Selection of and Evidentiary Considerations for Wearable Devices and Their Measurements for Use in Regulatory Decision Making:

Recommendations from the ePRO Consortium

Moderated by: Chris Watson, PhD (ERT)

Presented by: Bill Byrom, PhD (ICON)

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(ERT)

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Biographies

Chris Watson, PhD

Chris Watson, PhD, Director of Product Strategy at Digital Patient Solutions, ERT. He has a PhD in Behavioural Neuropharmacology and is an experienced product strategist with 18 years' experience in the delivery of business and consumer based solutions, the last 8 of which have been focused in the clinical technology industry.

Bill Byrom, PhD, is Senior Director of Product Innovation at ICON, UK. He has worked in the pharmaceutical industry for over 25 years in a variety of roles, specializing in eClinical technology. Bill has authored over 70 publications including an industry textbook on electronic patient reported outcomes (ePRO). Bill is the Vice Director of the ePRO Consortium.

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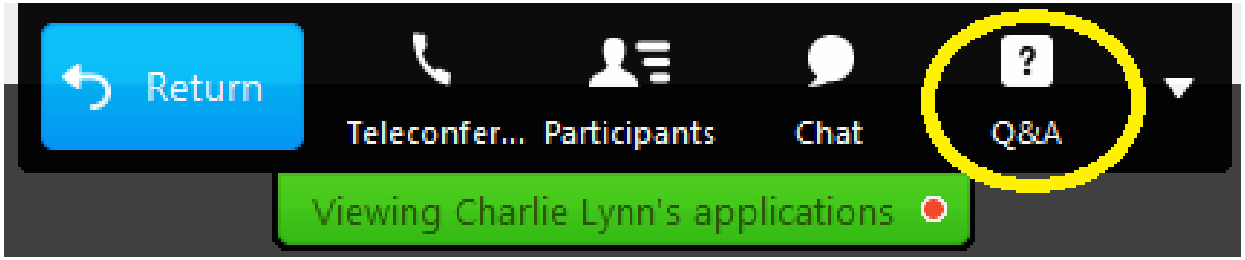

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ePRO Consortium

- The Electronic Patient-Reported Outcome (ePRO) Consortium was established by the Critical Path Institute (C-Path) in 2010. Along with C-Path, the members of the ePRO Consortium are firms that provide electronic data collection technologies and services for capturing patient-reported outcome (PRO) and other clinical outcome assessment (COA) data in clinical trials.

- The mission of the ePRO Consortium is to advance the science of clinical trial endpoint assessment by collaboratively supporting and conducting research, designing and delivering educational opportunities, and developing and disseminating best practice recommendations for electronic collection of clinical outcome data.

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Recommendations from the ePRO Consortium
Agenda

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1. Introduction – the growing interest in wearables
2. Evidence recommended to support device selection
3. Evidence recommended to support derived endpoints

Sensors and Microsensors

Sensors are a device or device component that detects and measures physical or chemical information from a surrounding physical environment, and translates this into an electrical output signal

The use of reliable, high performance microsensors in the medical field is of growing importance for patient health monitoring, personal wellness and clinical research.

Types of Sensors and Microsensors (1)

External Devices/Sensors: Physically separate from the user that can be interacted with

- movement detection camera
- weighing scales
- digital spirometer

Wearable Devices/Sensors: Integrated into clothing/accessories that are worn on the body

- activity monitors
- pulse oximeters
- heart rate monitors

Types of Sensors and Microsensors (2)

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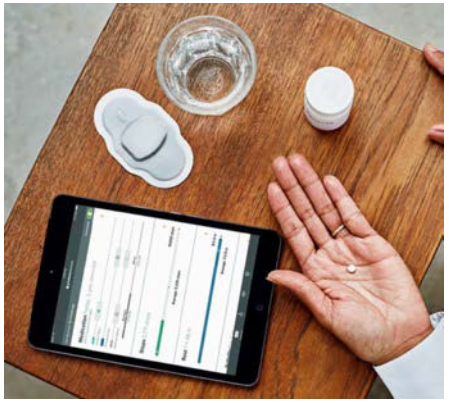
Implantable Devices/Sensors: Inserted into the human body

- cardiac arrhythmia monitors
- brain liquid pressure sensors

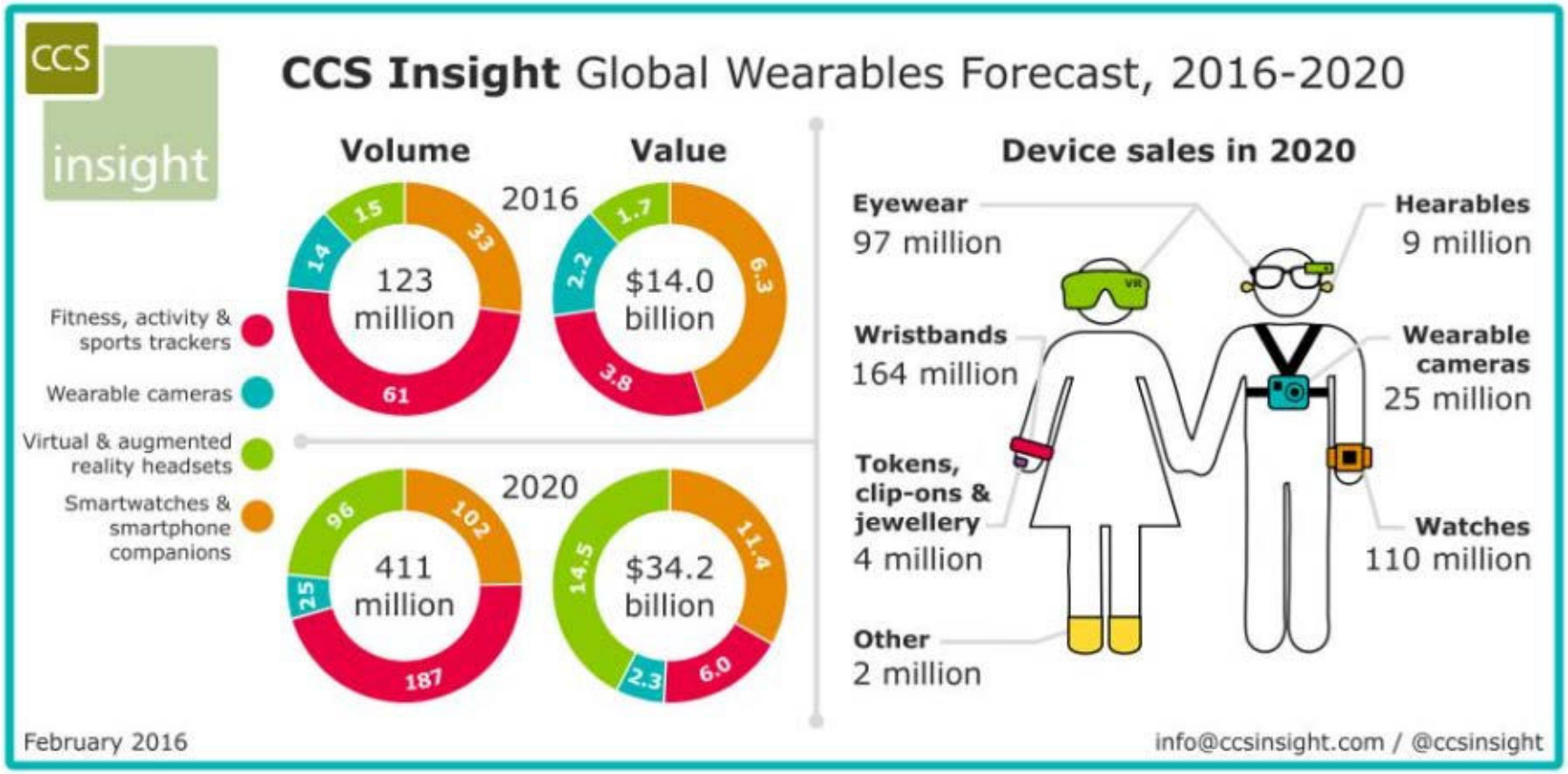
Ingestible Devices/Sensors: Swallowed by the user and data set to an external collection device

- ingestible temperature sensors
- ingestible medication tags



Introduction
Wearables as Sensors

A small electronic device containing one or more sensors that are integrated into clothing or other accessories that can be worn on the body that measures physical or chemical information.



Introduction
Wearables and Health

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FDA News Release

FDA expands indication for continuous glucose monitoring system, first to replace fingerstick testing for diabetes treatment decisions

For Immediate Release December 20, 2016

Wearable technology is here - Today

Can sponsors utilise this technology as an outcomes research tool?

Poll question

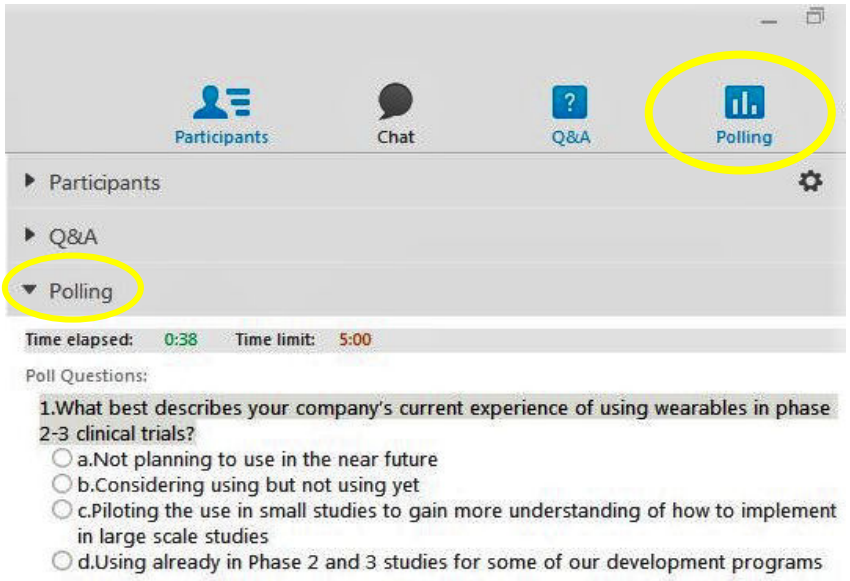
What best describes your company's current experience of using wearables in phase 2-3 clinical trials?

a. Not planning to use in the near future

b. Considering using but not using yet

c. Piloting the use in small studies to gain more understanding of how to implement in large scale studies

d. Using already in Phase 2 and 3 studies for some of our development programs



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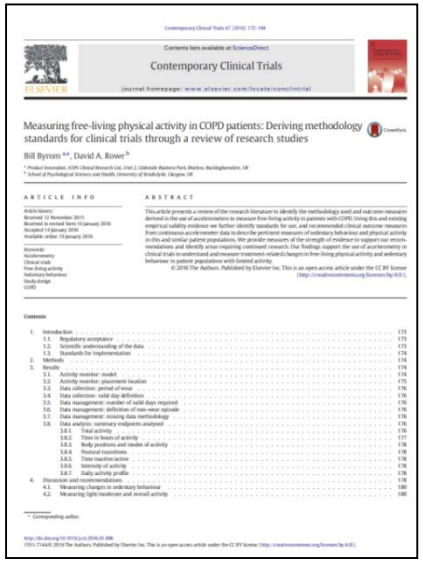
Recommendations from the ePRO Consortium
Barriers to adoption - *Example*


Contemporary Clinical Trials

Measuring free-living physical activity in COPD patients: Deriving methodology standards for clinical trials through a review of research studies

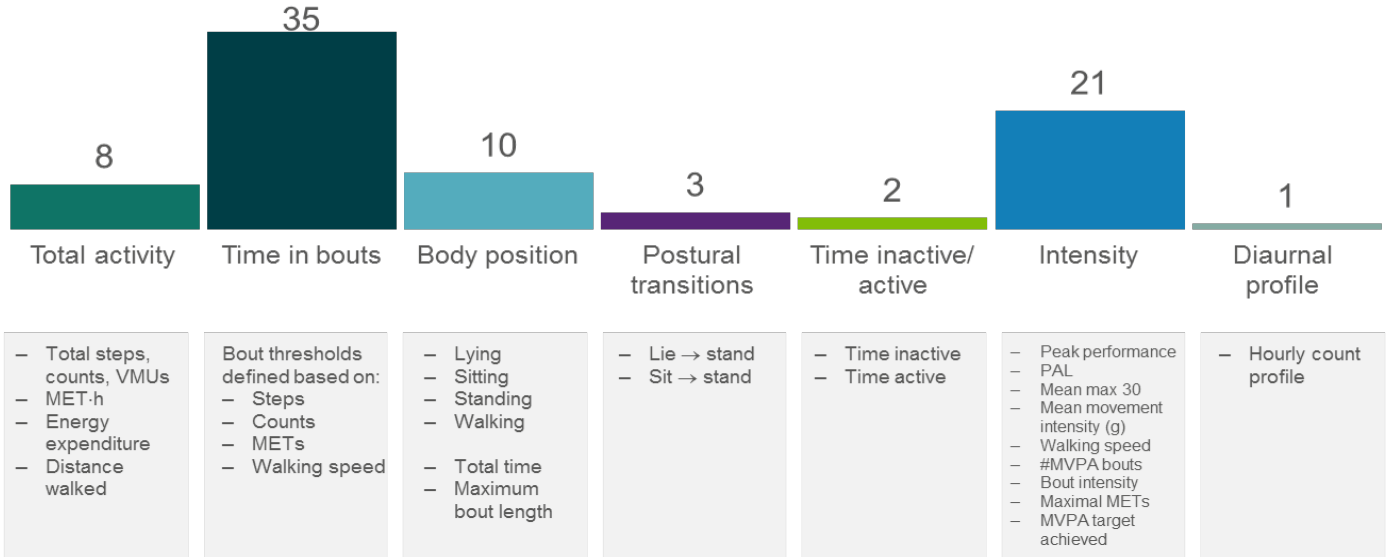
Bill Byrom, David A. Rowe

Large variation in methodology applied across 76 studies

- 27 different activity monitor models
- Different placement locations
  - Waist/hip (41%), arm (15%), ankle (8%), wrist (4%), lower back (3%), pocket (1%), shoe (1%), multiple sensors (9%), not reported (18%).
- Period of wear
  - 2 days to 26 weeks
  - Median 7 days

80 different derived performance outcome measures

Byrom, B, Rowe, D.A. (2016). Contemporary Clinical Trials; 47: 172-184.



Barriers to adoption

- No regulatory guidance specifically on the use of wearables
- How do we select a device that is appropriate for clinical research?
- What evidence do we need to support endpoints derived from wearable devices?

Evidence recommended to support selection of a device

Evidence to support device selection
Selection of a device

1. • Safe
2. • Suitable
3. • Valid and reliable data

Evidence to support device selection
Safety

Areas for consideration	Evidence recommended
• Mechanical performance • Electrical performance • Biological engineering performance • Electrical safety and electromagnetic compatibility (EMC) • Sterility • Stability/shelf life	• Statement, certification or data on performance and safety provided by manufacturer • Usage instructions • Maximum wear intervals • Wear locations • Instructions for preparation and (if appropriate) re-use

Evidence to support device selection

Suitability

- **Study Objectives**
- **Patient population**
- **Study design factors**
- **Vendor characteristics**

Evidence to support device selection
Suitability

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Study Objectives

Patient population

Study design factors

Vendor characteristics

Areas for consideration

Does the wearable device claim to measure the concept of interest as defined by the study objectives?

Evidence to support device selection
Suitability

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Study Objectives

Patient population

Study design factors

Vendor characteristics

Areas for consideration

- Acceptability
- Wear and usage considerations
- Ease of operation, removal and replacement, charge and maintenance

Evidence recommended

- Usability testing of device and training information may be helpful where usage considered complicated
- Cognitive interview and usability study in 6-10 patients

Evidence to support device selection
Suitability

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- Study Objectives
- Patient population
- **Study design factors**
- Vendor characteristics

Areas for consideration

- Does battery length and storage capacity match the wear interval?
- Non-volatile data storage and no over-write of data
- Patient burden in the light of other study requirements
- Set-up and maintenance processes
- Data acquisition processes
- Visibility of the data
- Is real-time access to data required/desirable?

Evidence to support device selection
Suitability

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Study Objectives

Patient population

Study design factors

Vendor characteristics

Areas for consideration

- Access and control of source data
  - 21 CFR part 11
- Control over firmware and cloud algorithm updates
- Vendor risk assessment: access to data in the event of device vendor changes/device withdrawal
- Deployment and logistics support
- Financial model

Evidence to support device selection
Valid and reliable data

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1. Reliability assessment: intra-device and inter-device agreement, including calibration methods where appropriate

2. Concurrent (criterion-related) validity: assessment of measurement accuracy and concordance with an alternative accepted approach, and where appropriate sensitivity and specificity in measurement

3. Ability to detect change

Valid and reliable data

Intra-device and inter-device reliability

Areas for consideration	Evidence recommended

• Intra-device reliability
• Inter-device reliability
• Manufacturing quality system certification to ensure continued reliability
	• Reliability data provided by vendor or in peer-reviewed literature
	• Simulated laboratory testing can be used but must be supplemented by tests in human subjects
	• Human study
	  • Include anchor measure to identify stability
	  • ICC (95% CI > 0.7)

Valid and reliable data

Concurrent (criterion-related) validity

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Areas for consideration	Evidence recommended

• Correlation with another instrument or measure that is regarded as a more accurate, criterion or 'gold standard' measure	• At least 1 study published in peer-reviewed literature, independent of vendor.
	• Example:
	  • 50 subject study
	  • Representative group
	  • Wearable and comparator method
	  • Ideally ICC analysis, but other methods also considered (e.g., ROC analysis)

Valid and reliable data

Ability to detect change

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Areas for consideration	Evidence recommended
• Sensitivity to detect change when a change exists • (see also evidence to support endpoint selection)	• At least 1 study published in peer-reviewed literature, independent of vendor. • Intervention to achieve a change • Additional measures to identify a change has truly occurred

Evidence recommended to support endpoints derived from device data

Evidence to support derived endpoints
What is an Endpoint?

> "A characteristic or variable that reflects how a patient feels, functions, or survives * "

A summary measure of clinical relevance derived from the data collected using the wearable device. Endpoint descriptions include:

- information defining how and when they are measured
- how they are calculated
- rules for missing data
- how they are analyzed.

For example, a potential trial endpoint (if demonstrated to predict clinical benefit) could be:

The change from baseline in mean daily activity count over a 7-day interval (with at least 3 valid days recorded) after 12 weeks of treatment, measured using a wrist-worn tri-axial accelerometer worn during non-bedtime hours.

* The Biomarkers Definition Working Group. See also BEST Resource (FDA-NIH Biomarker Working Group)

Evidence to support derived endpoints

1. • Responsiveness
2. • Interpretability

Evidence to support derived endpoints
Responsiveness

Areas for consideration	Evidence recommended
• Sensitivity to detect change when a change exists • (see also evidence to support device selection)	• At least 1 study published in peer-reviewed literature, independent of vendor. • Intervention to achieve a change • Additional measures to identify a change has truly occurred

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Meaningful change: statistical significance isn't enough

Individual change

- Responder definition
- The minimum degree of change deemed meaningful to the individual patient

Group mean change

- Minimal important difference (MID) or minimally clinically important difference (MCID)
- The minimum change in group mean deemed meaningful

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Methodology

- Anchor-based approaches
  - Relate observed change to another measure (anchor) where meaningful change is understood
  - Conduct for a number of different anchors if possible
    - Changes in anchors must be associated with changes in derived endpoint under consideration
  - Responder definition is estimated from the change scores from the wearable device in those experiencing a meaningful change (anchor measure)

- May be supplemented by other approaches such as distribution-based methods

Evidence to support derived endpoints
Interpretability - EXAMPLE

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Meaningful change in number of steps per day in MS patients

OPEN ACCESS Freely available online PLOS ONE

Clinical Importance of Steps Taken per Day among Persons with Multiple Sclerosis

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Abstract

Background: The number of steps taken per day (steps/day) provides a reliable and valid outcome of free-living walking behavior in persons with multiple sclerosis (MS).

Objective: This study examined the clinical meaningfulness of steps/day using the minimal clinically important difference (MCID) value across stages representing the developing impact of MS.

Methods: This study was a secondary analysis of de-identified data from 15 investigations totaling 786 persons with MS and 157 healthy controls. All participants provided demographic information and wore an accelerometer or pedometer during the waking hours of a 7-day period. Those with MS further provided real-life, health, and clinical information and completed the Multiple Sclerosis Walking Scale-12 (MSWS-12) and Patient Determined Disease Steps (PDDS) scale. MCID estimates were based on regression analyses and analysis of variance for between group differences.

Results: The mean MCID from self-report scales that capture subtle changes in ambulation (1-point change in PDSS scores and 10-point change in MSWS-12 scores) was 779 steps/day (14% of mean score for MS sample); the mean MCID for clinical/health outcomes (MS type, duration, weight status) was 1,455 steps/day (26% of mean score for MS sample); real-life anchors (unemployment, divorce, assistive device use) resulted in a mean MCID of 2,580 steps/day (45% of mean score for MS sample); and the MCID for the cumulative impact of MS (MS vs. control) was 2,747 steps/day (48% of mean score for MS sample).

Conclusion: The change in motion sensor output of ~800 steps/day appears to represent a lower-bound estimate of clinically meaningful change in free-living walking behavior in interventions of MS.

Citation: Motl RW, Pilutti LA, Learmonth YC, Goldman MD, Brown T (2013) Clinical Importance of Steps Taken per Day among Persons with Multiple Sclerosis. PLoS ONE 8(9): e73247. doi:10.1371/journal.pone.0073247

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Competing Interests: Acorda Therapeutics funded this study. RWM is a consultant for Acorda Therapeutics and Biogen Idec. LAP and YCL report no conflicts of interest. MDG has served as a consultant for Acorda Therapeutics and Novartis Pharmaceuticals, but does not report any current conflicts of interest. TB is a consultant for Acorda Therapeutics, Biogen Idec, Genzyme, Pfizer, and Teva. There are no patents, products in development or marked products to declare. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials.

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Introduction

There has been an ongoing debate regarding outcome measures in clinical research involving persons with multiple sclerosis (MS) [1], with increasing interest in approaches for objectively monitoring patients under real-world conditions [2]. This interest has highlighted the potential for the objective monitoring of free-living walking behavior using motion sensors such as accelerometers and pedometers in clinical research involving persons with neurologic diseases [3] including MS [2]. Such devices are worn around the waist or ankle during the waking hours of the day and over a representative sampling period (e.g., seven days). The motion sensors capture the total amount of walking undertaken in free-living conditions based on metrics such as steps taken per day (steps/day). The number of steps/day reflects a straight-forward metric of the overall amount of walking undertaken during one's everyday life, representing free-living walking behavior [2,3].

Accumulating data demonstrates that the number of steps/day provides a reliable and valid measure of free-living walking behavior in MS [4–7]. Steps/day has demonstrated acceptable test-retest reliability over a two-week time period in persons with MS [4], and as few as three days of data with an appropriate amount of wear time (i.e., 10 or more hours/day) yields a reliable estimate of usual ambulatory-based behavior [5]. Regarding validity, steps/day has correlated strongly with clinical (e.g., Expanded Disability Status Scale scores), performance (e.g., timed 25-foot walk and 6-minute walk), and patient-reported (e.g., 12-Item Multiple Sclerosis Walking Scale or MSWS-12 scores) measures of ambulation in persons with MS [6,7]. To date, there are no published data evaluating the clinical importance of differences in steps/day among those with MS (i.e., amount of difference in steps/day that actually reflects a difference) on a group level. Such minimal clinically important difference (MCID) values are necessary for designing and interpreting clinical trials

- 786 MS patients
- 157 healthy controls
- 3 – 7 days activity data (steps/day)
  - Yamax SW-200 pedometer
- Anchors
  - MSWS-12, a 12-item PRO measure assessing the impact of MS on walking-related activities
  - Patient-Determined Disease Steps (PDDS) scale

Evidence to support derived endpoints
Interpretability - EXAMPLE

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Meaningful change in number of steps per day in MS patients

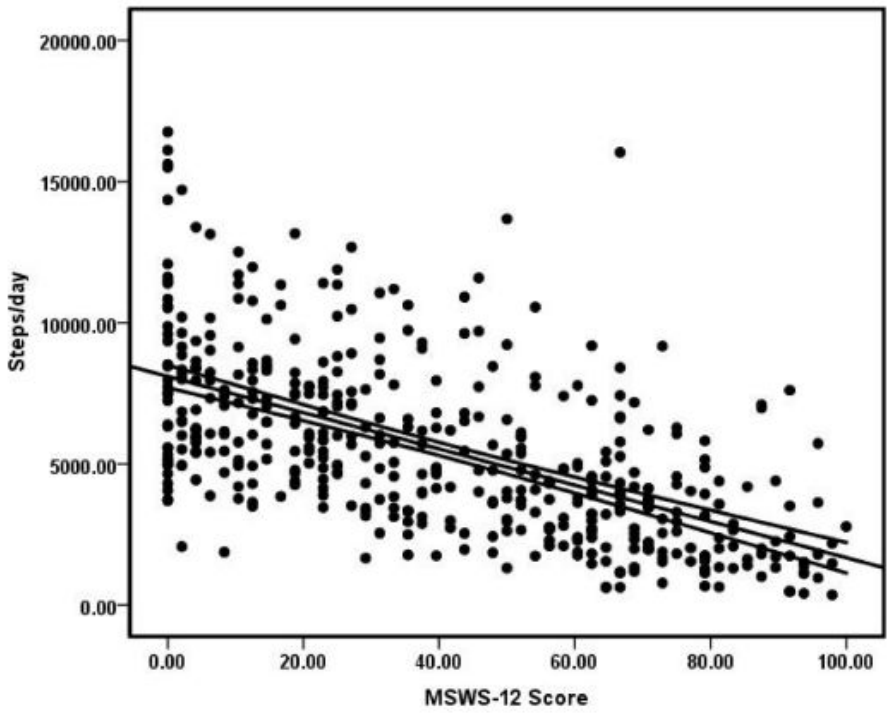
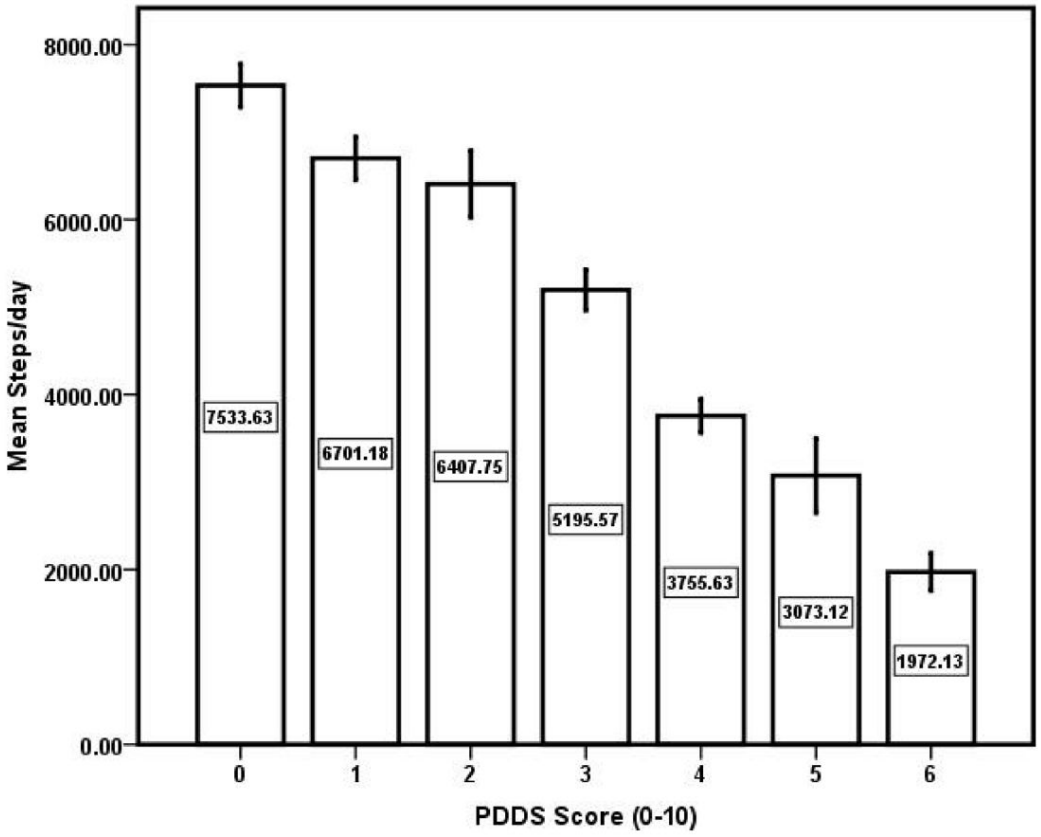


Figure 1. Scatter plot of the association between Multiple Sclerosis Walking Scale-12 (MSWS-12) scores and steps/day in persons with multiple sclerosis.
doi:10.1371/journal.pone.0073247.g001

1. Demonstrate steps/day is related to the anchor measure
2. MCID (MSWS-12) = 10
3. Corresponds to 642 steps/day
4. Repeat for additional anchor (Patient-Determined Disease Steps (PDDS) scale)

Evidence to support derived endpoints
Interpretability - EXAMPLE

Meaningful change in number of steps per day in MS patients



1. MCID (PDDS) = 1 point change
2. Corresponds to 915 steps/day

Figure 2. Bar graph of the association between Patient Determined Disease Steps (PDDS) scale scores and steps/day in persons with multiple sclerosis. The number within the bars represents the mean score for steps/day per level of the PDDS.
doi:10.1371/journal.pone.0073247.g002

Meaningful change in number of steps per day in MS patients

- MCID (steps) = 779 steps (642 – 915) steps per day

Responder definition could be estimated from the same data set

- Receiver operating characteristic curves

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Where endpoints are used in labeling claims

- Require evidence for validity and reliability as described above for all primary and secondary endpoints intended for inclusion in product labeling.

- Although not essential, available evidence supporting the measurement properties of the wearable device used to measure exploratory endpoints should also be assembled.

- Phase 2 studies may provide an ideal opportunity to implement devices and collect data required for endpoint validation and usability in preparation for the Phase 3 program.

Summary

Summary

Recommendations

Evidence to support device selection

- Intra-device and inter-device reliability
- Concurrent (criterion-related) validity
- Responsiveness (ability to detect change)
- Usability

Evidence to support derived endpoints

- Responsiveness (ability to detect change)
- Interpretability (responder definition)

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Questions?

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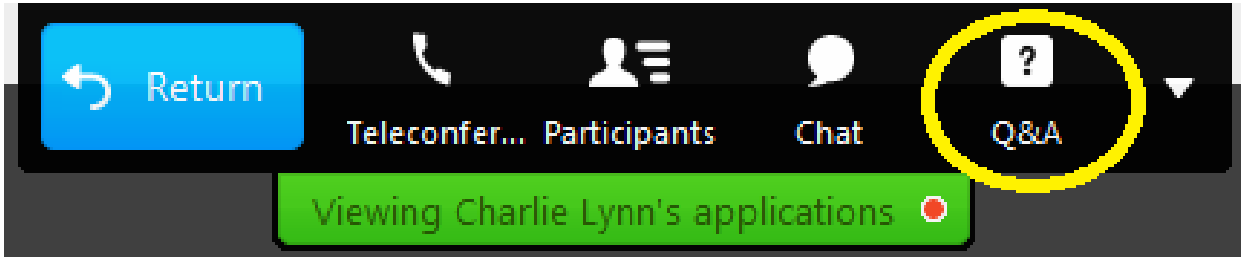

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