Digital Drug Development Tools Team: Building a Regulatory Roadmap

CAMD Annual Meeting & Regulatory Workshop

October 19, 2016

Co-Chair: Dan Karlin (Pfizer)

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DIGITAL DRUG DEVELOPMENT TOOLS

Qualifying Biosensor Outcome Assessments

WHAT

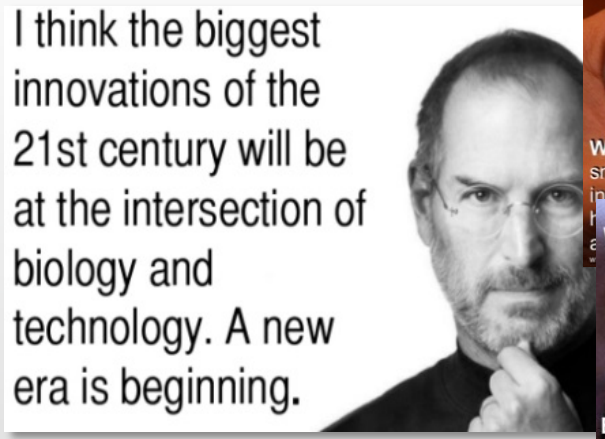
Data (signal) collected by a sensor or set of sensors measuring clinical or biological phenomena

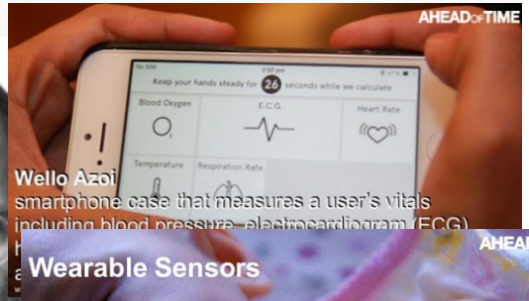
HOW

High temporal, spatial, and availability using novel digital and mobile devices containing sensors

WHY

Improve our understanding of real-time/real-world changes in function in health & disease





DIGITAL DRUG DEVELOPMENT TOOLS

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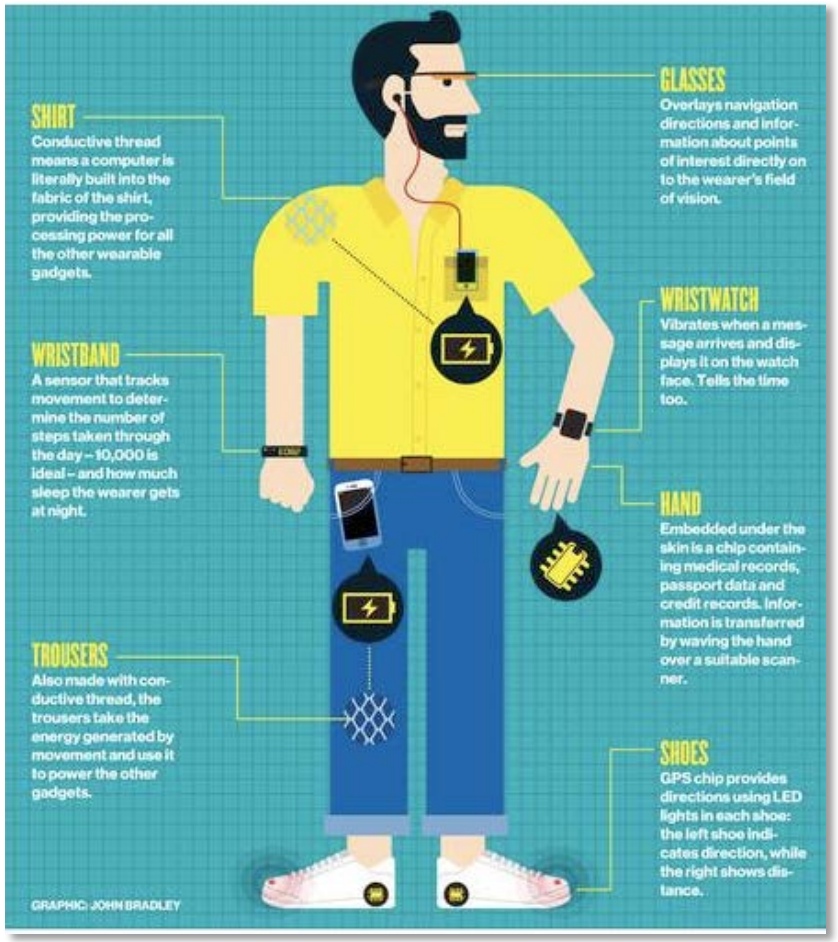
Sensor Systems

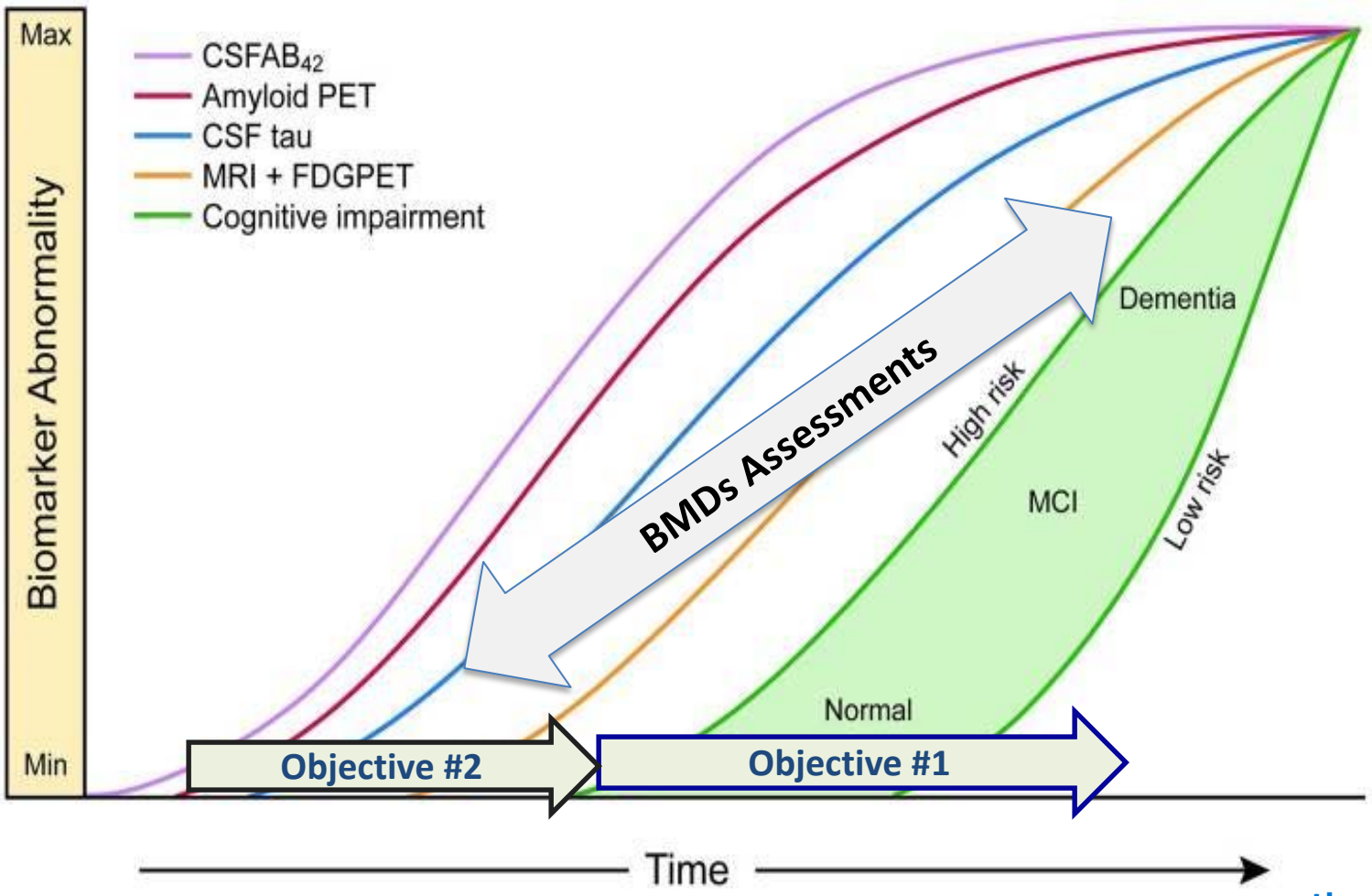
- Disease diagnosis improved ROC and phenotype definition
- Disease progression + regression characterize trajectory
- Response to intervention
- Continuous observation of ADLs

Measure Objective Signs of Function in Health, Disease & Treatment



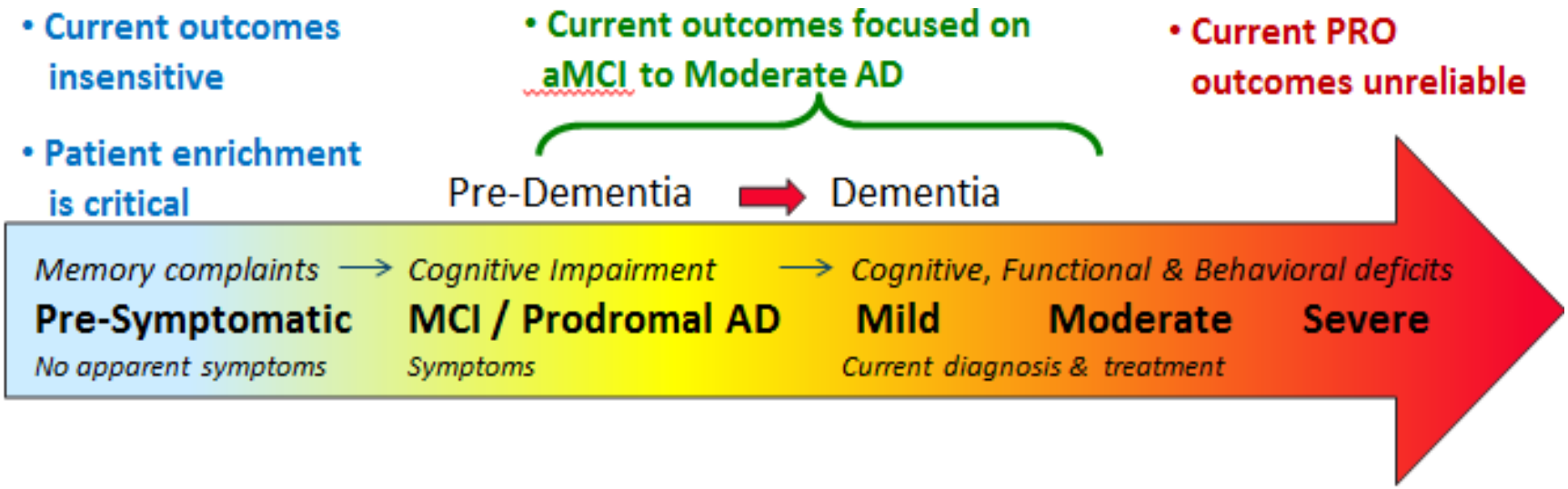
ALZHEIMER'S DISEASE (AD) STAGES

Framing the dilemma of what to measure and when?



ALZHEIMER'S DISEASE (AD) STAGES
(continued)

Framing the dilemma of what to measure and when?



USE OF BIOSENSORS IN CLINICAL TRIALS BARRIERS & SOLUTIONS TO THE CURRENT LANDSCAPE

https://c-path.org/camd-digital-biomarkers-conference/

March 31 – April 1, 2016

Bethesda North Marriott Conference Center

Interest in identifying, evaluating and qualifying innovative technologies for use in drug development is growing. While regulatory guidance documents exist for pursuing novel Drug Development Tools (DDTs) and Medical Devices Development Tools (MDDTs) for Qualification, the use of Digital Biomarkers (i.e., measured biological events or patient function captured through a device or sensor technology) for use in clinical development remains ill-defined. This conference examines the current landscape of our use of Digital Biomarkers in clinical trials, the challenges faced, and the need for solutions to these challenges.

Biometric Monitoring Devices for Objective Assessments of Clinically-Relevant Endpoints: Building a Roadmap for Digital Drug Development Tools in Clinical Trials

Stephen P. Arnerić, PhD[1], Jesse M. Cedarbaum, MD[2], Sean A. Khozin, MD[3], Spyros Papapetropoulos MD, PhD[4], Derek L. Hill, PhD[5], Klaus Romero, MS, MD[1], Jane Rhodes, MBA, PhD[2], Lynn D. Hudson, PhD[1], Mark Forrest Gordon, MD[6], Volker D. Kern, PhD[1], George Vrandenburg[7], Michael Ropacki[8], Rhoda Au, MBA, PhD[9], Daniel R. Karlin, MD[10], Maurizio F. Facheris, MD[11], Ottavio Vitolo[10], Cheryl Fitzer-Atlas[12],Jeffrey A. Kaye, MD[13]

DEFINING DISEASE REQUIRES COMPOSITE ASSESSMENT

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Signs + **Symptoms**

Observer / Performance Outcomes

Genetics | Examine | Temperature

Vision | Forgetfulness | Infection | Mobility

GI/Lung/ Glucose tests | Kidney function | EKG HR/BP | EEG/ Sleep/ Fatigue

Imaging Modalities

Patient & Physician Reported Outcomes

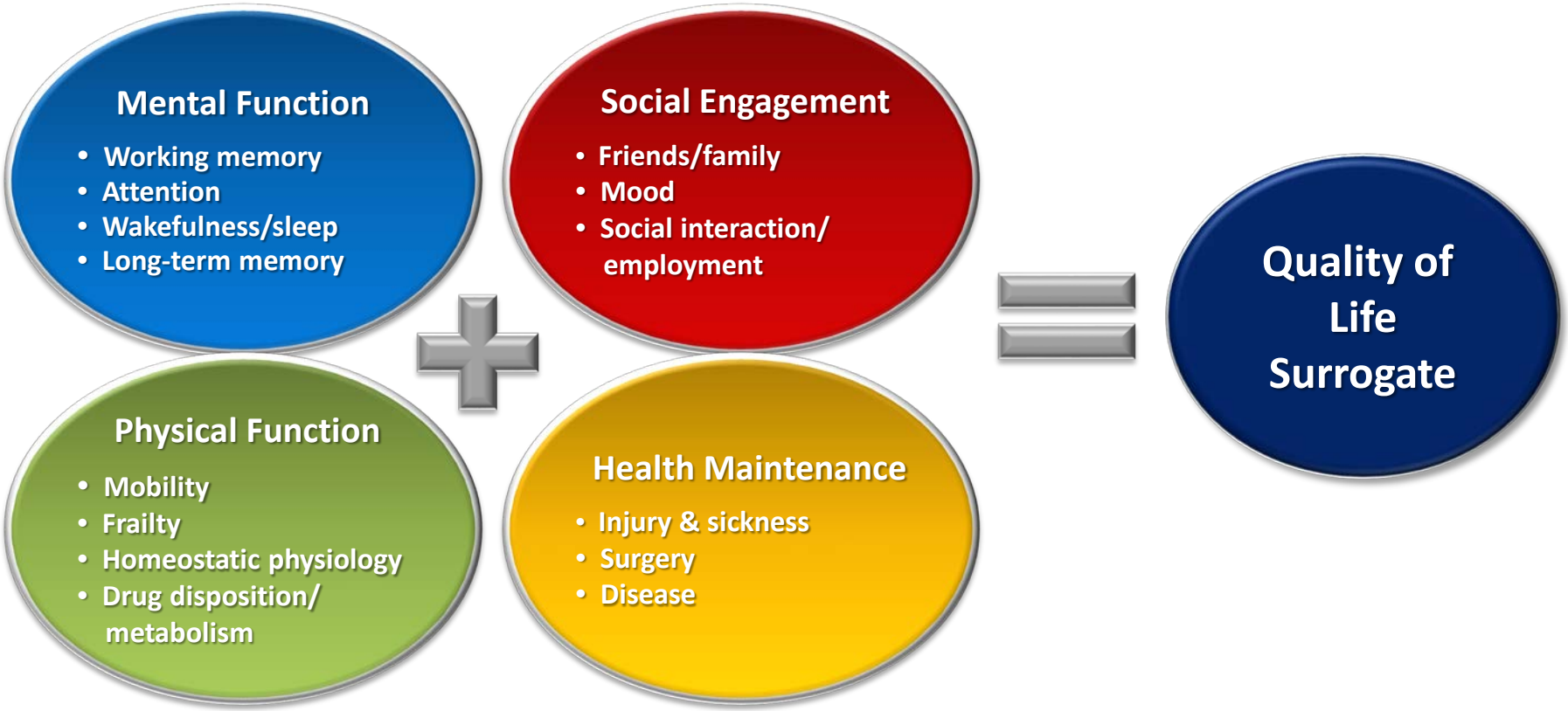
- Cognition (MMSE, CDR-SB, etc.)
- Behavior (sleep/mood scales – QOL-AD, GDS)
- Motor function (UDPRS)
- Sensation (NRS, etc.)
- Balance & Coordination
- Autonomic

Outcome Decisions

- Diagnoses
- Treatment Algorithm

MEASURING SIGNS RELATED TO QOL

BMDs have the potential to measure signs related to all domains of function comprising what is viewed as Instrumental Activities of Daily Living



DEFINING DATA STANDARDS IS ESSENTIAL

Currently, there is no interoperable uniformity across the various BMDs.

Data Standards are necessary to scale use of BMDs in research [goo.gl/IM85UD].

Data standards provide a science-based consensus on how to record, structure and report data generated by devices and align with the development and adoption of CDISC standards to:

- allow integration of data sources to quantify the predictive accuracy, utility and reliability of BMDs in clinical trials;
- enable prospective collection of data in standardized format in clinical trials and observational studies; and
- expedite regulatory submissions to FDA, EMA, and other regulatory authorities.

THE NEED FOR STANDARDS

MOBILE AND WEARABLE DEVICES WORKSHOP

Mobile and Wearable Devices

Role of Standards in Generating Evidence for Regulatory Decision-Making

8:30 a.m. – Noon, Wednesday, August 3, 2016
National Academies of Science
2101 Constitution Avenue, Washington, DC

Meeting Objectives:

- Identify barriers and approaches to addressing standards and standardized methods for the use of mobile and wearable devices in clinical trials.
- Use case studies to highlight both the progress and the gaps.
- Discuss next steps for filling gaps and aligning standards.

Regulators, Academics, Consortia

- FDA (CDER & CDRH)
- Duke/CTTI
- Imperial College
- PEW
- CAMD & ePRO
- Univ. Chicago

Pharma

- Allergan
- Amgen
- Biogen
- BMS/Transcelerate
- Merck
- Pfizer
- Sanofi

Technologies and CROs

- Google
- Verily Life Sciences
- Nokia
- Validic
- Medidata
- Garmin
- Becton Dickenson

DESIDERATA FOR DATA STANDARDS

Methods of Information in Medicine

J. J. Cimino

Desiderata for Controlled Medical Vocabularies in the Twenty-First Century

Department of Medical Informatics,
Columbia University, New York, USA

Abstract: Builders of medical informatics applications need controlled medical vocabularies to support their applications and it is to their advantage to use available standards. In order to do so, however, these standards need to address the requirements of their intended users. Over the past decade, medical informatics researchers have begun to articulate some of these requirements. This paper brings together some of the common themes which have been described, including: vocabulary content, concept orientation, concept permanence, nonsemantic concept identifiers, polyhierarchy, formal definitions, rejection of "not elsewhere classified" terms, multiple granularities, multiple consistent views, context representation, graceful evolution, and recognized redundancy. Standards developers are beginning to recognize and address these desiderata and adapt their offerings to meet them.

Keywords: Controlled Medical Terminology, Vocabulary, Standards, Review

DESIDERATA FOR CONTROLLED VOCABULARIES

Content: formal editorial policy and methodology; breadth and depth; don't just add terms

Concept orientation: exactly one and meaning per concept and concept per meaning

Concept permanence: old concepts not deleted; names can be changed, not meaning

Nonsemantic identifiers: meaningless integer

Polyhierarchy: multiple hierarchies to support tree walking, inferencing

Formal Definitions: structured descriptions that invoke internal relationships

Reject NEC: terminology changes induce semantic drift

Graceful evolution: fix mistakes; account for changes in knowledge

Recognize redundancy: redundant expressions are inevitable, no redundant concepts

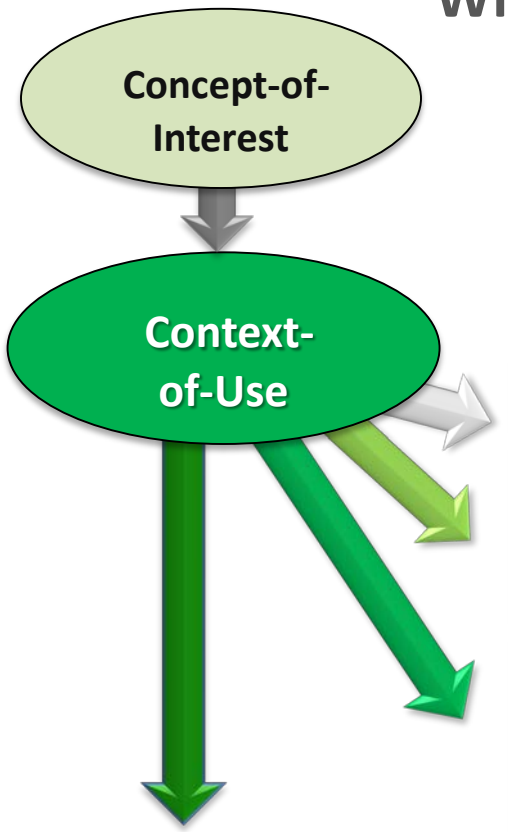
DESIDERATA FOR BMDs

Increasingly Open Data Sharing

- Kerckhoffs' desideratum: “A cryptosystem should be secure even if everything about the system, except the key, is public knowledge.”
- The inner working of a sensor system and/or device must be known to the extent possible.
- Concept of “raw data,” is non-specific and often incorrect.
- Increasing data standardization demands clear and careful use of terms and concepts.

DEFINING THE CONCEPT-OF-INTEREST IS FOUNDATIONAL

What patient-level decision will be made?



Aspect of clinical, biological, physical, or functional state, or experience that the assessment reflects.

A statement that fully and clearly describes the way the medical product development tool (MPDT) is to be used, and the medical product development-related purpose of the use.

Exploratory: Regulatory endorsement not required.

Fit-for-purpose: A conclusion that the level of validation associated with a medical product development tool is sufficient to support its context-of-use (e.g. Clinical Trial Simulation Tool).

Qualification: A conclusion, based on a formal regulatory process, that within the stated context -of-use, a medical product development tool can be relied upon to have a specific interpretation and application in medical product development and regulatory review.

Approval for Clinical Utility: The conclusion that a given use of a medical product will lead to a net improvement in health outcome or provide useful information about diagnosis, treatment, management, or prevention of a disease. Clinical utility includes the range of possible benefits or risks to individuals and populations.

KEY CONSIDERATIONS FOR COI & COU:

- Context is essential and tricky
- Validating signals reported, and interpretation, is paramount to moving forward.
- The further BMDs move away from measuring physiology, the more important context becomes.
- Use cases for BMDs need to be developed and BMDs need to be evaluated together with PROs to correlate sensor data with how the patient reports they feel.

- What if the biosensor is more sensitive to the measure than patient perception?
- More sensitive than gold standard?

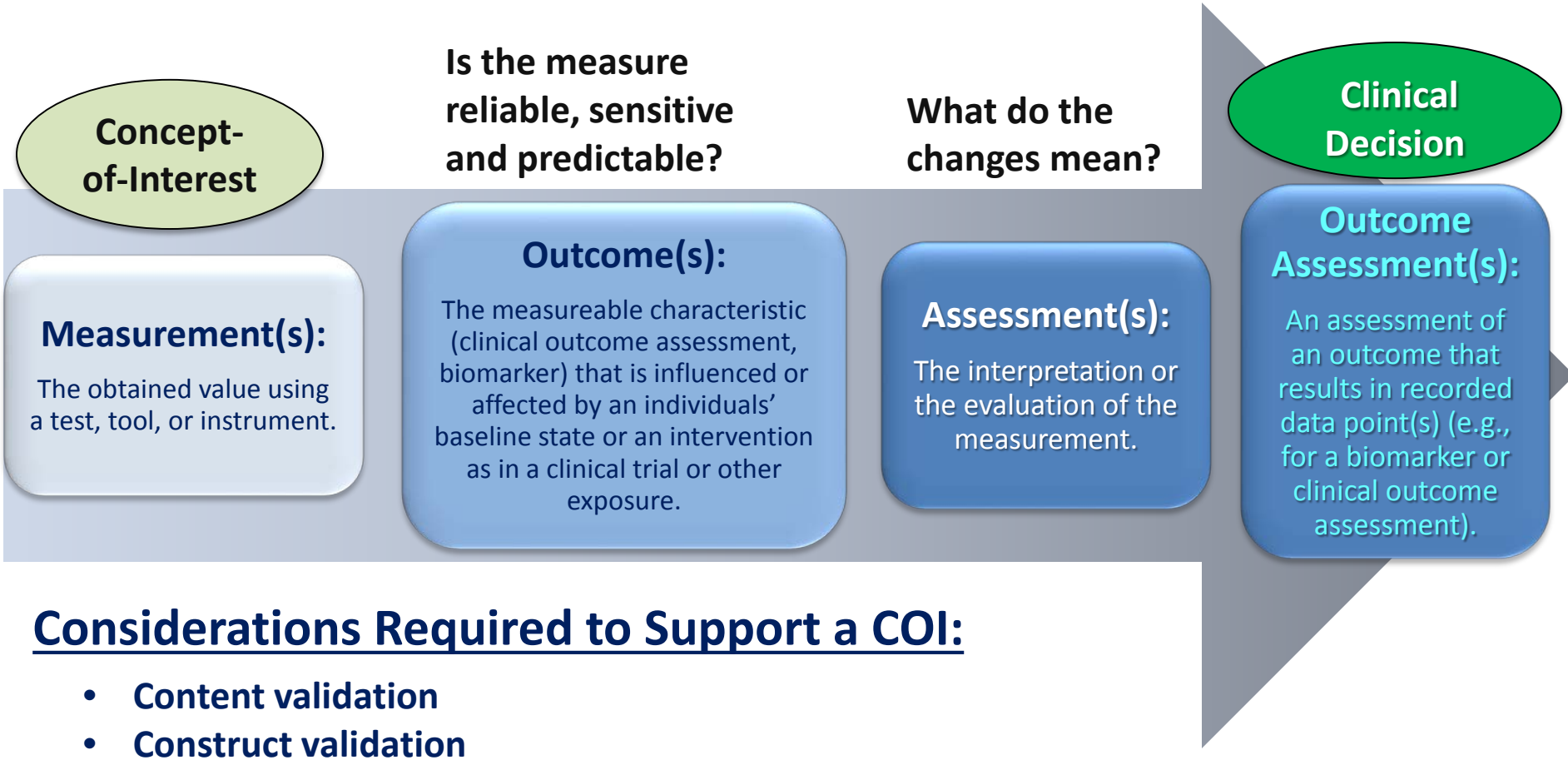
or

,

or

PROGRESSIVE DATA VALIDATION

Measurements Guiding Clinical Decisions



Considerations Required to Support a COI:

- Content validation
- Construct validation
- Criterion validation
- Analytical validation
- Clinical validation

ASSURANCE OF GOOD CLINICAL PRACTICE (GCP)

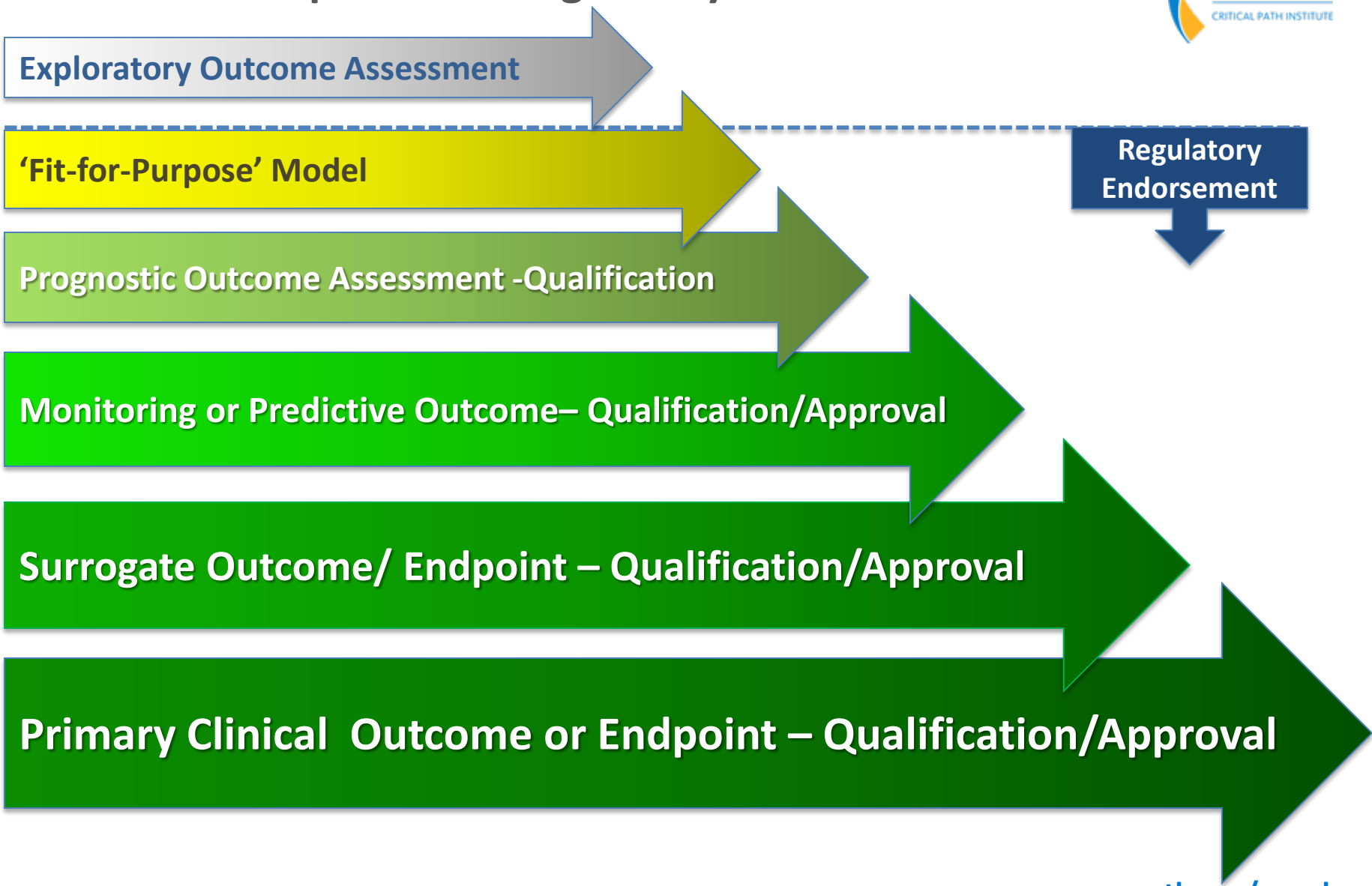
Researchers will only use BMDs assurance of GCP compliance.

Particularly challenging with “bring your own device” approach.

Authentication, Authorization and Access	Audit trail	Data quality control
Computer System Validation	Privacy	Device Safety
Impact on Blinding	Safety Data Monitoring	Access to Source Data

CONTEXT-OF-USE (RISK/BENEFIT)

Drives Data Required For Regulatory Endorsement



BIOMETRIC MONITORING DEVICES TO ASSESS CLINICAL SIGNS - Uses in Clinical Drug Trials

Context-of-Use	Definition	CDISC Standards	Evidentiary Standards
Internal Decisions	Commercial devices that is not a medical device (e.g., Smartphones, Fitbits™, Home-sensor monitoring, etc.).	No	Arbitrary
Exploratory Measures	Commercial devices that is not a medical device for potential patient stratification (e.g., Smartphones, Home-sensor monitoring, etc.,)	No	
Prognostic Assessment	Medical devices for use in in trial enrichment to predict rate of disease progression.	YES	
Predictive Assessment	Medical devices for trial enrichment to identify individuals who are more likely than similar patients without the outcome to experience a favorable or unfavorable effect from a specific intervention/ exposure.	YES	
Susceptibility/ Risk Assessment	Medical devices for use in in trial enrichment to indicate the potential for developing a disease or medical condition or sensitivity to an exposure in an individual without clinically apparent disease or medical condition.	YES	
Surrogate Endpoint	Medical devices in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.	YES	
Clinical Endpoint	Medical devices measuring precisely defined variable(s) intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.	YES	

Regulatory Endorsement

Robust; Multi-trial; Longitudinal

ELEMENTS REQUIRED TO DEVELOP A BALANCE AND PRODUCTIVE GLOBAL ECO-SYSTEM FOR BMDs

Perspective	Action
Patients, Caregivers & Advocacy Organizations	• Input of patients and caregivers. How to obtain the best input will be based on use case (both disorder-specific as well as function-specific) of patient acceptability, availability, usability and sustainability. Input on clinical meaningfulness from patients is a key cornerstone, as must concerns about loss of privacy arising from technologies that are used continuously to collect data from them, instead of much less frequent tests in a clinic. • Engagement of patient advocacy groups to help determine which symptoms are most-concerning to patients and what issues need to be addressed first. While the literature has numerous studies documenting the spectrum of symptoms experienced by patients with neurological diseases, there is a paucity of studies that have quantified these symptoms, or how these evolve from the presymptomatic to late-stages of the disease. This clarification may help to determine which functional aspects should be measured and help target the definition of the COU. • The attitudes and beliefs toward using BMD technologies by the end-users must also be more clearly understood to ensure proper application and successful use. • Patient Advocacy groups to provide educational tools (e.g., websites, educational forums, and dissemination of leading edge opportunities) • Proactive, clear, and broad informed consent to allow patients (or caregivers) to make de-identified data available for existing and future unanticipated data mining uses.

ELEMENTS REQUIRED TO DEVELOP A BALANCE AND PRODUCTIVE GLOBAL ECO-SYSTEM FOR BMDs

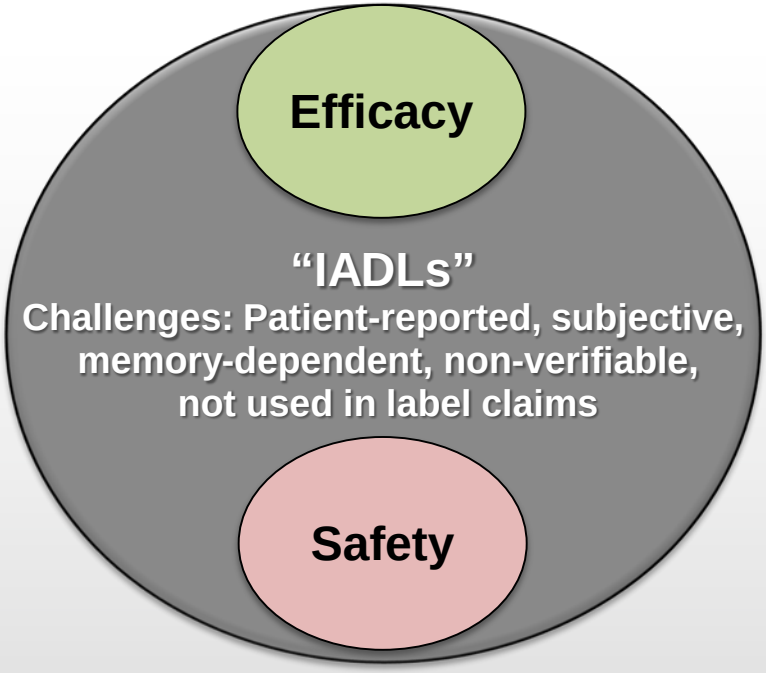
Regulators (FDA, EMA, PMDA, TGA, etc.)	• Input from regulators to help define the evidentiary standards & corresponding regulatory path for different COUs. • Provide guidance to ensure scientific rigor, data privacy, and data security.
Research & Developers, Academia, Pharma & Device Makers	• Engagement of the consumer device industry with the pharma industry to share anonymized, patient-level data for research purposes must be more robust. We must find innovative ways to inform and lower barriers for this fragmented industry to join digital healthcare efforts in a responsible way, without hampering their ability to innovate. • Define and develop a library of proposed BDMs documenting the measures, COU, data types and other descriptive data defining primary and secondary objectives. Create a structured, interoperable format for cross-industry use of BMDs. • Using CDISC standards, transform data into structured, real-world evidence. • Sponsor pre-competitive data repositories of aggregated, anonymized data for use in developing models of disease progression and treatment response across therapeutic areas. • Sponsor and perform studies that generate real-world evidence for the use of BMDs-drug treatments to enhance healthcare.
Payers & Providers	• Provide pay for performance access to drug-device combinations that reduce overall healthcare costs and improve healthcare management.

BMDs ENABLE A PARADIGM SHIFT IN ASSESSING IADLs

SUBJECTIVE

Current Practice

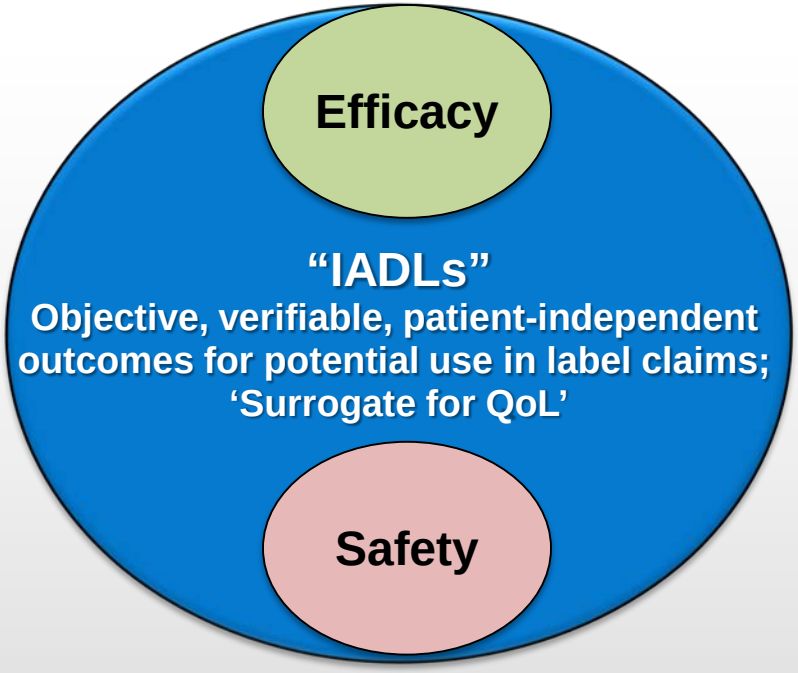
In Drug Development



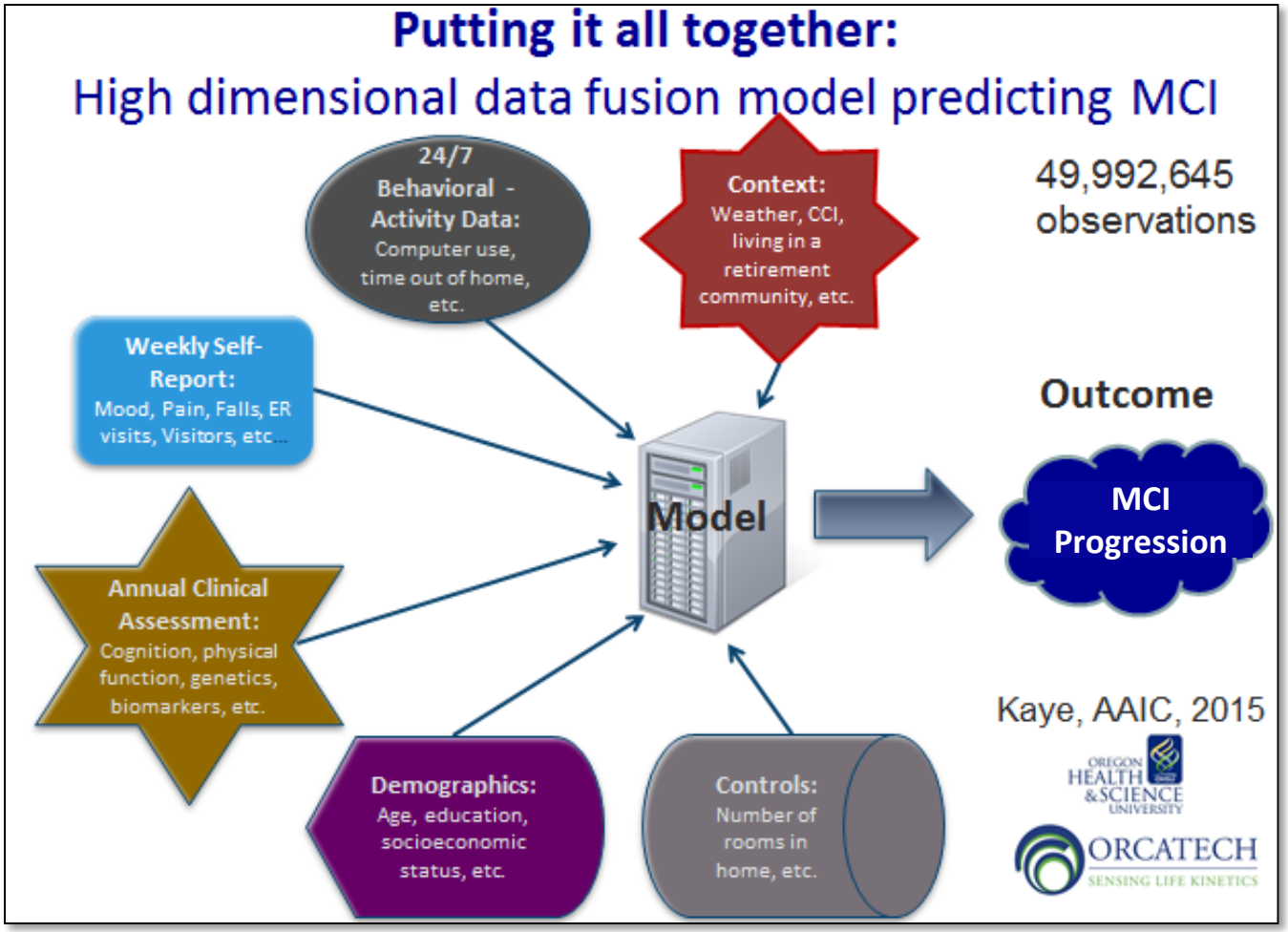
OBJECTIVE

Biometric Monitoring Devices

In Drug Development



MODELING AND SIMULATION AS A TOOL TO ENHANCE UNDERSTANDING OF DEMENTIA



BMDS– POTENTIAL ROLES IN FILLING REGULATORY SCIENCE GAPS

BARRIERS	GAP	CAMD Approach
Lack of qualified biomarkers for decision making	Highly variable subpopulations recruited into randomized clinical trials	Regulatory biomarker qualification for enrichment in randomized clinical trials
No effective therapy for modifying disease progression	Inadequate outcome measures for assessing functional efficacy of drugs in early pre-symptomatic stages	Innovative/sensitive clinical outcome assessments for efficacy of novel drug candidates
High risk and increasing costs for drug development	Huge uncertainty in design of clinical trials	Regulatory endorsed AD clinical trial simulation tool

Thank you!

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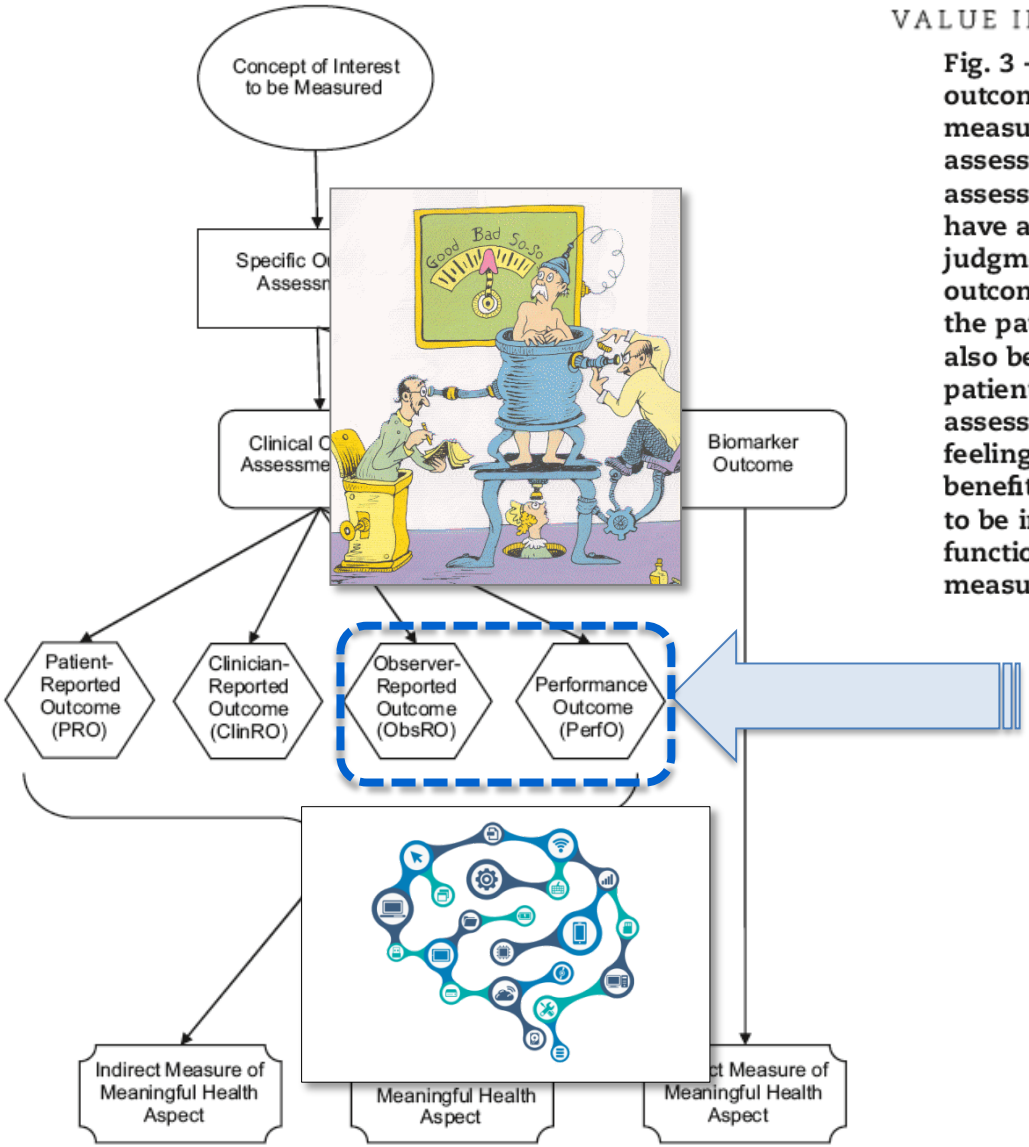
BIOMETRIC MONITORING DEVICES (BMDs)



VALUE IN HEALTH 18 (2015) 741–752

Fig. 3 – Attributes of outcome assessments. A specific outcome assessment is selected or created to operationalize measurement of the concept of interest. Outcome assessments are of two major types: clinical outcome assessments and biomarkers. Clinical outcome assessments have an attribute identifying the type of person whose judgment can influence the reported measurement. Clinical outcome assessments may be influenced by the judgment of the patient, clinician, or a nonclinician observer; they may also be a nonjudged recording of a task performed by the patient (performance outcome). Clinical outcome assessments may be directly reporting the meaningful feelings or functions selected as the potential treatment benefit, or may be reporting measurements that are thought to be indirectly informative regarding those feelings or functions (see Fig. 1). Biomarkers can only indirectly measure the meaningful aspect of health.

Biometric Monitoring Devices

- Less "observer specific bias"
- No need for "observer training"
- Potential for lower cross-site variance of measures
- Reduced clinical fees

Transforming clinical trials with high frequency, objective, continuous data: "Big Data" for each subject

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ORCATECH SENSING LIFE KINETICS

MCI Prevention Trial – Sample Size Estimates

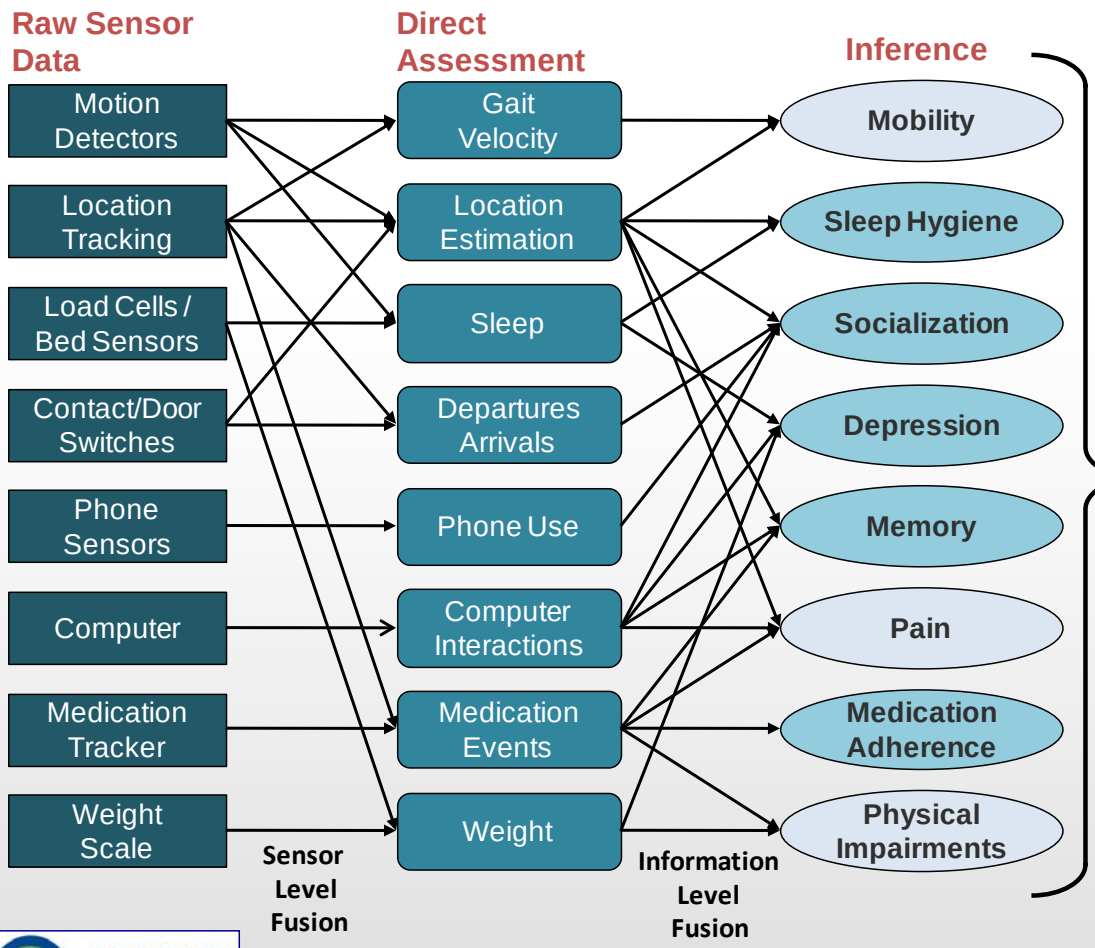
		Continuous Measures	
	LM Delayed Recall*	Computer Current Method Use**	Walking Speed**
SAMPLE SIZE TO SHOW **50% EFFECT**	688	10 [1.5%]	94 [13.7%]
SAMPLE SIZE TO SHOW **40% EFFECT**	1076	16 [1.5%]	148 [13.7%]
SAMPLE SIZE TO SHOW **30% EFFECT**	1912	26 [1.4%]	262 [13.7%]
SAMPLE SIZE TO SHOW **20% EFFECT**	4300	58 [1.4%]	588 [13.7%]

- Reduces required sample size and/or time to identify meaningful change
- Reduces exposure to harm (fewer needed/ fewer exposed)
- More precise estimates of the trajectory of change; allows for *intra-individual* predictions
- Provides the opportunity to substantially improve efficiency and inform go/no-go decisions of trials. **<14% of current patient costs with standard measures.**

Dodge, et al., PLoS One, 2015

NOVEL ASSESSMENT TOOLS
BIOSENSOR DATA FUSION ANALYTICS

Correlations with Validated Outcome Assessments



Change Detection

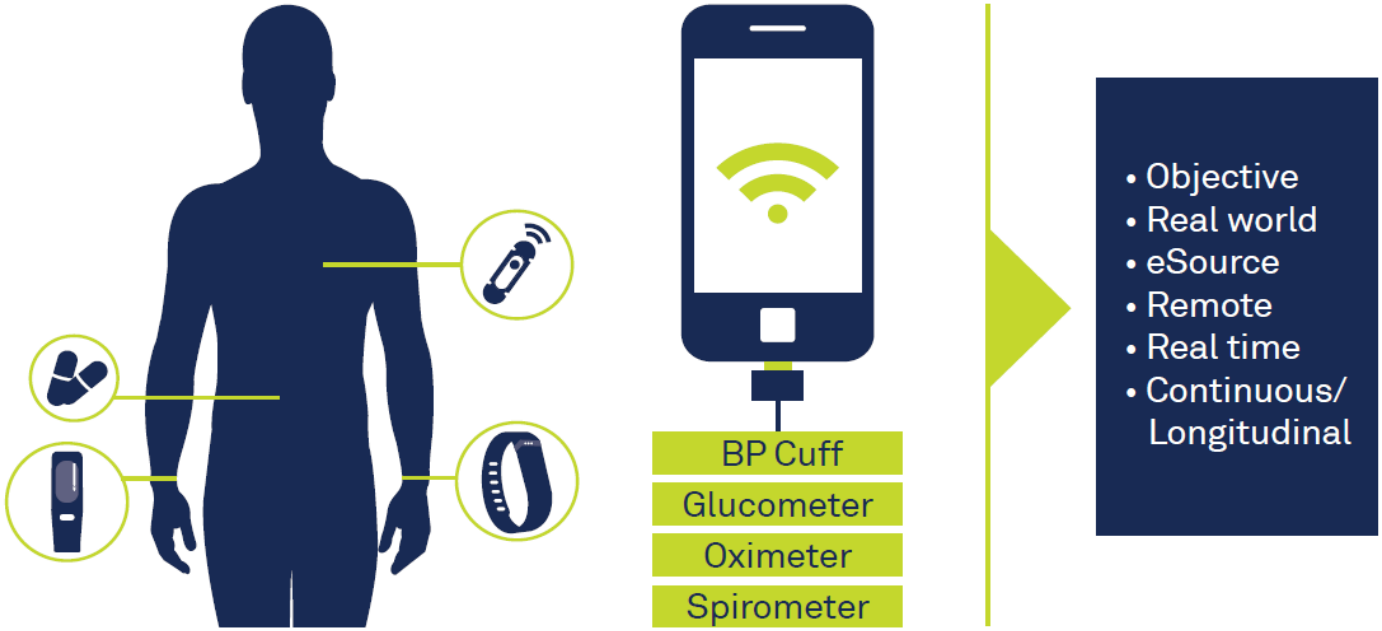
Cross-correlation of functional biosensor measurements with fluid & imaging biomarkers & PROs to develop BOAs

Quality of Life Surrogate

- Independence
- Social Life & Social Participation
- Work Life
- Relationships & Family

CONTINUOUS UNOBTRUSIVE BIOSENSOR DATA COLLECTED IN THE CONTEXT OF DAILY LIVING

Figure 1: Instrumenting produces a new class of data



medidata

04/2015 WHITE PAPER
COMBINING THE DISCIPLINE OF CLINICAL R&D WITH THE PROMISE OF MHEALTH

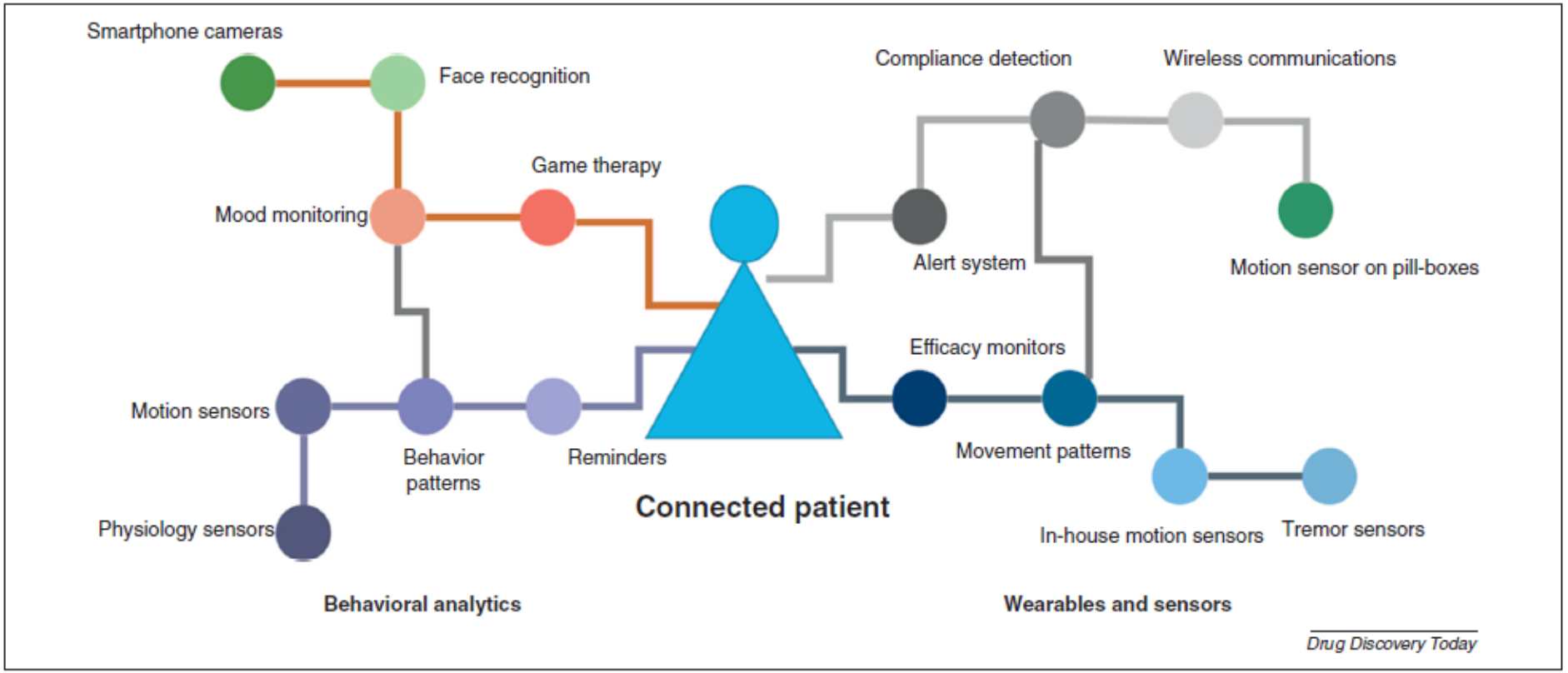


FIGURE 2

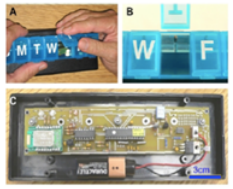
Connected patient. With a side variety of sensors, wearable devices and personal health monitors becoming readily available, it is becoming increasingly important to connect these diverse devices and data to provide benefit to patients in a holistic manner.

"Digital Biomarkers: Sensing Life Kinetics"

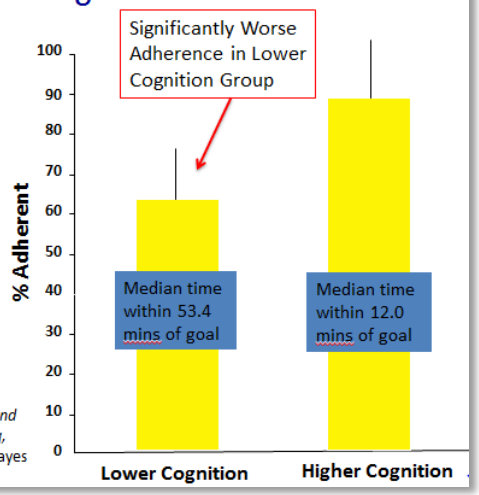
- Dr. Jeffrey Kaye, Director, Oregon Center for Aging & Technology

CAMD

Every Day Cognition:
Medication adherence as a measure of cognitive function

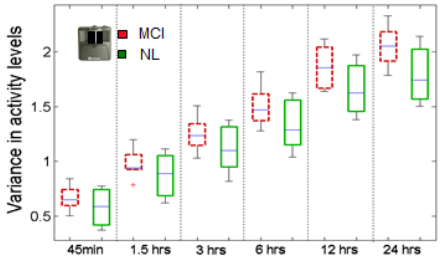


- Adherence assessed continuously x 5 wks with MedTracker taking a
- Mean Age - 83 yrs
- Based on ADAScog: Lower Cognition Group vs Higher Cognition Group



Hayes et al., *Proceedings : Engineering in Medicine and Biology Soc*, 2006; Leen, et al., *Technology and Aging*, 2007 ; Hayes et al. *Journal of Aging Health*, 2009; Hayes et al. *Telemedicine Jounal and E-Health*, 2009

Differentiation of early MCI: Total Activity & Walking



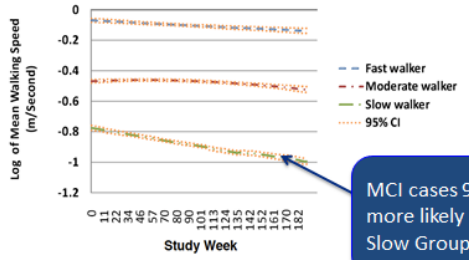
Activity patterns associated with mild cognitive impairment

Hayes et al. Alzheimers Dement, 2008

Trajectories of walking speed over time

Dodge, et al. Neurology, 2012

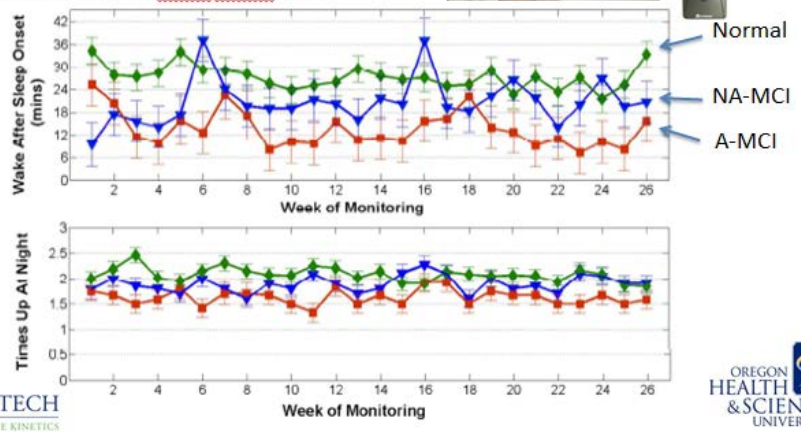
ORCATECH SENSING LIFE KINETICS



MCI cases 9X more likely in Slow Group

Differentiation of early MCI:
Night-time Behavior & Sleep

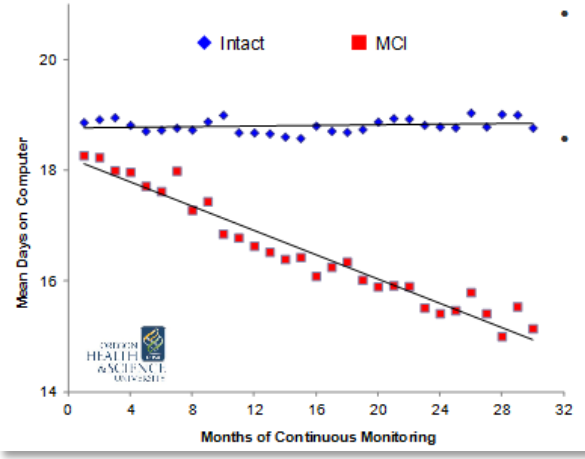
Hayes, et al. Alzheimer Dis Assoc Disord. 2014



ORCATECH SENSING LIFE KINETICS

OREGON HEALTH & SCIENCE UNIVERSITY

Routine home PC use over time (*without formal tests or queries*) detects change in those with MCI



- Mean 1.5 hours on computer/per day at baseline month
- Over time:
  - *Less use days per month*
  - *Less use time when in session*
  - *More variable in use pattern over time*

Kaye, et al. AAIC, 2011

DEFINING DISEASE

Disease (ICD-10 code) = **Symptoms** + **Signs**

Use in Drug Development & Reimbursement

- Alzheimer's disease
- Parkinson's disease
- Huntington's disease
- Multiple Sclerosis
- Duchenne's

Patient Outcome

- Cognition
- Behavior (sleep/mood)
- Motor function
- Sensation
- Balance & Coordination
- Autonomic

Observer / Performance Outcome

- Cognition
- Behavior (sleep/mood)
- Motor function
- Sensation
- Balance & Coordination
- Autonomic

- **Independence**
- **Social Life & Social Participation**
- **Work Life**
- **Relationships & Family**

Functional Impact Domains

Cross- correlation of functional biosensor measurements with fluid & imaging biomarkers & PROs

Cedarbaum et al. (2015) Commonalities and challenges in the development of clinical trial measures in Neurology, Neurotherapeutics , 12:151–169.

DEFINITIONS OF MEASURED OUTCOMES

Used in Developing a Biomarker or COA

- **Measurement:** The obtained value using a test, tool, or instrument.
- **Test, Tool, or Instrument:** An assessment system comprising three essential components: 1) signs or symptoms for measurement; 2) an assay for obtaining the measurement; and 3) method and/or criteria for interpreting those measurements.
- **Biomarker:** A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives .
- **Assessment:** The interpretation or the evaluation of the measurement.
- **Outcome:** The measureable characteristic (clinical outcome assessment, biomarker) that is influenced or affected by an individuals' baseline state or an intervention as in a clinical trial or other exposure.
- **Outcome assessment:** An assessment of an outcome that results in recorded data point(s) (e.g., for a biomarker or clinical outcome assessment).
- **Clinical outcome:** An outcome that describes or reflects how an individual feels, functions or survives.
- **Clinical outcome assessment (COA):** Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician, observer or through a performance-based assessment. There are four types of COAs.
  - clinician-reported outcome; observer-reported outcome; patient-reported outcome; performance outcome
- **Endpoint:** A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.

BIOSENSORS CAN PROVIDE ObsROs

Observer-reported outcomes (ObsROs): A type of clinical outcome assessment. A measurement based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than the patient or a health professional. Generally, ObsROs are reported by a parent, caregiver, or someone (*biosensor*) who observes the patient in daily life and are particularly useful for patients who cannot report for themselves (e.g., infants or individuals who are cognitively impaired). An ObsRO measure does not include medical judgment or interpretation. ObsRO measures include:

- Rating scales, such as: Acute Otitis Media Severity of Symptoms scale (AOM-SOS), a measure used to assess signs and behaviors related to acute otitis media in infants
- Face, Legs, Activity, Cry, Consolability scale (FLACC), a measure used to assess signs and behaviors related to pain
- Counts of events (e.g., observer-completed log of seizure episodes)

DISEASES ARE DEFINED BOTH BY SIGNS & SYMPTOMS

Signs

(Objective and Observable)

A medical sign is an objective feature indicating a medical fact or characteristic that is detected by a physician, nurse, or medical/laboratory device during the examination of a patient.

Sometimes, a sign may not be noticed by the patient, or not seem relevant to them, but it is meaningful for the physician.

High blood pressure is a sign - this may indicate a cardiovascular problem, a reaction to medication, an allergy, as well as many other possible conditions or diseases.

Symptoms

(Patient Reported and Subjective)

There are three main types of symptoms:

Chronic symptoms - long lasting or recurrent symptoms. These are often seen in diabetes, asthma, and cancer.
Relapsing symptoms - symptoms which had occurred in the past, disappeared, and then come back. For instance in depression, multiple sclerosis, and also cancer.
Remitting symptoms - when symptoms improve, and sometimes go away completely.
Diseases and conditions can also be described as:

Asymptomatic diseases/conditions - this means the disease is present, but there are no symptoms. For example, during the early stages of breast cancer, the patient may feel no symptoms at all. High blood pressure (hypertension) is often asymptomatic.

NEW MEDICAL DEVICE GUIDANCE

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications

Document issued on August 24, 2016.

The draft of this document was issued on August 15, 2011.

As of October 23, 2016, this document supersedes "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications" dated March 28, 2012.

For questions about this document concerning devices regulated by CDRH, contact the Office of the Center Director at 301-796-5900. For questions about this document concerning devices regulated by CBER, contact the Office of Communication, Outreach and Development (OCOD) by calling 800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Decision Summaries and Device Labeling

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

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For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537 (Anindita.Saha@fda.hhs.gov)..

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

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MOBILE IN CLINICAL TRIALS

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Craig Lipset, MBA
Head of Clinical Innovation, **Pfizer Inc**
Cal Collins
CEO, **OpenClinica**
Jennifer Goldsack, MChem, MA, MBA, CPHQ
Clinical Project Manager, **CTTI**
David Haddad
Executive Director, **Open mHealth**
Nicole Miskel, RPh
Advisor, Clinical Innovation, **Eli Lilly & Co**
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Global Head Early Development Workflows, pRED Informatics, **Roche Pharmaceutical**
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VP, Global Head Clinical Development Movement Disorders & Neurodegenerative Diseases, **Teva Pharmaceuticals**
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Medical Affairs Lead, **ContinUse Biometrics**
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Leader, Otsuka Information Technology, **Otsuka Pharmaceuticals**
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Faculty Director and Entrepreneur-in-Residence, **MIT**
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Research Fellow, **National Cancer Institute**
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CEO, **mProve Health**
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Managing Director, Mobile Health, **Medidata Solutions**
Julian Jenkins, PhD
VP, Innovation Performance & Technology, **GSK**
Jane Rhodes, MBA, PhD
Director of New Initiatives, **Biogen Idec**
Panelists:
Willie Muehlhausen
VP, Head of Innovation, **ICON plc**
William Shaw
IP Counsel, **Biogen Idec**

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