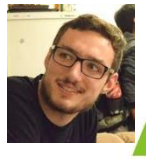
from Angelini et al. (2021)

Challenge 3: computational pipeline

Luca Palmerini

Anisoara Ionescu

Abolfazl Soltani



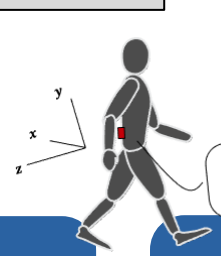
Arne Küderle

Martin Ullrich

80+ algorithms compared !
(mostly existing algorithms)

Data Standardization

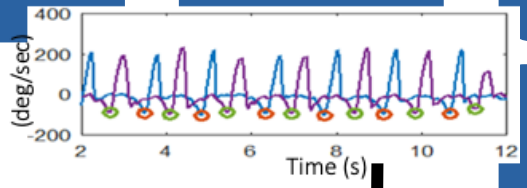
Walking contex
- Turning
- Stairs
- ...



Gait sequence Detection

Pre-Processing

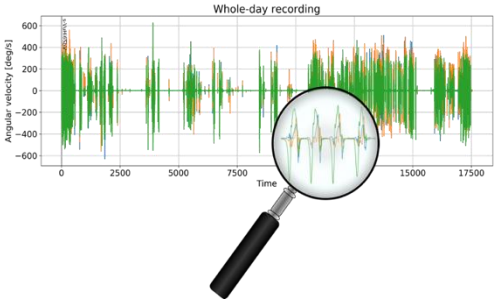
Step detection



Step Length

Real-World Walking Speed

Cadence (Temp/Freq)



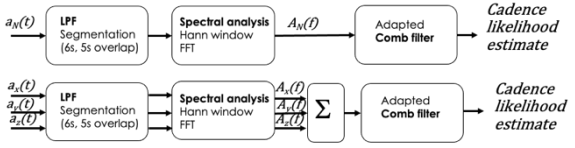
Left/Right Stride detection

- Time domain

$$AverageCadence = \frac{\sum_{k=1}^{n\_steps} \left(\frac{60}{Step\_duration_k}\right)}{n\_steps}$$

$Step\_duration_k$ is the duration of the k – step in the WB
n_steps is the number of steps identified in the WB

- Frequency domain



Stride Interpolation

Walking Bout Assembly (WBA)

WB DMOs

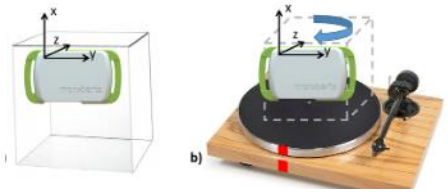
Secondary DMOs

Challenge 4: establishing a technical validation framework

Three-level validation

1 - Device testing

Bench test and spotchecks



2- Algorithm validation

With reference ("knowing the truth")

- In-Lab motor tests
- 2.5 hr Free-living

3- Acceptability

Context

7 days Real World

In the cohort(s) of interest:

- Older Healthy Adults
- Parkinson's Disease
- Multiple Sclerosis

N ~ 120

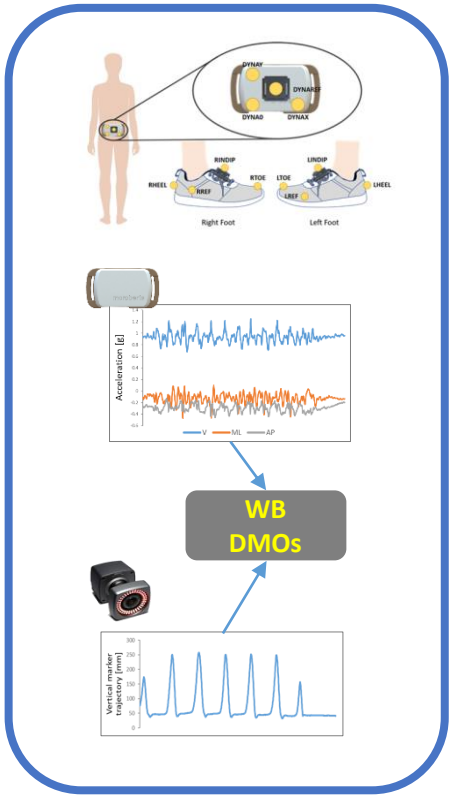
- Chronic Obstructive Pulmonary Disease
- Congestive Heart Failure
- Proximal Femur Fractures

In the context(s) of interest:

Technical validation of real-world monitoring of gait: a multicentric observational study Mazzà et al. BMJ Open 2021

Challenge 4.1: Algorithms validation In-Lab with stereophotogrammetry

In-Lab Assessment



SP#1

SP#2

SP#3

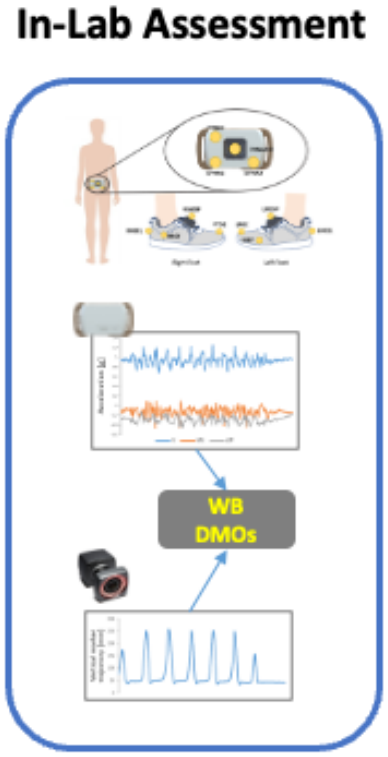
SP#4

SP#5

Multi-centric data collection

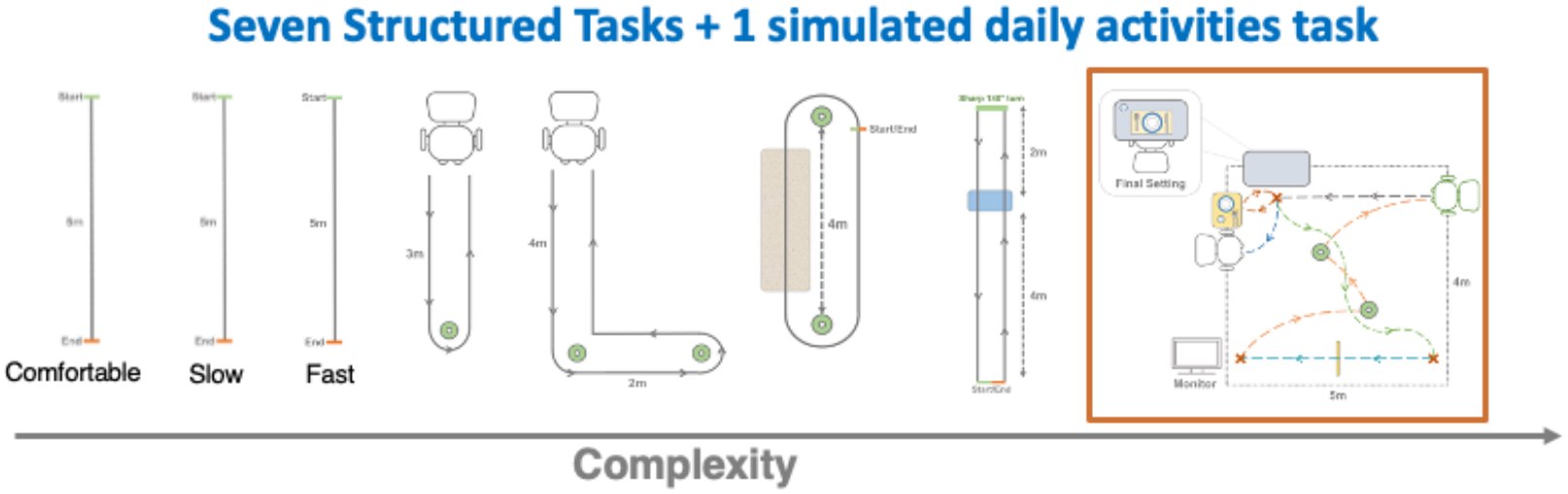
Algorithm performances under **known circumstances**

Challenge 4.1: Capturing significant data in the Lab



The experimental Protocol was conceived to:

- Ensure participant safety and well-being (clinical acceptability)
- Capture a broad range of gaits similarly to Real World (technical acceptability)

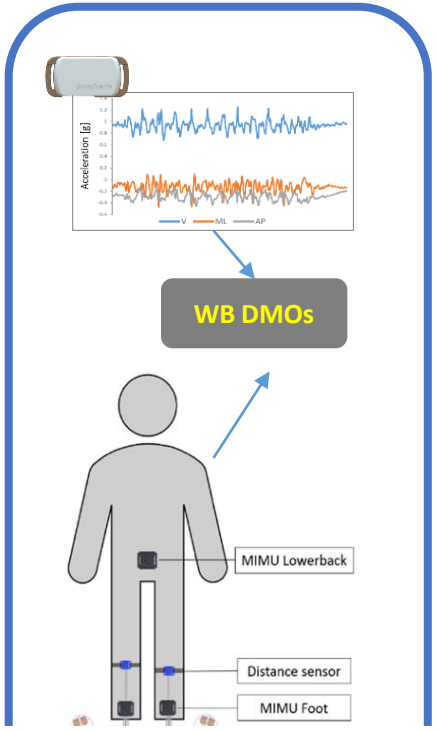


Kirsty Scott

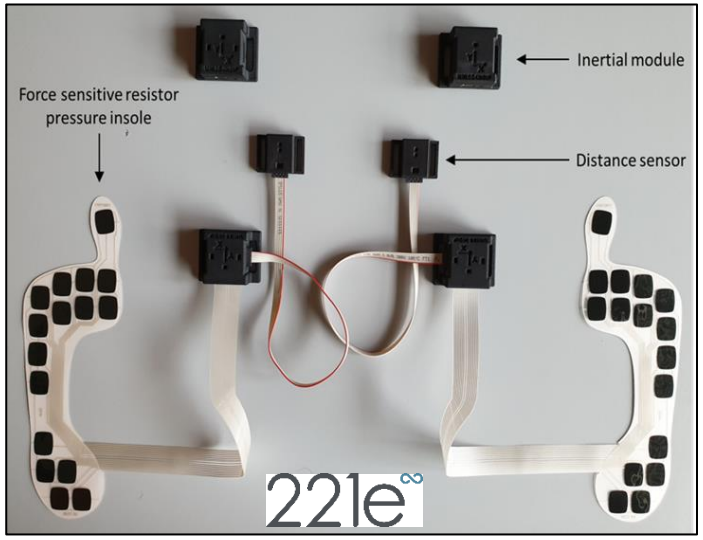
Tecla Bonci
The University Of Sheffield.

Challenge 4.2: Algorithm validation in free living conditions

2.5 hr free-living



INDIP system




Stefano Bertuletti


Francesca Salis


Marco Caruso


Andrea Cereatti

uniss UNIVERSITÀ DEGLI STUDI DI SASSARI

POLITECNICO DI TORINO

	Walking Speed		
Cohort	**Mean ± Standard Deviation (INDIP, m/s)**	**Mean ± Standard Deviation (SP)**	**Median Relative Error (%)**
HA	0.97 ± 0.25	0.97 ± 0.25	0.95 %
PD	0.82 ± 0.30	0.81 ± 0.29	1.16 %
MS	0.84 ± 0.29	0.79 ± 0.30	0.31 %
COPD			
CHF	0.92 ± 0.34	0.90 ± 0.33	0.67 %
PFF	0.73 ± 0.35	0.72 ± 0.35	1.57 %

Walking Speed mean error < 1.6%

A multi-sensor wearable system for the assessment of diseased gait in real-world conditions, Salis et al. Frontiers in Bioengineering and Biotechnology 11, 1143248 (2023)

Challenge 5: statistical data analysis

Anne-Elie Carsin

ISGlobal Barcelona Institute for Global Health

Sarah Koch

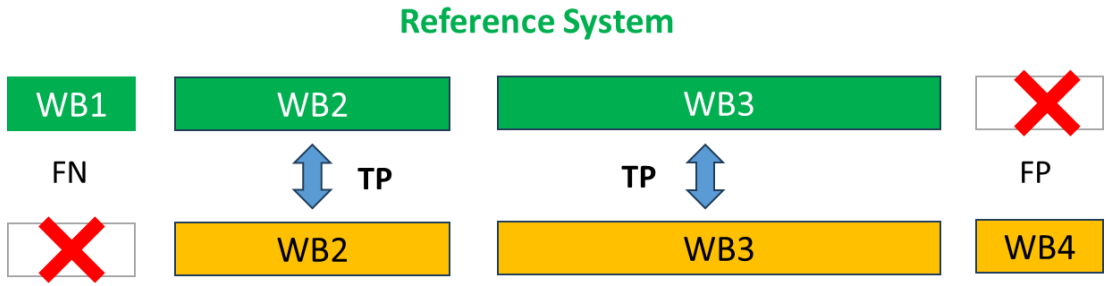
Encarna Micó -Amigo

Newcastle University

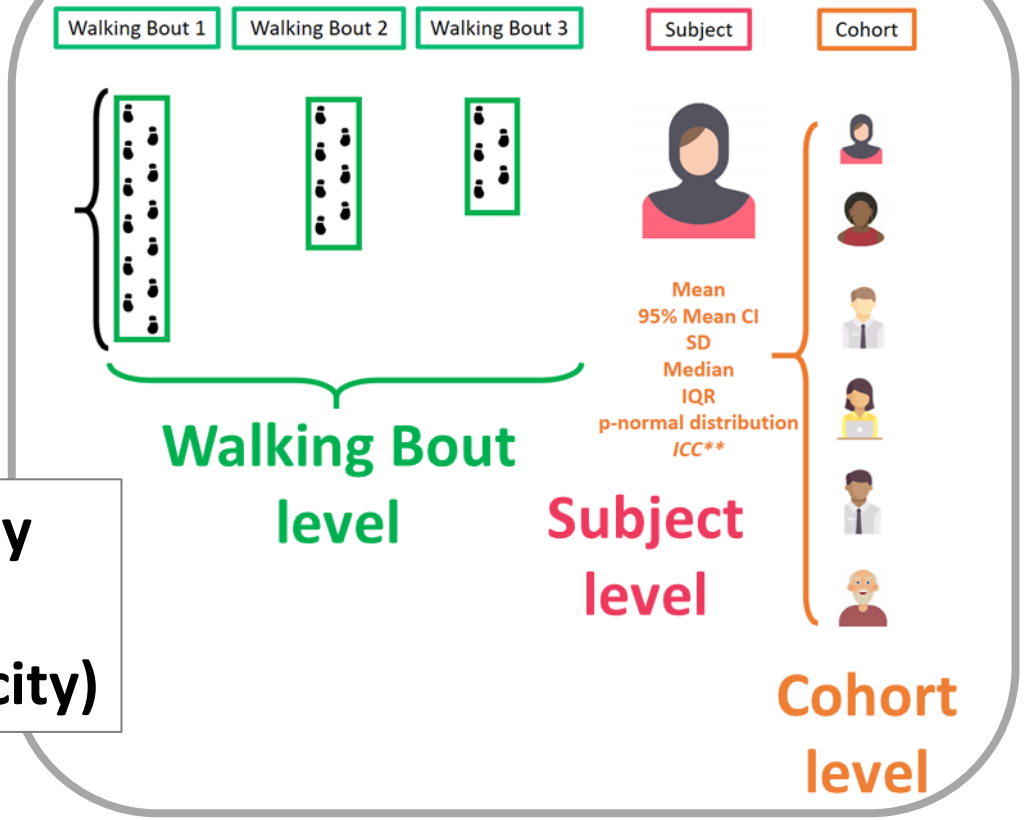
Silvia Del Din

Walking bout matching

For each true WB & DMO



Performance Metrics



Statistical analysis plan

Criterion Validity Metrics (ICC, sensitivity/specificity)

Challenge 5.1: DMOs validity & results at a Glance

	DMOs	All Walking Bouts	Walking Bouts >10s
Walking activity Volume	Number of steps	✓	✓
	Number of Turns	✓	✓
Walking activity Pattern	Number of Walking Bouts	✓	✓
	Walking Bout Duration	✓	✓
	Turn duration	✓	✓
Gait - Pace	Walking Speed	X →	✓
	Stride Length	X →	✓
Gait - Rythm	Step Duration	✓	✓
	Cadence	✓	✓
	Swing Phase Duration	X	X
	Stance Phase Duration	X	X

Criteria for DMO validity recommendation "✓"
Relative error <20%, Performance Metrics > 0.7 (ICC>0.7)

Critical factors

- Short WB (< 10 s)
- Gait complexity (strong asymmetries)
- Very low gait speed (<0.3 m/sec)
- Two mobility pipelines depending of the use case (impaired gait vs limited performance)


Silvia Del Din


Kameron Kirk

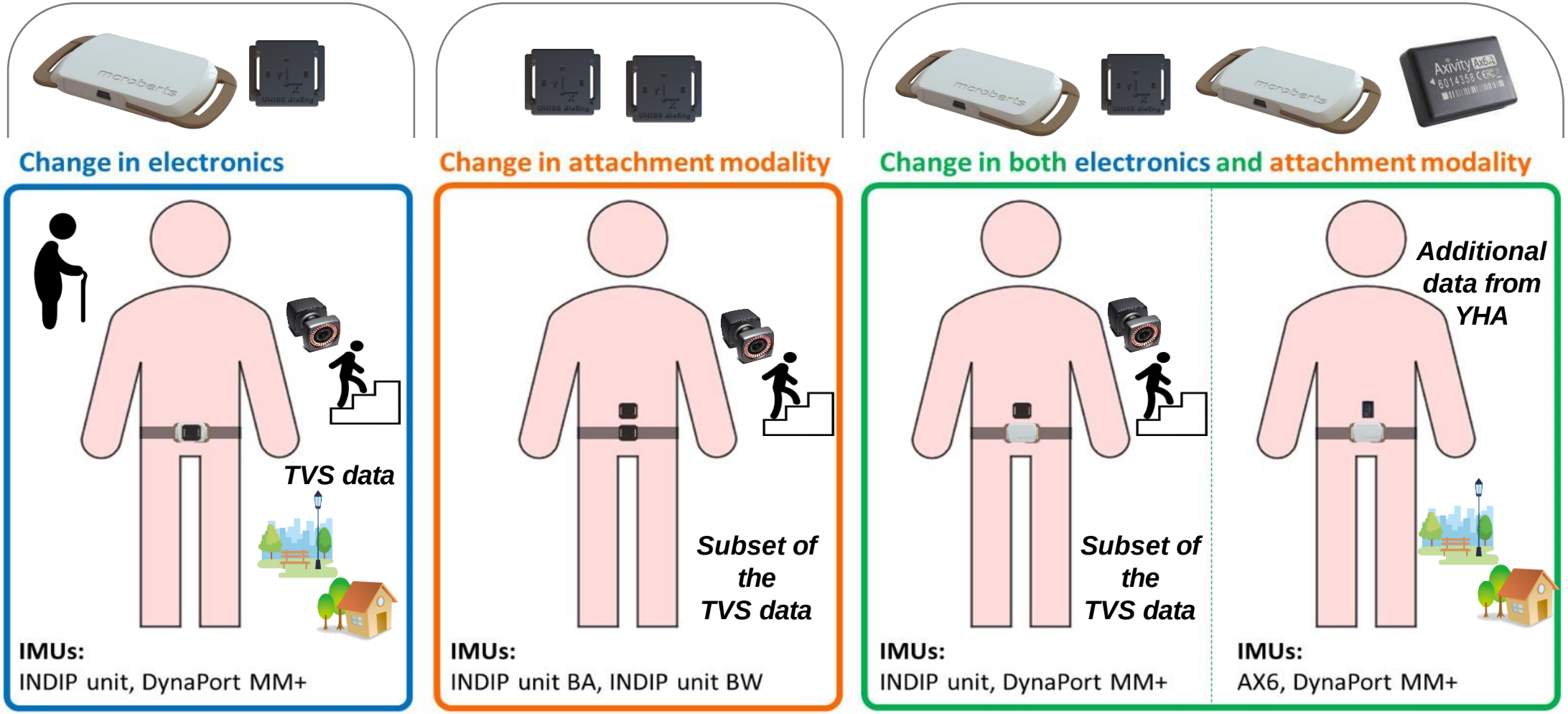

Encarna Micó -Amigo

Assessing real-world gait with digital technology? Validation, insights and recommendations from the Mobilise-D consortium. ME Micó-Amigo et al. Journal of NeuroEngineering and Rehabilitation 20 (1), 1-26, 3, 2023.

Mobilise-D insights to estimate real-world walking speed in multiple conditions with a wearable device. C Kirk, et al. Scientific reports 14, 1754 (2024)

Validity of device agnostic approach

Equivalence & comparison



Impact and perspectives

- Provides first-ever systematic approach to mobility measurement that is standardised and freely available.
- *Research/tech companies:* Data availability and the benchmarking framework enables the development of new algorithms.
- *Pharma companies:* Increased robustness and trustworthiness of mobility endpoints enables use in clinical trials.
- *Health authorities:* Technical validation is one of the foundations for qualification of DMOs.

MOBILISE-D
Towards Qualification of Digital Mobility Outcomes

Gül Erdemli MD, PhD, Novartis Pharmaceuticals Corporation, Cambridge MA, USA
&
Nicholas Wong MS, Sanofi, Cambridge MA, USA
FNIH - Digital Measures Workshop, June 24-25, 2024

A staged qualification advice approach

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**
- Pre-LoI meeting in May 2023

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

Introductory meeting feedback

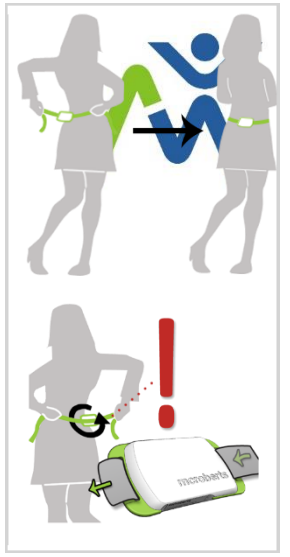
- The mobility should be correlated to each patient's daily activities and the information on what the participants are actually doing would be important for interpretation
- Collecting data to determine what the patients and caregivers consider important to them is essential
- The parameters measured 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.

FDA COA Qualification Program

Pre-LoI meeting package (DMOs for multiple sclerosis)

- **Objective:** To obtain feedback on the draft LOI for the Mobilise-D DMO in multiple sclerosis and its suitability of the proposal for scientific review.
- Pre-LoI materials included:
  - Intended benefit for a more effective assessment tool to provide greater sensitivity to changes of disability
  - Conceptual framework for linking the COA to the meaningful aspects of health and activities of daily life (ADLs)
  - Device agnostic approach and considerations to evaluate changing between sensors
  - Technical validation data to support concurrent validity of a device and algorithm
  - Clinical validation objectives and plan:
    - 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 minimally important difference (MID) of DMOs to measure change in disease state (worsened or improved)

Device Agnostic Outcome Assessment



- When developing the DMO, the goal was to define the minimum performance requirements to enable a device agnostic digital measure
- Evaluation criteria for a new device would need to consider:

Output Data Compatibility

- Raw data output in .csv file at a sampling frequency of 100hz
- 3D Linear acceleration
- 3D angular velocities

Sensing Capability & Metrological Requirements

- Clock jitter of at least +/-20ppm
- Sampling Frequency at 100hz
- Tri-axial accelerometer:
  - Range: ≥ ±8g
  - Resolution: 1mg (at ±8g)
- Tri-axial gyroscope:
  - Range ≥ ± 2000dps
  - Resolution: 70mdps (at ± 2000dps)
- At least 7 days of recording 3D angular velocities and acceleration signals

Wearing Modality

- If changing from Body worn (BW) to body-attached (BA), apply algorithms on output data when wearing the device simultaneously
- Acceptability should be determined based on the errors associated with the BW or BA wear configuration from the Technical Validation Study

Human Factors

- Acceptability
- Wearability
- Patients' compliance

FDA COA Qualification Program

Pre-LoI meeting feedback (DMOs for multiple sclerosis)

- **Objective:** To obtain feedback on the draft LOI for the Mobilise-D DMO in multiple sclerosis and its suitability of the proposal for scientific review.
- The Agency commented that
  - How the proposed DMO would be used in the MS clinical trials and what value it would provide to MS drug development should be clarified.
  - The proposed endpoint should be described in more detail: particularly how clinical fluctuations in the MS patients would be adequately assessed and how changes in self-limiting mobility behavior (e.g., due to symptom burden) are captured.
  - Additional qualitative research to understand why and to what extent the DMO is important to patients with MS is needed.
  - Additional clarification is needed for mapping the meaningful aspects of health to CoI and how the CoI will be evaluated.

Lessons learned

- Concept of Interest should be relevant and clinically meaningful to the target population
- Context of Use, a detailed description of how the outcome measure to be used, is essential for the regulatory assessment
- Needs assessment for the COA in a specific disease area should be justified
- 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 :
    - Initial 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 – 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

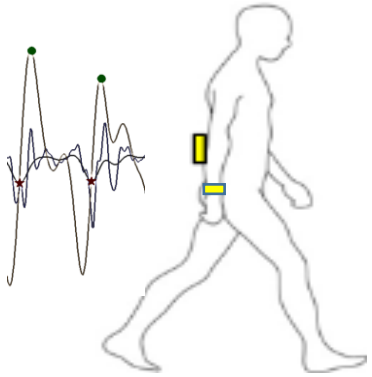
https://mobilise-d.eu/

Clinical Validation Study

Daniel Rooks, PhD
Translational Medicine, Novartis
Mobilise-D Industry Lead

Overall plan

Technical Validation Study	Clinical Validation Study
from device to digital mobility outcomes	*from digital mobility outcomes to health status*



Digital data from wearable device + algorithm

- Mobility Performance
- Digital mobility outcome(s) (DMO)
- Walking speed, walking bouts; stride length, turning, etc.

Health status

Patients

Regulatory authorities

Rochester et al., 2020

Clinical Validation Study: What do mobility outcomes tell us about health?

- 2388 participants
- ~600 per cohort (PD, MS, COPD, Hip Fracture)
- Every 6 months for 2 years (2021-2024)
- 16 sites/10 countries
- 7-day digital mobility assessment
- Clinical characterisation
- Mobility characterisation - secondary mobility outcomes & generic mobility loss
- Generalisable (geography; inclusivity; degree of disability)

Mikolaizak et al., PLOS ONE, 2022

Enrollment of PD, MS, COPD, and PFF cohorts

Parkinson's disease:

- n=602 from 5 sites
- 4/2021 – 5/2022

Multiple sclerosis:

- n=602 from 4 sites
- 5/2021 – 10/2022

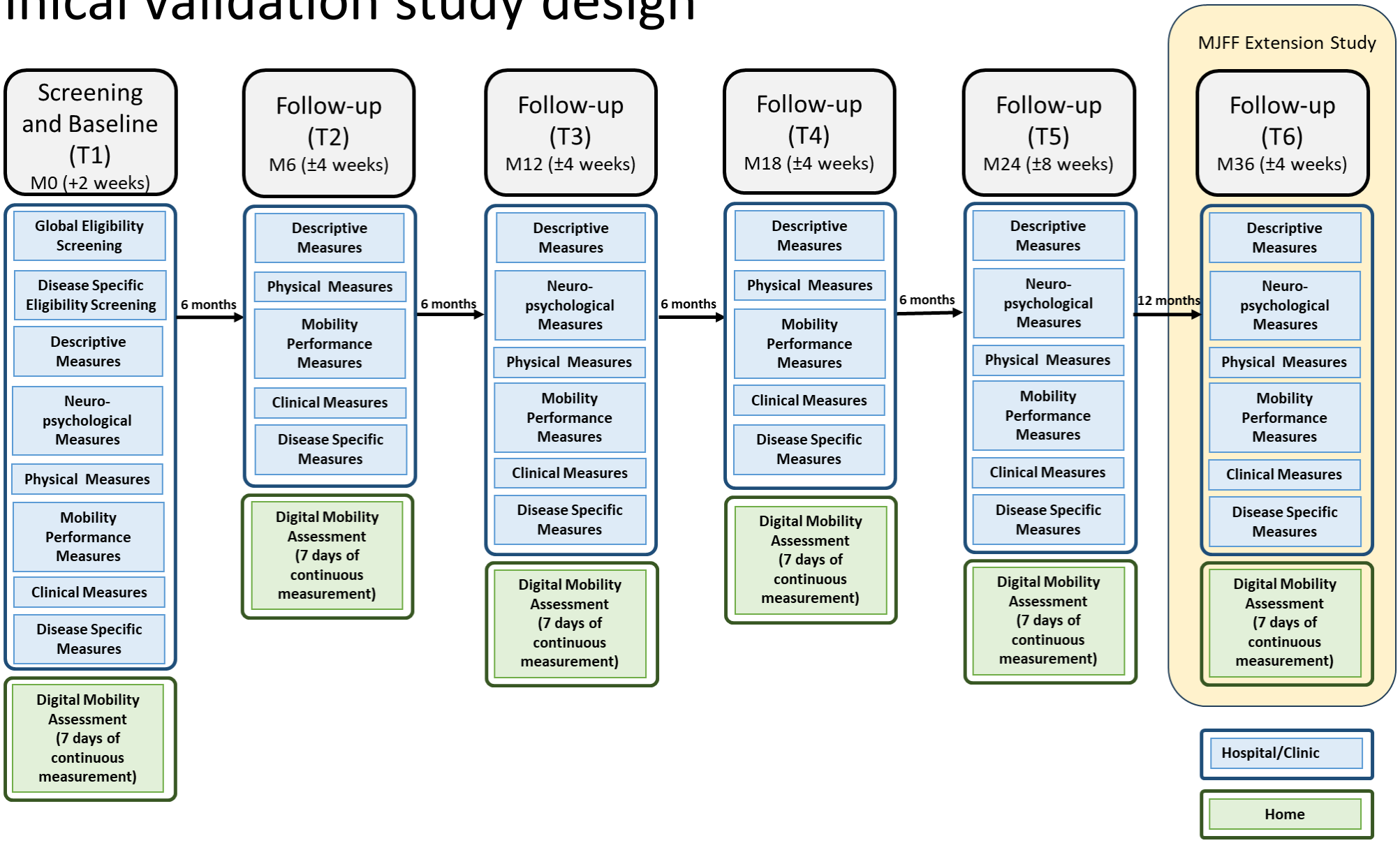
Chronic Obstructive Pulmonary Disease

- n=613 from 7 sites
- 4/2021 – 4/2022

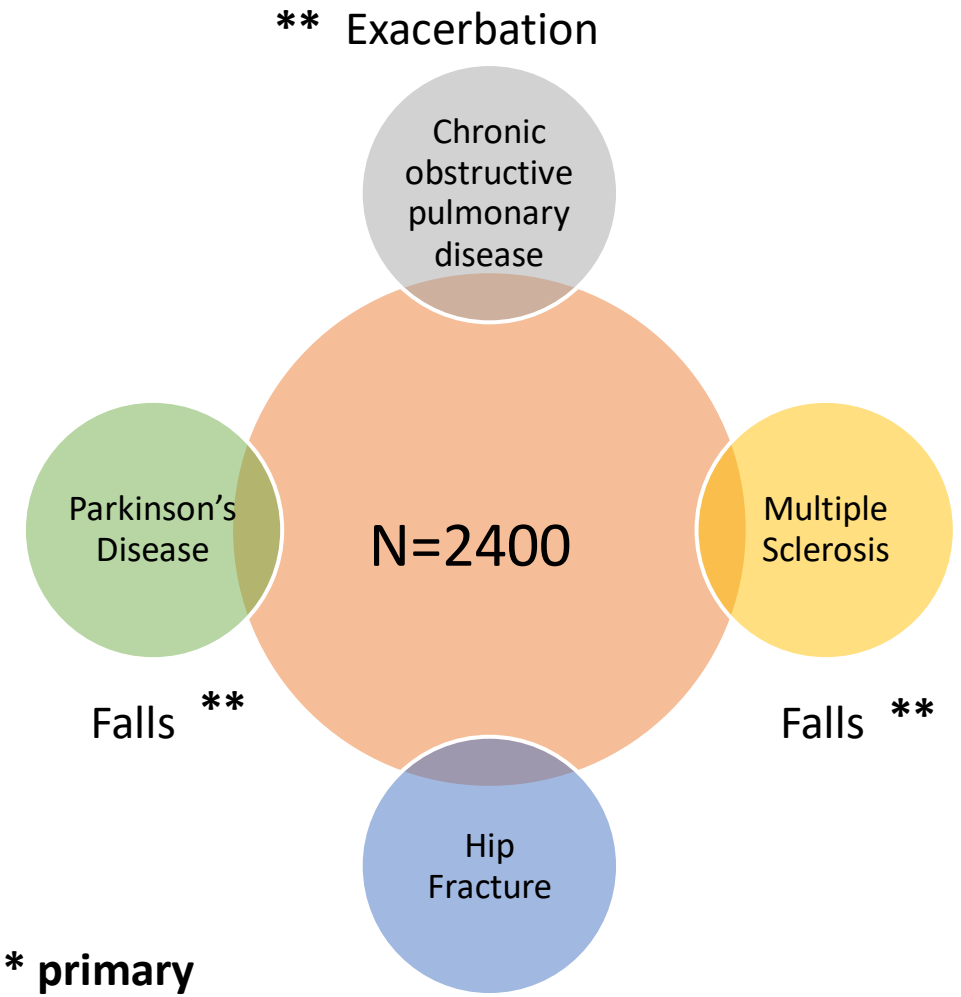
Proximal femoral fracture

- n=572 from 3 sites
- 4/2021 – 7/2023

Clinical validation study design



Clinical Validation Study - Aims



Identify the **best disease** specific & **global** digital mobility outcome & cut-off scores where relevant:

- Measure & monitor mobility performance
- Detect change – progression & responsiveness
- Clinically meaningful
- Predictive capacity
- Superior to standard mobility outcomes
- Acceptable, reliable, implementable

Descriptive Measures:

Year of birth, gender, height, weight, shoe size, leg length, education, employment, marital status, living arrangement, overall health status, smoking history, alcohol consumption, ethnicity, comorbidities, vision and COVID-19 history.

Clinical outcome measures:

- **Late-Life Functional Disability Index (LLFDI)** - function and disability in older adults
- Mortality
- Care home admission and length of stay
- Hospital admission
- **Fall events** (occurrence and frequency) and fall related injuries.
- Fracture history
- Medication and non-pharmacological interventions
- Blood pressure
- **Euro-Qol (EQ-5D)** – Quality of life
- Pain - Visual Analogue Scale (VAS) during rest and walking
- **Groll Functional Comorbidity Index** (FCI Groll).
- Frailty Index (FI).
- **Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale**
- **Minimal Important Difference (MID)** -Anchor questions to measure change in mobility constructs (distance, speed, safety, effort and overall perception)
- Bioelectrical Impedance Analysis (BIA)- body composition

Physical measures (all assessments will be instrumented using a wearable sensor):

- Use of mobility aids
- **Short Physical Performance Battery (SPPB)** - lower extremity function and mobility.
- **Hand grip strength**
- **Timed Up and Go** (TUG) - common clinical measure used to assess mobility, balance and walking ability in older adults.
- **Six-minute walking test** (6MWT) - functional exercise capacity.

Mobility life space measures:

- University of Alabama at Birmingham **Life Space Assessment** (LSA) - extent and frequency of movement
- Nursing Home Life Space Diameter (NHLSD) - extent and frequency of movement (nursing home resident)

Neuropsychological measures:

- **Short Falls Efficacy Scale International** (Short FES-I) – measure of concern about falling
- Patient Health Questionnaire (PHQ-2) - severity of depression.
- Social isolation and loneliness (UCLA Loneliness scale)
- **Mini-Mental State Examination** Short version (SMMSE) - measure of cognitive impairment

PD Specific Assessments:

- Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) – disease progression
- Mini balance Evaluation Systems Test (Mini BESTest) - measure to assess dynamic balance.
- New Freezing of Gait Questionnaire (NFOGQ) - impact and severity of freezing of gait.
- Montreal Cognitive Assessment (MoCA) - measure of cognitive impairment.

MS Specific Assessments:

- MS Descriptives - MS symptoms and diagnosis date, subtype and use of Disease Modifying Treatments.
- Modified Fatigue Impact Scale (MFIS)
- The Multiple Sclerosis Functional Composite (MSFC) - measure of MS in three key clinical dimensions: leg function and ambulation (Timed 25-Foot Walk), arm and hand function (9-Hole Peg Test), and cognitive function (Paced Auditory Serial Addition Test).
- Expanded Disability Status Scale (EDSS) - used to quantify disability in MS.
- Patient Determined Disease Steps (PDDS) scale - patient reported measure of disability in MS.
- Multiple sclerosis walking scale-12 (MSWS-12) - patient reported measure of impact of MS on walking ability.
- Symbol Digit Modalities Test (SDMT) - severity of cognitive dysfunction.
- Low-contrast letter acuity (LCLA) - vision testing.
- Fatigue Severity scale (FSS)
- Mobility Importance - importance of mobility (Sheffield sub-study)

Summary and impact

- Mobilise-D algorithm has been rewritten to be easier to use and is undergoing revalidation then release to the public.
- Patient input to clinical trials and feedback on participation expands the understanding of disease burden and experience as study participants. Educational materials accessible on the Mobilise-D website (https://mobilise-d.eu/).
- Technical Validation Study data describe required wearable DHT specifications, are published, and accessible for use by public.
- Regulatory interactions provided valuable insights into what is needed to develop a validated digital mobility outcome and has been shared through publication and presentations and will be accessible to the public.
- Clinical validation study process provided important insights for integrating DHT into clinical trials and collecting quality data. Ongoing analysis will deliver the needed evidence of clinical meaningfulness and relevance of specific DMOs to fill the knowledge gap in people with the four conditions (PD, MS, COPD, PFF).

SUSTAIN Mobilise-D – SUSTainability And Impact Now for Mobilise-D

- Objective: Build on foundational knowledge of Mobilise-D algorithm, data, and clinical research experience; promote best practices from MOBILISE-D to improve the adoption and advancement of digital mobility outcomes (DMOs)
- Financial support from select EFPIA partners and in-kind support from select academic and EFPIA partners
- Two years (1 July 2024 – 30 June 2026)
- Focused activities
  - Algorithm rewrite (Python) and data release to public
  - Support further data analyses and publication of results
  - Promote implementation of DMOs in intervention clinical trials
  - Advance DMOs towards qualification for use in the development of therapeutics

AstraZeneca CLARIO. ICON NOVARTIS Pfizer SANOFI teva

Mobilise-D Network

The Network's proposed objectives are to:

- Create and develop methodologies for advancing the field of digital mobility measurements and application.
- Work with members to highlight and communicate research and other funding opportunities.
- Establish a forum for multidisciplinary discussion and collaboration in the field.
- Develop and promote a research agenda in the field of digital mobility biomarkers.
- Advance mobility assessment into research (including, but not limited to clinical trials) and practice (including regulators and HTA).
- Encourage skill development and training in the field.

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

CRITICAL PATH INSTITUTE

CPP
CRITICAL PATH FOR PARKINSON'S

Critical Path for Parkinson's Consortium:

Creating collaborations worldwide with the lived experience at the forefront

Diane Stephenson, PhD

Executive Director, CPP,

Critical Path Institute

Regulatory Agency Guidances are Driving Change

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

December 2023

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

WORKSHOP | VIRTUAL

Co-sponsored Public Workshop - Using Patient-Generated Health Data in Medical Device Development: Case Examples of Implementation Throughout the Total Product Life Cycle

JUNE 26 - 27, 2024

Date: June 26 - 27, 2024
Day1: Wed, Jun 26 11:00 AM - 3:00 PM ET
Day2: Thu, Jun 27 11:00 AM - 3:00 PM ET

June 26, 2024

Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products

Discussion Paper and Request for Feedback

COMMENT

Nat Rev Drug Discovery, v19 | 2020 | 57

Digital technologies for medicines: shaping a framework for success

Francesca Cerreta[1] ✉, Armin Ritzhaupt[1], Thomas Metcalfe[2], Scott Askin[3], João Duarte[4], Michael Berntgen[1] and Spiros Vamvakas[1]

Regulatory agencies can provide advice to support developers of digital technologies for medicines use, but what are the best strategies to maximize the chance of a successful regulatory interaction? Here, EMA and industry representatives comment on the experience so far.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 June 2020
EMA/219860/2020
Human Medicines Division

Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products

Status as of June 2020

Evidence Generation For a Novel PD tool in an Evolving Landscape

Forging the Path in Advancing Regulatory Maturity of Digital Health T

Engaging regulators prior to study start

Study execution, data sharing and Clinical Validation

WATCH-PD


npj | parkinson's disease

Article

Published in partnership with the Parkinson's Foundation

https://doi.org/10.1038/s41531-024-00721-2

Using a smartwatch and smartphone to assess early Parkinson's disease in the WATCH-PD study over 12 months

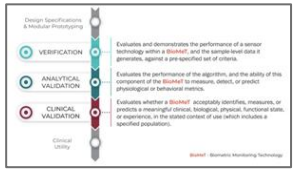
Check for updates

Jamie L. Adams[1,2], Tairmae Kangarloo[2], Yishu Gong[2], Vahe Khachadourian[2], Brian Tracey[2], Dmitri Volfson[2], Robert D. Latzman[2], Joshua Cosman[2], Jeremy Edgerton[2], David Anderson[2], Allen Best[2], Melissa A. Kostrzebski[2,3], Peggy Auinger[2,4], Peter Wilmot[2], Yvonne Pohlson[2], Stella Jensen-Roberts[2], Martijn L. T. M. Müller[2], Diane Stephenson[2], E. Ray Dorsey[1,2] & the Parkinson Study Group Watch-PD Study Investigators and Collaborators*

June 2024

2018 2019 2020 2018 2020 2021 2022 2024

DIME v3 Framework Released (Fall 2019)



EMA Q&A on Digital Technology-Based Methodologies (June 2020)


EUROPEAN MEDICINES AGENCY

Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products

Status as of June 2020

Draft Guidance (Dec 2021)


Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

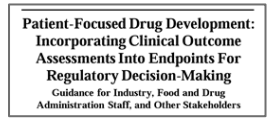
Guidance for Industry, Investigators, and Other Stakeholders

Draft Guidance #3 (June 2022)


Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

Draft Guidance #4 (April 2023)


Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

Final Guidance (Dec 2023)


Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

WATCHPD device platforms®

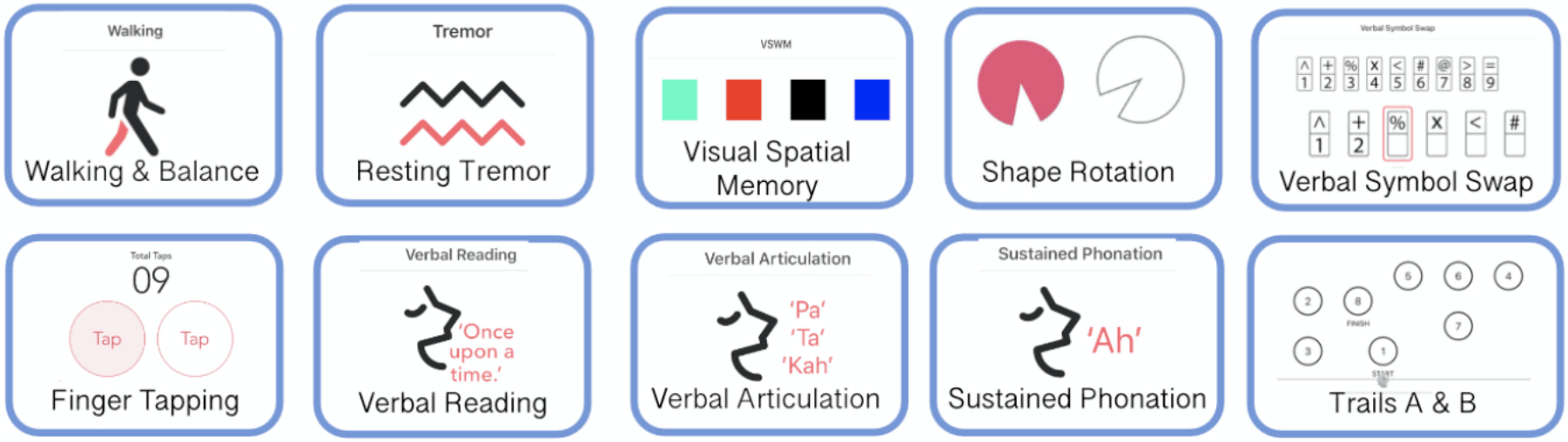
Apple Watch

Commercialised by Clario (Opal APDM), ClinicalInk

(**W**earable **A**ssessments in **T**he **C**linic and **H**ome in **PD**)

Mapping smartphone tasks to symptoms
WATCH-PD Qualitative Sub-study

- Participants incorporate picture card of each task into the personal symptom map
- Clarify/confirm relevance of the task to personal symptoms
  - Relevant to more or less bothersome symptoms



Jamie Adams, Univ Rochester; *Jennifer Mammen*; Univ Massachusetts in collaboration with CPP 3DT Qual substudy team; Mammen et al *Journal of Parkinson's disease*, vol. 13, pp. 619-632, 2023.
Journal of Parkinson's disease, vol. 13, pp. 589-607, 2023.

Tackling Clinical Meaningfulness by Listening to Patients:
WATCH-PD Qualitative Sub-study

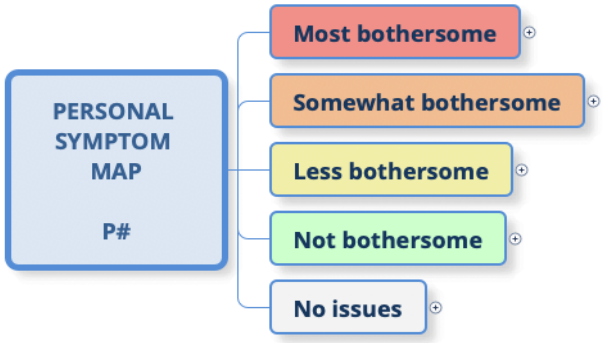
Surveys (N=80 – all participants in WATCH-PD)

- Sliding scale ratings of relevance of tasks
- Open response evaluation of symptoms and tasks
- Approx 100 mins/participant

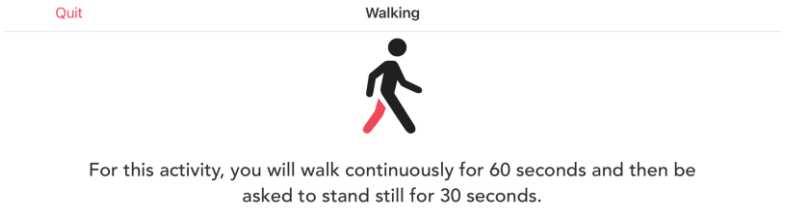
Interviews (N=40 – purposeful subset)

1. Map Patient Reported Symptoms (PRS)
   - with details on defining characteristics
2. Cognitive debriefing re:WATCH-PD tasks
3. Map WATCH-PD tasks to PRS
4. Map symptom concepts to PRS

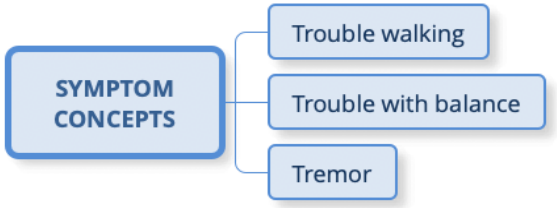
Step 1: Map Patient Reported Symptoms



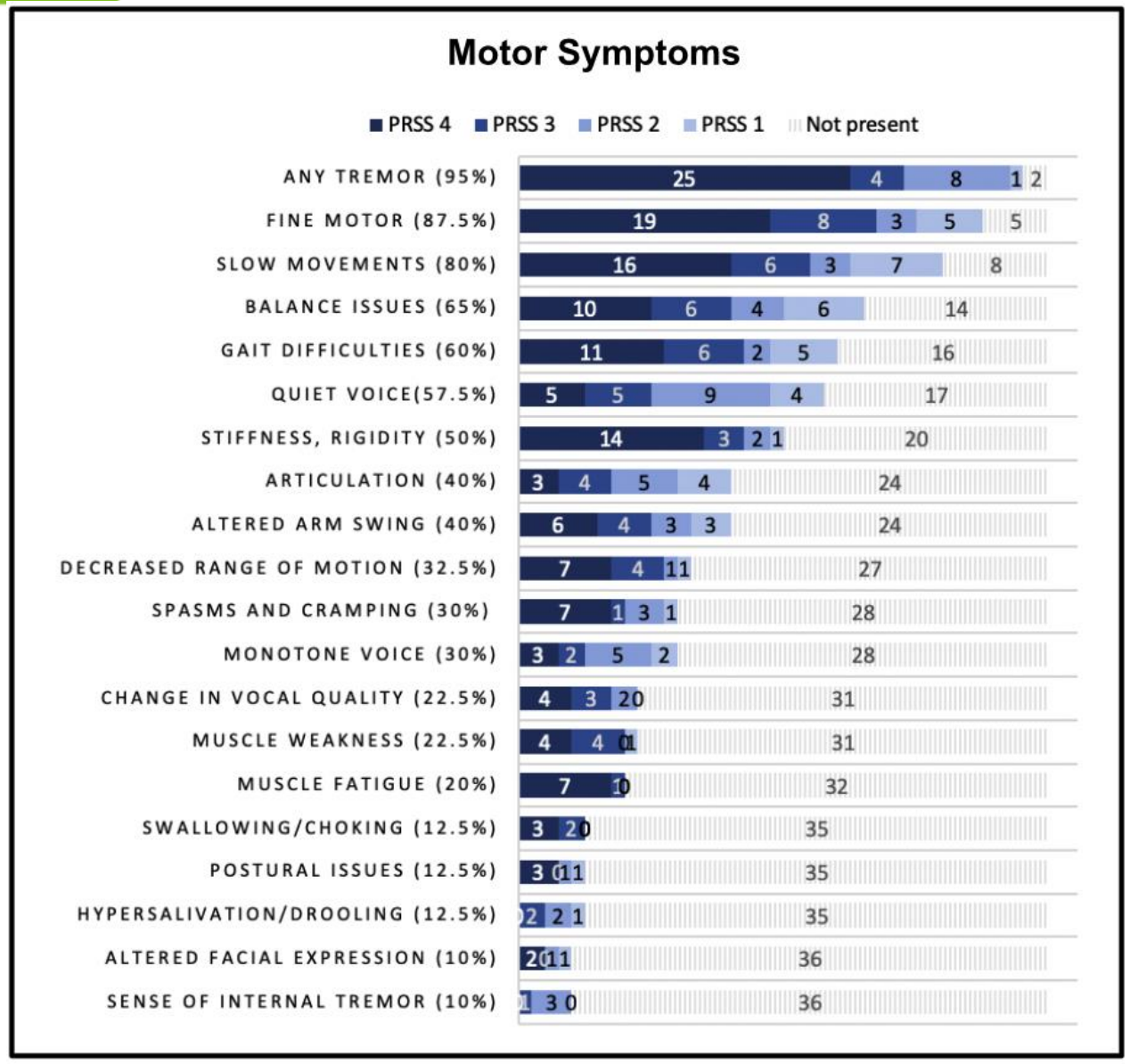
Step 2: Debrief on WATCH Tasks
Step 3: Map tasks back to PRS

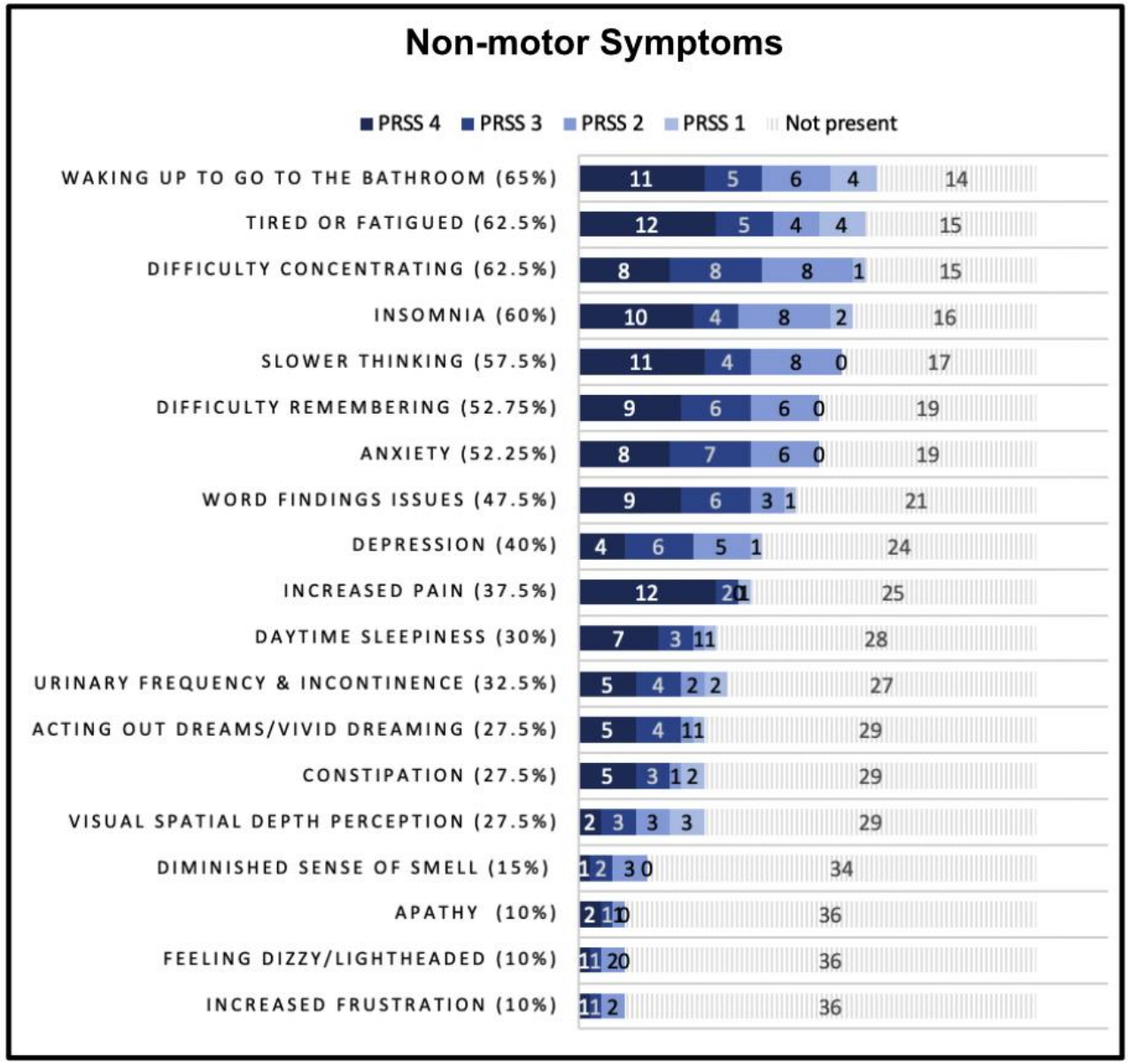


Step 4: Map Symptom Concepts to PRS



Example health experiences resulting from PD (WATCH-PD qualitative substudy, Case study 1)





Sharing of data with participants is transformational

WATCHPD participants experiences:

- Comfortable process (computer or smartphone/tablet)
- 39/40 (97.5%)- improved ability to discuss symptoms/impacts
- 2/40 (5%) experienced emotional distress
- 38/40 (95%) wanted copies of their symptom maps

P1: *When I was asked for this study, [they] said there was an option to get the map back—that was very encouraging. I assumed like the other [studies], I wouldn't get any feedback. That was a delightful option.*

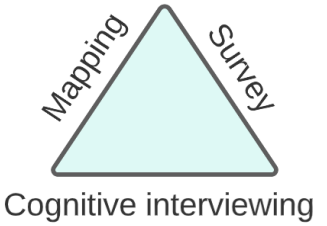
P37: *I would love to have [the maps]. I feel like I'm in all these studies, but I'm like, "I have no results"…**Until now.** …It's eye-opening… I would love to see my progression [over time]. Did anything change?*

Participant experience with mapping

P31: It was great that you had the survey to start with, but this was much easier. I think with surveys, you tend to just [answer] whatever. You're not [un]truthful, it's just you're not quite sure…This picture is a really good way of taking that survey and organizing my thoughts and putting it correctly.

P39: It's really hard to track your symptoms in a way that shows what's most important, what's not, and why….A lot of times, when you try to tell people about your symptoms, they don't really understand what you're saying. [This is a] very good way of trying to describe it.

- 39/40 felt mapping improved ability to explain symptoms
- 38/40 wanted copies of their maps



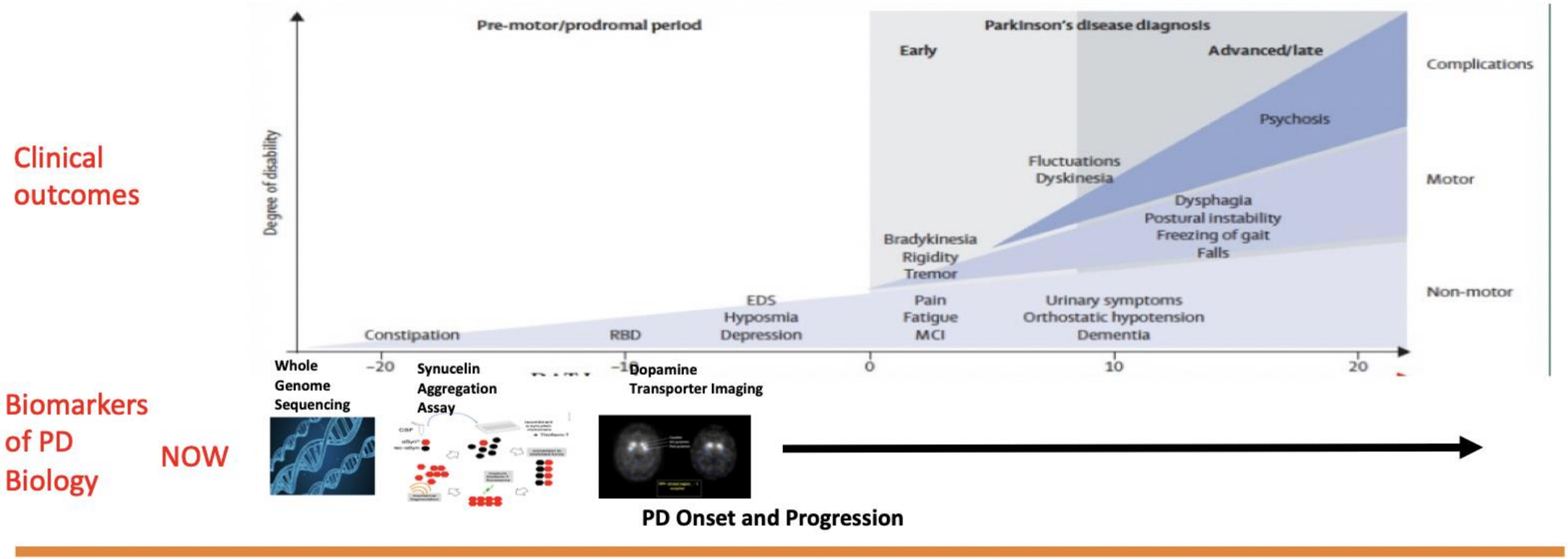
Transforming the DHT landscape
WATCHPD-2 new findings & needs for the future

New manuscript being finalized reporting meaningful change in DHT measures from year 1 to year 2

Continued worldwide collaborations sharing data, knowledge and costs together

- WATCH-PD 3 and beyond
- WATCH-PD in alignment with Digital Mobility outcomes (CPP and Mobilise-D)
- Incentivize open science and data efficiencies (e.g. Dime crowdsourcing library)
- Continue to leverage WATCHPD to inform improved and novel endpoints
- Redefine clinical meaningfulness strategies by driving qual & quant strategies -- align with C-Path's expertise in endpoints (COA Program)
- Embrace novel data innovative strategies: Federated Learning
- Align with Biological staging initiatives

Redefining the PD continuum, *Biology lights the way*



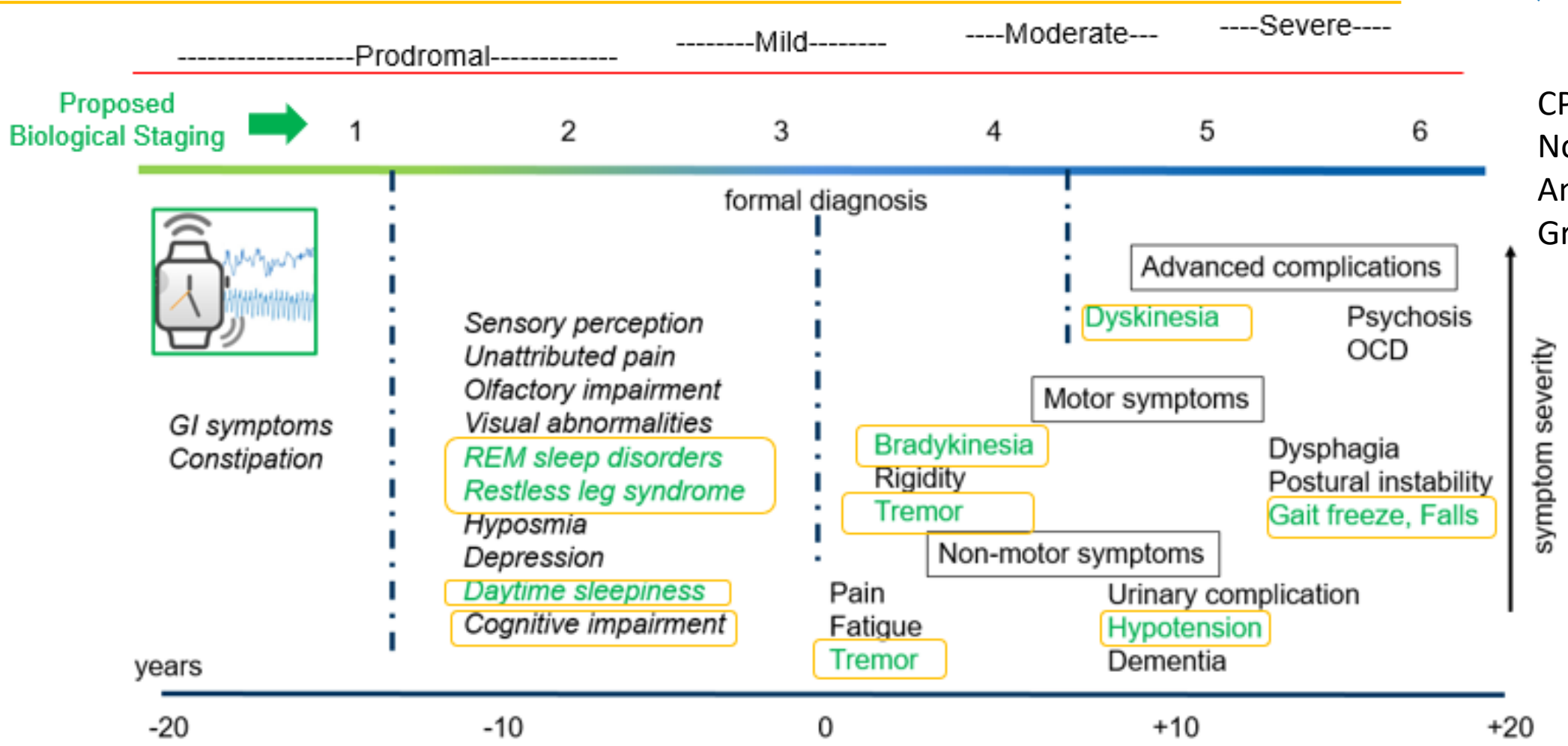
Future PD Biomarkers | 3-5yr | Immune Function | Mitochondrial Function | Lysosomal markers | Synaptic density markers | Protein aggregation markers

Simuni et al., Lancet Neurology, 2024 Feb;23(2):178-190

Hollinger et al., Lancet Neurology, 2024 Feb;23(2):91-204

Ken Marek
CPP advisor
Michael J Fox Fdn

Digital Health Technologies, the future



CPP members
Novartis:
Amit Khanna
Graham Jones

***Khanna & Jones* Toward Personalized Medicine Approaches for Parkinson Disease Using Digital Technologies**
JMIR Form Res 2023;7:e47486

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- Critical Path Institute Drug Development Tool team (3DT)
- University of Rochester collaborators Jamie Adams, Ray Dorsey, Jennifer Mammen (UMass)
- CPP scientific advisors and academic collaborators

  Tanya Simuni, Ken Marek, Jesse Cedarbaum, Derek Hill

  Jamie Adams, Jennifer Mammen
- Food and Drug Administration, CDER

  Michelle Campbell, Gerald Podskalny, Kevin Krudys, Teresa Buracchio
- European Medicines Agency

  Pavel Balabanov, Maria Tome, Corrine de Vries, Efthymios Manolis

Tribute to Dr. Ira Shoulson, Making Patients Heard

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