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)
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.
Please use Q&A feature to submit questions to presenter

- If in full screen mode, select following:

- If not in full-screen mode, the Q&A box is open to your right.

- When asking questions, be sure to select “All Panelists”
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.
Membership
Recommendations from the ePRO Consortium

Agenda

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

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.
Introduction
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 spirometers

Wearable Devices/Sensors: Integrated into clothing/accessories that are worn on the body
- activity monitors
- pulse oximeters
- heart rate monitors
Introduction
Types of Sensors and Microsensors (2)

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.

CCS Insight Global Wearables Forecast, 2016-2020

Volume 2016
- Fitness, activity & sports trackers: 15 million
- Wearable cameras: 2.2 million
- Virtual & augmented reality headsets: 6.3 million
- Smartwatches & smartphone companions: 3.8 million

Value 2016
- Fitness, activity & sports trackers: $14.0 billion
- Wearable cameras: 1.7 billion
- Virtual & augmented reality headsets: 3.3 billion
- Smartwatches & smartphone companions: 6.1 billion

Device sales in 2020
- Eyewear: 97 million
- Wristbands: 164 million
- Tokens, clip-ons & jewellery: 4 million
- Watches: 110 million

February 2016
Introduction
Wearables and Health

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

Select a response and press Submit at the bottom of your screen.
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

Recommendations from the ePRO Consortium

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

• Mechanical performance
• Electrical performance
• Biological engineering performance
• Electrical safety and electromagnetic compatibility (EMC)
• Sterility
• Stability/shelf life

Evidence recommended

• 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
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

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

Study Objectives

Patient population

Study design factors

Vendor characteristics
Evidence to support device selection
Suitability

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

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

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

- Intra-device reliability
- Inter-device reliability
- Manufacturing quality system certification to ensure continued reliability

Evidence recommended

- 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

Areas for consideration

- Correlation with another instrument or measure that is regarded as a more accurate, criterion or ‘gold standard’ measure

Evidence recommended

- 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

Areas for consideration

- Sensitivity to detect change when a change exists
- (see also evidence to support endpoint selection)

Evidence recommended

- 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
“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

• Sensitivity to detect change when a change exists
• (see also evidence to support device selection)

Evidence recommended

• 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
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
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

Meaningful change in number of steps per day in MS patients

- 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
Meaningful change in number of steps per day in MS patients

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)
Meaningful change in number of steps per day in MS patients

1. MCID (PDDS) = 1 point change

2. Corresponds to 915 steps/day
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
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)
Questions?

http://c-path.org/programs/e-pro
Please use Q&A feature to submit questions to presenter

- If in full screen mode, select following:

- If not in full-screen mode, the Q&A box is open to your right.

- When asking questions, be sure to select “All Panelists”
Thank you for attending this ePRO Consortium webinar