Understanding Priorities for the Use of Digital Health Technologies to Support Clinical Trials for Drug Development and Review

Duke-Margolis Center for Health Policy | Virtual Public Meeting

March 28-29, 2023

Duke | MARGOLIS CENTER *for* Health Policy

Welcome and Overview | Day 2

Mark McClellan

Director, Duke-Margolis Center for Health Policy

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Disclaimer

Funding for this workshop was made possible in part by a cooperative agreement from the U.S. Food and Drug Administration. The views expressed in written workshop materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsements by the U.S. Government.

Meeting Agenda (Day 2)

1:00 pm Welcome and Overview

1:10 pm Session 3: Actigraphy in Clinical Trials to Support Drug Development

2:30 pm Break

2:40 pm Session 4: Use of Other Sensor-Based DHTs in Clinical Trials for Drug Development

3:40 pm Break

3:50 pm Session 5: Key Priorities for the Advancement and Integration of DHTs into Clinical Trials for Drug Development

4:35 pm Closing Remarks

4:45 pm Adjournment

Session 3: Actigraphy in Clinical Trials to Support Drug Development

1:10 pm – 2:30 pm EST

Jeremy Wyatt

CEO

Actigraph

ActiGraph™

PIONEERING THE DIGITAL TRANSFORMATION OF CLINICAL RESEARCH™

Digital Health Technologies in Clinical Trials

Actigraphy Overview

March 29, 2023

Jeremy Wyatt
CEO, ActiGraph

THEACTIGRAPH.COM

Safe Harbor Statement

The following is intended to outline our general product direction. It is intended for information purposes only and may not be incorporated into any contract.

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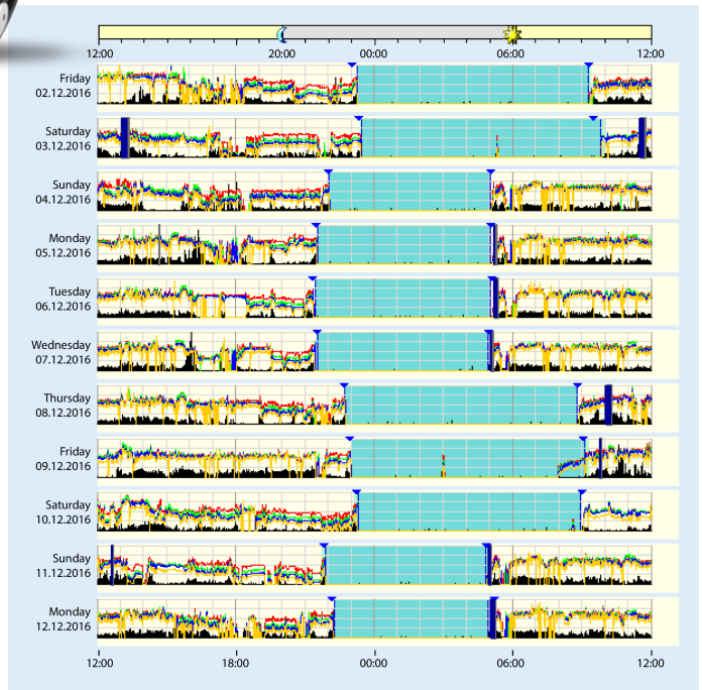
Actigraphy Introduction

- A non-invasive method of monitoring human activity/rest cycles.
- Small device(s) worn on the body (wrist, ankle, thigh) over a period of days to weeks.
- Primary sensor: Accelerometer.
- Other components: Battery, storage (memory), connectivity (USB, Bluetooth®).
- Data captured is used to interpret movement which is then translated into specific measurements (sleep, mobility, physical activity, caloric expenditure, etc)



Sleep cycles measured by actigraphy[1]

1 - Acker, J.G., Becker-Carus, C., Büttner-Teleaga, A. *et al.* The role of actigraphy in sleep medicine. *Somnologie* **25**, 89–98 (2021). https://doi.org/10.1007/s11818-021-00306-8

Clinical Uses of Accelerometers trace to 1950s

> J Bone Joint Surg Am. 1953 Jul;35-A(3):543-58.

The major determinants in normal and pathological gait

J B SAUNDERS, V T INMAN, H D EBERHART

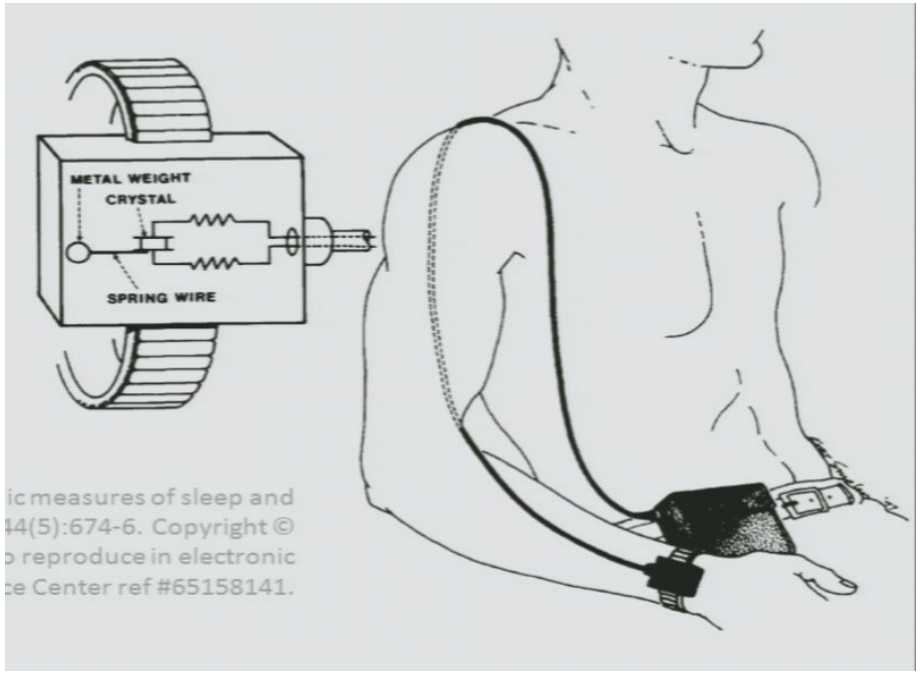
PMID: 13069544 Paperpile

> Am J Ment Defic. 1959 Nov;64:455-6.

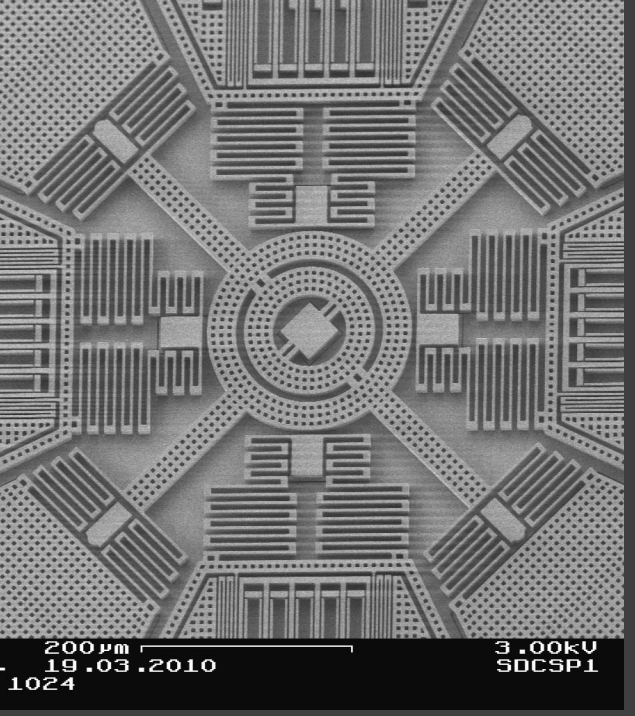
An objective measure of hyperactivity

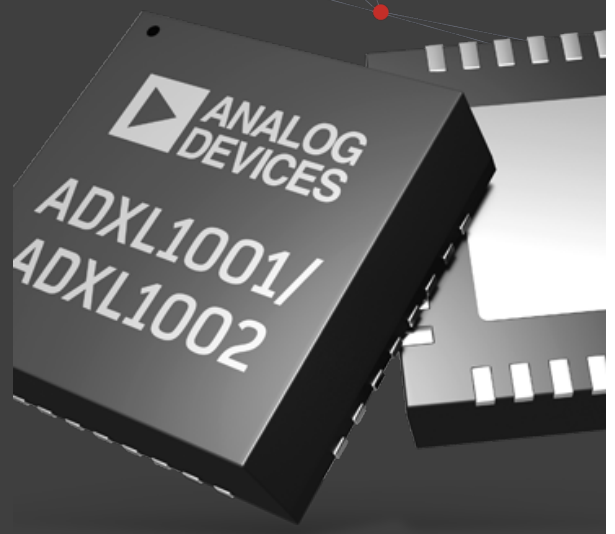
J L SCHULMAN, J M REISMAN

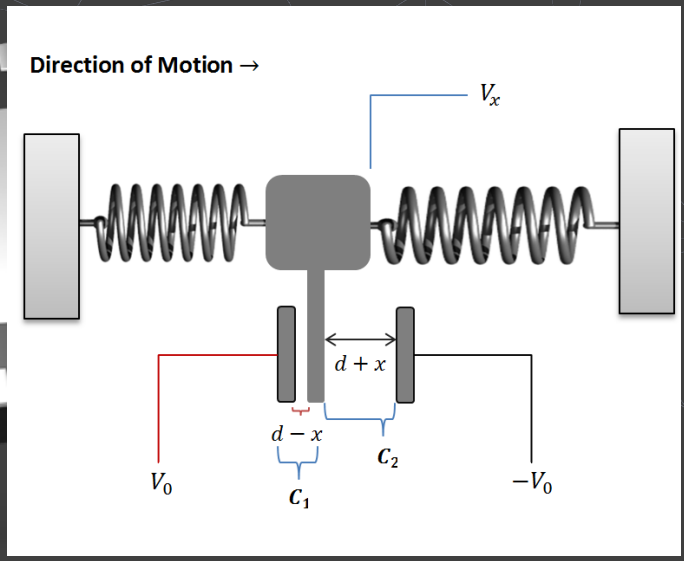
PMID: 14443747 Paperpile

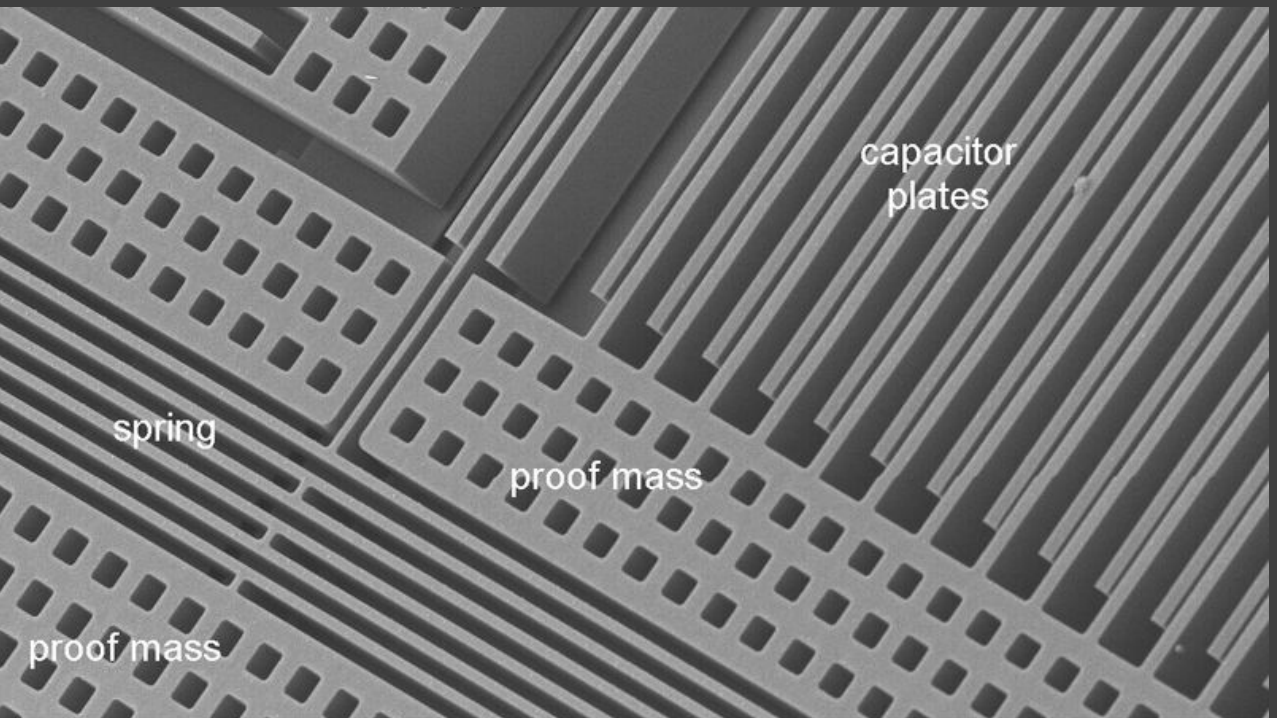


1970s





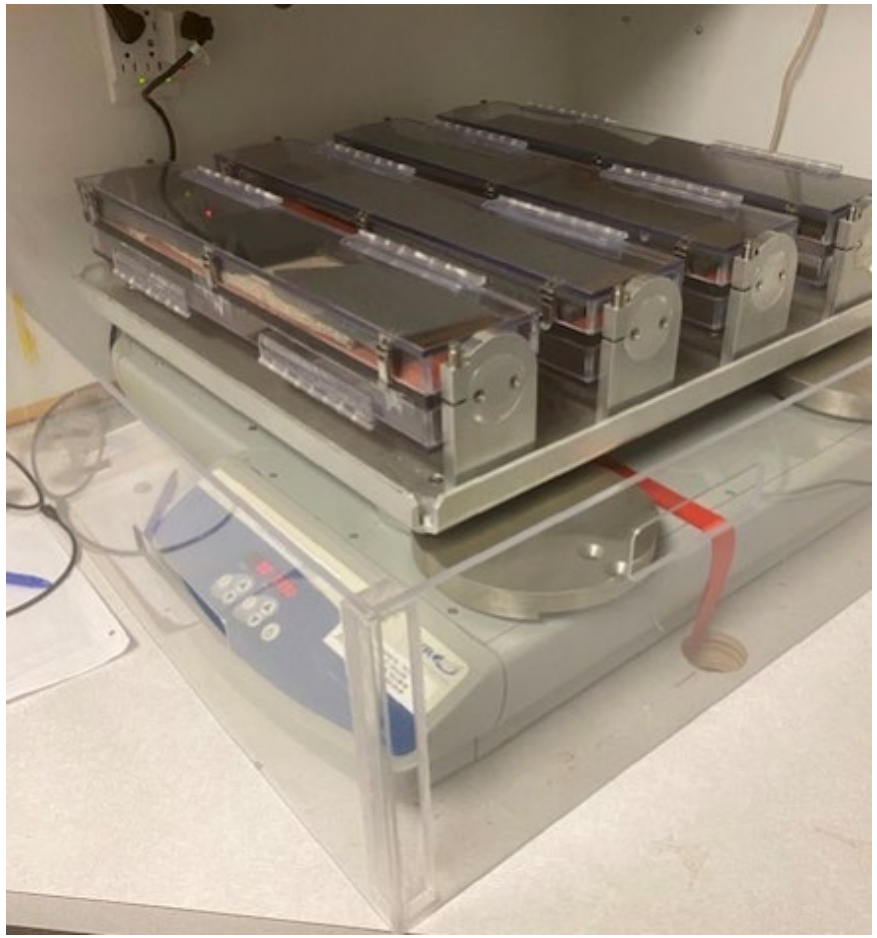


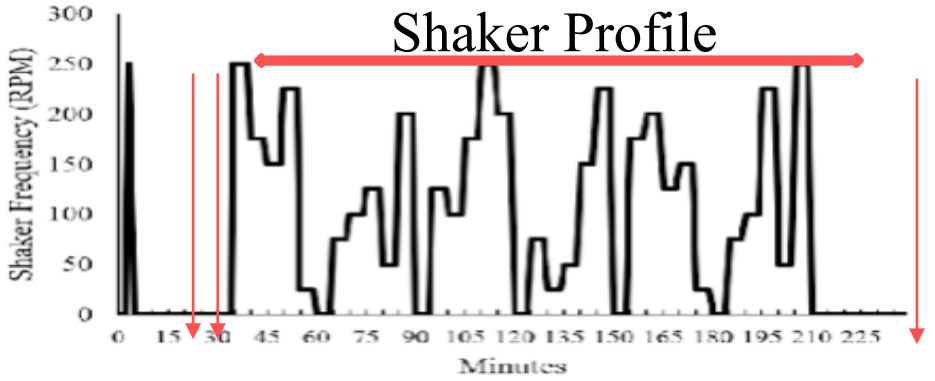


Accelerometer – The Basis of Actigraphy

- Accelerometer – Core sensor technology behind actigraphy
  - Measures proper, instantaneous acceleration
- MEMS - Micro-electromechanical systems
- Physical (mechanical) movement of floating mass, usually in three axes
- Analog signal typically converted to digital on most modern MEMS accelerometers

How do we test Raw Data – Technical Verification



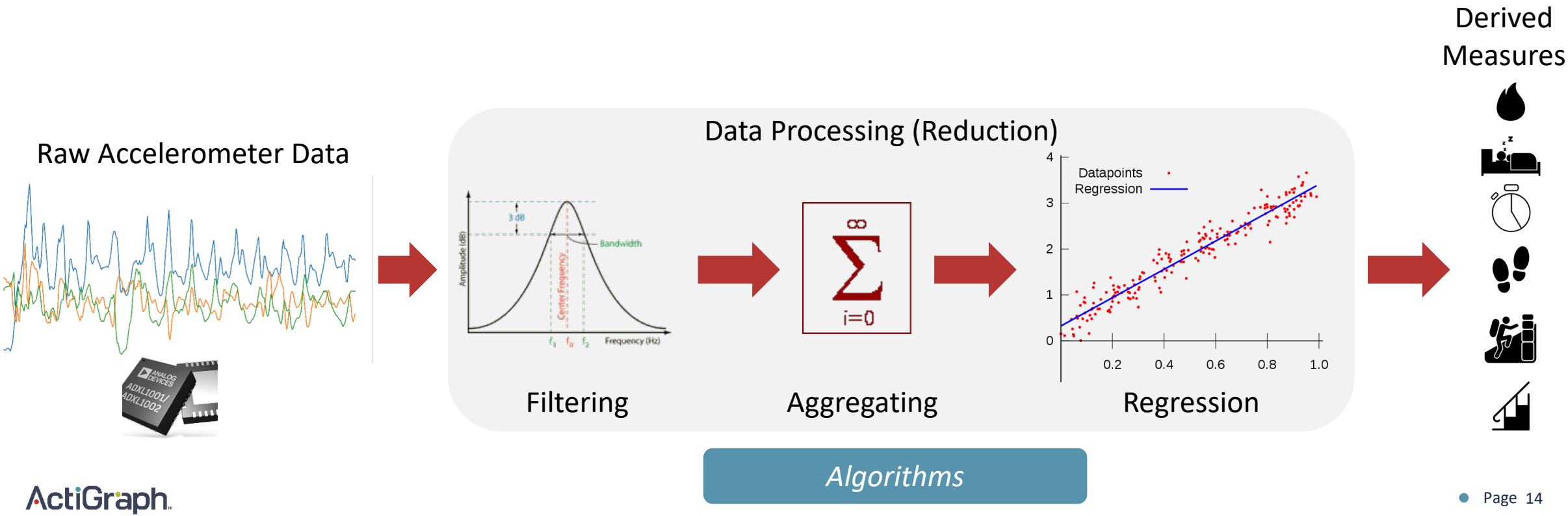


Components to Characterize

- Baseline Offset
  - Difference from 1 g vector magnitude at rest
- Signal Drift
  - Change in the baseline sensor signal over time.
- Dynamic Response
  - The change in the sensor signal during applied accelerations above the force of gravity
  - Compared to National Institute of Standards and Technology (NIST) accelerometer

High-Fidelity Raw Accelerometry Data Provides Foundation for Digital Measures

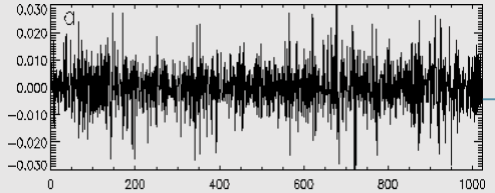
- **Raw data**: Direct measurements of accelerometer, typically between 30-100 Hz
- **Processed data**: Any measures derived from the raw data through a data transformation process (compression, feature extraction, etc)



Two Approaches to Measurement

Consumer Model

Raw Accelerometer Data

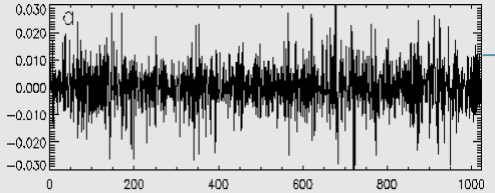


Sleep Detection Algorithm → Sleep Efficiency

Data Collection & Processing Performed Together

Clinical Model

Raw Accelerometer Data



Data Collection & Processing Performed Separately

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

Actigraphy in Clinical Research

ENABLE CONTINUOUS DATA COLLECTION

PROVIDE SURROGATE ENDPOINTS FOR EFFICACY

SUPPORT PARTICIPANT ENGAGEMENT TO IMPROVE ADHERENCE AND RETENTION

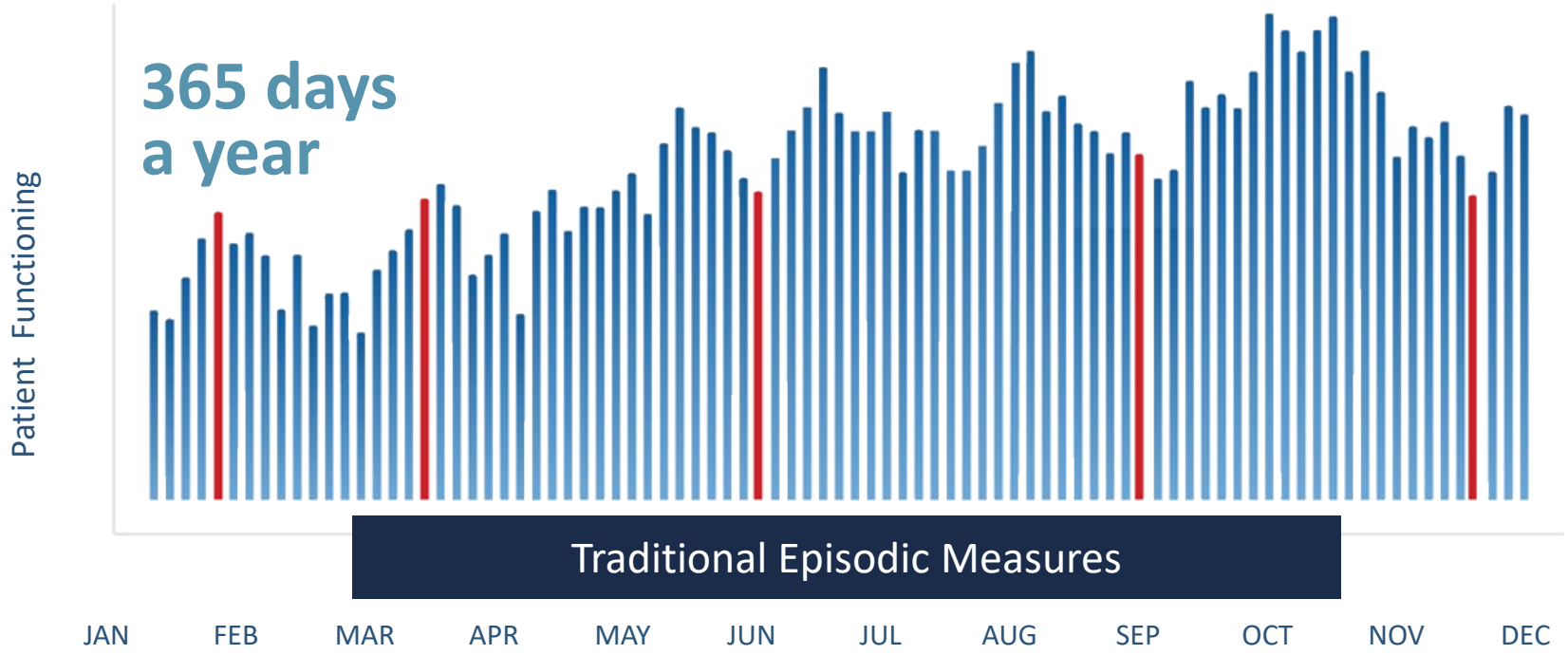
BROADEN ACCESS TO AND INCREASE REPRESENTATION OF CLINICAL RESEARCH

Taken from: Shore C, Beachy SH, Nicholson A, et al. NIH National Library of Medicine - *The Role of Digital Health Technologies in Drug Development* - https://www.ncbi.nlm.nih.gov/books/NBK563608/

Measurement Challenges in Drug Development

Measurable:
Conventional outcomes: Episodic & Subjective

Unmeasurable:
Function in real life: Chronic and progressive with fluctuations



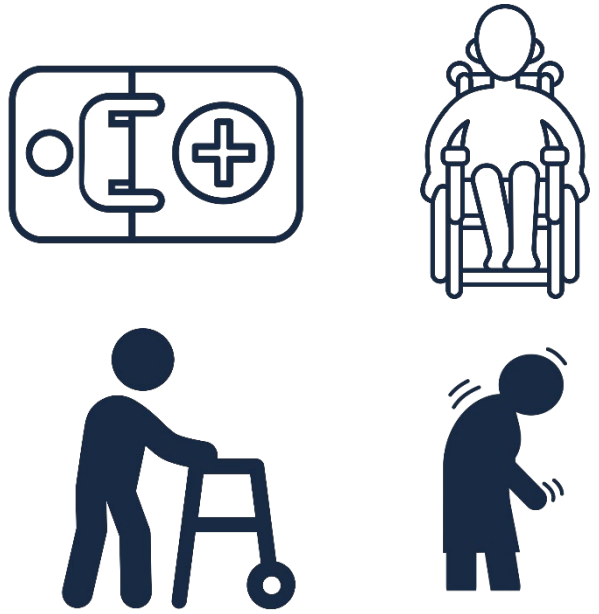
If you cannot measure it, you cannot improve it.

~ Lord Kelvin

- Inadequate measures of the course of disease trajectory
- Long and big clinical trials, and low confidence in detecting clinical benefits.

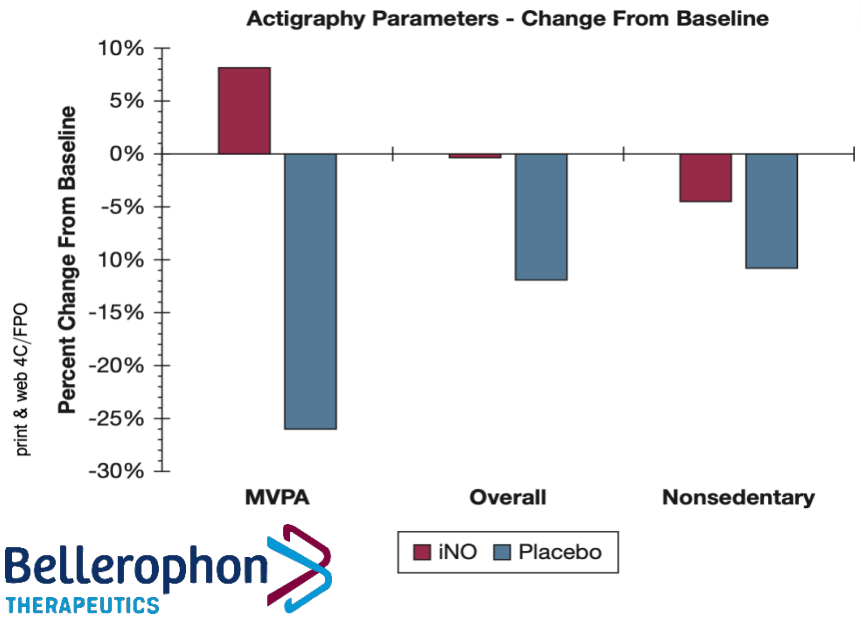
Actigraphy Offers a Better Approach to Clinical Outcomes in Many Indications

- Actigraphy presents new ways to measure behaviors where gold-standards do not exist or are insufficient.
- FDA defines clinical outcomes as a measure that describes or reflects how a patient feels, functions, or survives.
- Measuring treatment benefit is the most challenging, but essential step for drug development
  - E.g., Aduhelm for AD, Tofersen and Relyvrio for ALS



CASE STUDY:

Physical Activity as Primary Endpoints in Cardiopulmonary



Bellerophon THERAPEUTICS

Nathan, Steven D., Kevin R. Flaherty, Marilyn K. Glassberg, Ganesh Raghu, Jeffrey Swigris, Roger Alvarez, Neil Ettinger, et al. 2020. "A Randomized, Double-Blind, Placebo-Controlled Study of Pulsed, Inhaled Nitric Oxide in Subjects at Risk of Pulmonary Hypertension Associated With Pulmonary Fibrosis." *Chest* 158 (2): 637–45.

- MVPA (Moderate-Vigorous Physical Activity) show clinically significant changes to treatments whereas traditional COAs showed non-significant trends in the same direction
- First FDA endorsed actigraphy endpoints in a pivotal trial
- Reduction of sample size by more than 50% with accelerated clinical development timeline

TABLE 4] Oxygen Saturation and 6MWD

	Placebo	iNO	Difference	*P*
Relative oxygen desaturation	10.5% (12.6%)	-9.3% (8.0%)	19.8% (14.2%)	.31
SpO_2 nadir	-1.4% (1.6%)	0.3% (0.7%)	1.7% (1.5%)	.35
6MWD (m)	0.5 (6.7)	7.2 (11.7)	6.7 (18.8)	.83
Distance saturation product (meter %)[a]	-2.0 (16.4)	8.5 (11.2)	10.5 (19.1)	.97

Relative oxygen desaturation is calculated as: (desaturation at end of study − desaturation at baseline) ÷ desaturation at baseline; a negative number indicates a reduction in desaturation as compared with baseline. SEs for each parameter are provided in the parentheses. Statistical analysis was conducted for active vs placebo via Mann-Whitney test at week 8 on available data. See Table 1 legend for expansion of abbreviations.
[a]Distance saturation product is calculated as: 6MWD × SpO_2 Nadir.

P
.31
.35
.83
.97

Thank you!

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Steve Xu

Ruth K. Freinkel, MD, Professor

Northwestern University

Speaker requested that his slides not be shared publicly

Diane Stephenson

Executive Director

Critical Path for Parkinson's Consortium

Critical Path Institute

Creating Consensus for Advancing Digital Health Technologies for Parkinson's Disease

Diane Stephenson, PhD; Critical Path Institute, March 28, 2023 [dstephenson@c-path.org]

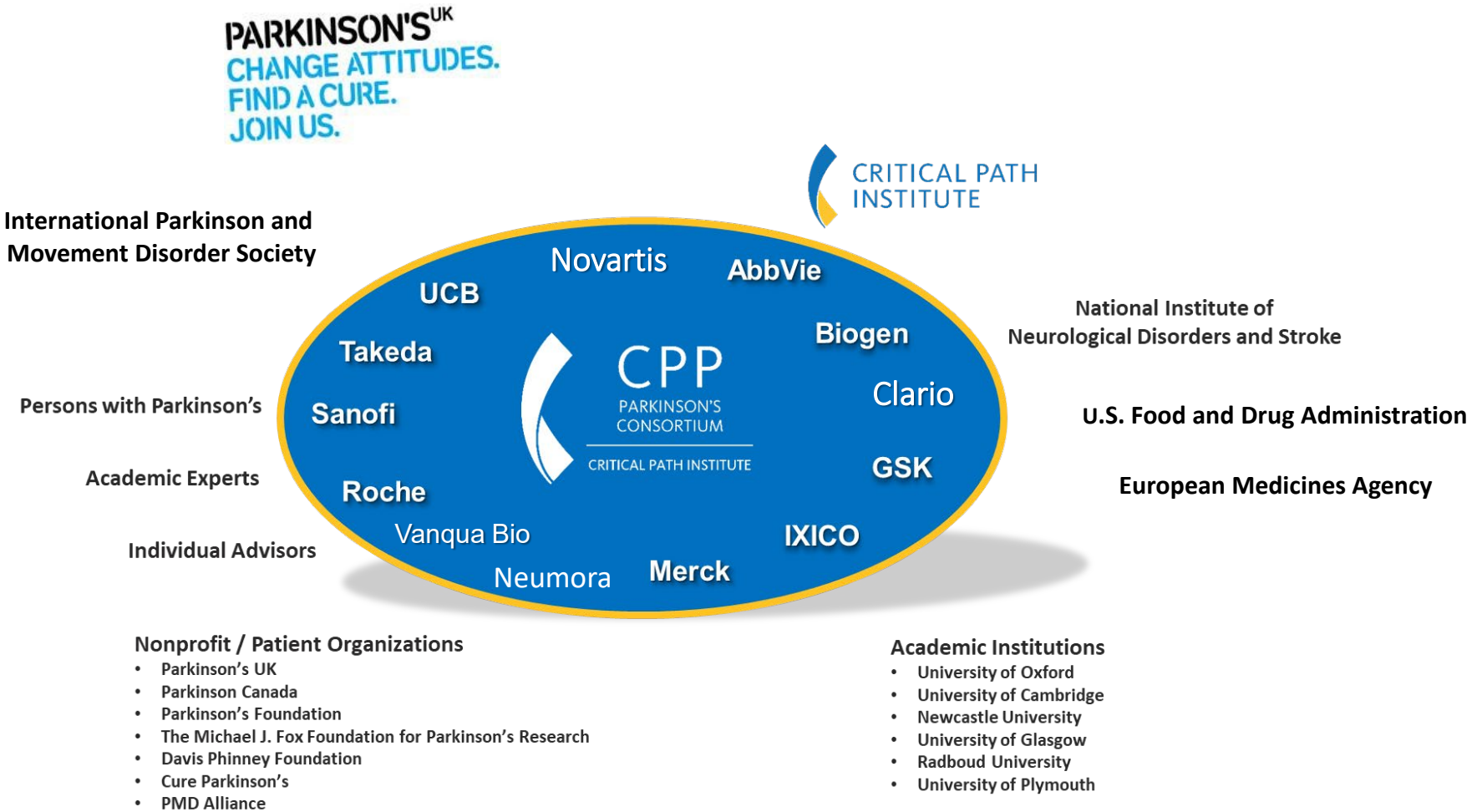
No Conflicts of Interest
To Disclosure

CPP PARKINSON'S CONSORTIUM

CRITICAL PATH INSTITUTE

Critical Path for Parkinson's Consortium

- CPP was launched in 2015 with a major goal to develop tools to quantify disease progression
- Successfully acquired and integrated patient level data from >13000 PD patients
- Qualification of imaging biomarker for enrichment of trials in early PD
- Current CPP focus is regulatory endorsement of PD drug disease trial model
- **Digital Drug Development Tools (3DT) team was launched under CPP with the goal of advancing regulatory readiness of digital health technologies in PD trials targeting early stages**



Using Digital Health Tools to Measure Function in People with Parkinson's at an Early Stage

Primary issues for tracking functional outcomes in response to treatment in 'early PD':

- Semi-quantitative and subjective scales not purpose-built for early PD
- Infrequent measurement doesn't capture fluctuations over time
- Limited assessment of non-motor aspects of PD (e.g., mood/cognition) despite high burden to people with Parkinson's

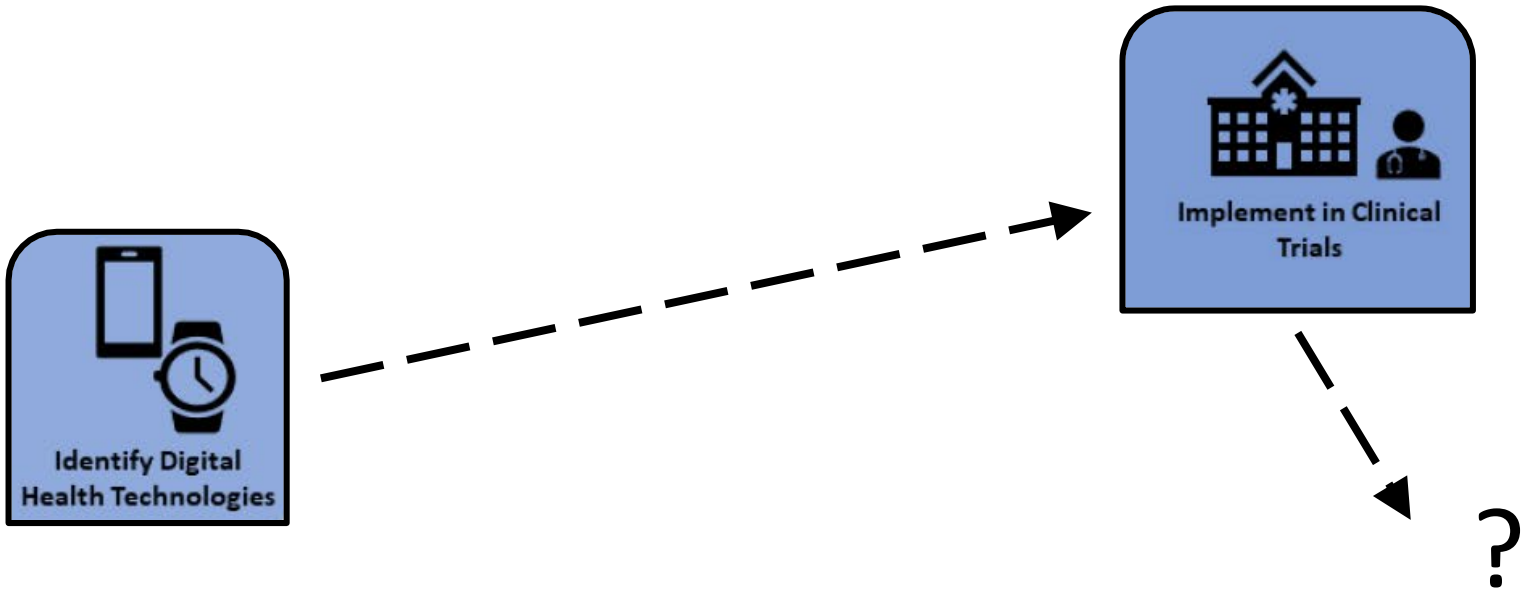
Digital Health Technologies (DHTs) present an opportunity to enhance PD therapeutic development, but to date their impact has been limited

- 'Digital' still a young scientific discipline with many unknowns
- Siloed development has delayed standardized measurement methodologies/rapid iteration
- Issues with data standards, provenance, privacy, and security
- ***Lack of regulatory precedent for use of these measures beyond exploratory endpoints***

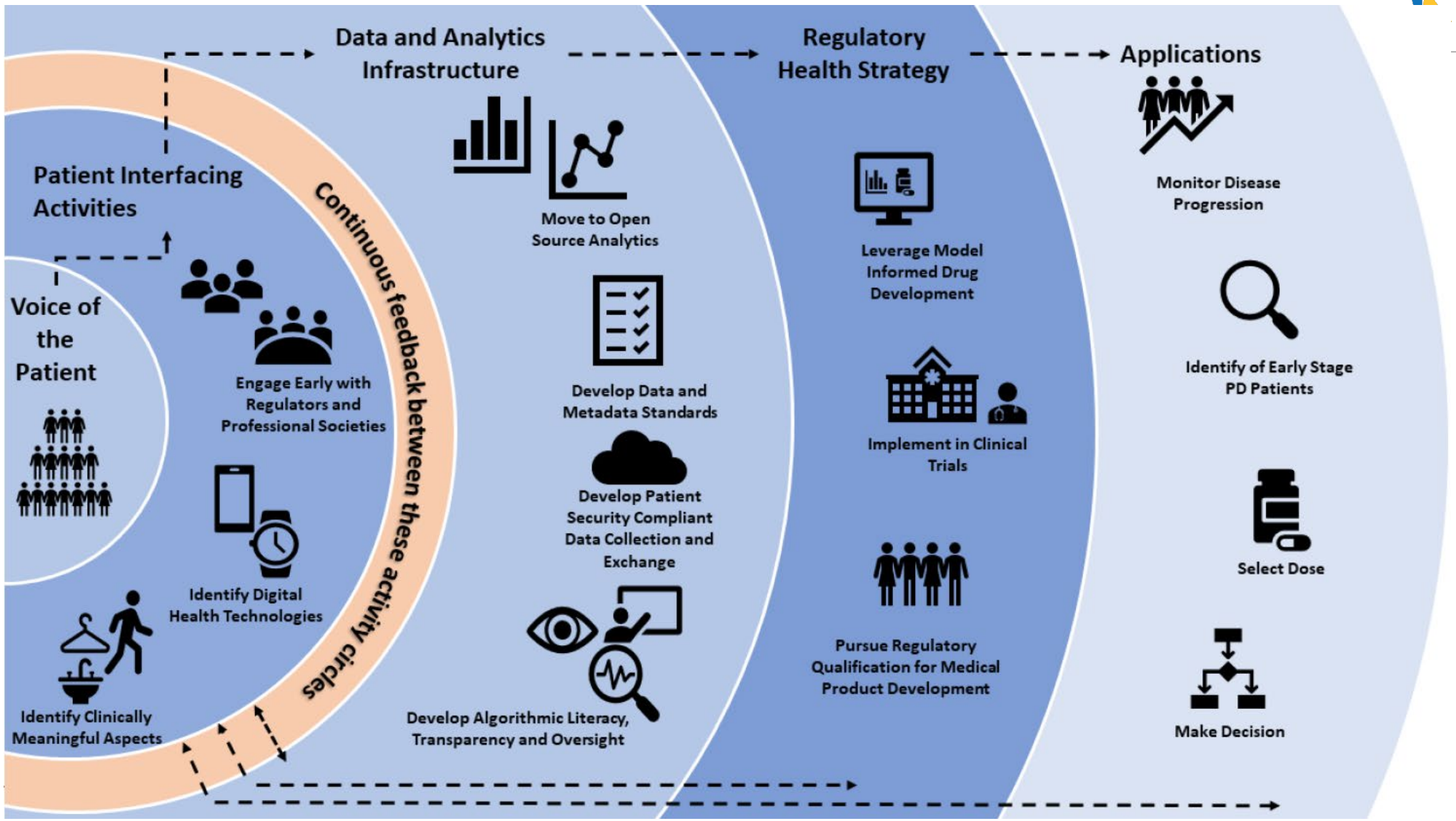
CPP 3DT Goals: Advance a device agnostic regulatory strategy for DHTs to be endorsed by regulators as drug development tools in PD clinical trials

For Sponsors Embarking on a DHT Exploratory Study

what are the factors to consider?



Josh Cosman, 3DT industry co-director, AbbVie



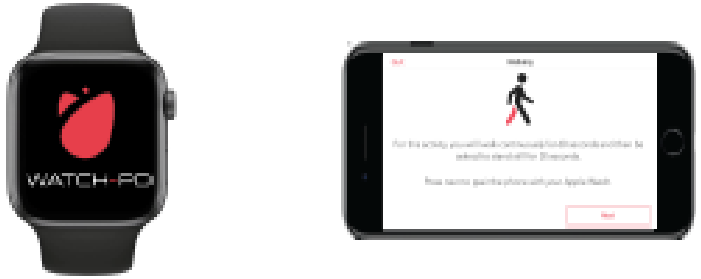
Stephenson et al., "Precompetitive Consensus Building to Facilitate the Use of Digital Health Technologies to Support Parkinson's Disease Drug Development through Regulatory Science." *Digital Biomarkers* 2020 Nov 26;4(Suppl 1):28-49.

Case Study : Questions and Approach

RESEARCH-GRADE WEARABLE SENSORS USED ALONGSIDE SMARTWATCH + SMARTPHONE IN CLINIC

Can objective kinematic measures acquired via wearable sensors differentiate individuals with early, untreated PD from healthy age-matched controls and capture PD motor symptom progression better than subjective clinical standards?

SMARTWATCH + SMARTPHONE USED OUTSIDE CLINIC



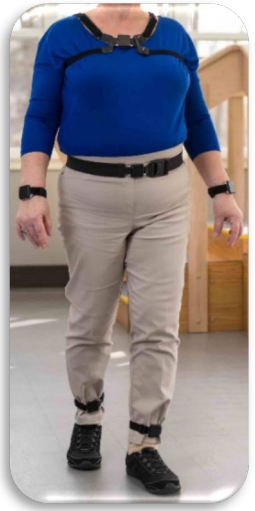
Can a custom designed wearable/mobile platform used outside of the clinic meaningfully supplement in clinic measures of PD *motor and non-motor* symptom progression?

Jamie Adams, Ray Dorsey, University of Rochester

WATCH-PD Data-Collection Platforms

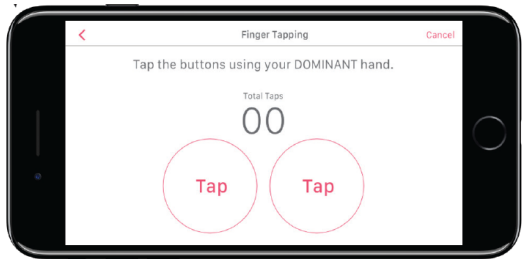
Wearable Assessments in the Clinic and Home in Parkinson's Disease

APDM Opal/Mobility Lab
(worn in clinic) *Clario*



Motion sensors only

Apple Watch + iPhone *ClinicalInk*
(worn in clinic and at home)



- *Motion sensors*
- *Microphone (for speech)*
- *Patient-Reported Outcomes (PROs)*

3DT Strategy: Engage Regulatory Agencies
Early and Often

FDA U.S. FOOD & DRUG ADMINISTRATION

Memorandum

Date: 7/10/2019

Subject: Critical Path Innovation Meeting: Parkinson's Disease Digital Drug Development Tools

Date of meeting: 5/14/2019

Requestor: Critical Path Institute, Critical Path for Parkinson's

Note: Discussions at Critical Path Innovation Meetings are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants.

FDA Representatives

Center for Drug Evaluation and Research
Office of Business Informatics (OBI)

EMA initiatives to support drug development

EUROPEAN MEDICINES AGENCY

What do we provide?

2. Innovation Task Force (ITF) platform and meetings

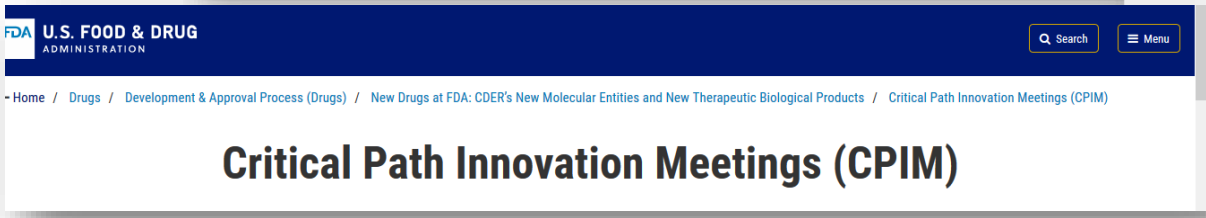
5 August 2019

ITF Briefing Meeting Report

Critical Path Institute Ltd, Critical Path for Parkinson's (CPP) Consortium

Briefing meeting held at the European Medicines Agency (EMA) on 15th July 2019.

ective of the ITF briefing meetings is to provide for a preparatory discussion on scientific and
ory topics relevant to the development of new medicinal products and technologies
menting and reinforcing existing formal procedures.



FDA U.S. FOOD & DRUG ADMINISTRATION

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Home / Drugs / Development & Approval Process (Drugs) / New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products / Critical Path Innovation Meetings (CPIM)

Critical Path Innovation Meetings (CPIM)

EMA: Innovative Task Force suggested taking a stepwise approach. Identify a small, well-defined meaningful measure and come back to them with a focused data-driven path for a future Scientific Advice and potential for qualification.

FDA: The appropriate FDA review divisions will continue to have iterative, disease-specific discussions with CPP, including strategies for establishing meaningful clinical endpoints.

Advice from Regulatory Agencies Informs the Path

- Technical issues, data quality, transparency of algorithms
- Evaluation of both motor, non-motor manifestations of PD is key
- Link to the voice of patients and function .

.

- It is critical to establish **normative databases**
- <u>A suggestion that it may be beneficial to enroll subjects at the earliest point possible</u>

WATCH-PD Baseline Results are Promising

News > Medscape Medical News > Conference News > MDS 2021

Apple Devices Identify Early Parkinson's Disease

Daniel M. Keller, PhD

September 24, 2021

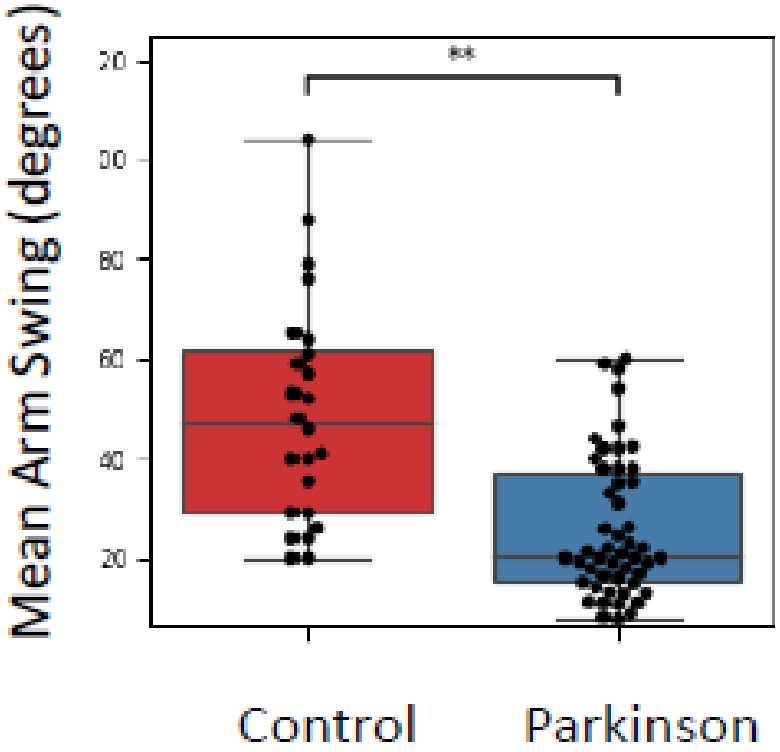
1 Read Comment Add to Email Alerts

Apple Watches and iPhones can differentiate between individuals with early, untreated Parkinson's disease (PD) and healthy controls, new research shows.

Results from the WATCH-PD study show clear differences in a finger-tapping task in the PD vs control group. The finger-tapping task also correlated with "traditional measures," such as the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), investigators report.

Adams J et al., Movement Disorders Congress, Sept 2021
Funded by Biogen, Takeda, CPP 3DT and led by Univ Rochester

A smartwatch can differentiate arm swing between individuals with Parkinson's disease and controls



Adams et al., npj Parkinson's disease , *in press*

The Data Informs the Intended Application

Arm Swing deficits can be measured in asymptomatic LRRK2 gene carriers

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

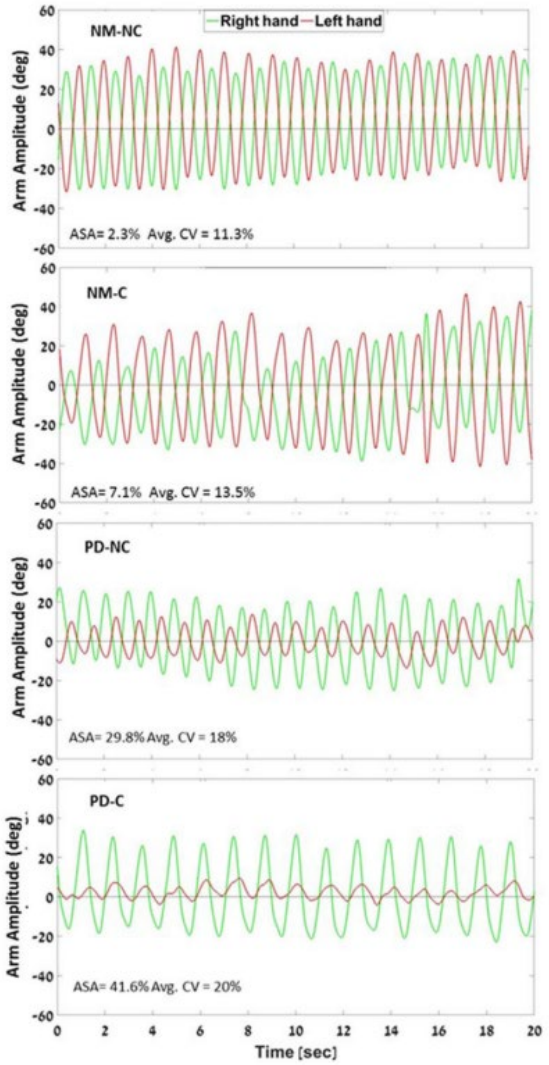
Research Article

Arm swing as a potential new prodromal marker of Parkinson's disease

Anat Mirelman PhD, Hagar Bernad-Elazari BSc, Avner Thaler MD, PhD, Eytan Giladi-Yacobi MD, Tanya Gurevich MD, Mali Gana-Weisz PhD, Rachel Saunders-Pullman MD, Deborah Raymond MSc, Nancy Doan MD, Susan B. Bressman MD, Karen S. Marder MD, Roy N. Alcalay MD, Ashwini K. Rao PhD, Daniela Berg MD, Kathrin Brockmann MD, Jan Aasly MD, Bjørg Johanne Waro MD, Eduardo Tolosa MD, Dolores Vilas MD, Claustre Pont-Sunyer MD, Avi Orr-Urtreger MD,PhD, Jeffrey M. Hausdorff PhD, Nir Giladi MD
... See fewer authors

First published: 06 October 2016 | https://doi.org/10.1002/mds.26720 | Citations: 80

Mov Disorders 2016 Oct;31(10):1527-1534

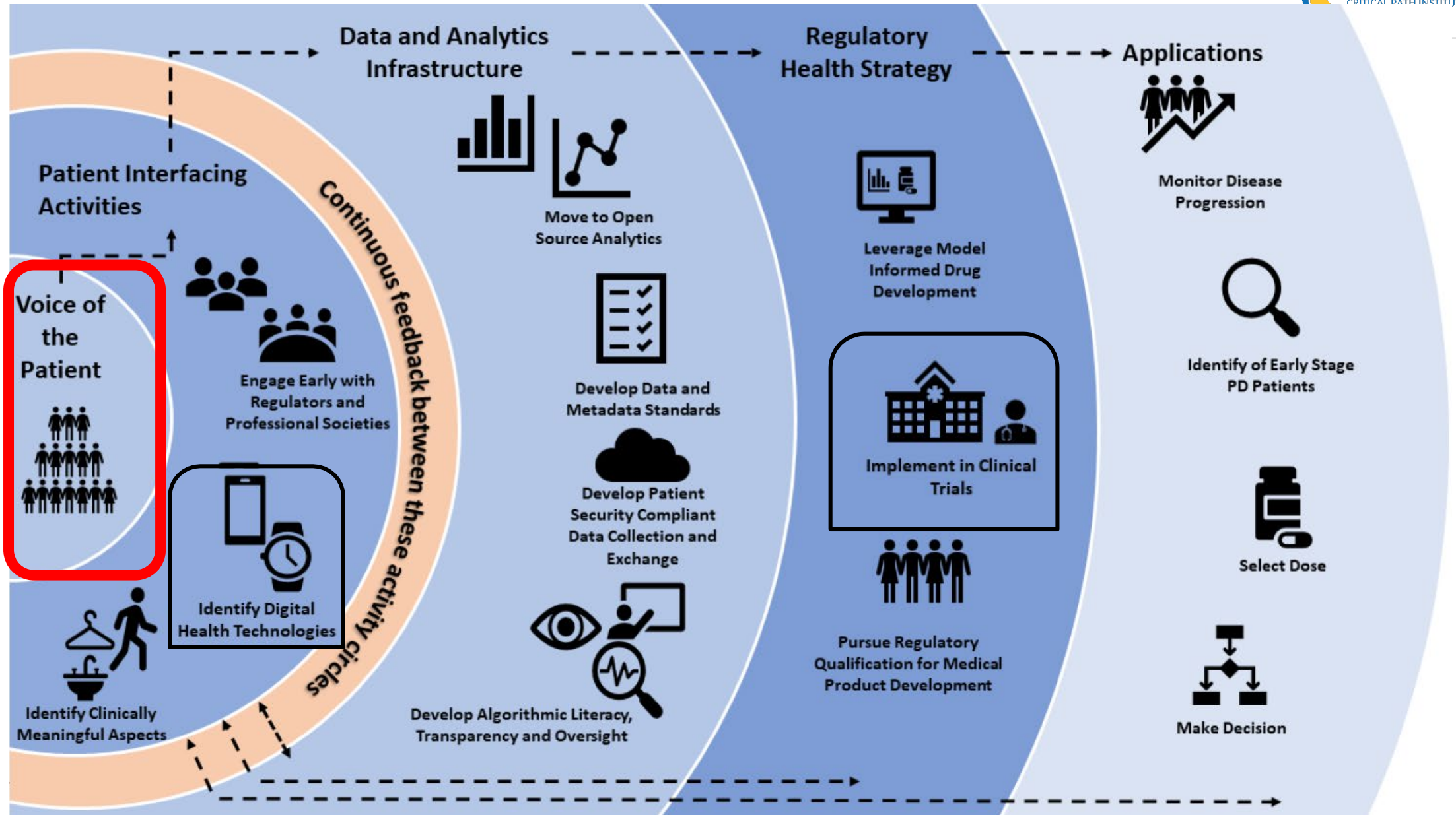


Nonmanifest noncarriers

Non-manifesting carriers

PD noncarriers

PD carriers



Digital Biomarkers 2020 Nov 26;4(Suppl 1):28-49

npj | digital medicine

www.nature.com/npjdigitalmed

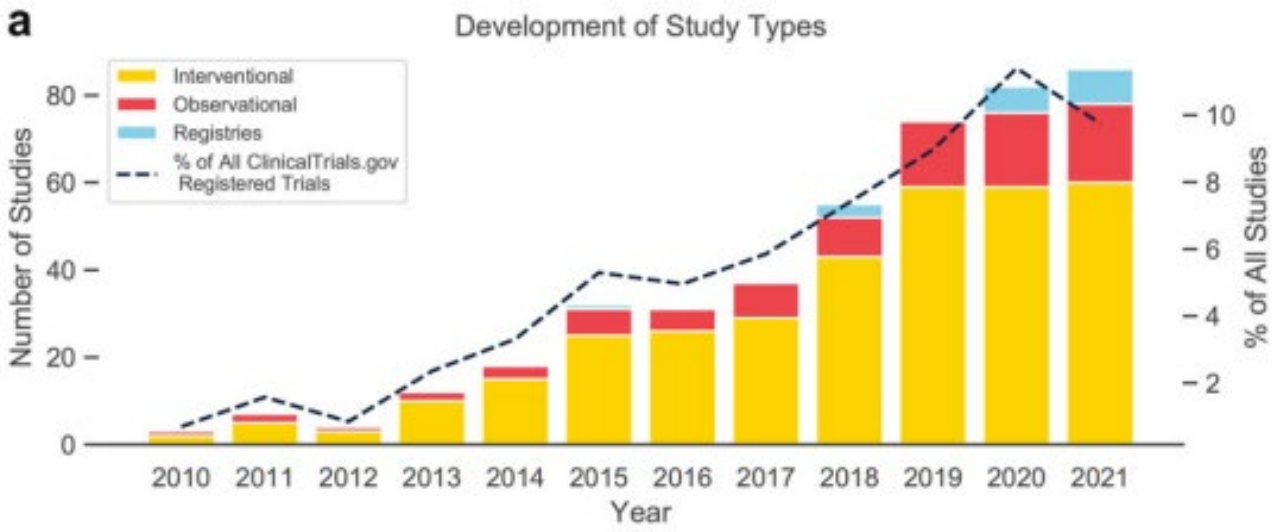
CPP CRITICAL PATH INSTITUTE

BRIEF COMMUNICATION OPEN

Check for updates

Evidence from ClinicalTrials.gov on the growth of Digital Health Technologies in neurology trials

Lars Masanneck[1,2], Pauline Gieseler[2], William J. Gordon[3,4,5], Sven G. Meuth[1] and Ariel D. Stern[2,6,7]✉



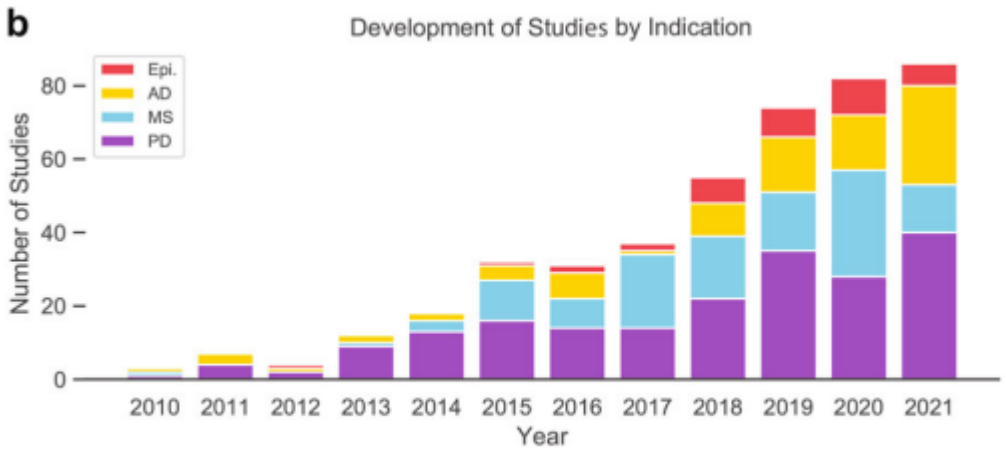


Fig. 1 Development of clinical trials for chronic neurological diseases by year of initiation, trial type and indication. a Number

Masanneck, L., Gieseler, P., Gordon, W.J. *et al. npj Digit. Med.* **6**, 23 (2023).

What is Needed for Success in the Future?

Current state

Medical practitioners aspire for prodromal diagnosis

Clinicians & drug developers aspire to enrol large diverse patient cohorts at minimal cost to validate studies

Patients want to increase their quality of life

Stakeholders

Voice of the patient

Regulators

Clinicians

Device vendors

Engineers, data scientists, statisticians

Success

Patient-centric outcomes

- Improved quality of life
- Patient centric digital biomarker

Data sharing

- Reduce duplication of effort
- Clinical and technical validation through data harmonisation

Data Standards

- Increase data interoperability and data management
- Data used beyond its purpose of collection

Global Collaboration

- Reduce discrepancy between research utility & clinical value

Stephenson D, Badawy R, Mathur S, Tome M, Rochester L.
Digital progression biomarkers as novel endpoints in clinical trials – a multistakeholder perspective
J. Parkinson's Disease, *11*(s1), S103–S109, 2021.

CPP 3DT Initiative Stakeholders

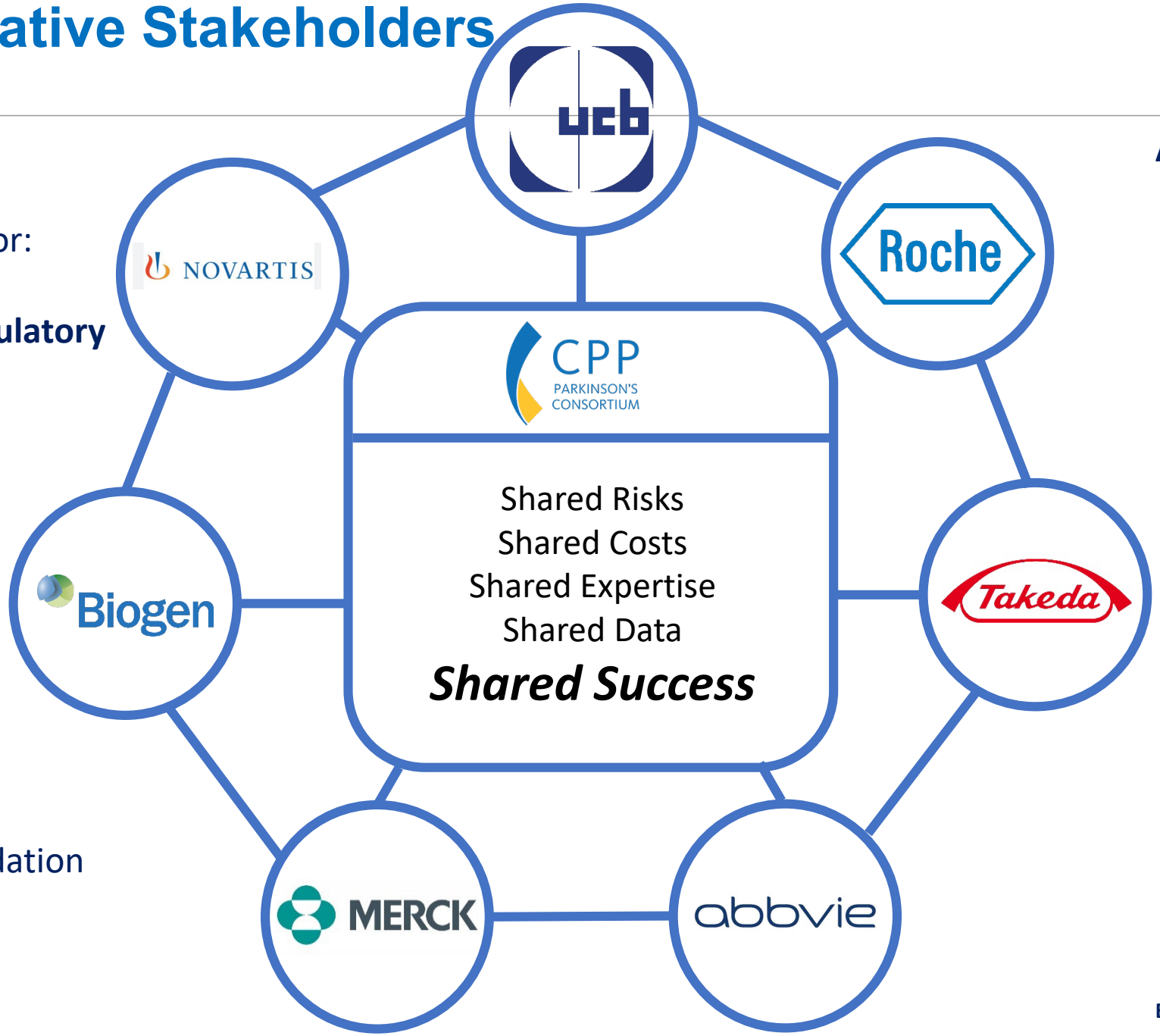
Critical Path Institute

3DT industry codirector:
Josh Cosman

Government and Regulatory Agencies
European Medicines Agency (EMA)
U.S Food and Drug Administration (FDA)
Michelle Campbell,
Billy Dunn

Patient/Research Organization
Parkinson's UK
Michael J. Fox Foundation

People living with Parkinson's



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New Publication: Learnings from Traditional Biomarkers to Defining Regulatory Success

Received: 28 July 2022 | Revised: 27 September 2022 | Accepted: 3 November 2022

DOI: 10.1111/cts.13461

REVIEW

Empowering drug development: Leveraging insights from imaging technologies to enable the advancement of digital health technologies

Elena S. Izmailova[1] | R. Paul Maguire[2] | Timothy J. McCarthy[3] | Martijn L. T. M. Müller[4] | Philip Murphy[5] | Diane Stephenson[4]

Clinical Translational Sciences 2023 Mar;16(3):383-397. doi: 10.1111/cts.13461.

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Critical Path Institute Staff

Critical Path for Parkinson's Consortium Members

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European Medicines Agency

Maria Tome, Spiros Vamvakas

Billy Dunn

People living with Parkinson's, the hidden pandemic

Abhinav Sharma

Assistant Professor of Cardiology

McGill University

Use of Actigraphy in Heart Failure Clinical Trials

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DREAM-CV Lab, McGill University Health Centre
March 29th, 2023
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Centre universitaire de santé McGill
McGill University Health Centre

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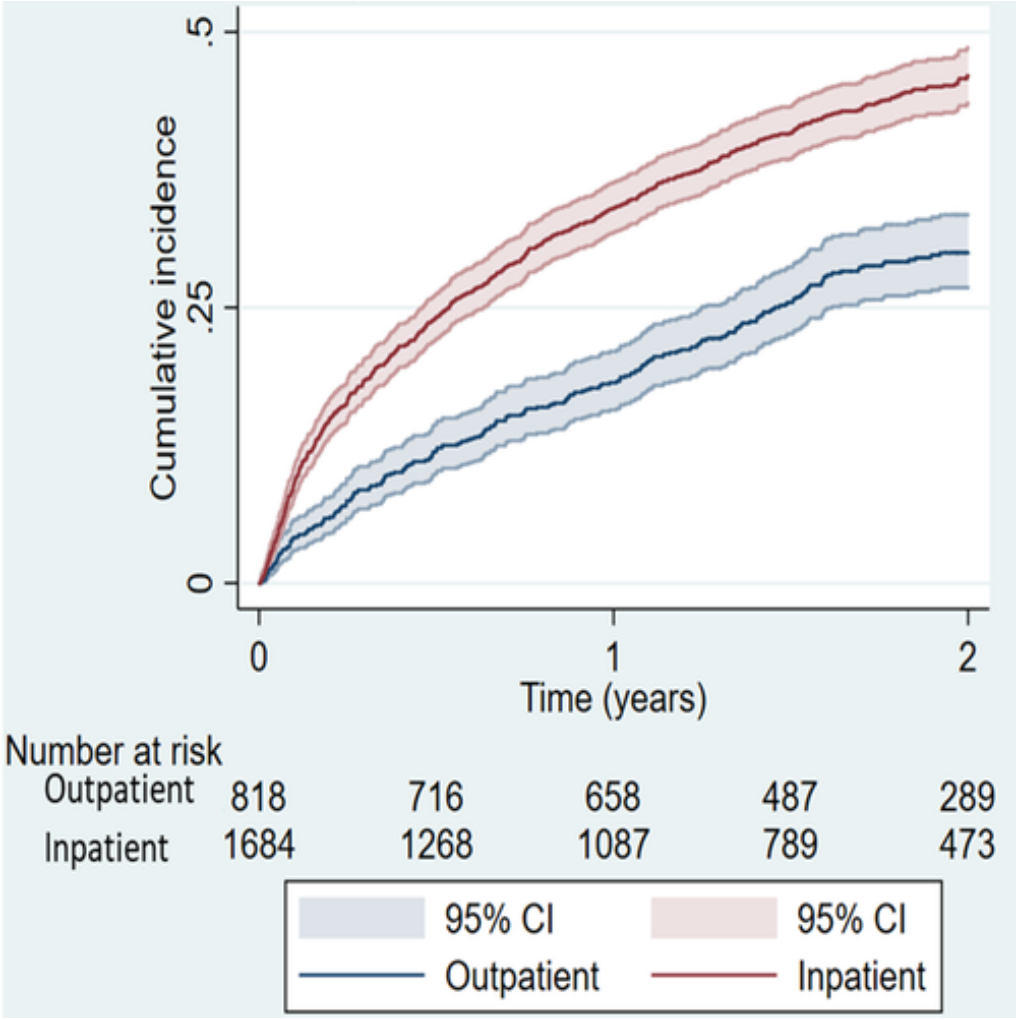
- Takeda
- BMS-Pfizer

Agenda

- The role of actigraphy in heart failure
- Evidence for use of actigraphy in heart failure
- Current gaps in how we can use actigraphy
- Framework for validation of actigraphy and next steps

The Role of Actigraphy in Heart Failure Clinical Trials

Morbidity and Mortality In Heart Failure



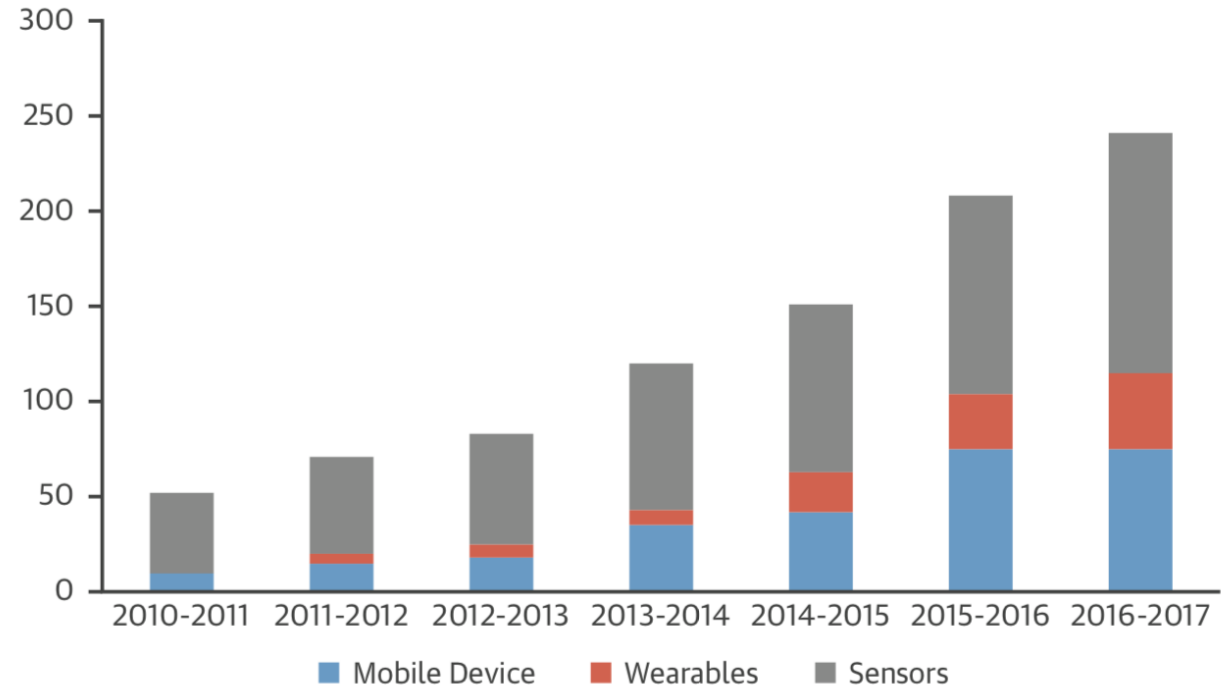
European Journal of Heart Failure (2019)21,112–120

Digital Innovation

- Healthcare industry, until recently has been largely excluded from the advances in digital health
- Availability of powerful yet low-cost computing + funding from government and industry resulted in major advances in the use of digital technologies
- Facilitate healthcare delivery + optimize clinical trials

Sharma A et al, JACC 2018

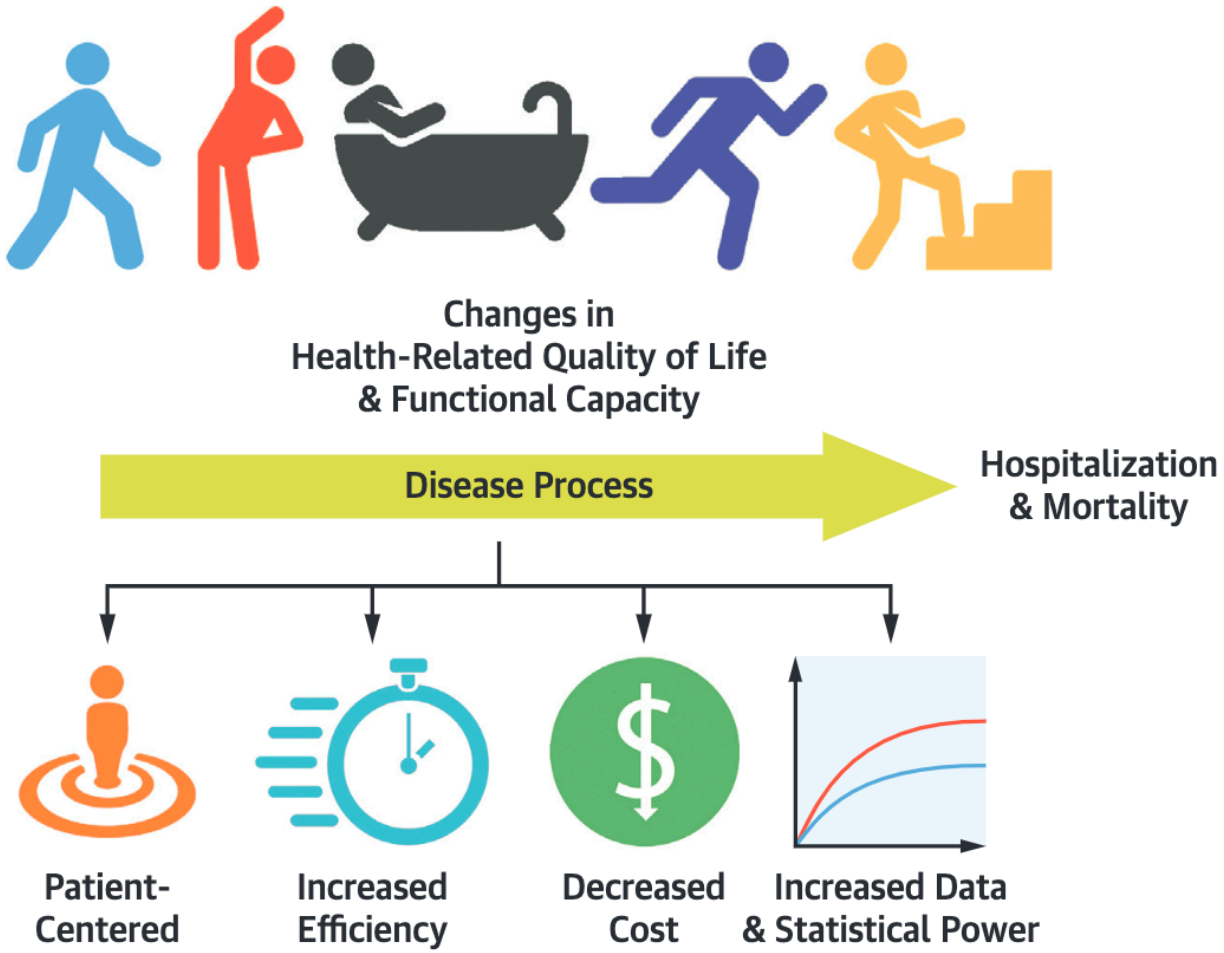
FIGURE 2 Use of Digital Health Technologies Within Clinical Trials



Data reflect the number of initially registered trials on clinicaltrials.gov per year (accessed March 20, 2017). Posted entries are defined based on investigator description of proposed devices used.

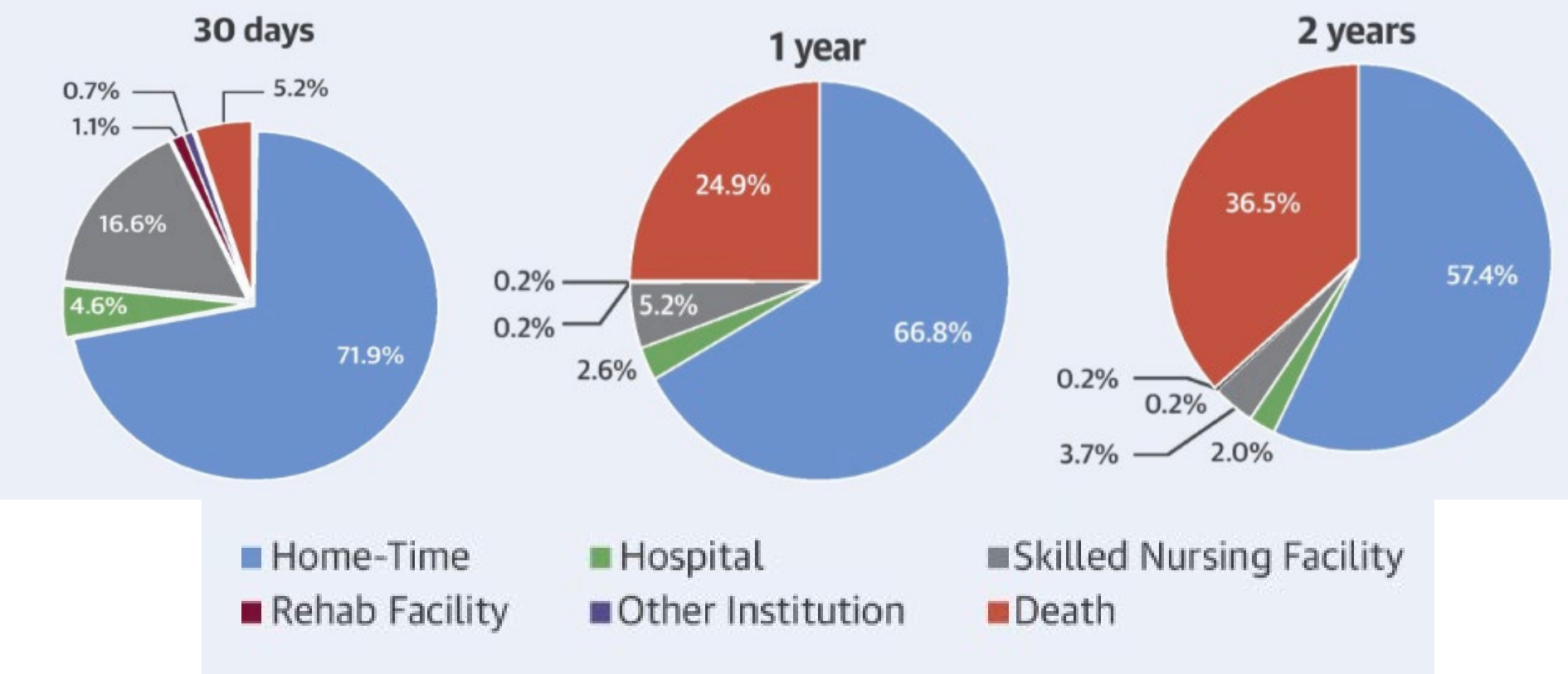
Sharma A et al, JACC 2018

CENTRAL ILLUSTRATION **Utility of Functional and Symptomatic Endpoints for Heart Failure Clinical Trials**



Psotka MA, et al. J Am Coll Cardiol HF. 2022;10(12):889-901.

Why Actigraphy in Heart Failure Trials



Greene et al. J Am Coll Cardiol. 2018 Jun 12;71(23):2643-2652

Use of Actigraphy in Heart Failure Trials

1 **Broadly Available**

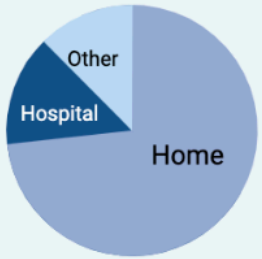
- Increasing comfort in using DHT
- Broadly available with lower cost
- Increasing R+D to create devices for specific diseases

2 **Current Functional Assessment**

6MWD *VO2*

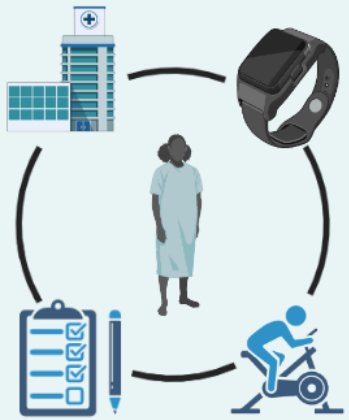
- Traditional functional assessment 6MWD and VO2
- Generally conducted in standardized settings
- Need for trained personnel

3 **Need For Real-World Data**



- Majority of peoples lives are not within a healthcare setting
- There is need to determine functional outcomes within real-world settings

4 **Actigraphy To Support Drug Development**



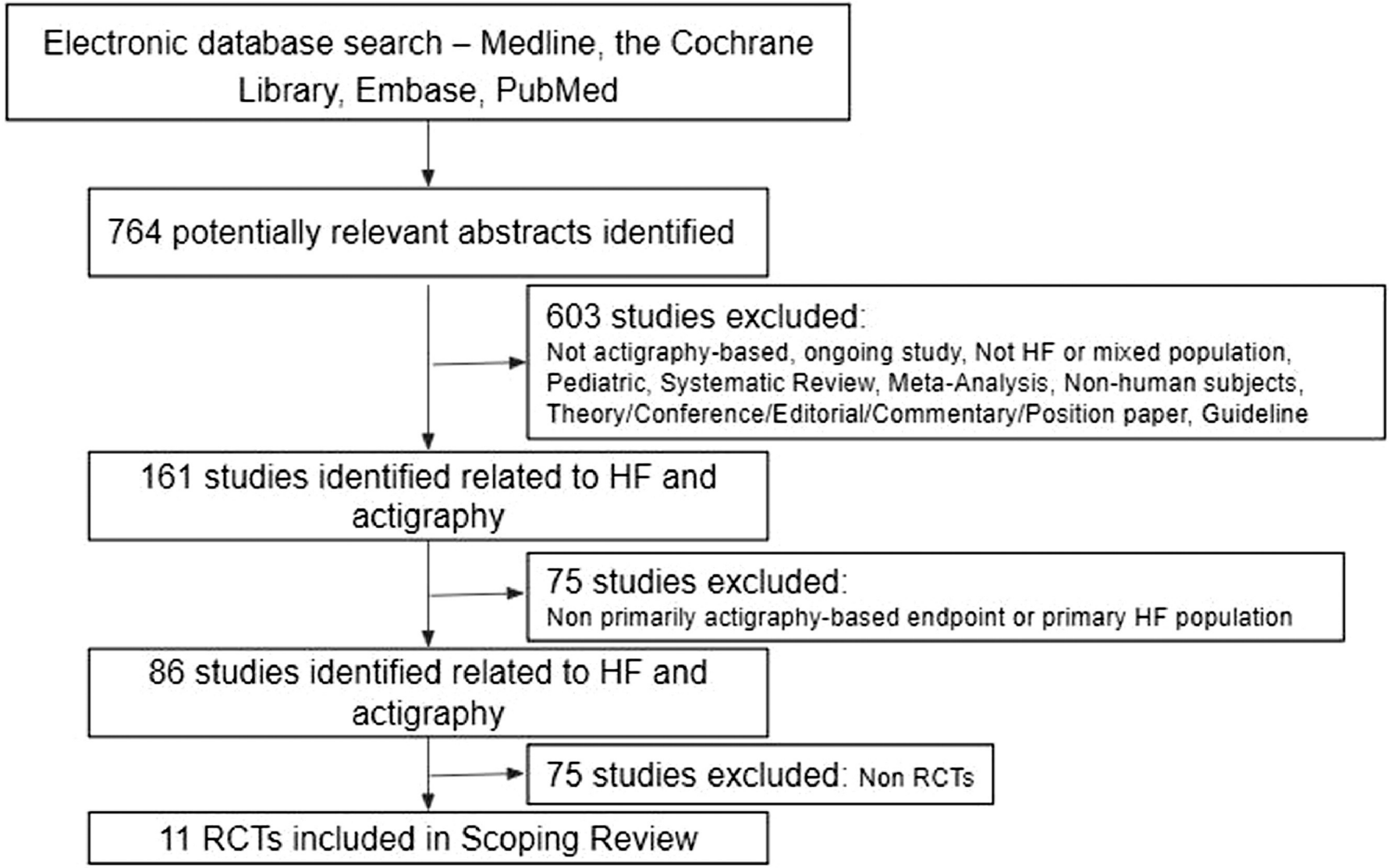
- Actigraphy can facilitate to democratize HF trials
- Provide a holistic picture in addition to traditional endpoints

Current State of Evidence

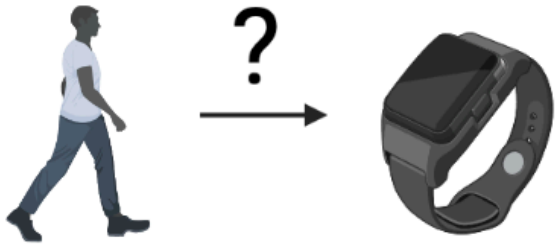
Use of Actigraphy (Wearable Digital Sensors to Monitor Activity) in Heart Failure Randomized Clinical Trials: A Scoping Review

Khalil Anchouche, MD * • Malik Elharram, MD, MSc * • Emily Oulousian, BSc • Amir Razaghizad, BSc • Robert Avram, MD, MSc • Guillaume Marquis-Gravel, MD, MSc • Varinder Kaur Randhawa, MD, PhD • Richard Nkulikiyinka, PhD • Wei Ni, PhD • Mona Fiuzat, PharmD • Christopher O'Connor, MD • Mitchell A. Psotka, MD, PhD • Jonathan Fox, MD, PhD • Benoit Tyl, MD • David Kao, MD • Abhinav Sharma, MD, PhD • Show less • Show footnotes

Can J Cardiol. 2021 Sep;37(9):1438-1449.


Electronic database search – Medline, the Cochrane Library, Embase, PubMed
764 potentially relevant abstracts identified
603 studies excluded:
Not actigraphy-based, ongoing study, Not HF or mixed population, Pediatric, Systematic Review, Meta-Analysis, Non-human subjects, Theory/Conference/Editorial/Commentary/Position paper, Guideline
161 studies identified related to HF and actigraphy
75 studies excluded:
Non primarily actigraphy-based endpoint or primary HF population
86 studies identified related to HF and actigraphy
75 studies excluded: Non RCTs
11 RCTs included in Scoping Review

1 VALIDATION



- Majority of devices did not have validation data among patients with HF
- Unclear if therefore measures have a certainty of accuracy

2 OUTCOMES

Peak movement | Average over day | Distance vs steps

- Significant heterogeneity between studies regarding outcomes

3 DISCREPANCIES

- Functional outcomes based on actigraphy did not align with the larger phase 3 trials
- Actigraphy results and handing of data not completely reported

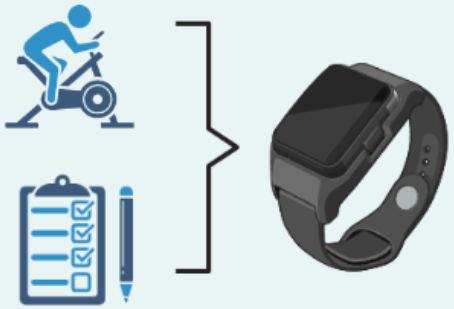
Future Directions

METHODOLOGY FRAMEWORKS

1

- Develop validation methodology for devices
- Collaborations between academia-industry-FDA (e.g. Heart Failure Collaboratory)

2



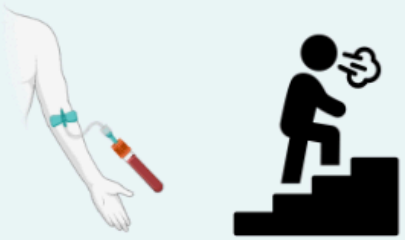
- Develop guidance on minimal change criteria in heart failure
- Anchor this to established and accepted FDA endpoints

PROSPECTIVE STUDIES

3

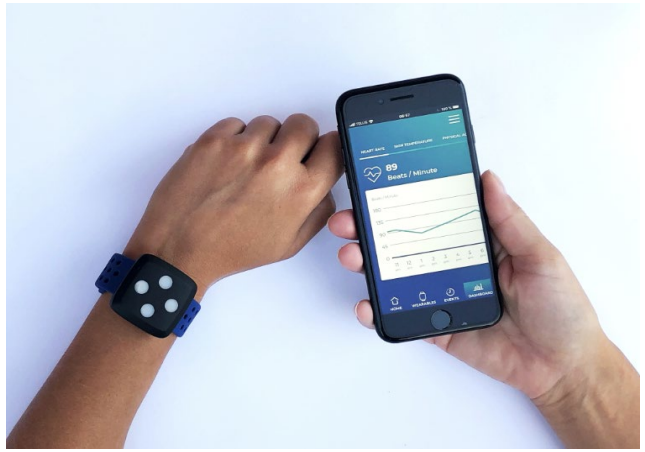
- Conduct prospective studies to demonstrate the utility of actigraphy
- Confirming and validating minimal change - 6MWD +VO_2

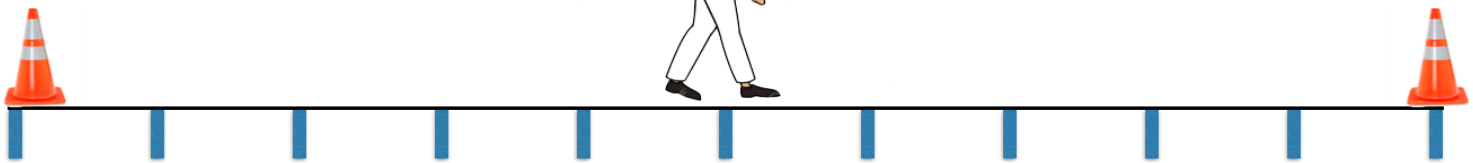
4



- Further evaluation of actigraphy measures against FDA accepted patient reported outcomes (KCCQ)
- Explore associations with biomarkers (NTproBNP)

Some Studies Underway



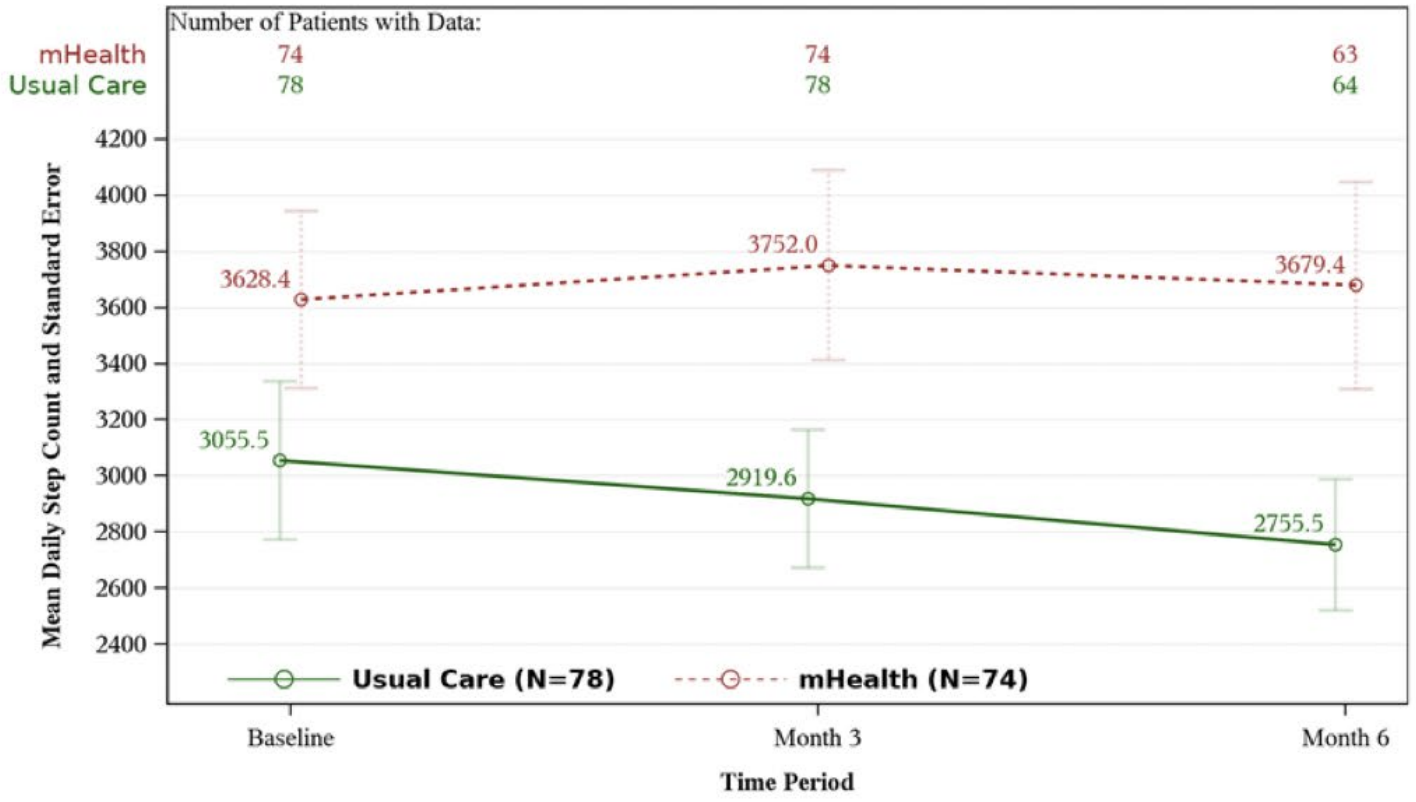


TARGET-HF-DM Trial

- 1:1 randomization to mHealth intervention or usual care
- Both groups received step counter and weekly text reminder to wear it
- mHealth group received feedback and incremental personalized activity goals (based on prior week's activity) sent by text 3x/week
- 3 months of active intervention followed by 3 months of additional data collection

Sharma A et al. AHJ 2021

TARGET-HF-DM Trial



Change in daily step count baseline to month 3:

between group difference of 313 steps/day

95% CI 8, 619
p = 0.04

Felker M, Sharma A et al. Journal of Cardiac Failure 2022

Conclusions

- Actigraphy can play a substantial role in advancing clinical trials evaluating heart failure therapies
- Potential to democratize trials, improve evaluation of real-world outcomes, supplement traditional clinical trial outcomes across Phase I-IV
- Need for more guidance and framework around actigraphy based validation, minimal change criteria, and associations with accepted outcomes

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- Duke Clinical Research Institute – Dr M. Felker
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- DREAM-CV Team at MUHC
- All the patients and families

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Jennifer Mammen

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University of Rhode Island

Mapping relevance of digital measures to meaningful symptoms in early Parkinson's disease

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Jennifer Mammen, PhD, University of Rhode Island

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FDA Center for Drug Evaluation Research
- Michelle Campbell

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Rationale for Qualitative Study

- DHT captures finer variation in symptoms
- Unclear if capturing what is meaningful to patients
- "Meaningfulness" is needed for regulatory approval of new devices
- **FDA PFDD Section IV, Part D, #3**:
  - endpoint is clinically relevant + data is adequately captured
  - meaningful reflection of an aspect of health that is important to patients

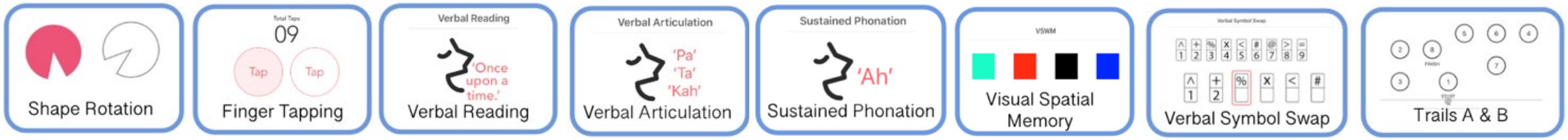
USDHHS. (2022). Patient-focused drug development: Methods to identify what is important to patients (Guidance for industry, food and drug administration staff, and other stakeholders). Retrieved from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-methods-identify-what-important-patients

Background: WATCH-PD study

WATCH-PD - *Wearable Assessments in The Clinic and at Home in PD*

- **Approach**: 12-month multi-center observational trial
- **Testing**: Smartwatch and smartphone apps → monitor PD
- **Sample**: early, untreated PD (N=82) and 50 controls
  - ≤ 2 years diagnosis, Hoehn & Yahr stage ≤ 2
- **Procedures**:
  - in-clinic visits: 0, 1, 3, 6, 9, and 12 months
  - **in-home assessments: 10 smartphone + smartwatch-based tasks**
    - motor and cognitive function

Adams et al. (2023). A Multicenter Study Using a Smartwatch, Smartphone, and Wearable Sensors to Assess Early Parkinson's Disease: Baseline Results of the WATCH-PD Study. *Research Square, Preprint*. Retrieved from https://assets.researchsquare.com/files/rs-2289246/v1/6e9df279-2bd5-4e8e-ba7b-18a0af828c0e.pdf?c=1669746436



TASK NAME	ACTIONS REQUIRED TO PERFORM ASSESSMENT	PICTOGRAPH
Walking & Balance	(1) Walks in straight line - 1 minute. (2) Stands with arms at sides - 30 seconds.	
Tremor Task	(1) Rests hands in lap - 10 seconds. (2) Extends arms out in front - 10 seconds.	

Table 1. Smart watch-based measures of activity evaluated for relevance

**Brainbaseline application screenshots used with permission from Clinical Ink*

WATCH-PD Qualitative study aims

Aims were to explore participants perceptions of:

Aim 1 Meaningful symptoms and impacts of early Parkinson's.

Aim 2 Relevance of WATCH-PD smartphone/smartwatch technology.

Study Design

Approach: Integrated (hybrid) mixed methods

Sample: all PD participants from WATCH-PD

- Exited within 6-months for interview group

Data collection: November 2021—March 2022

- Brief survey followed by online interview
  A. Symptom mapping
  B. Cognitive interviewing on 10 tasks (content validity)
  C. Map tasks back to personal symptoms

Data analysis: content coding and thematic analysis

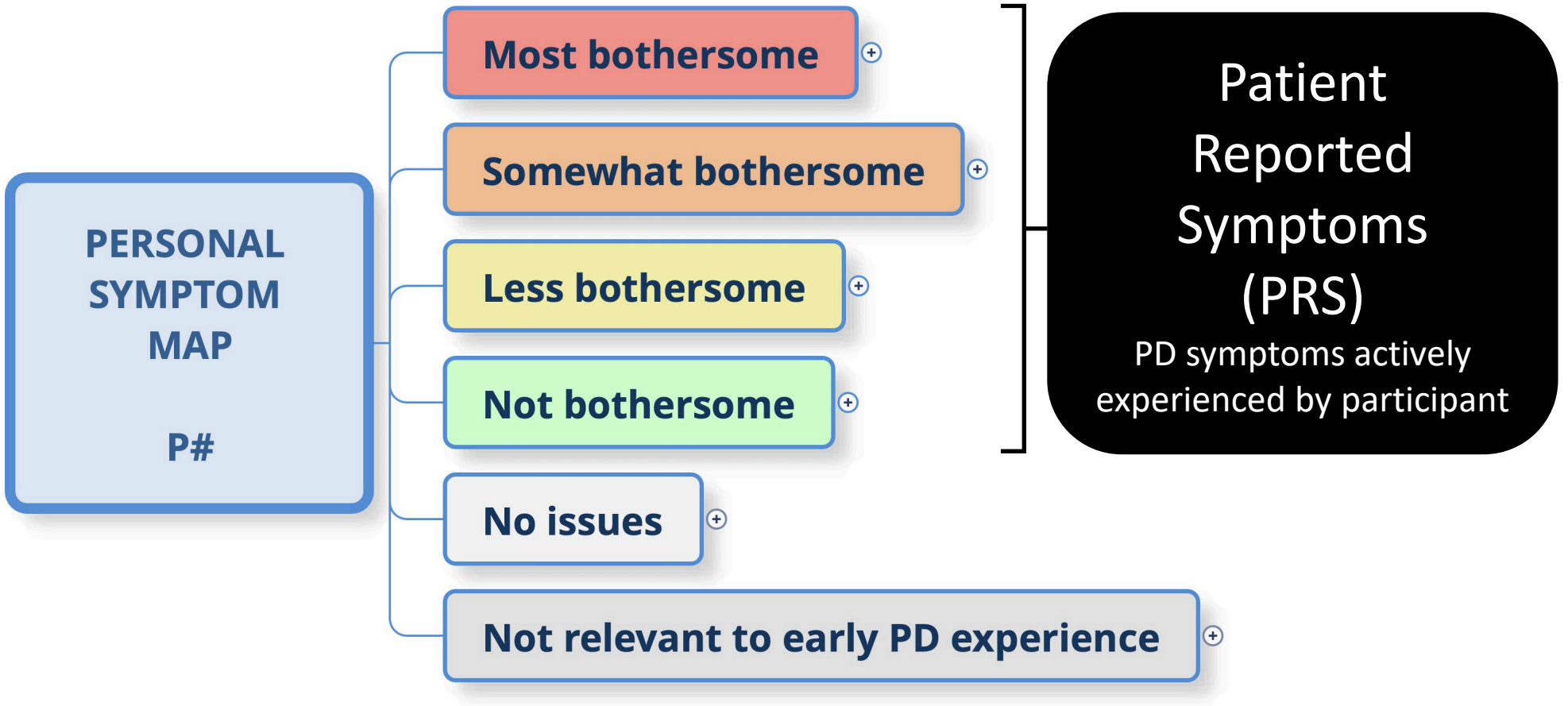
Demographics

Predominantly:

- White
- Male
- Higher SES
- PD 2 years

	Sample n = 40
Age, years	63.9 (SD 8.8)
Female, n (%)	19 (47.5%)
Race/ethnicity, n (%)	
White	37 (92.5%)
Asian	3 (7.5%)
Not specified	-
Hispanic or Latino, n (%)	1 (2.5%)
Education > 12 years, n (%)	40 (100.0%)
PD duration, years	2.1 (SD 0.9)
Taking medications for PD, n (%)	16 (40.0%)

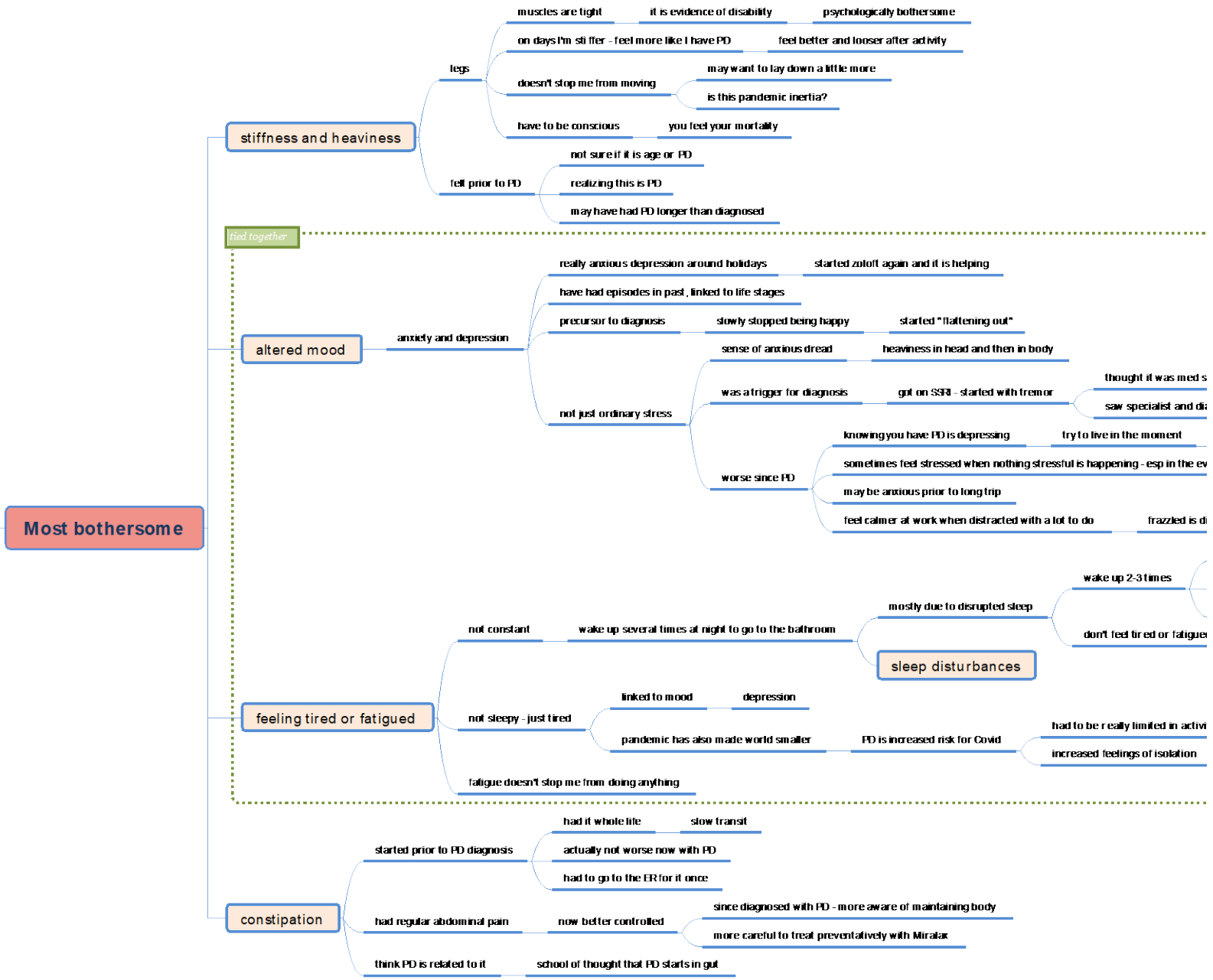
SYMPTOM MAPPING



Hybrid data collection approach – qualitative data collected *inside* a quantitative framework.

STEP 1.

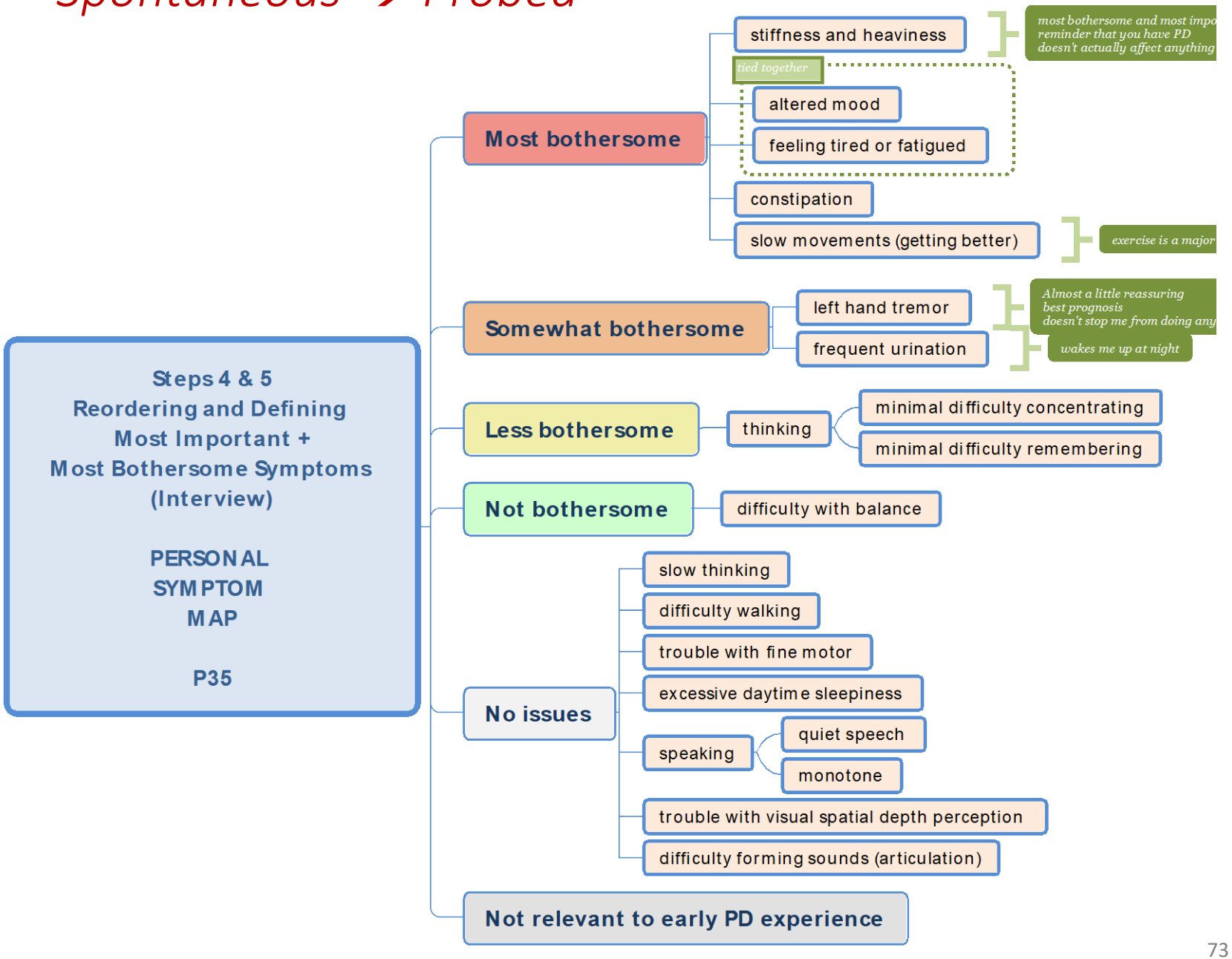
A. MAP SYMPTOMS
B. MAP IMPACTS



STEP 2.

A. RANK ORDER
B. IDENTIFY MOST IMPORTANT

Spontaneous → Probed



Interview part 2: Cognitive interviewing

Did the participant understand how to complete the task?

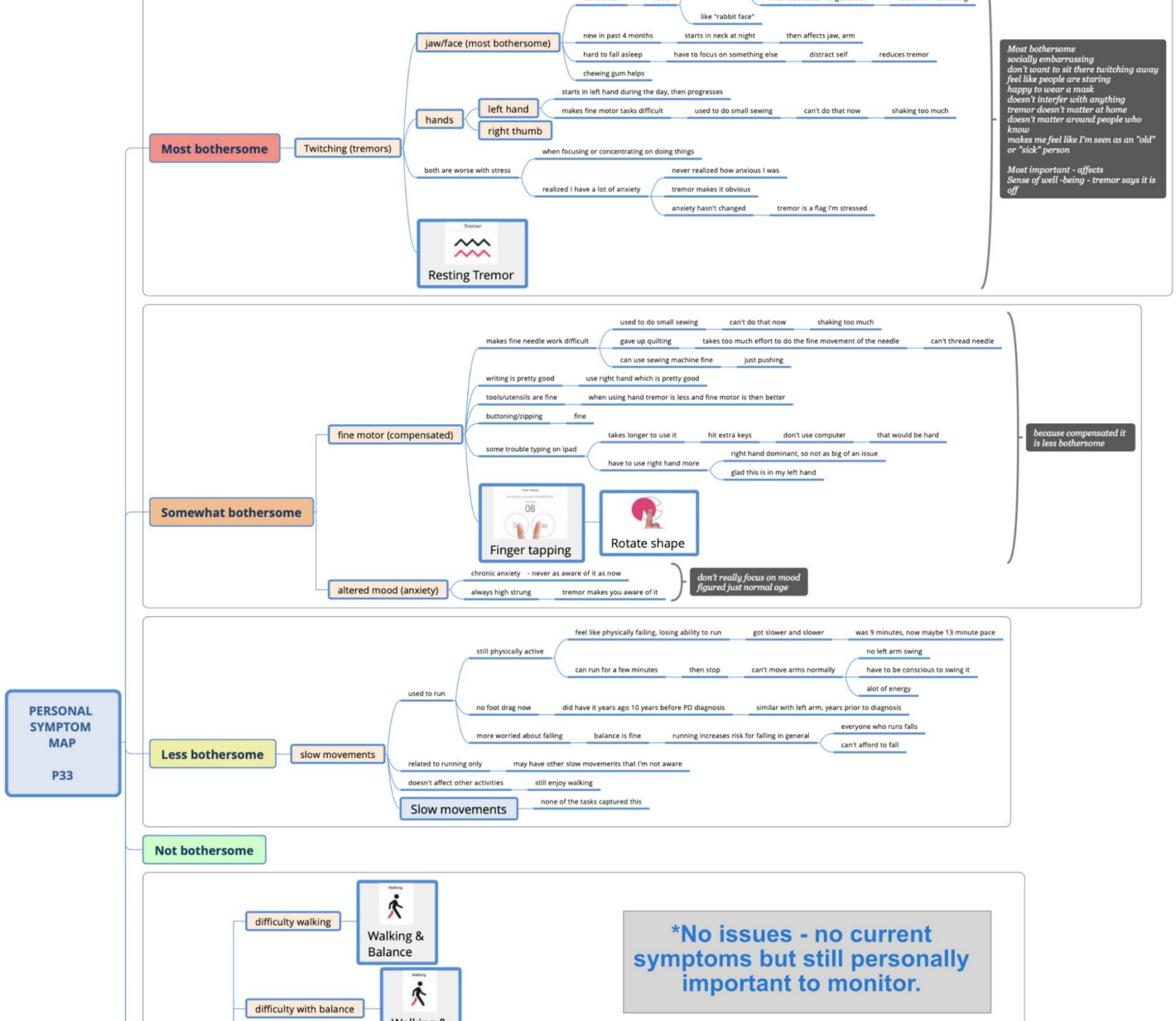
Did the task relate to the participant's PD symptoms?

Was the task similar/relevant to activities in daily life?

Was the task relevant to measuring progression of their PD?

STEP 3:

MAP DHT TO SYMPTOMS



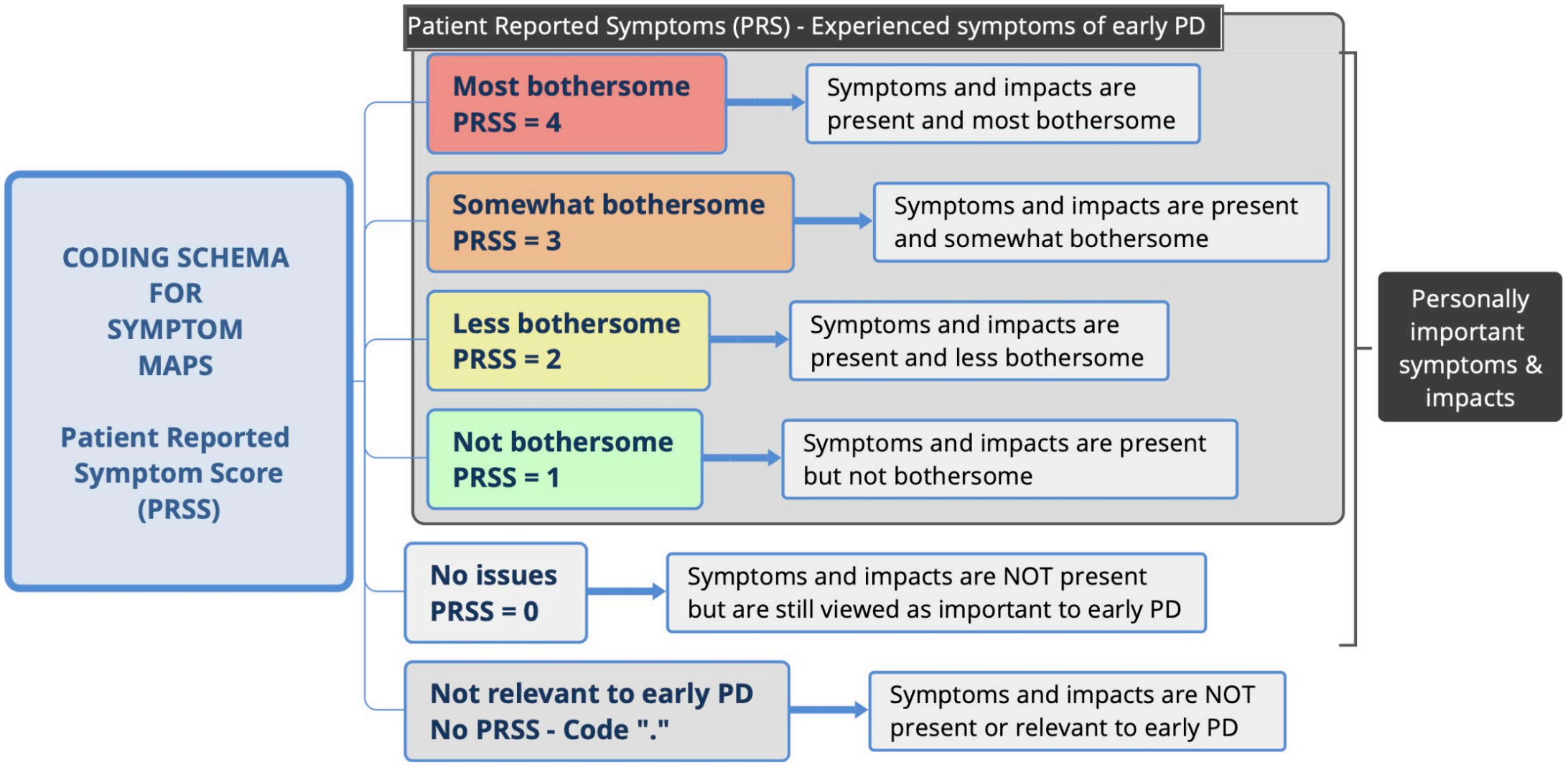
Participant experience with mapping

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.

Reciprocity: Copies of maps were returned to participants

Interviews 102 minutes on average

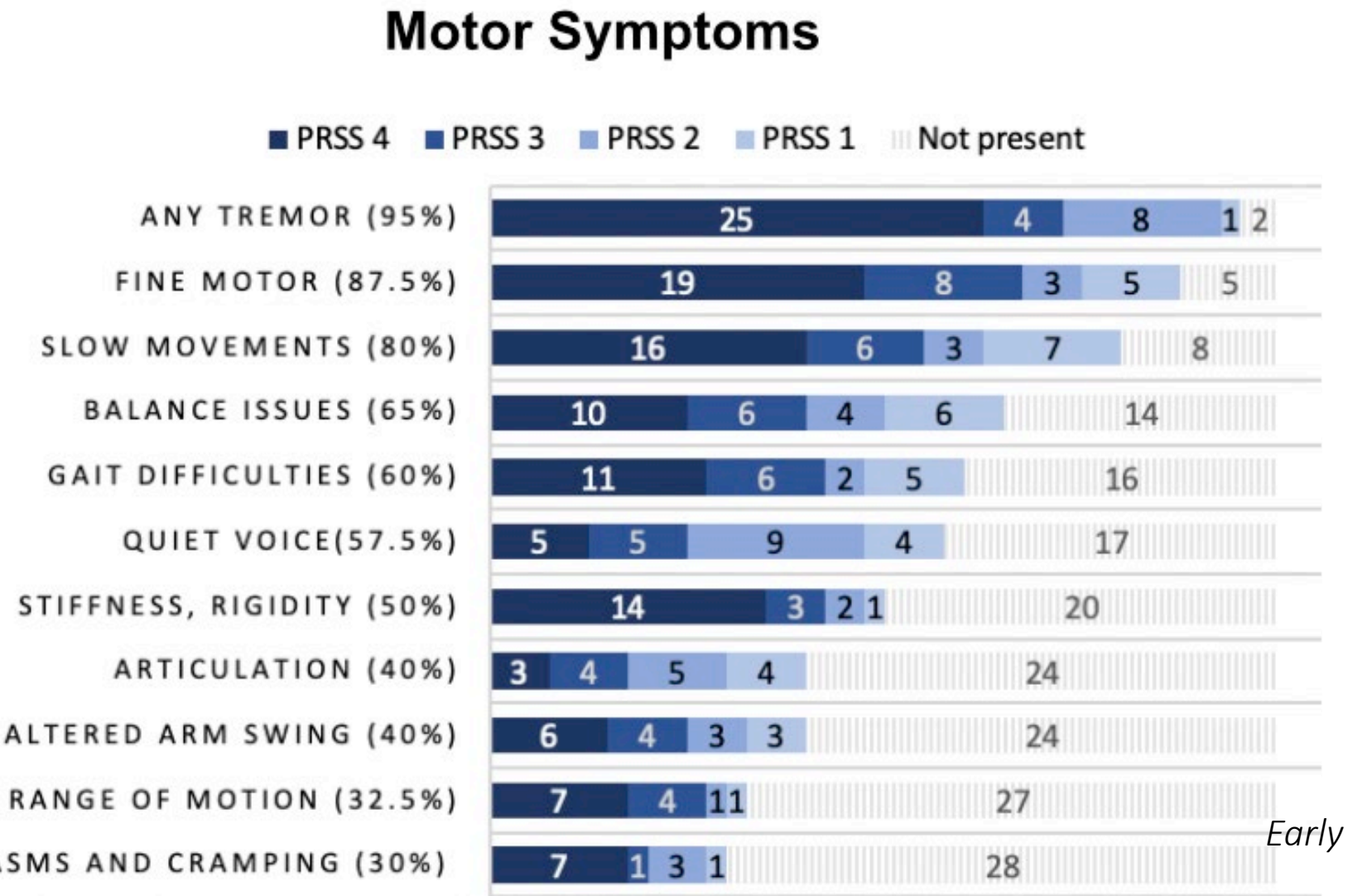
Content coding



Results from the WATCH-PD qualitative study

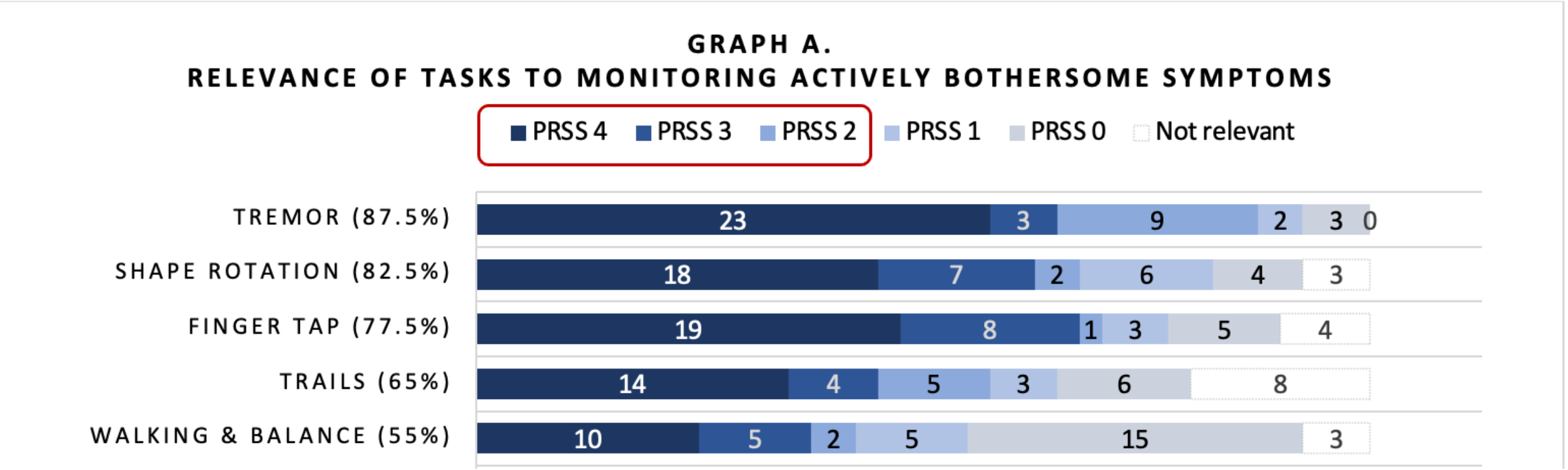
Activity based symptoms were some of the most important:

Tremor
Fine motor
Slow movement
Gait & balance



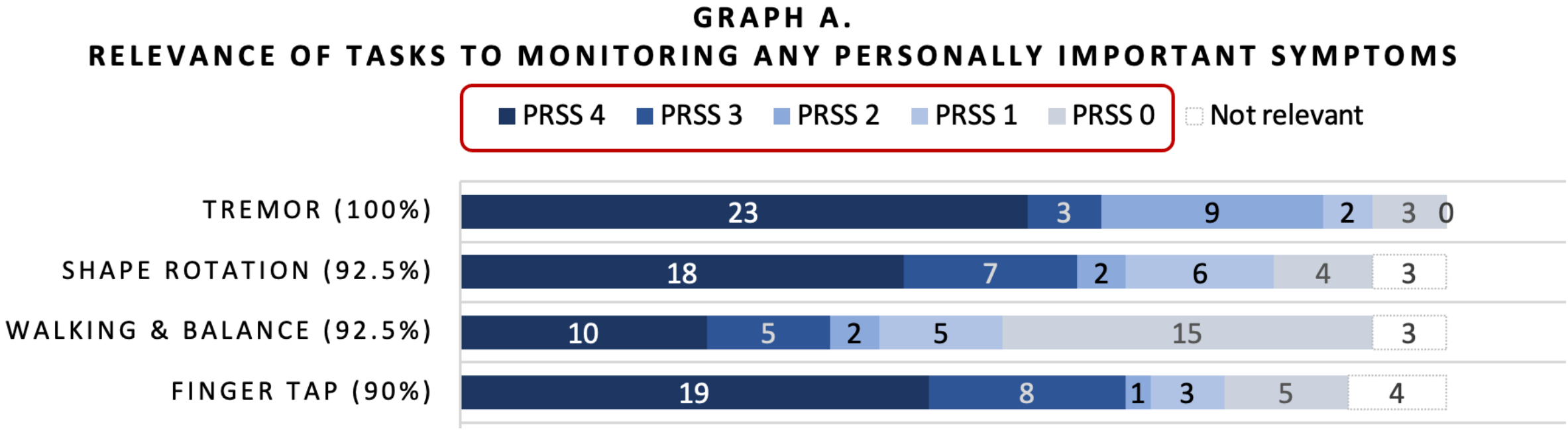
Early PD

Relevance of tasks to actively bothersome symptoms



Early PD

Relevance of tasks to important symptoms

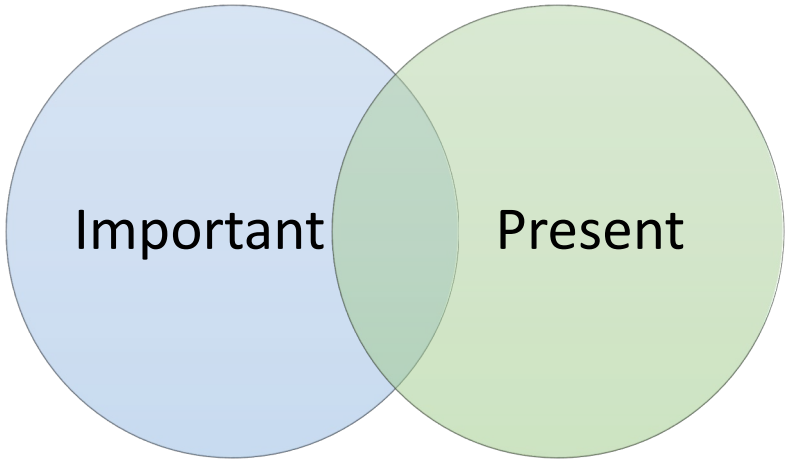


Early PD

THEMES

Symptoms can be important <u>even when not present</u>, or present but not important.

Important PD symptoms can impact physical and psychosocial functioning



Important Past Symptoms → Important Present Symptoms → Important Future Symptoms

***P6**: I don't experience [trouble speaking] but I want to be able to speak clearly. Speaking is important to me.*

Measure important symptoms

Many patients with early PD want to measure symptoms they do not currently experience.

P24: It's not so much what you have currently, it's the progression. It's about whether new symptoms develop and if those symptoms become more severe over time. …Symptoms change, they get worse, or they suddenly show up, and you didn't have it before

Patient criteria for evaluating relevance

Relevance" based on belief that a task effectively measured an important symptom—regardless of whether the symptom was present or the task related to ADL.

Criteria 1	Believed they understood what is being assessed
Criteria 2	Believed measure assessed an important symptom (past, present or future)
Criteria 3	Believed measure is a good test of that symptom

Tremor Task

100% Relevant in early PD

P33: [I have] tremor in my hand. I don't sit around with my hands in my lap or my hands out. [But it's important] Because if the watch was picking up the intensity of the tremor, it would show that it was is getting worse.

P6: I don't have tremors… I understand why you're testing, and I think it's important to test…[it isn't like anything I do in real life, but] I can see where it would be very important. I absolutely believe it's valid, as valid as the walking, yes.

Walking & Balance Task

92.5% Relevant in early PD

P26: [I don't have this symptom [but] I do a lot of walking [and] I'm worried. This is one of the worrisome symptoms of PD, for me, not being able to get around, [so the task is important]. I mean I'm watching myself. When I stub my toe, I sit there and I go, was that [Parkinson's]? Yeah. I'm already monitoring it.

Transparency increases relevance

P5: I don't feel like I have enough information [to decide if the measure is relevant]. … It would be nice to see results … [The digital measures could be] seeing things that I'm not.

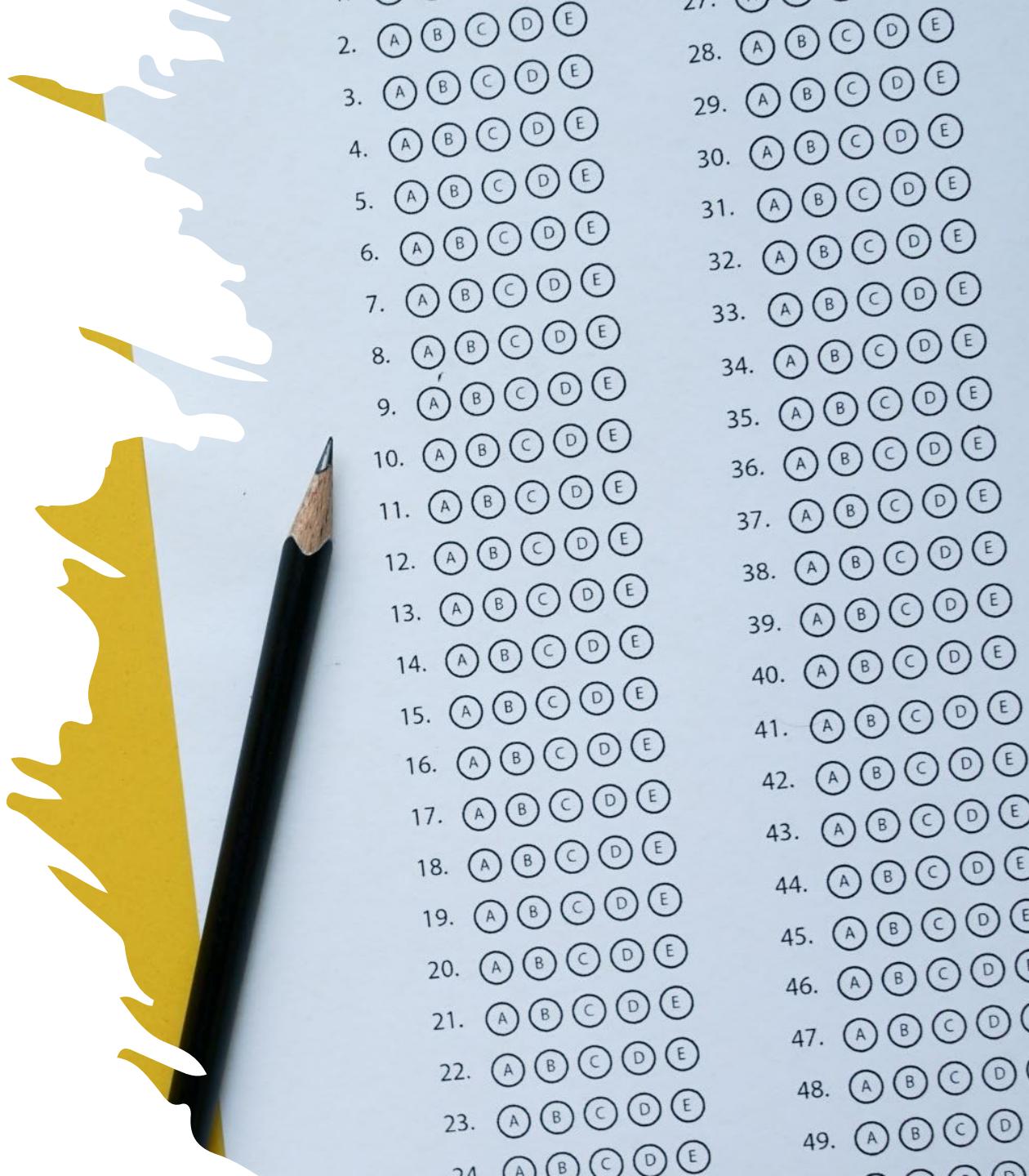
P3: I don't know what they were measuring, so it's hard for me to know whether it was related. If it is able to measure the things I care about, yes [it's important]. It's hard to know without seeing the data.

P6: I don't have tremors… I understand why you're testing, and I think it's important to test, but, for my daily life, it wasn't particularly important to me at this point …[it isn't like anything I do in real life, but] I can see where it would be very important. I absolutely believe it's valid, as valid as the walking, yes. [Tremor Task]

Assessing personal relevance (context validity)

KEY THINGS TO ASK:

- What symptom was being assessed by the task/measure?
- Was this a personally important symptom?
- Does the symptom limit/get in the way of doing things?
- How bothersome is that limitation?
- Is this a good way to test the symptom?
- Is the task/measure relevant to monitoring disease progression?
- Is the task/measure relevant to the person now?



Limitations

- Higher SES and health/tech literacy
- Predominantly white
- Single time-point
- Early PD group
- Smaller sample N=40

References:

Mammen, J., Speck, R., Stebbins, G. . . Adams, J. (preprint). Mapping meaningful symptoms and impacts of disease to digital outcome measures. From: https://digitalcommons.uri.edu/nursing_facpubs/343/

Mammen, J., Speck, R., Stebbins, G . . . Adams, J. (preprint). Relevance of digital health technologies to people with early Parkinson's for monitoring meaningful symptoms in the WATCH-PD study. From https://digitalcommons.uri.edu/nursing_facpubs/345/

Mammen, J., Speck, R., Stebbins, G. . . Adams, J. (preprint). Relative meaningfulness and impacts of symptoms in people with early-stage Parkinson's disease. From https://digitalcommons.uri.edu/nursing_facpubs/344/

Important.
Transparent.
Relevant.

Session 3: Actigraphy in Clinical Trials to Support Drug Development

Moderator:

- Christina Silcox, Duke-Margolis Center for Health Policy

Panelists:

- Jeremy Wyatt, ActiGraph
- Steve Xu, Northwestern University
- Diane Stephenson, Critical Path Institute
- Abhinav Sharma, McGill University
- Jennifer Mammen, University of Rhode Island

Break

We will be back momentarily.

The next panel will begin at 2:40 p.m. (U.S. Eastern Time)

Session 4: Use of Other Sensor-Based DHTs in Clinical Trials for Drug Development

2:40 pm – 3:40 pm EST

Kuldeep Singh Rajput

CEO and Founder

Biofourmis

Biofourmis

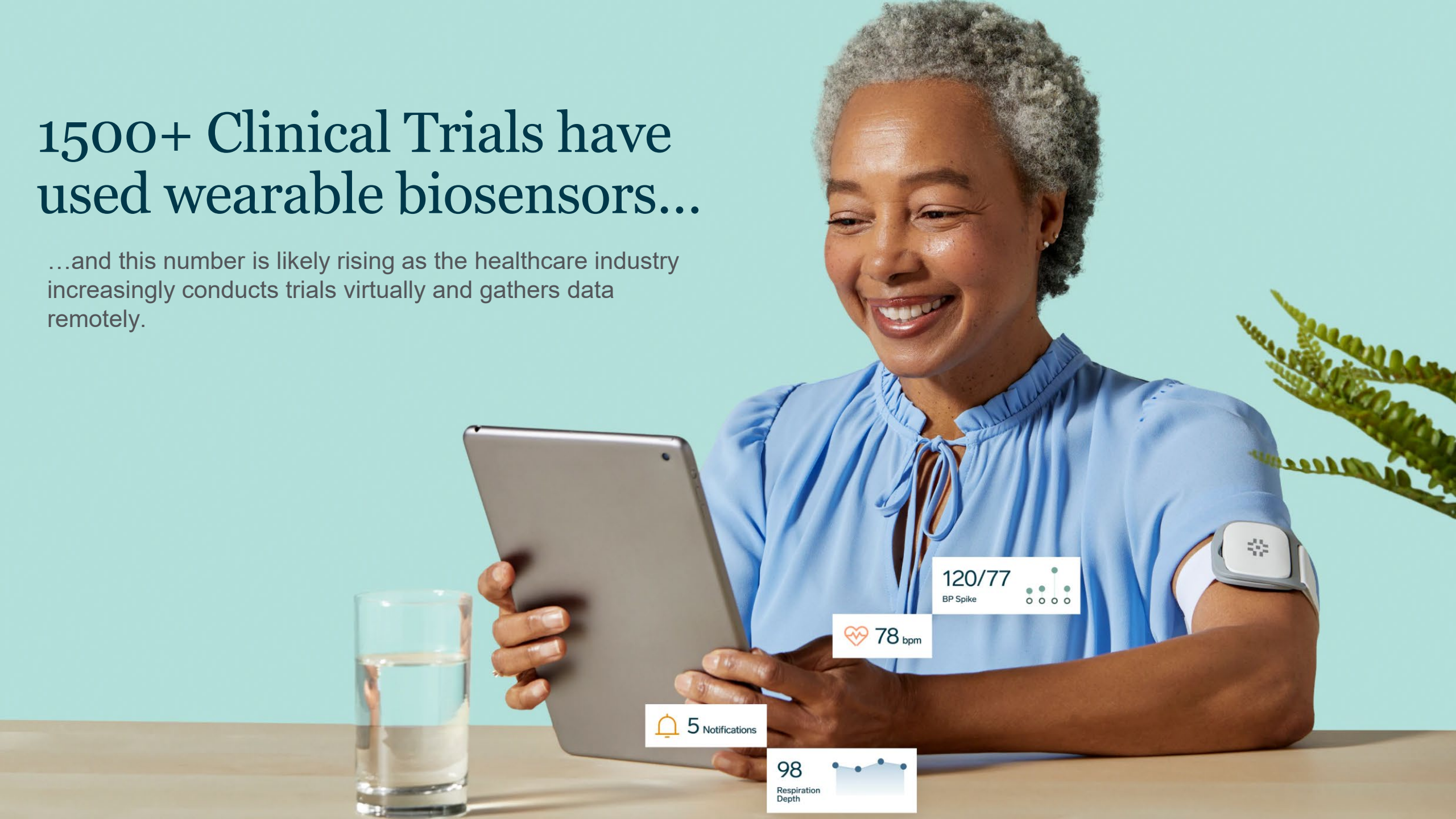
Connecting drug development to care delivery

Use of Other Sensor-Based DHTs in Clinical Trials for Drug Development

March 2023

1500+ Clinical Trials have used wearable biosensors…

…and this number is likely rising as the healthcare industry increasingly conducts trials virtually and gathers data remotely.



Opportunity: Wearable Biosensors (DHTs) in Clinical Trials

	Safety Monitoring & Patient Phenotyping	Novel Endpoints	Medication monitoring & Intervention	Patient enrollment & Retention in Clinical Trials
Application				
Benefits	▪ Early safety signal, dose and frequency adjustments, discontinuation of certain drug candidates ▪ Better understanding of mechanistic and pharmacological drug profile if combined with PK and wet lab test data	▪ Mobility as a measure of quality of life ▪ Sleep studies in the home settings for extended periods of time ▪ More sensitive measures than traditional clinical scales in movement disorders	▪ Improved adherence ▪ Informed decisions about dose adjustments ▪ Increased efficiency in post-market data collection	▪ Fewer obstacles to enroll in clinical trials ▪ Reduced burdens for patients to participate ▪ Increased patient outreach
Examples	▪ Vital sign, e.g., HR, RR, skin temperature, BP, and actigraphy ▪ CRS Detection in Oncology	▪ Actigraphy in Oncology & CV ▪ Pain Measurement post-intervention (Acute/Chronic)	▪ Drug intake reminder apps ▪ GDMT in Heart Failure	▪ Remote enrollment and consent apps ▪ Reminder apps about study procedures and clinical trial progress

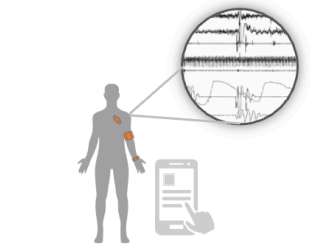
Izmailova, E.S., Wagner, J.A. and Perakslis, E.D., 2018. Wearable devices in clinical trials: hype and hypothesis. Clinical Pharmacology & Therapeutics, 104(1), pp.42-52.

Biovitals® Platform to support clinical trials

An end-to-end platform that combines FDA-cleared wearable biosensors, and analysis/interpretation software (SaMD) that enable continuous remote data collection, and digital endpoints to measure drug efficacy and safety.

Platform for Remote Data Collection & Analysis in Drug Trials

FDA 21 CFR, ISO 13485, SDLC, HIPAA, GDPR compliance

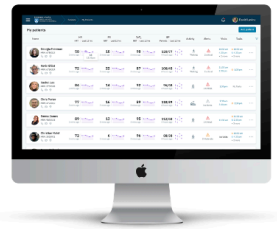


WEARABLE BIOSENSORS & COMPANION APP

- ALERT MANAGEMENT & INTERVENTIONS
- DETECTION OR PREDICTION OF A CLINICAL EVENTS
- MULTI-VARIATE PHYSIOLOGY ANALYSIS (DETECT DEVIATIONS FROM BASELINE)
- DISEASE SPECIFIC DIGITAL BIOMARKERS OR DIGITAL ENDPOINTS
- RAW BIOSENSOR PROCESSING & PHYSIOLOGY MONITORING

DATA LAKE

APIs
API Integrations into EDC/CTMS/Registry



INVESTIGATOR PLATFORM FOR MONITORING & INTERVENTION

Operational Infrastructure to support use of DHTs in Drug Trials

Logistics Support

Compliance Monitoring Technical Support

Safety Monitoring

In-Home Services

Picking the right sensors for your study…

As wearable biosensors proliferate, we have put together a framework to evaluate sensors based on various criteria (shown below) to be used in clinical studies – enabling us to pick the right sensor for the right patient population, ensuring higher compliance rate.

Example FDA-cleared Wearables

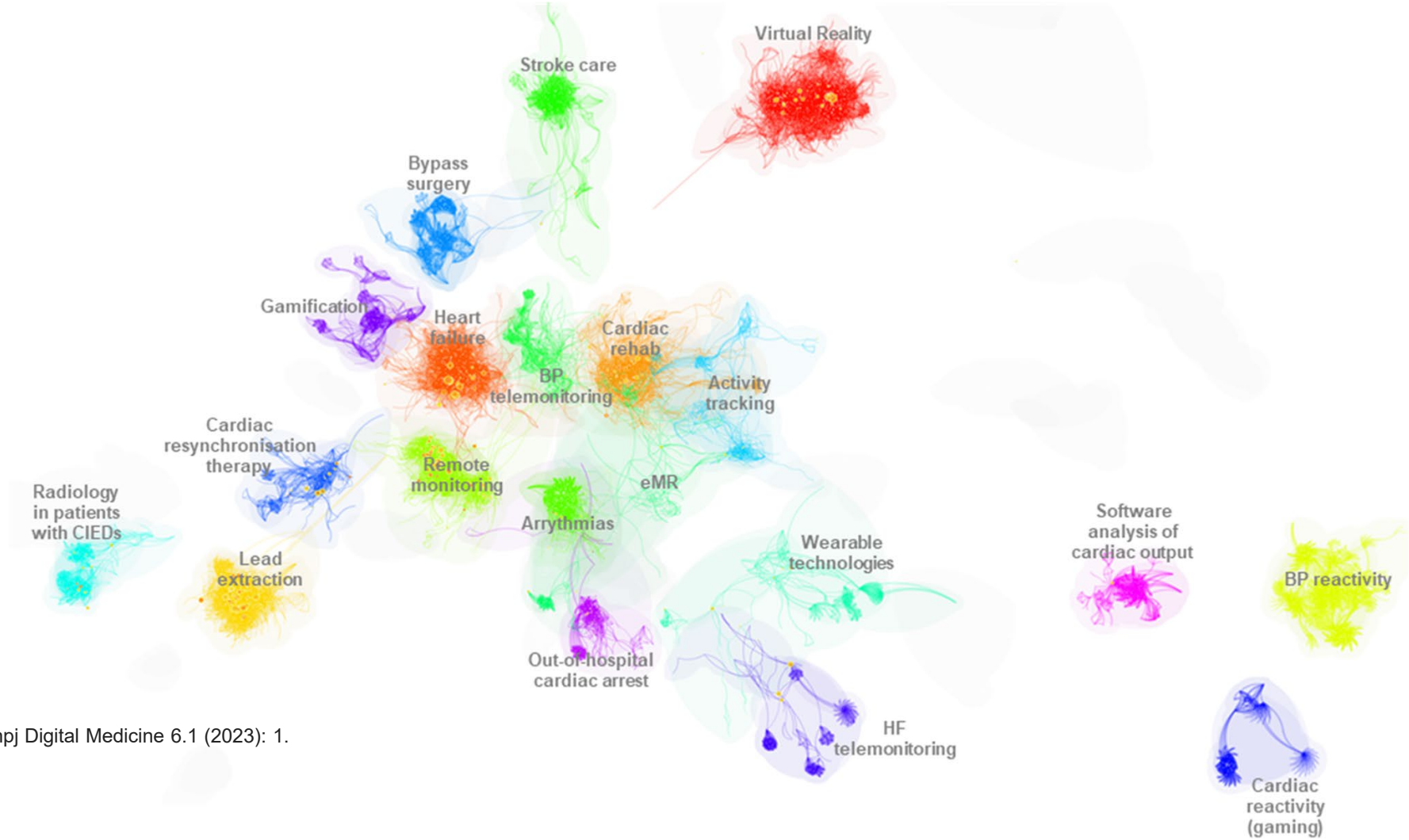
Everion
OMRON
VitalConnect
biobeat Medical Smartmonitoring
iHealth
Oxitone
empatica
Viatom
WelchAllyn

Sample Criteria focused on multi-parameter wearable biosensors

	Topic	Requirement
1	Raw Signals	ECG, PPG, Accelerometer, GSR, etc.
2	Vital signs	Heart Rate, Respiration rate, temperature, Blood Pressure, SpO2, Activity, etc…
3	Regulatory	FDA cleared; CE marked
4	Form Factor	Patch, wearable armband, wristband, Ring
5	Tech	BTLE 4.2+ compliant (FIPS 128 encryption)
6	Tech	Local device data storage (incase connection with phone is lost)
7	Tech	Continuous vitals data capture & transfer (some devices are only spot measurements)
8	Tech	SDK access with support (to have access to raw data and integrate with our App)
9	Data Quality	Evaluation of bench-top and clinical trial results for evaluation performance compared to gold standards
10	Manufacturability	Should have an existing manufacturing line and commenced commercial activity
11	Battery	Preferably rechargeable (at least 24 hrs life per charge)
12	Reusability	Ideally reusable, but disposable are also ok

Evolution of DHTs in Cardiovascular Research

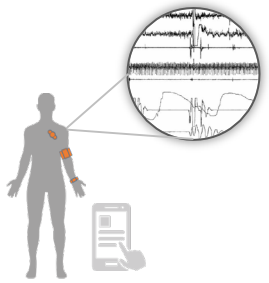
Birds-eye view of the research areas that digital technologies have been applied in cardiovascular medicine for Monitoring, Surrogate Endpoints, and Safety



Zwack, Clara C., et al. npj Digital Medicine 6.1 (2023): 1.

DHTs in CV drug trials for safety and efficacy

Using passively collected physiology data from wearable biosensors to derive digital endpoints and detect clinical events for safety and efficacy monitoring in cardiovascular drug trials.



WEARABLE BIOSENSORS & COMPANION APP

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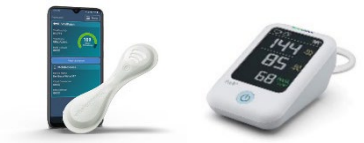
- RAW BIOSENSOR PROCESSING & PHYSIOLOGY MONITORING

Example CV Drug Trials	
Safety & Efficacy in HF patients (NCT03016325)	Safety & Efficacy of Etripamil (NCT03016325)
ECG Morphology change from baseline (QTc, QT, PR, QRS Duration)	Arrhythmia Detection using RhythmAnalytics®++ - PSVT, Sinus Rhythm
Changes in Vital Signs from baseline+: HR, RR, Temp, Activity	N/A
Dyspnea, Hypotension, Physical Function	N/A
ECG, HR, RR, Temp, BP	ECG + other vital signs



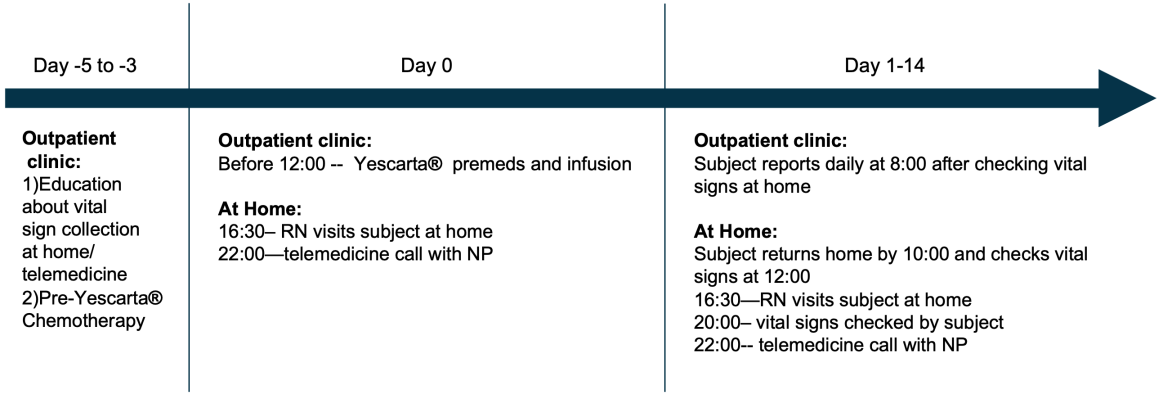
+ Biovitals® Analytics Engine (K183282): FDA 510(k) cleared SaMD to detect changes in baseline physiology

++ RhythmAnalytics® (K182344): FDA 510(k) cleared SaMD for detection of cardiac arrhythmias by beat-to-beat analysis

DHTs for Safety Monitoring

Cytokine release syndrome (CRS) Events

Chimeric Antigen Receptor (CAR) T Cell Therapy With YESCARTA in the Outpatient Setting (NCT05108805)



- Feasibility of treating participants with YESCARTA in the outpatient setting
- Continuous collection of physiology data from patients – Blood Pressure, Heart Rate, Respiration Rate, and Temperature
- Multi-variate analysis of continuous physiology signals to detect/predict CRS events
- Alert escalation and management – development of out-patient care protocols

DHTs for Safety Monitoring

Cytokine release syndrome (CRS) Events

Chimeric Antigen Receptor (CAR) T Cell Therapy With YESCARTA in the Outpatient Setting (NCT05108805)

Day -5 to -3	Day 0	Day 1-14
Outpatient clinic: 1)Education about vital sign collection at home/ telemedicine 2)Pre-Yescarta® Chemotherapy	**Outpatient clinic:** Before 12:00 -- Yescarta® premeds and infusion **At Home:** 16:30– RN visits subject at home 22:00—telemedicine call with NP	**Outpatient clinic:** Subject reports daily at 8:00 after checking vital signs at home **At Home:** Subject returns home by 10:00 and checks vital signs at 12:00 16:30—RN visits subject at home 20:00– vital signs checked by subject 22:00-- telemedicine call with NP

- Feasibility of treating participants with YESCARTA in the outpatient setting
- Continuous collection of physiology data from patients – Blood Pressure, Heart Rate, Respiration Rate, and Temperature
- Multi-variate analysis of continuous physiology signals to detect/predict CRS events
- Alert escalation and management – development of out-patient care protocols

DHTs for Novel endpoints

Pain Assessment

Objective Pain Measurement Using a Wearable Biosensor and a Mobile Platform in Patients With Endometriosis (NCT04318275)

- Numeric rating scale (NRS) are mainly used in clinical trials to determine the presence and severity of pain associated with endometriosis; however, they are subjective, containing recall bias, and can vary over time.
- Continuous collection of raw biosensor signals: PPG, Accelerometer, Galvanic Skin Response (GSR)
- Algorithms for feature extraction, and analysis to objectively quantify presence and severity of pain

The Healthcare Revolution At Home

Connecting Drug Development, Digital Health Tools, and Care Delivery at-scale!

Biofourmis

Thank you

Neeta Sharma

Vice President of Global Regulatory Affairs

Dexcom

Use of Digital Health Technologies (DHTs) to Support Clinical Trials for Drug Development and Review

Continuous Glucose Monitors

March 29, 2023

Continuous glucose monitoring (CGM) systems

- CGM systems regularly measure glucose levels in the interstitial fluid and send readings to display devices (such as receivers, smartphones, smart watches) or automated insulin delivery devices
- CGM systems measure glucose in the interstitial fluid either using a thin sensor filament that is inserted into the subcutaneous space (transcutaneous) or by insertion of the sensor itself into the subcutaneous tissue in the upper arm (ie, implantable)
- CGM systems offer the opportunity to observe and follow glucose levels in real-time for an extended period yielding insights for people with diabetes, clinicians, researchers, and others
- Provide remote monitoring features and capabilities including electronic health record (EHR) integration

Transcutaneous*

Implantable*

*Images are not to scale

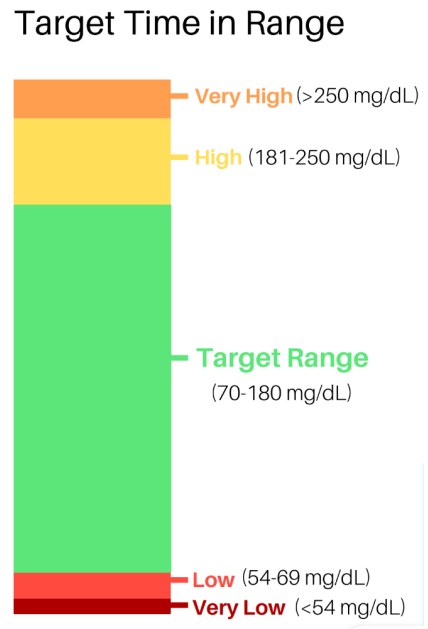
Metrics from a CGM

CGM devices produce additional useful metrics beyond A1c, such as

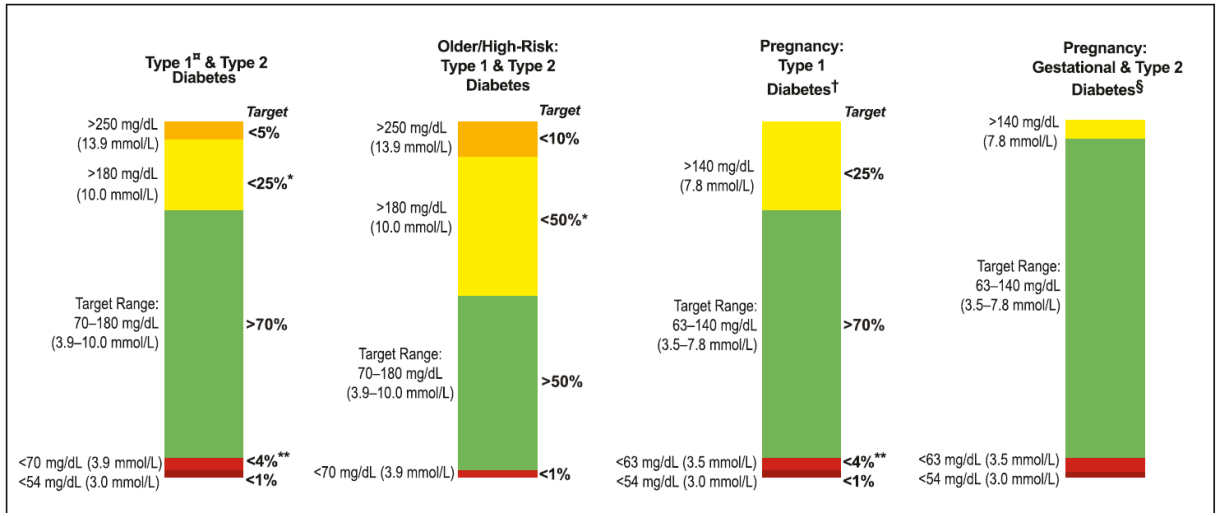
- Mean glucose (measured by SD or coefficient of variation)
- Patterns and daily glucose highs, lows
- Glycemic variability
  - time in range (TIR)
  - time below range (TBR)
  - time above range (TAR)
- Estimated A1C(eA1C)
- Ambulatory glucose profile (AGP)

What is Time In Range (TIR)?

- Time in Range (TIR) is a helpful metric that can provide people with diabetes with actionable information to improve their health
- The most common target range for people with diabetes is 70-180 mg/dL, however target range may differ for certain groups such as pregnant women and the elderly
- The goal for people with diabetes is to spend more “time-in-range” each day



Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-603



Clinical Implications of TIR : Neuropathy

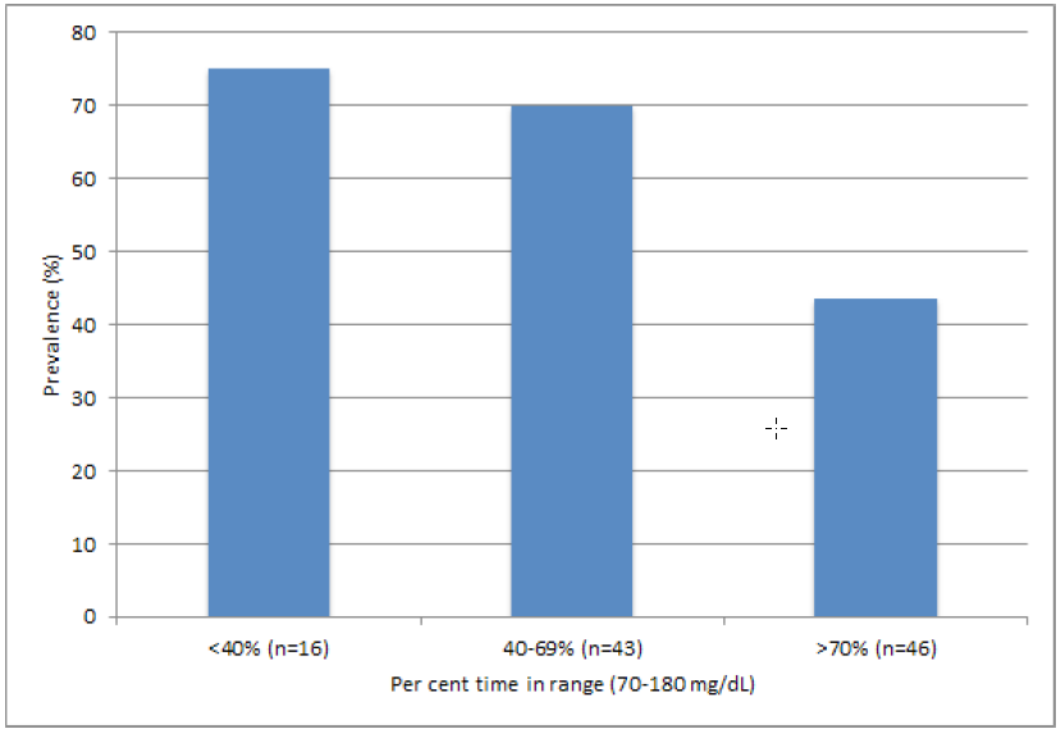


Figure 2 Prevalence of distal peripheral neuropathy according to time in range asceratined by continuous glucose monitoring.

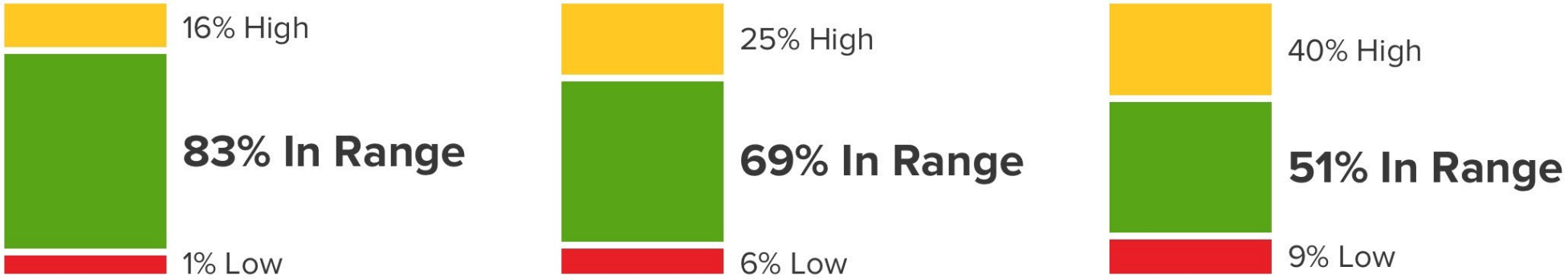
(1) Mayeda, 2020. Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease. *BMJ Open Diabetes Res Care.* 8

(2) Beck, 2019. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. *Diabetes Care.* 42(3):400-405.

(3) Lu, 2021. Time in Range in Relation to All-Cause and Cardiovascular Mortality in Patients With Type 2 Diabetes: A Prospective Cohort Study. *Diabetes Care.* 44(2):549-555.

Moving Beyond A1c

Time in Range (70-180 mg/dL) for 3 Patients



- A1C has been used to demonstrate the efficacy of interventions
- However it is not a comprehensive marker of overall glycemia
- It does not provide information of day-to-day glycemic control, or may mask significant issues such as clinically important hypoglycemia

All 3 patients had the same A1c

International consensus on Time in Range

- **2017**, International Consensus on the Use of the Continuous Glucose Monitoring standardizing the use of CGM and recommendations together with A1c
- **2019**, the International Consensus on Time in Range published a report standardizing CGM metrics, including TIR
- **2020**, TIR was added to the ADA's Standards of Care in Diabetes for the first time
- **2023**, the ADA's Standards of Care in Diabetes[2,3] offer the following recommendations:
  - **Recommendation 6.1** - Assess glycemic status (A1C or other glycemic measurement such as time in range or glucose management indicator) at least two times a year in patients who are meeting treatment goals
  - Recommendation 6.2 - Assess glycemic status at least quarterly and as needed in patients whose therapy has recently changed and/or who are not meeting glycemic goals.
  - Recommendation 7.12 - CGM "should be offered" for basal-only patients
  - Recommendation 7.15 - people with diabetes on MDI or CSII "should have uninterrupted access" to CGM

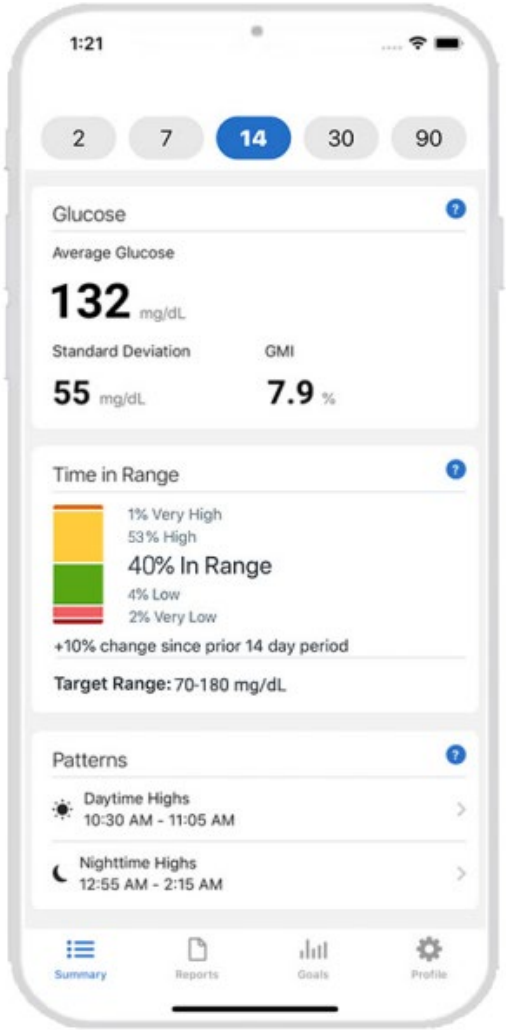
1 Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, Cobelli C, Dassau E, DeVries JH, Donaghue KC, Dovc K, Doyle FJ 3rd, Garg S, Grunberger G, Heller S, Heinemann L, Hirsch IB, Hovorka R, Jia W, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Levine B, Mayorov A, Mathieu C, Murphy HR, Nimri R, Nørgaard K, Parkin CG, Renard E, Rodbard D, Saboo B, Schatz D, Stoner K, Urakami T, Weinzimer SA, Phillip M. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019 Aug;42(8):1593-1603. doi: 10.2337/dci19-0028. Epub 2019 Jun 8. PMID: 31177185; PMCID: PMC6973648.
2 ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Leon J, Lyons SK, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Gabbay RA, on behalf of the American Diabetes Association. 6. Glycemic Targets: Standards of Care in Diabetes-2023. Diabetes Care. 2023 Jan 1;46(Suppl 1):S97-S110. doi: 10.2337/dc23-S006. PMID: 36507646; PMCID: PMC9810469.
3 ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Leon J, Lyons SK, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Gabbay RA, on behalf of the American Diabetes Association. 7. Diabetes Technology: Standards of Care in Diabetes-2023. Diabetes Care. 2023 Jan 1;46(Suppl 1):S111-S127. doi: 10.2337/dc23-S007. PMID: 36507635; PMCID: PMC9810474.

Use of CGM in clinical trials and research

- CGM is increasingly becoming the standard of care in people with type 1 diabetes
- CGM device provide accurate data in addition to convenience for researchers and study subjects
- Additional information provided by new CGM technologies provides relevant, reliable outcome measures for people living with type 1 diabetes
- Interest in the use of CGM in clinical trials is growing
- An analysis published in 2021, showed an increase in CGM usage in clinical trials over time.
    - The authors considered “2,032 clinical trials of 40 antihyperglycemic therapies currently on the market with a study start date between January 2000 and December 2019.”
    - In 2005, less than 5% of these trials used CGM, by 2019, 12.5% did.
- Number of clinical trials which include CGM quadrupled since 2015 going from 26 trials in 2015 to 101 trials in 2021.

https://www.medpace.com/wp-content/uploads/2022/12/Whitepaper-Benefits-and-Challenges-of-Continuous-Glucose-Monitoring-in-Clinical-Trials.pdf

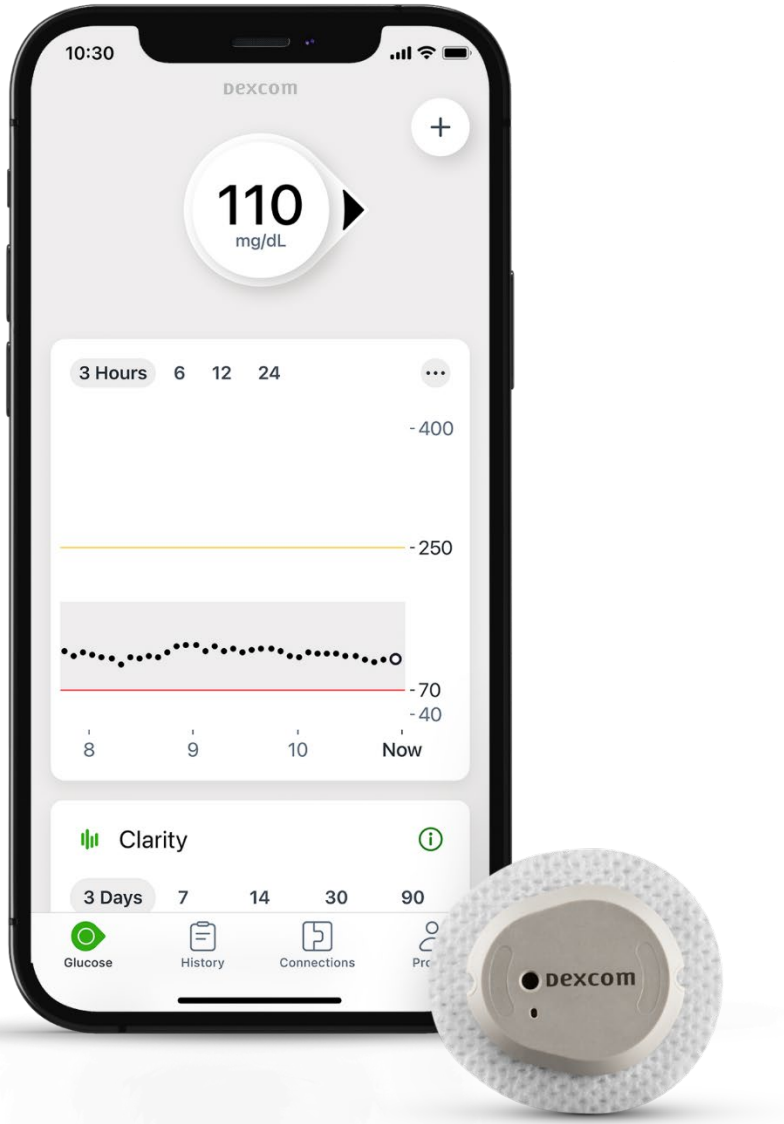
Time in Range as an outcome measure



- TIR has been validated as an outcome measure for clinical Trials complementing other components of glycemic control like A1c
- CGM can detect unrecognized hypoglycemia - an important benefit for use in clinical trials
- International consensus has accepted that a change of at least 5 percentage points in time in range is clinically meaningful for an individual participant
- InRange is the first randomized controlled trial to use continuous glucose monitoring (CGM)-based time-in-range (TIR) as a primary efficacy endpoint to compare second-generation basal insulin (BI) analogs insulin glargine (Gla-300) and insulin degludec (IDeg-100) in adults with type 1 diabetes (T1D).

CGM device selection for use in clinical trials

1. Technical Specifications
   - Warm up time, calibration (factory, code, 1x/day) wear period, ease of use
2. Performance
   - Researchers should review accuracy data before selecting a device
3. Special considerations
   - Blinded mode, alerts and alarms, data extraction capability
4. Clinical study considerations
   - Clinical trial personnel and participants should be aware of drug interferants for selected CGM device
   - Same brand and model for entire study, identified in methodology
   - For isCGM, participants must scan at least 3 times per day and at least once every 8 hours
   - For CGMs that require calibration – participants should be provided same model of BGM; burden of BGM can affect user compliance



SURPASS-3 sub-study: Tirzepatide associated with higher TIR than insulin degludec in T2D

ARTICLES | VOLUME 10, ISSUE 6, P407-417, JUNE 2022

Efficacy of once-weekly tirzepatide versus once-daily insulin degludec on glycaemic control measured by continuous glucose monitoring in adults with type 2 diabetes (SURPASS-3 CGM): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial

Tadej Battelino, MD • Richard M Bergenstal, MD • Angel Rodríguez, MD • Laura Fernández Landó, MD • Ross Bray, PhD • Zhentao Tong, PhD • et al. Show all authors

Published: April 22, 2022 • DOI: https://doi.org/10.1016/S2213-8587(22)00077-8 • Check for updates

Lilly

Lilly's tirzepatide led to greater time in range compared to insulin degludec in adults with type 2 diabetes in SURPASS-3 CGM sub-study

September 30, 2021

Participants taking highest dose of tirzepatide experienced 91.2% time in range (71-180 mg/dL) and 72.6% time in tight target range (71-140 mg/dL)
CGM sub-study achieved its primary and secondary endpoints

INDIANAPOLIS, Sept. 30, 2021 /PRNewswire/ -- All three tirzepatide doses led to more time in tight target range (71-140 mg/dL), improved glycemic variability and numerically less time in hypoglycemia compared to titrated insulin degludec in adults with type 2 diabetes in a continuous glucose monitoring (CGM) sub-study[1] of Eli Lilly and Company's (NYSE: LLY) phase 3 SURPASS-3 clinical trial. The CGM sub-study was presented today at the 57th European Association for the Study of Diabetes (EASD) Annual Meeting in an EASD-sponsored symposium.

The international consensus for time in range recommends a target of >70% time in range (70-180 mg/dL) for most people with diabetes as well as a target of <4% time below range 70 mg/dL and <25% time above range 180 mg/dL.[2] In an exploratory endpoint of this CGM sub-study, participants taking tirzepatide 15 mg experienced 91.2% time in range (71-180 mg/dL) at 52 weeks.

"The CGM data collected through this SURPASS-3 sub-study show that tirzepatide helped participants have less variability in their blood glucose levels throughout the day, including spending less time below target range and more time in a tighter target range reflecting a normal blood glucose range," said Richard Bergenstal, M.D., Executive Director of the International Diabetes Center at Park Nicollet. "Improving glycemic variability, increasing time in range and reducing time below range are important metrics in the management of type 2 diabetes because they reflect glucose control throughout the day, offering context beyond the three-month average of A1C."

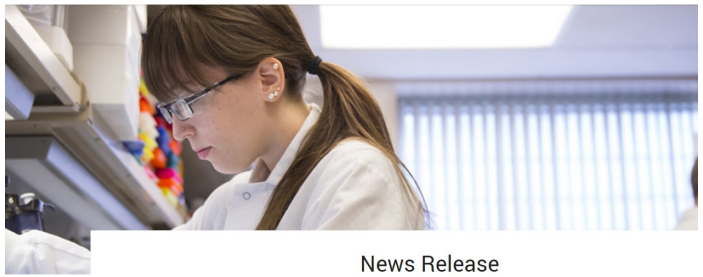
Tirzepatide is a novel investigational once-weekly dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that integrates the actions of both incretins into a single molecule, representing a new class of medicines being studied for the treatment of type 2 diabetes.

SURPASS-3 was a 52-week, multi-center, randomized, phase 3, open-label trial evaluating the efficacy and safety of tirzepatide 5 mg, 10 mg and 15 mg compared to titrated insulin degludec[i] in adults with type 2 diabetes who have inadequate glycemic control on stable doses of metformin with or without an SGLT-2 inhibitor. Study participants were insulin-naïve and had a mean duration of diabetes of 8.4 years, a baseline A1C of 8.17 percent and a baseline weight of 94.3 kg.

In the SURPASS-3 CGM sub-study, a subpopulation of 243 participants wore a CGM for 7 to 10 days at baseline, at 24 weeks and at 52 weeks to evaluate the effect of tirzepatide compared to insulin degludec on time in the hyper- and hypoglycemic range and on glycemic variability. Glycemic variability was measured during 24-hour periods by several measures, including the coefficient of variation (CV).

The CGM sub-study achieved its primary and secondary endpoints. Specifically, at 52 weeks, the primary endpoint showed that participants taking tirzepatide:

- Spent 72.6% of the 24-hour period in tight target range (71-140 mg/dL) for pooled 10 mg and 15 mg arms, an average of approximately six more hours than those taking insulin degludec (48.0%).



News Release

Lilly's tirzepatide led to greater time in range compared to insulin degludec in adults with type 2 diabetes in SURPASS-3 CGM sub-study

September 30, 2021

In substudy of the SURPASS-3 trial for tirzepatide:

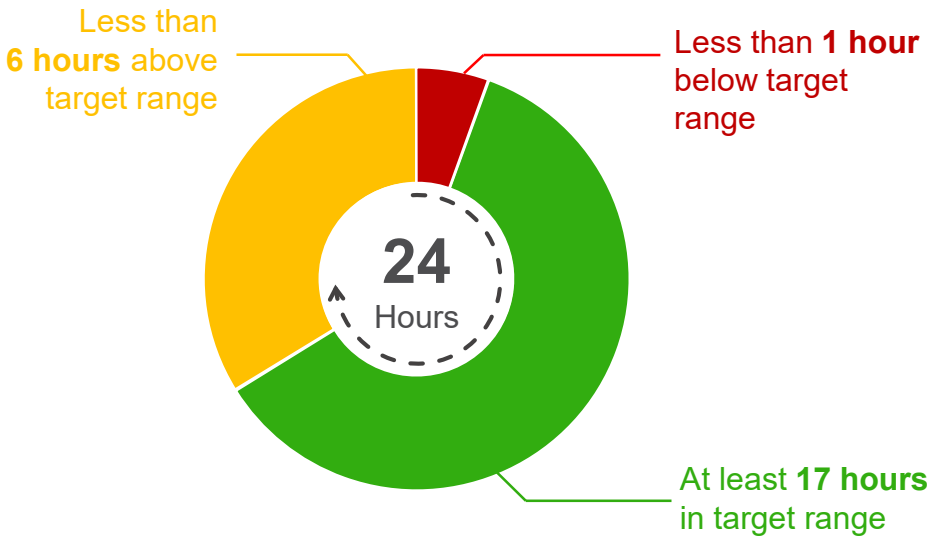
- Tirzepatide high-dose group had 91.2% TIR vs 75% TIR for insulin degludec group

Challenges when using CGM devices

1. Access to CGM
2. Study design challenges
3. Data collection and storage
4. Prior use of CGM in Clinical Practice
5. Training study participants

Conclusion

- CGM offers many potential benefits in the development of medical products
  - *Continuous, real time, accurate*
  - *Measure novel features such as TIR*
  - *Offer remote monitoring capabilities*
- Prospective and randomized controlled clinical studies in diabetes, especially with new pharmaceutical agents, can benefit from incorporating CGM devices
- CGM can offer clinically relevant outcome measures to complement established A1c outcomes
- Consensus statements provide clear guidance regarding use of CGM devices for incorporation into glucose management protocols



dexcom

Thank you

https://www.dexcom.com/en-us

Dina Katabi

President and Co-Founder

Emerald Innovations

Emerald: From Wearables to Invisibles!

Dina Katabi, PhD
President and Co-Founder, Emerald Innovations Inc.
Thuan and Nicole Pham Professor, MIT

EMERALD

Data-driven Drug Development

- Continuous clinical data from patients' homes

- Objective and sensitive biomarkers for difficult diseases

But how to collect continuous clinical data from the sick and old?

BREATHING

SLEEP

Emerald AI

SCRATCHING

GAIT SPEED

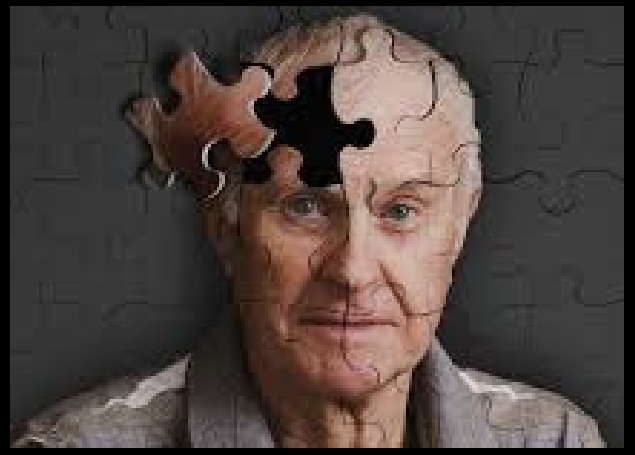
Behavioral Symptoms, Eating, Toileting, etc.

Sleep Studies and Publications

- Mingmin Zhao, Shichao Yue, Dina Katabi, Tommi Jaakkola, Matt Bianchi. Learning Sleep Stages from Radio Signals: A Conditional Adversarial Architecture, International Conference on Machine Learning (ICML'17)
- Chen-Yu Hsu, Aayush Ahuja, Shichao Yue, Rumen Hristov, Zachary Kabelac, Dina Katabi. Zero-Effort In-Home Sleep and Insomnia Monitoring using Radio Signals, ACM International Joint Conference on Pervasive and Ubiquitous Computing (Ubicomp) 2017.
- Third party validation and comparison to PSG in UMASS Sleep Lab.

Emerald is an exploratory endpoint in clinical trials

Alzheimer's



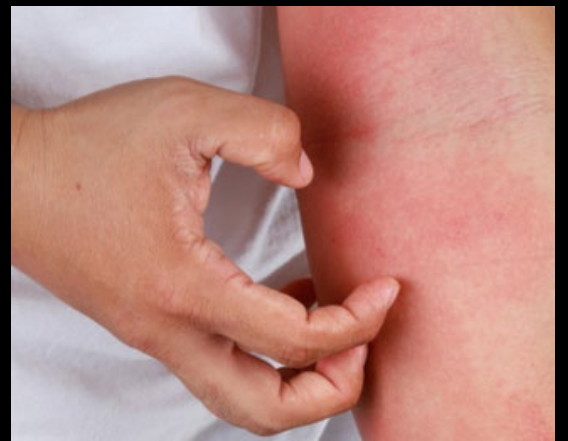
Parkinson's

FSHD

Crohn's

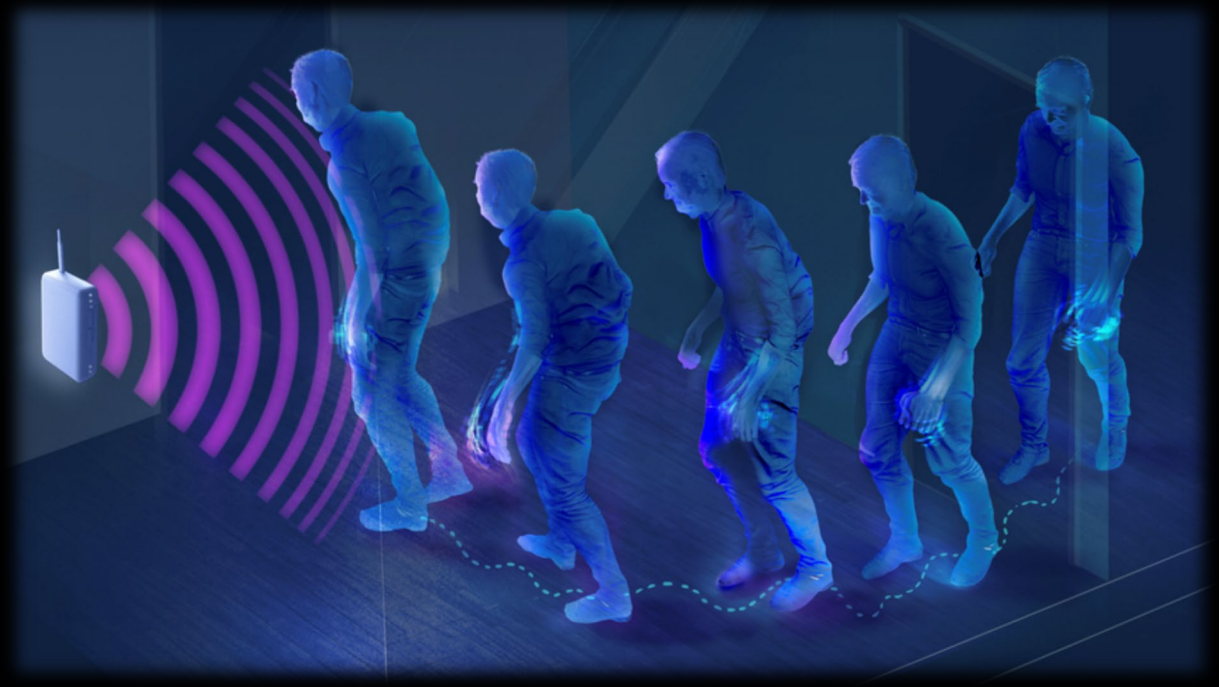
COVID-19

Atopic Dermatitis

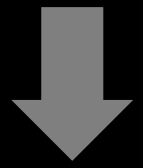


Parkinson’s Disease

In Science Translational Medicine Journal, September, 2022



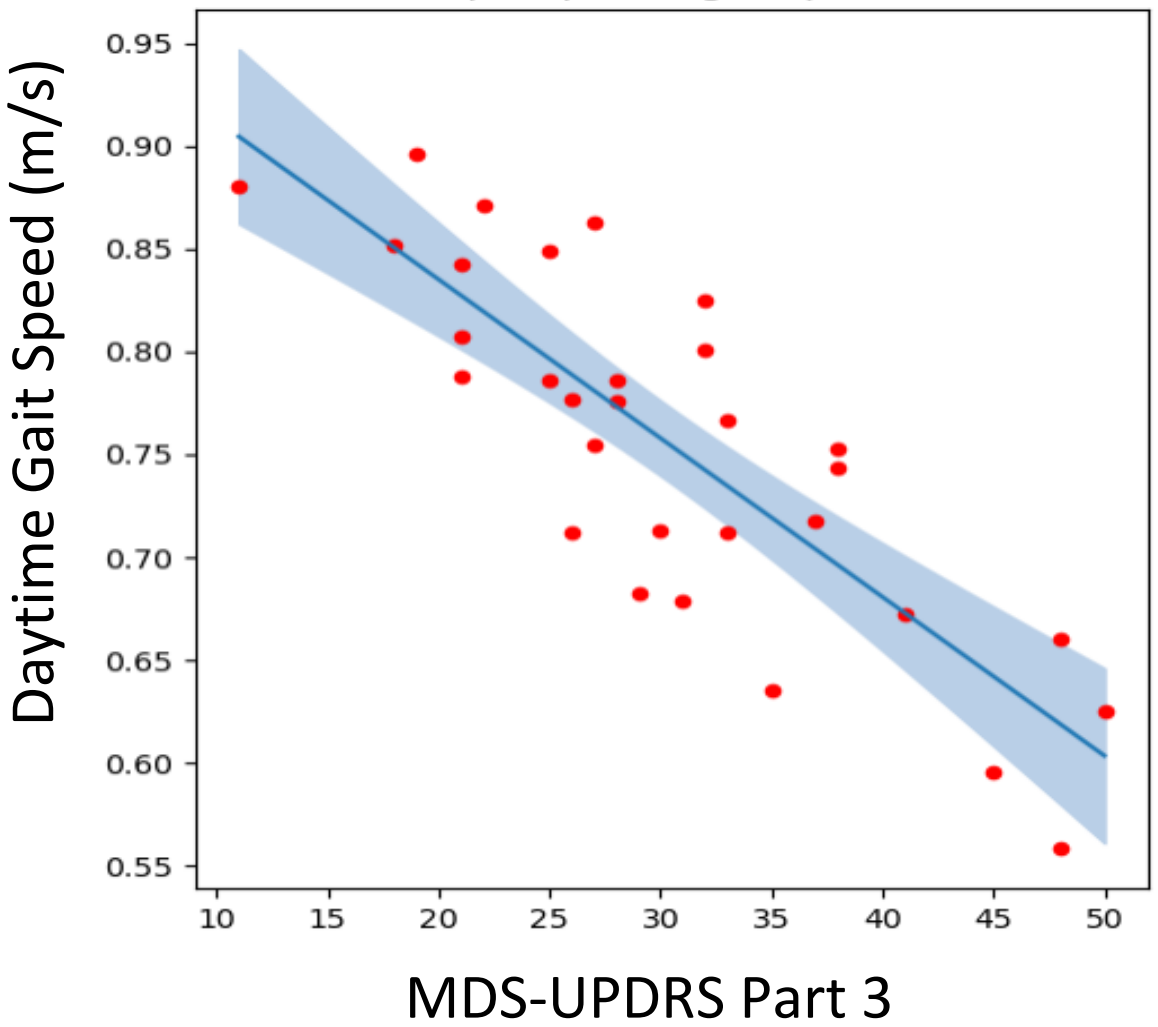
- Population: 50 participants (34 PD and 16 Controls)
- Monitored at home for up to one year



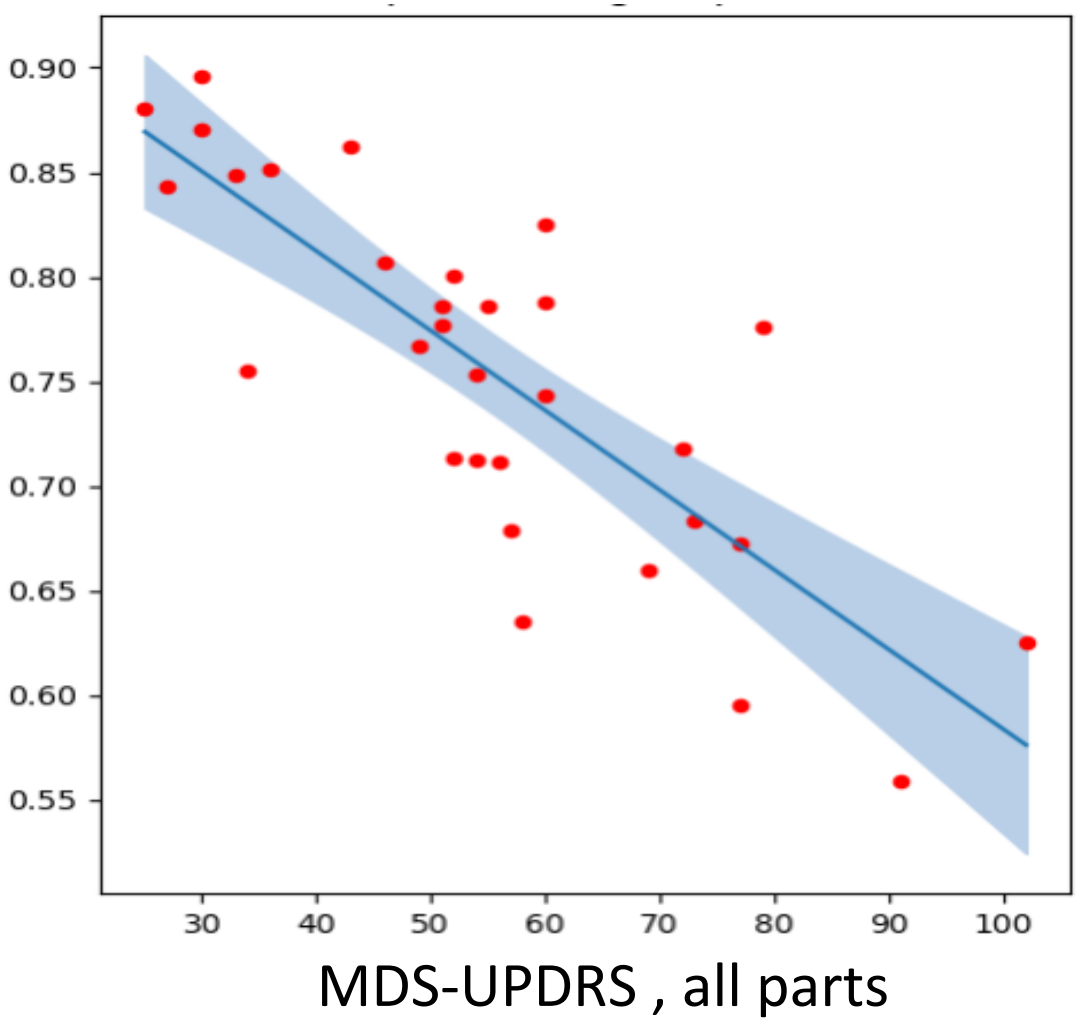
Over 200,000 unscripted gait measurements

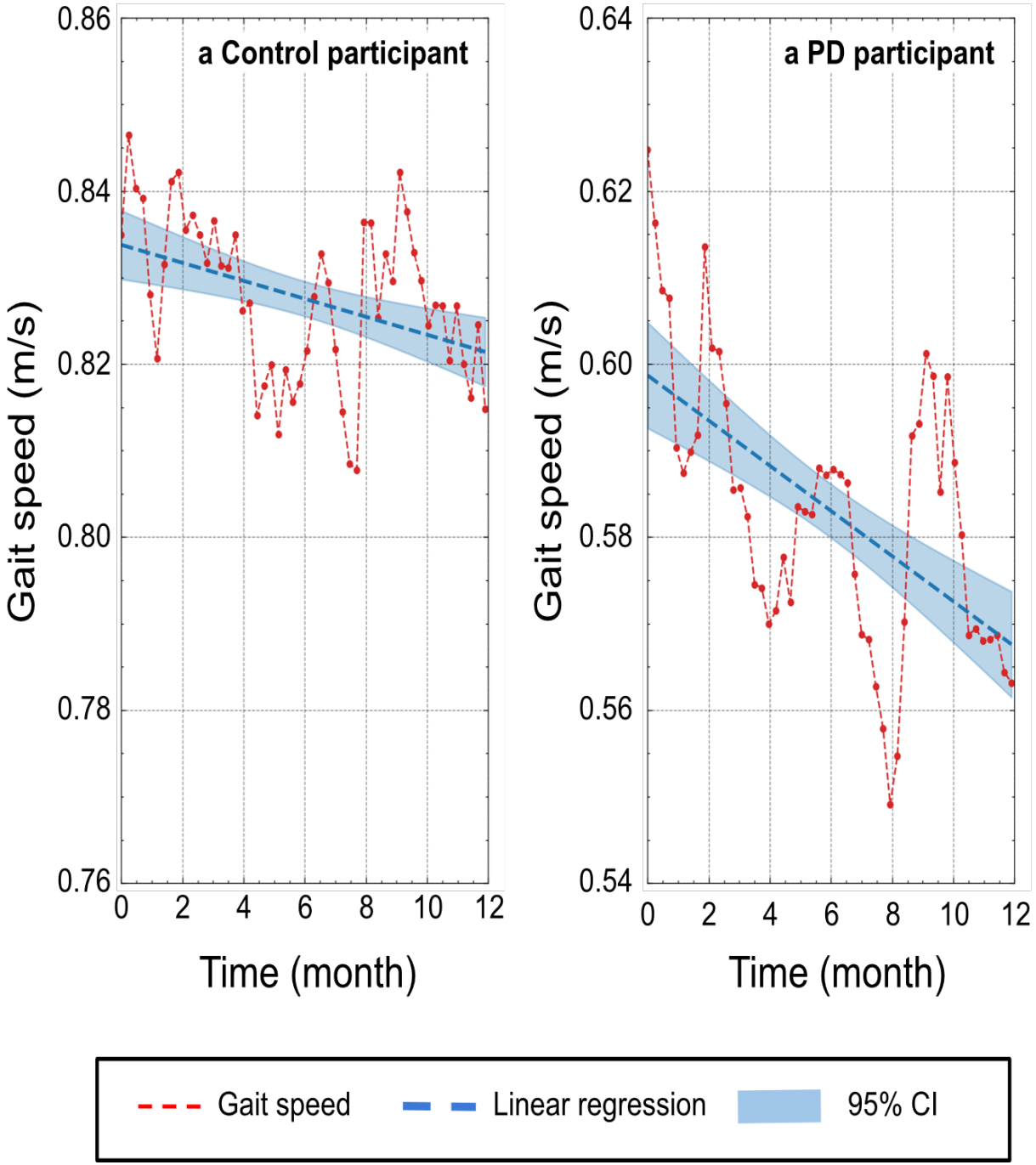
In-Home Gait Speed vs. MDS-UPDRS

r = -0.83, p < 0.001

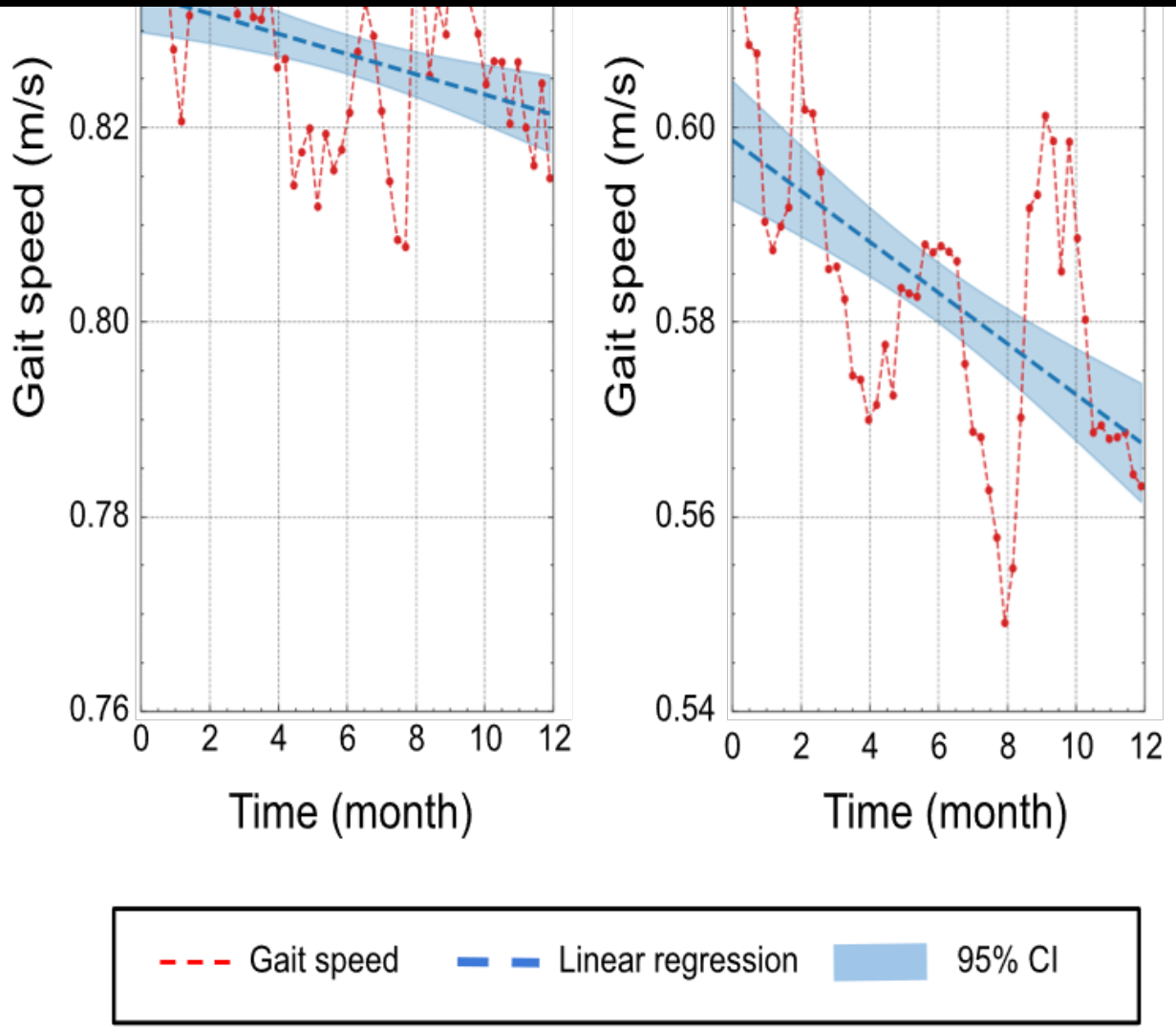


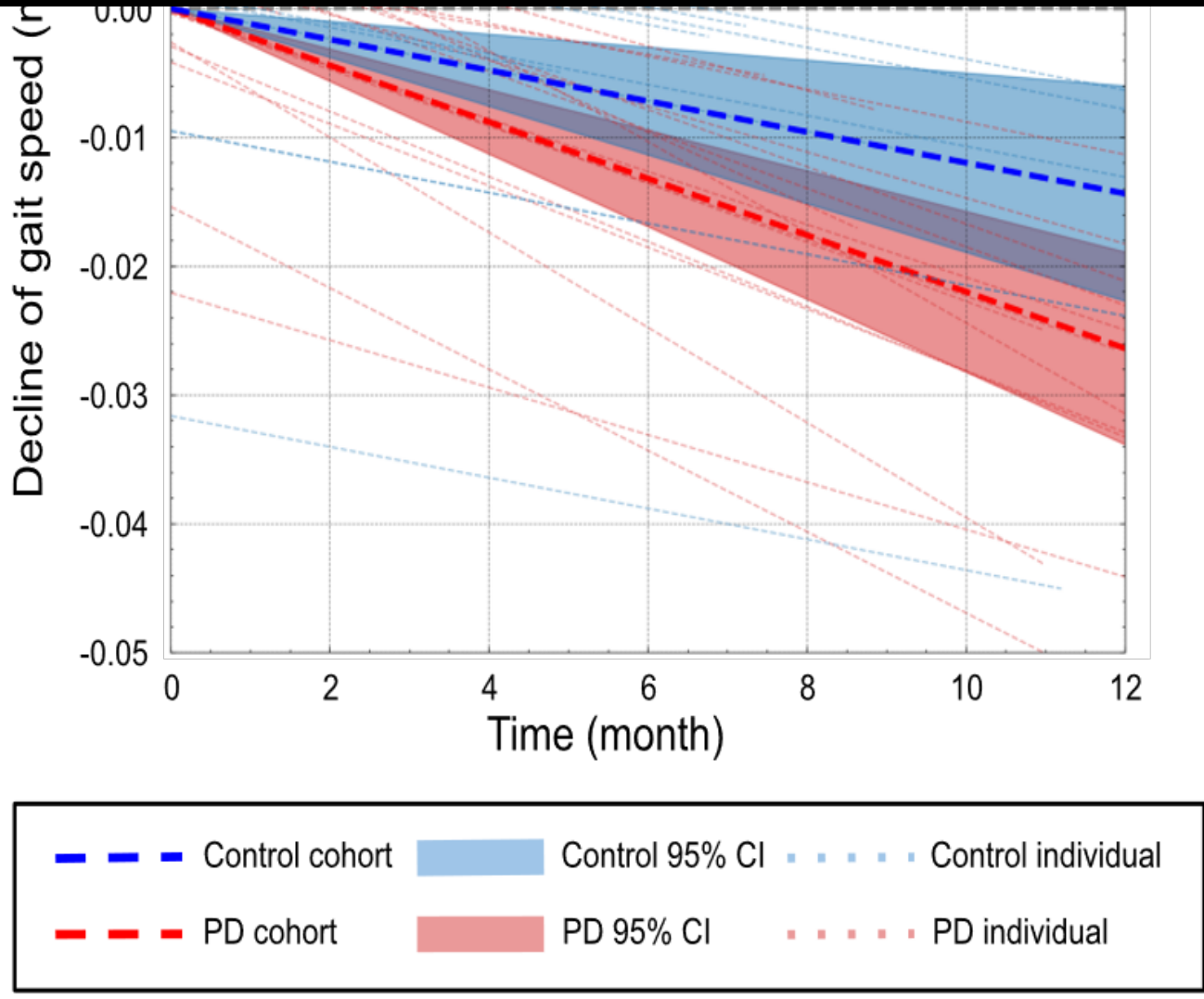
r = -0.81, p < 0.001



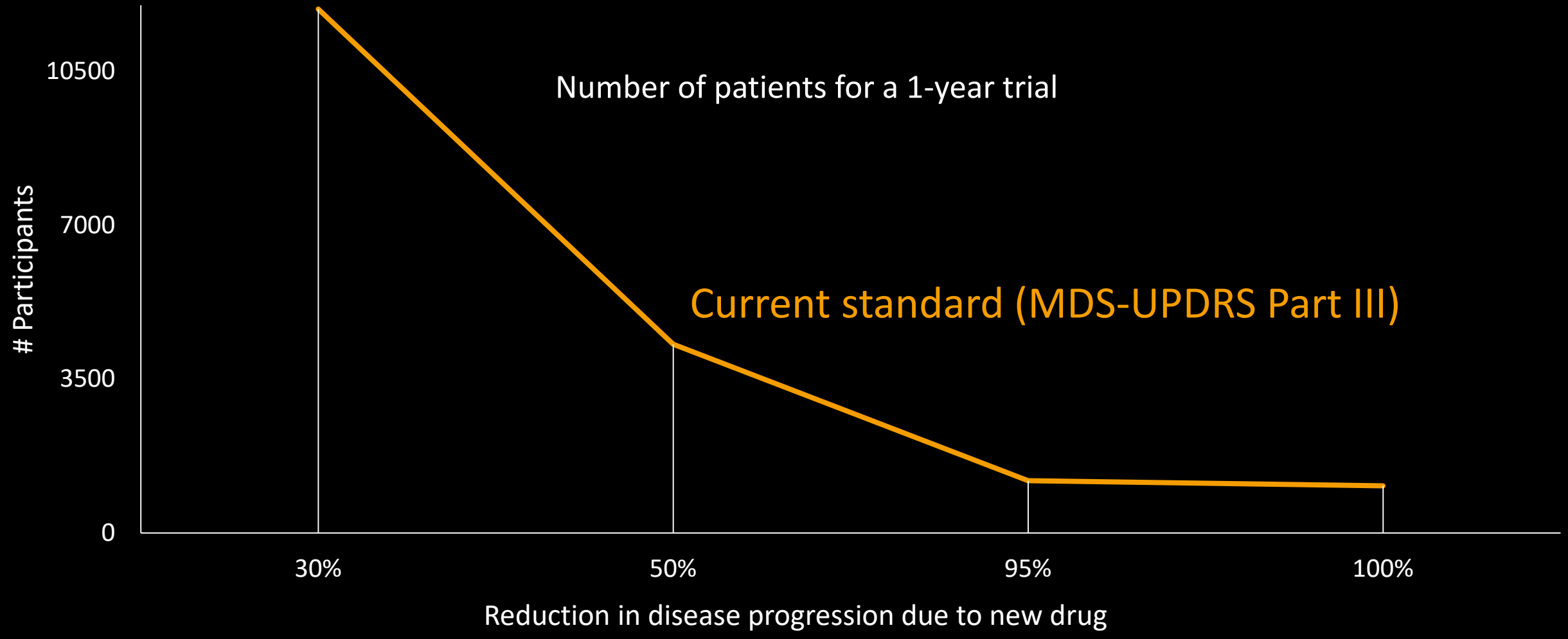

a Control participant
a PD participant
Gait speed (m/s)
Time (month)
0.86
0.84
0.82
0.80
0.78
0.76
0.64
0.62
0.60
0.58
0.56
0.54
0
2
4
6
8
10
12
Gait speed
Linear regression
95% CI

Gait decline is a statistically robust progression marker (p=0.04)
→ Major reduction in sample size and trial duration

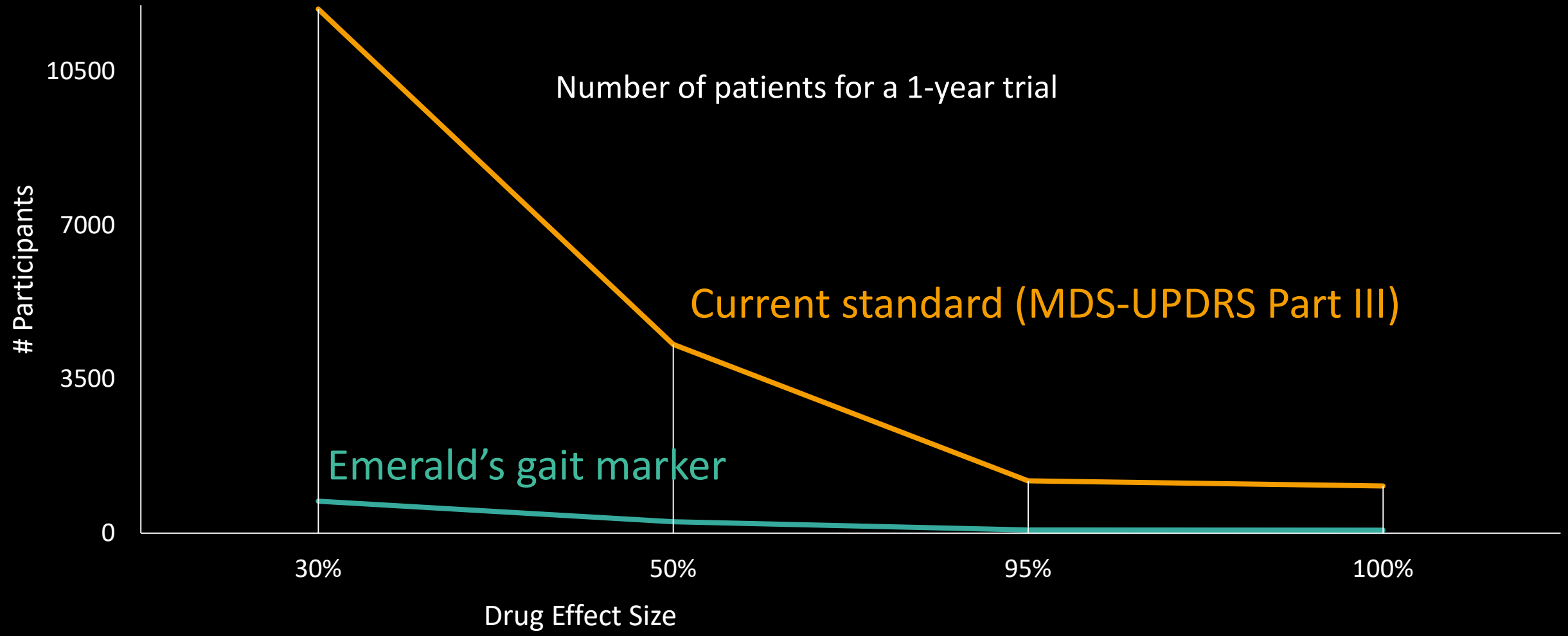




Impact on clinical trials (statistics based on PPMI)



Impact on clinical trials (statistics based on PPMI)



Objective and Sensitive Measure of Itch

Today pharma asks patients to rate their itch on a scale of 0 to 10

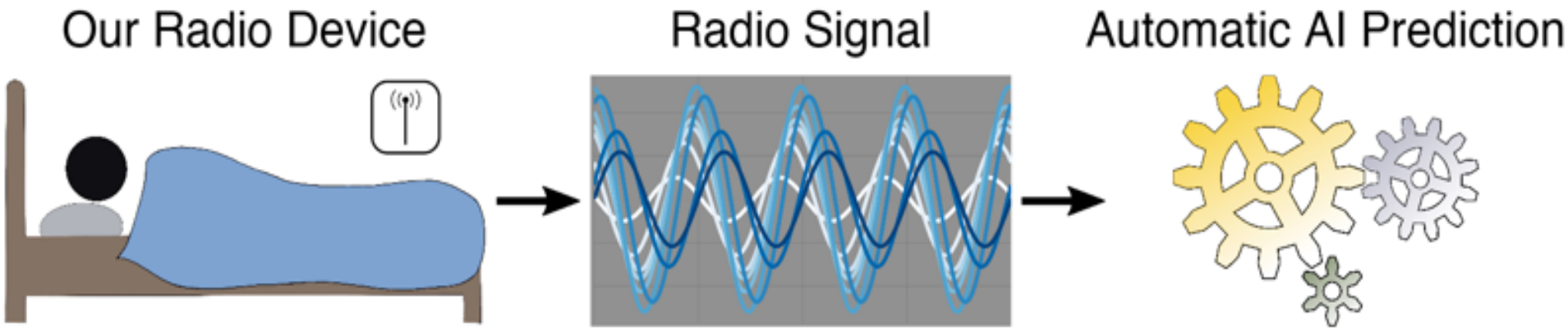
Collaboration with Dr. Brian Kim, at Mount Sinai

Measuring Scratching with Cameras vs. Radio Signals

(a) Measuring Scratching Using Video Cameras.

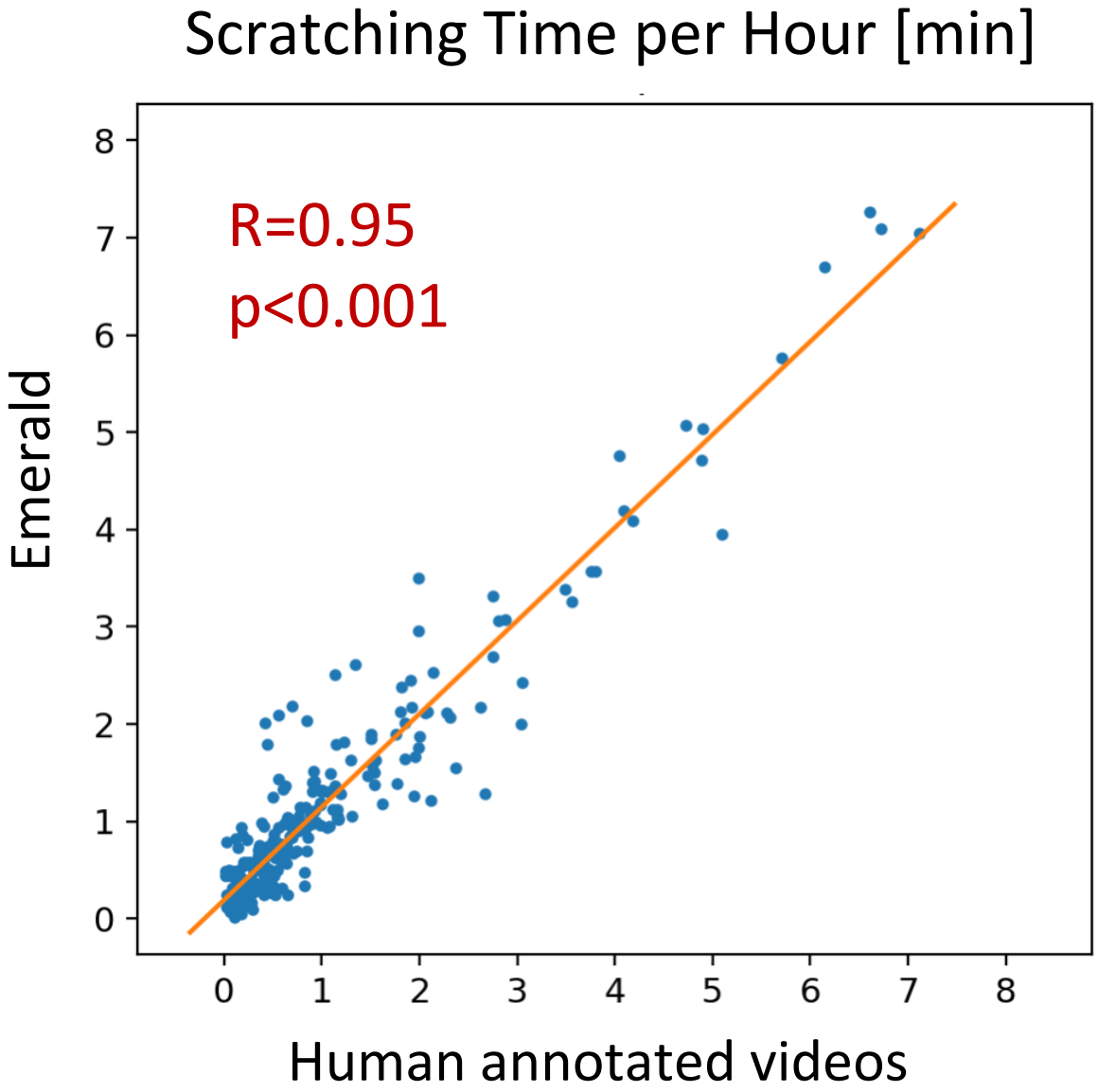
Measuring Scratching with Cameras vs. Radio Signals

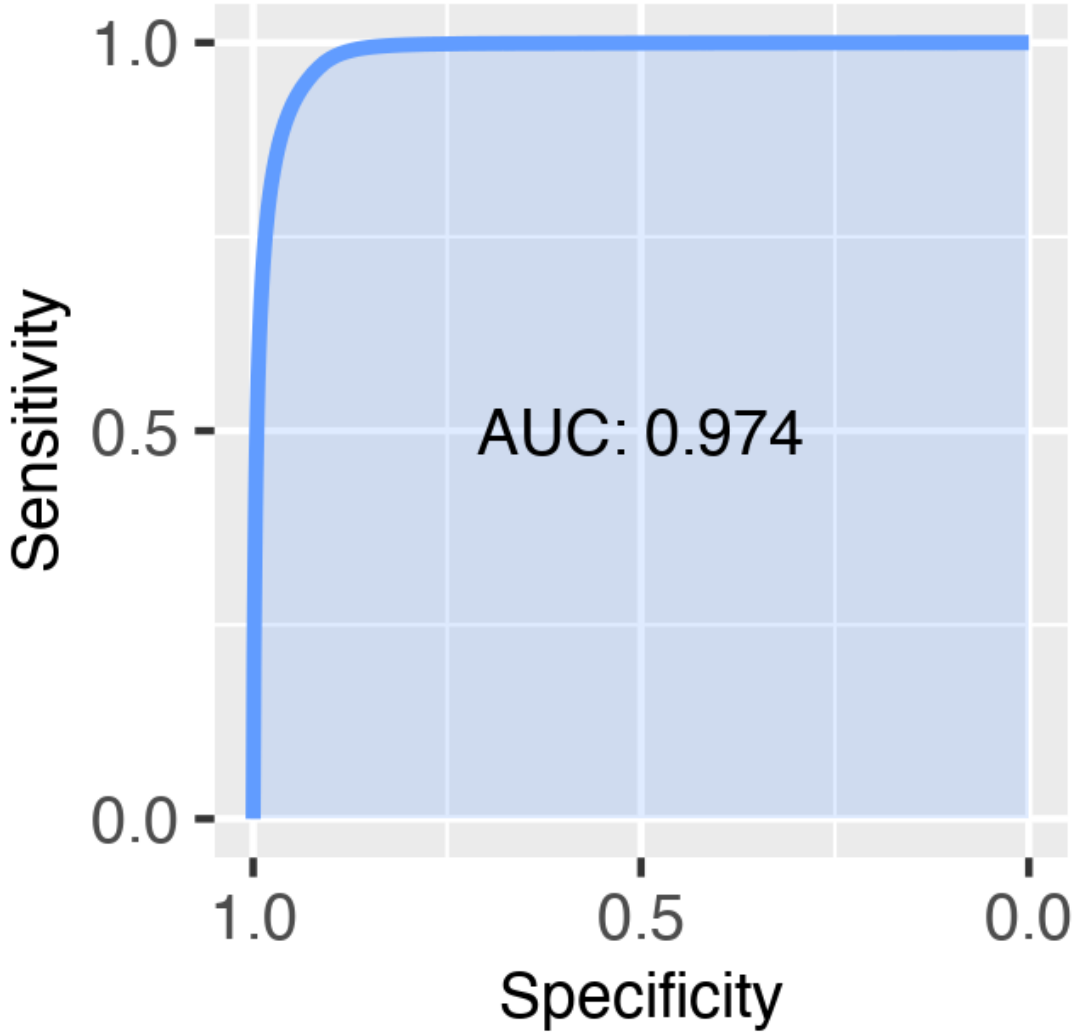
(a) Measuring Scratching Using Video Cameras.



(b) Measuring Scratching Using Radio Signals And Machine Learning.

Scratching Measured by Emerald vs. Videos






Emerald: From Wearables to Invisibles!
dina@emeraldinno.com

Session 4: Use of Other Sensor-Based DHTs in Clinical Trials for Drug Development

Moderator:

- Jennifer Goldsack, Digital Medicine Society

Presentations:

- Kuldeep Singh Rajput, Biofourmis
- Neeta Sharma, Dexcom
- Dina Katabi, Emerald Innovations

Break

We will be back momentarily.

The next panel will begin at 3:50 p.m. (U.S. Eastern Time)

Session 5: Key Priorities for the Advancement and Integration of DHTs into Clinical Trials for Drug Development

3:50 pm – 4:35 pm EST

Session 5: Key Priorities for the Advancement and Integration of DHTs into Clinical Trials for Drug Development

Moderator:

- Christina Silcox, Duke-Margolis Center for Health Policy

Panelists:

- Leonard Sacks, US Food and Drug Administration
- Yuge Xiao, Michael J Fox Foundation
- Danielle Friend, Janssen Pharmaceuticals
- Rebecca Nebel, PhRMA

Closing Remarks | Day 2

Marianne Hamilton-Lopez

Senior Research Director, Duke-Margolis Center for Health Policy

Thank You!

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