Current perspectives on digital biomarker development in early clinical research

17 May 2019

Better Health, Brighter Future

Outline

- Background
- Digital biomarker: definition
- Device selection
- Clinical trial implementation
- Regulatory Framework
- Challenges and future directions

Background

- Wearable technology is being increasingly implemented in clinical drug development (330 clinical trials: clinicaltrials.gov; 2017).
- Allows the collection of observable data non-invasively, in real-time, in a patient's natural setting.
- Enhances understanding of the effects of treatment and how symptoms change during daily life.
- Much enthusiasm contrasted with the need for more rigorously produced data for the field to progress and establish validated methodologies.
- Opportunities and challenges related to emergence of digital biomarkers.

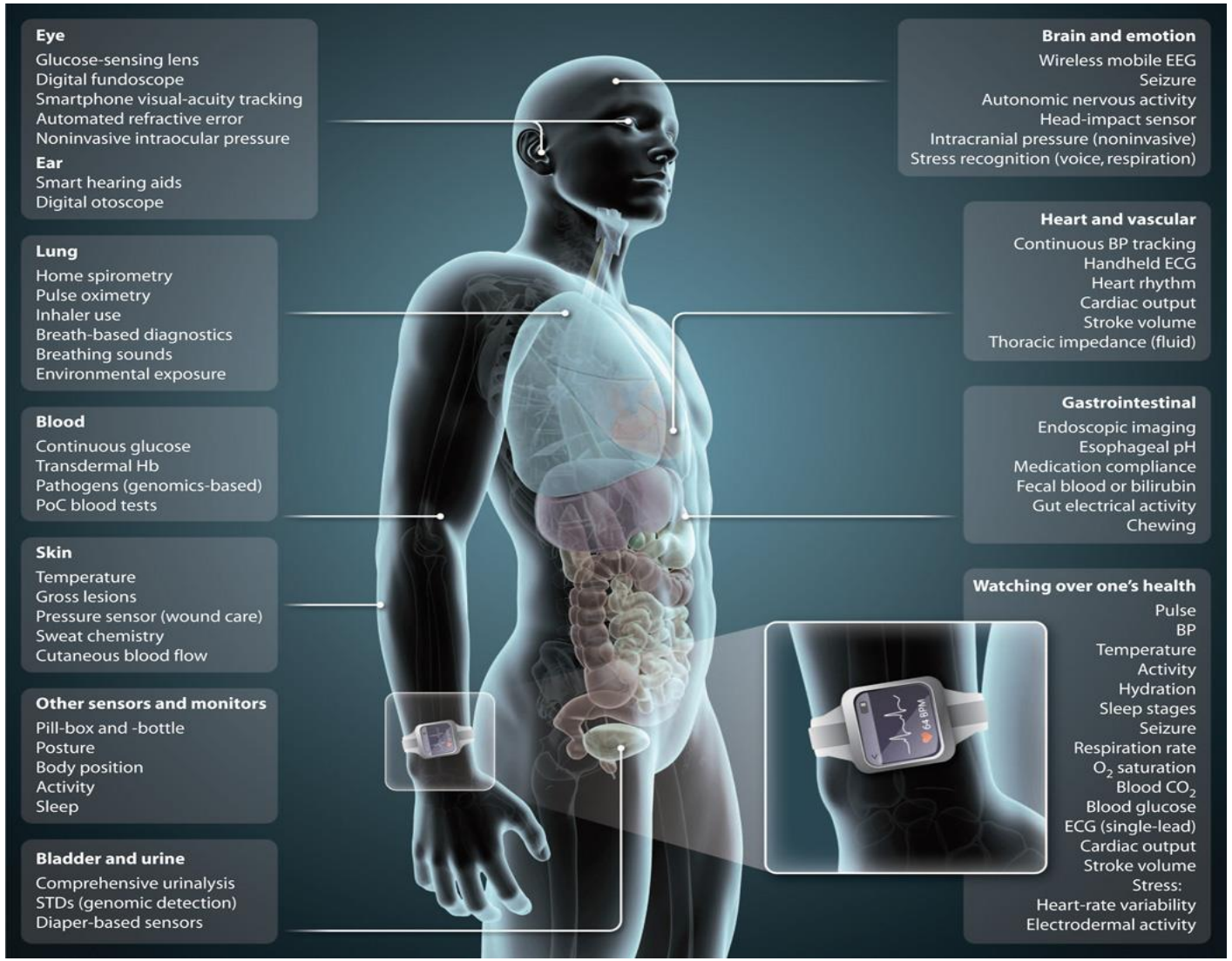
Rogozinska, M. Z. (2018). Can the use of novel digital devices improve the productivity of drug development?. *Clinical Pharmacology & Therapeutics*, *104*(1), 35-37.

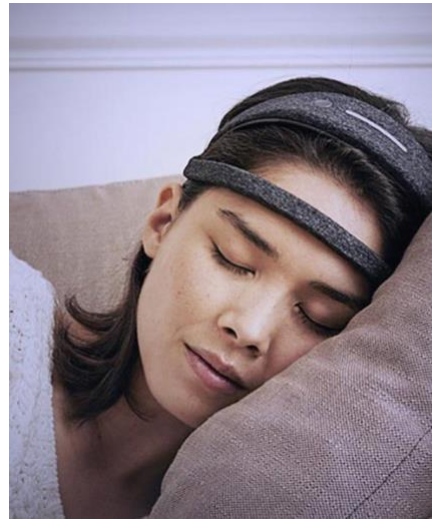
Digital Biomarker: Definition

Objective measurements of biological processes that reflect physiological responses to disease progression or therapeutic intervention collected using a digital device. These can ideally be correlated to clinical endpoints of interest or can access novel or additional markers of disease prognosis or progression

Kothare, P. A., Jadhav, P. R., Gupta, P., Harrelson, J. C., & Dickmann, L. (2018). Harnessing the Potential of Emerging Digital Health and Biological Sampling Technologies for Clinical Drug Development: Promise to Reality. *Clinical Pharmacology & Therapeutics*, *104*(6), 1125-1135.

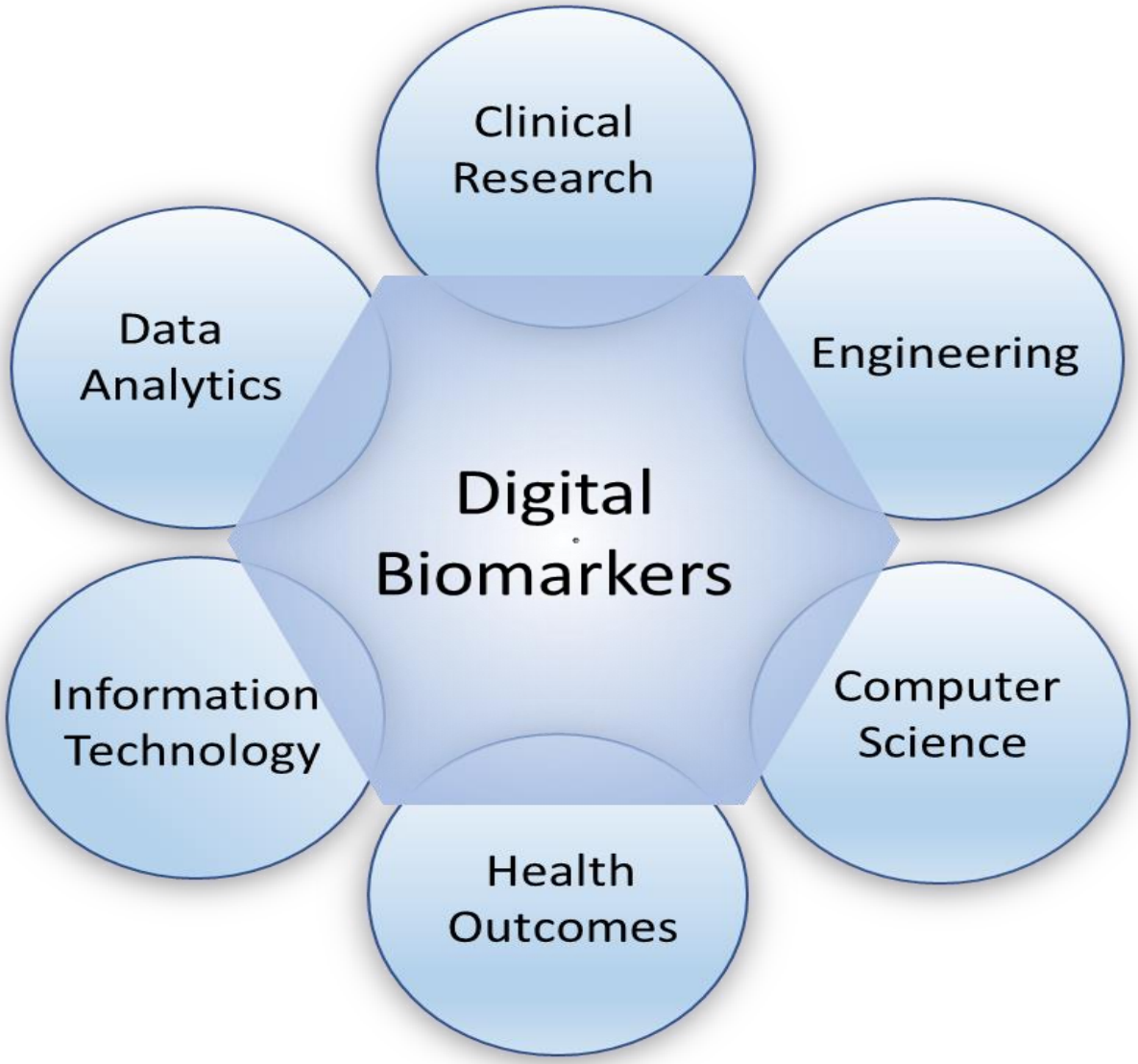
Use of a biosensor to collect objective data on a biological, anatomical, or physiological parameter



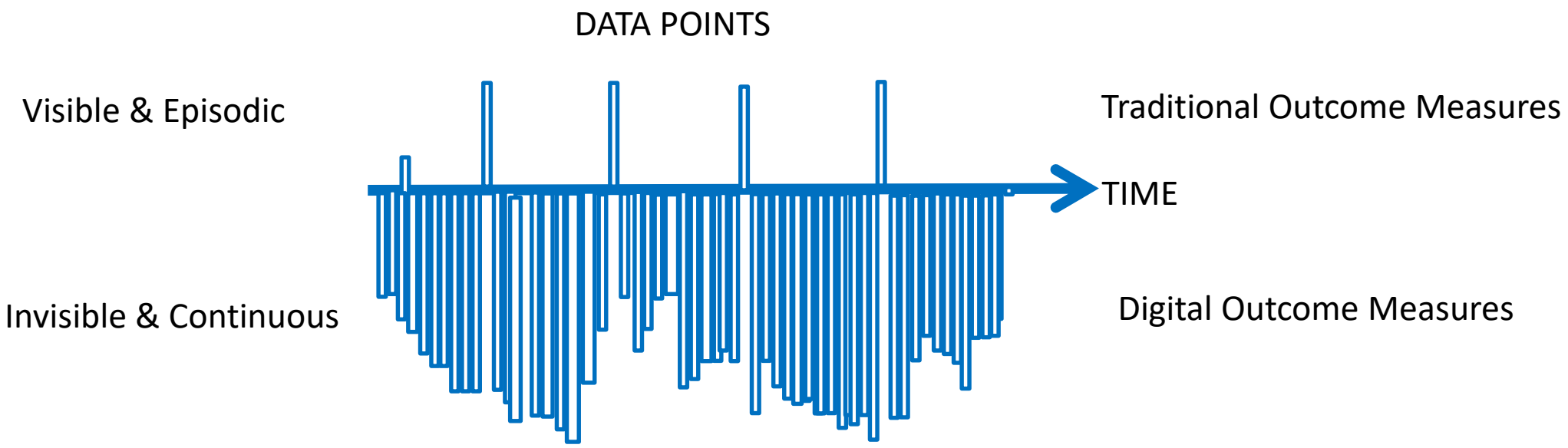


3. Steinhubl, S. R., Muse, E. D., & Topol, E. J. (2015). The emerging field of mobile health. *Science translational medicine*, *7*(283), 283rv3-283rv3.

Multi-Stakeholder Collaboration

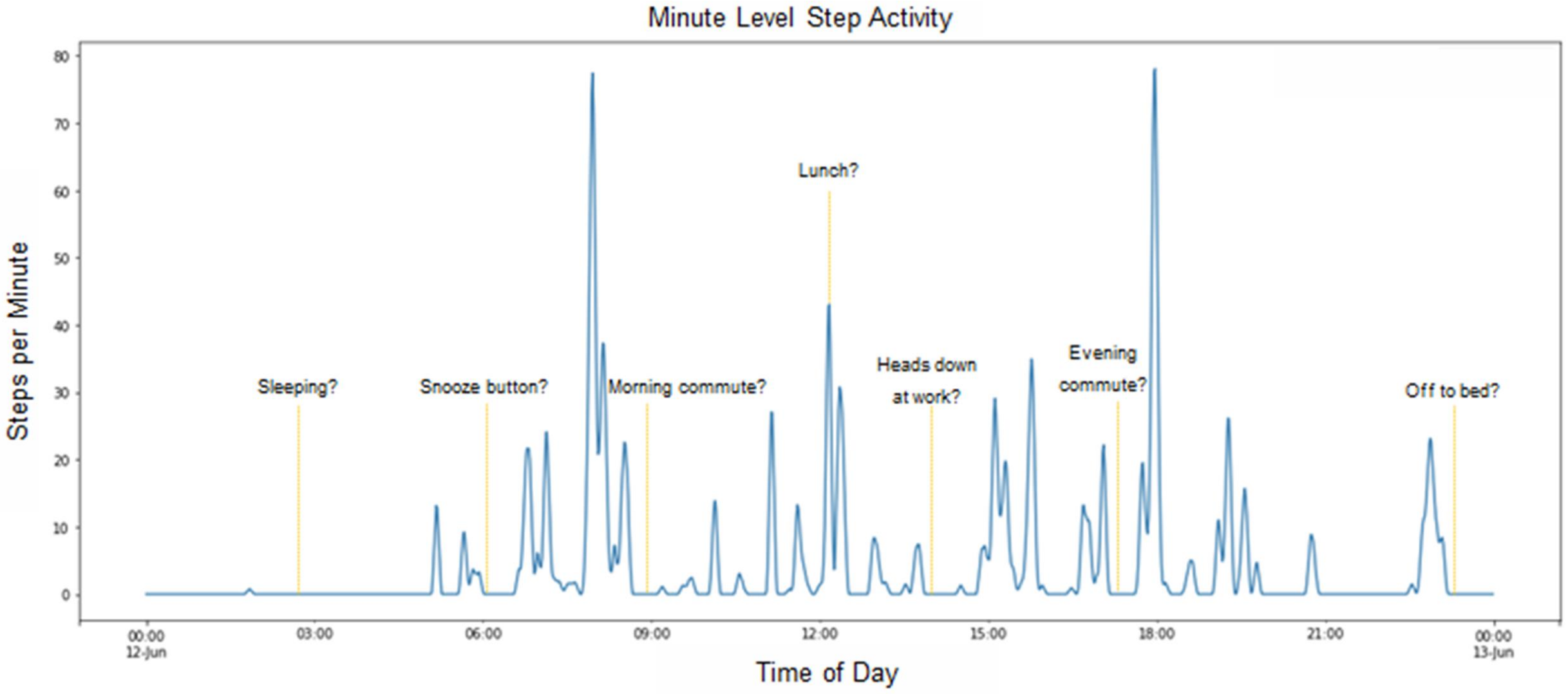


Limited data-sets have been used to characterize endpoints



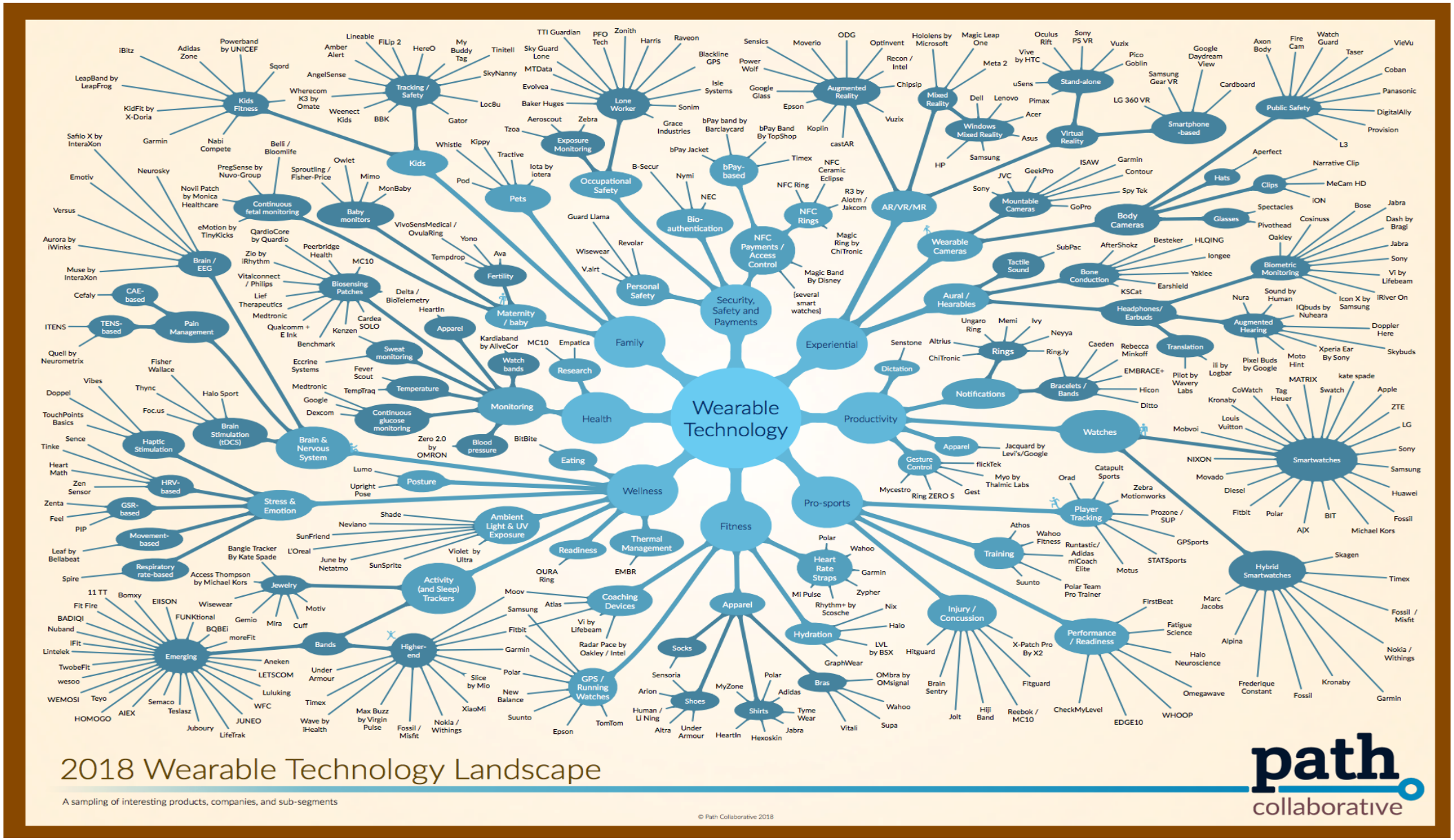
- Currently data collection occurs with a protocol-specified schedule of events
- *New paradigm* includes continuous measurements outside the clinic
- Consider how we interpret the data and how we think about validating the methods?

Minute level data provides insights on an individual's activity patterns via accelerometry.



The Importance of Metadata for Interpretation

Device Selection



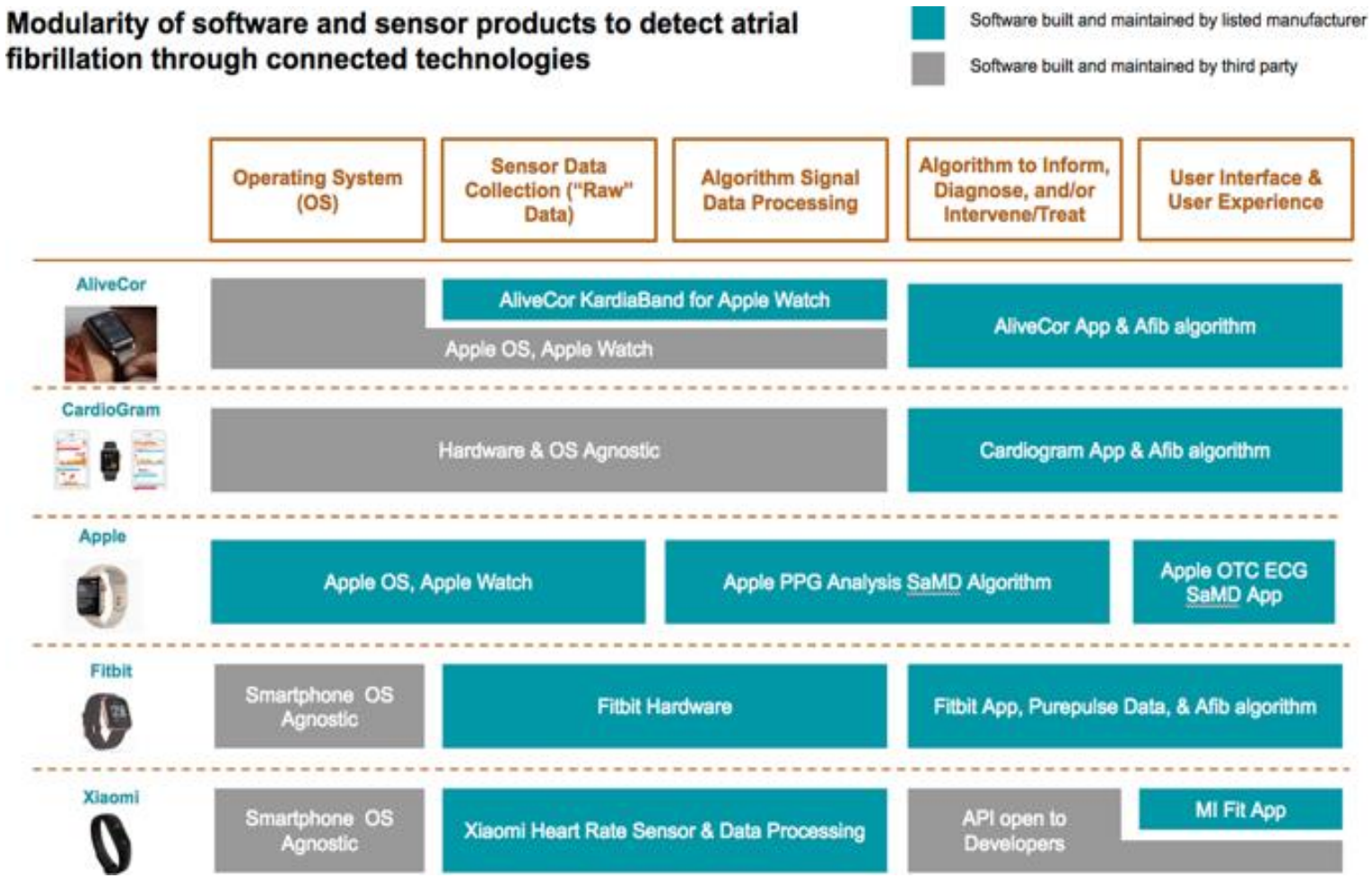
Fit-for-Purpose Device Selection

- The device chosen should have an **explicit context of use**; meet appropriate requirements for **accuracy and precision**.
- Accompanied by the metadata required for analysis and interpretation.
- Both **consumer grade and research grade devices** are being assessed for the development of digital biomarkers e.g. Fitbit.
- **Data protection and security.** In the EU the **General Data Protection Regulation** not specific to device type and covers all data generated by wearables or apps in a medical context.

Wright, S. P., Collier, S. R., Brown, T. S., & Sandberg, K. (2017). An analysis of how consumer physical activity monitors are used in biomedical research. *The FASEB Journal*, *31*(1_supplement), 1020-24.

Research vs Consumer-Grade Wearables

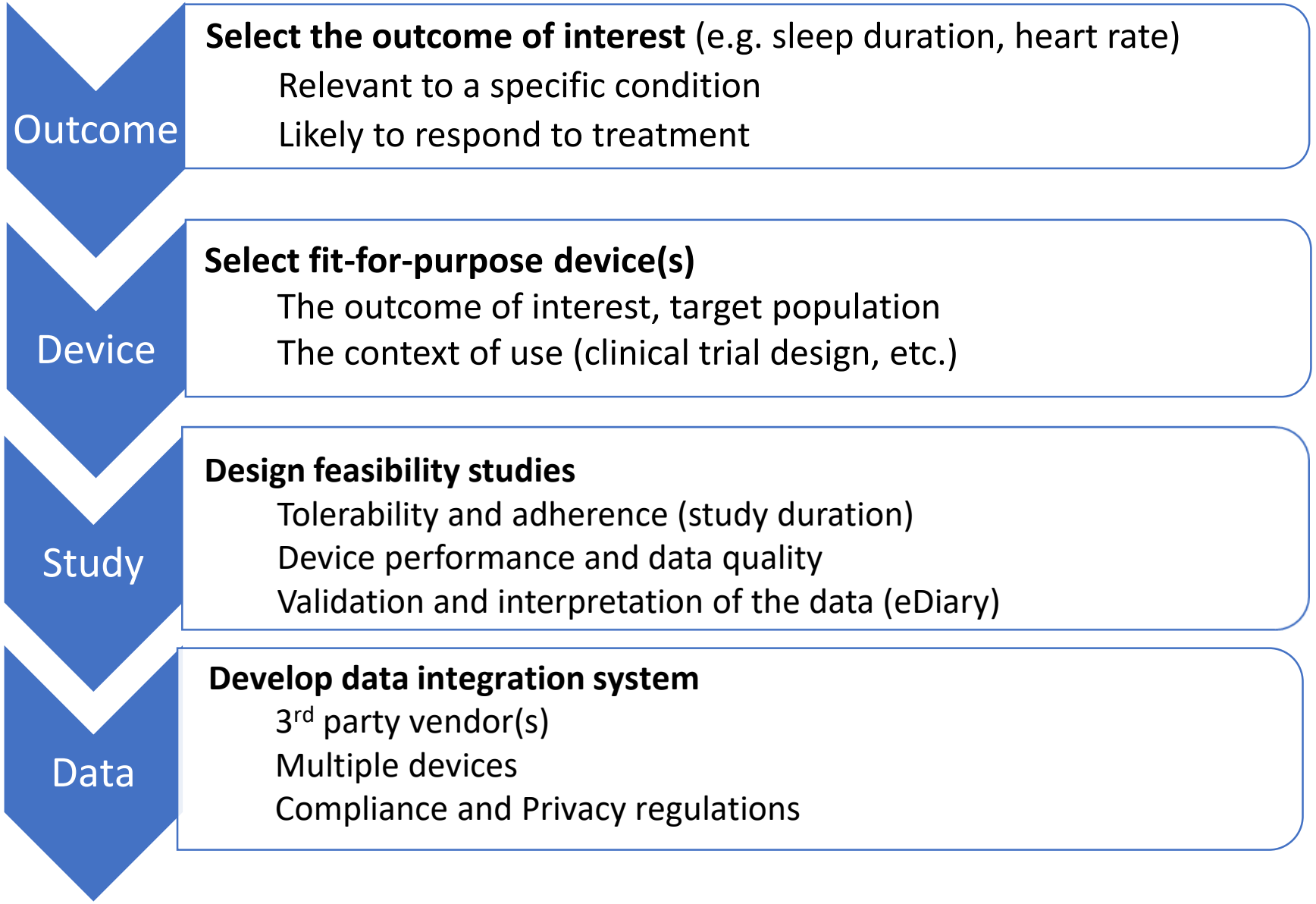
- **Research devices**:
  - Large scientific evidence base e.g. ActiGraph
  - Raw data for algorithm development
- **Consumer devices:**
  - Influence of Real World Data.
  - Challenging to meet clinical trial grade outcomes.



Coravos, Khozin, and Mandi. Npj Digital Medicine (2019) 14

Framework for FDA's Real World Evidence Program. December 2018. www.FDA.gov

Designing studies with Digital Devices



Examples of Digital Biomarkers

Research

JAMA Neurology | Brief Report

Using Smartphones and Machine Learning to Quantify Parkinson Disease Severity The Mobile Parkinson Disease Score

Andong Zhan, MS; Srihari Mohan; Christopher Tarolli, MD; Ruth B. Schneider, MD; Jamie L. Adams, MD; Saloni Sharma, MD; Molly J. Elson, BA; Kelsey L. Spear, MPH; Alistair M. Glidden, BS; Max A. Little, PhD; Andreas Terzis, PhD; E. Ray Dorsey, MD; Suchi Saria, PhD

RESEARCH ARTICLE

Evaluation of Smartphone-Based Testing to Generate Exploratory Outcome Measures in a Phase 1 Parkinson's Disease Clinical Trial

Florian Lipsmeier, PhD,[1] Kirsten I. Taylor, PhD,[1] Timothy Kilchenmann, MSc,[1] Detlef Wolf, MSc,[1] Alf Scotland, MSc,[1]

Location Patterns from Phone Sensors May Help Predict Depressive Symptoms: A Longitudinal Pilot Study

E. Howe[1], A. Ghandeharioun[2], P. Pedrelli[1,3], D. Mischoulon[1,3], R. Picard[2,4] S. Fedor[2,5]

[1]Massachusetts General Hospital, Boston, MA, USA, [2]Massachusetts Institute of Technology Media Lab, Cambridge, MA, USA, [3]Harvard Medical School, Boston, MA, USA [4]Empatica, Cambridge, MA, USA, [5]University of Cambridge, Cambridge, UK

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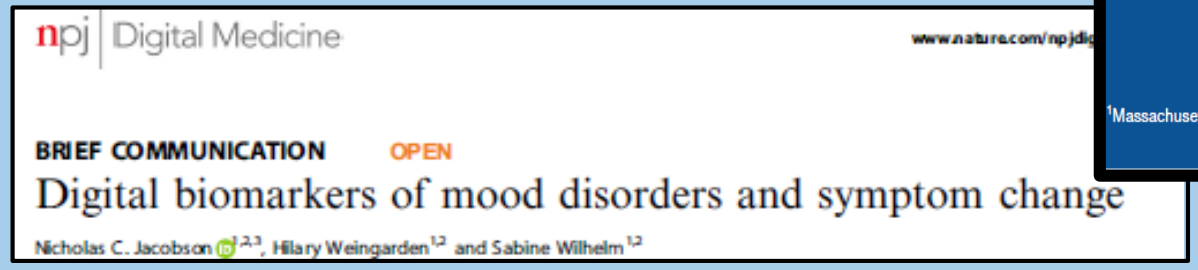


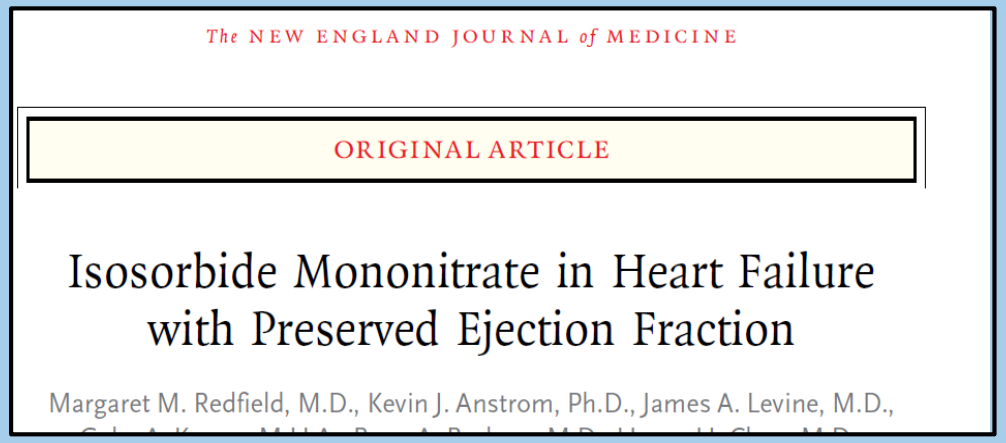
npj | Digital Medicine

www.nature.com/npjdi

BRIEF COMMUNICATION OPEN

Digital biomarkers of mood disorders and symptom change

Nicholas C. Jacobson[1,2,3], Hilary Weingarden[1,2] and Sabine Wilhelm[1,2]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

Margaret M. Redfield, M.D., Kevin J. Anstrom, Ph.D., James A. Levine, M.D.,

EMB IEEE ComSoc IEEE JOURNAL OF BIOMEDICAL AND HEALTH INFORMATICS, VOL. 22, NO. 4, JULY 2018 1011

Detection of Nocturnal Scratching Movements in Patients with Atopic Dermatitis Using Accelerometers and Recurrent Neural Networks

Arnaud Moreau, Peter Anderer, Marco Ross, Andreas Cerny, Timothy H. Almazan, and Barry Peterson

Guidelines and Frameworks for Deploying Wearables

CTTI & ePRO CONSORTIUM RECOMMENDATIONS FOR OPTIMIZING NOVEL ENDPOINT SELECTION

- Focus on measures that are **meaningful to patients**
- Select the device after selecting an **outcome assessment**.
- Is the device **fit for purpose** to measure concepts of interest identified?
- Is there satisfactory evidence of data **reliability** and **validity** from the device?
- Include novel **endpoints as exploratory endpoints** in existing clinical trials.
- **Early regulatory engagement is essential** if the dossier reliant on these data

Developing Novel endpoints generated by mobile technology for use in clinical trials. Available at: <https://www.ctti-clinicaltrials.org/projects/novel-endpoints>

Byrom, B., Watson, C., Doll, H., Coons, S. J., Eremenco, S., Ballinger, R., ... & ePRO Consortium. (2018). Selection of and evidentiary considerations for wearable devices and their measurements for use in regulatory decision making: recommendations from the ePRO Consortium. *Value in Health*, *21*(6), 631-639.

Moving Forward

- Value of incorporating new technologies will need to be justified against upfront investment and costs.
- A reliable and robust evidence base for demonstrating the clinical validation of devices relative to existing “gold standards” is largely missing.
- Still need systems that are configured to ensure privacy and security of patient information powerful analytic platforms capable of real-time analysis.
- **Early development expertise essential** to enabling rapid clinical evaluation of technologies and advancement of the field.


Questions ?
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