Recent advances towards fit-for-purpose biometric monitoring technologies in early clinical development

V. Parks

Association Francaise de Pharmacologie Translationnelle, Le Club Phase 1, Thursday, 16th June

Outline

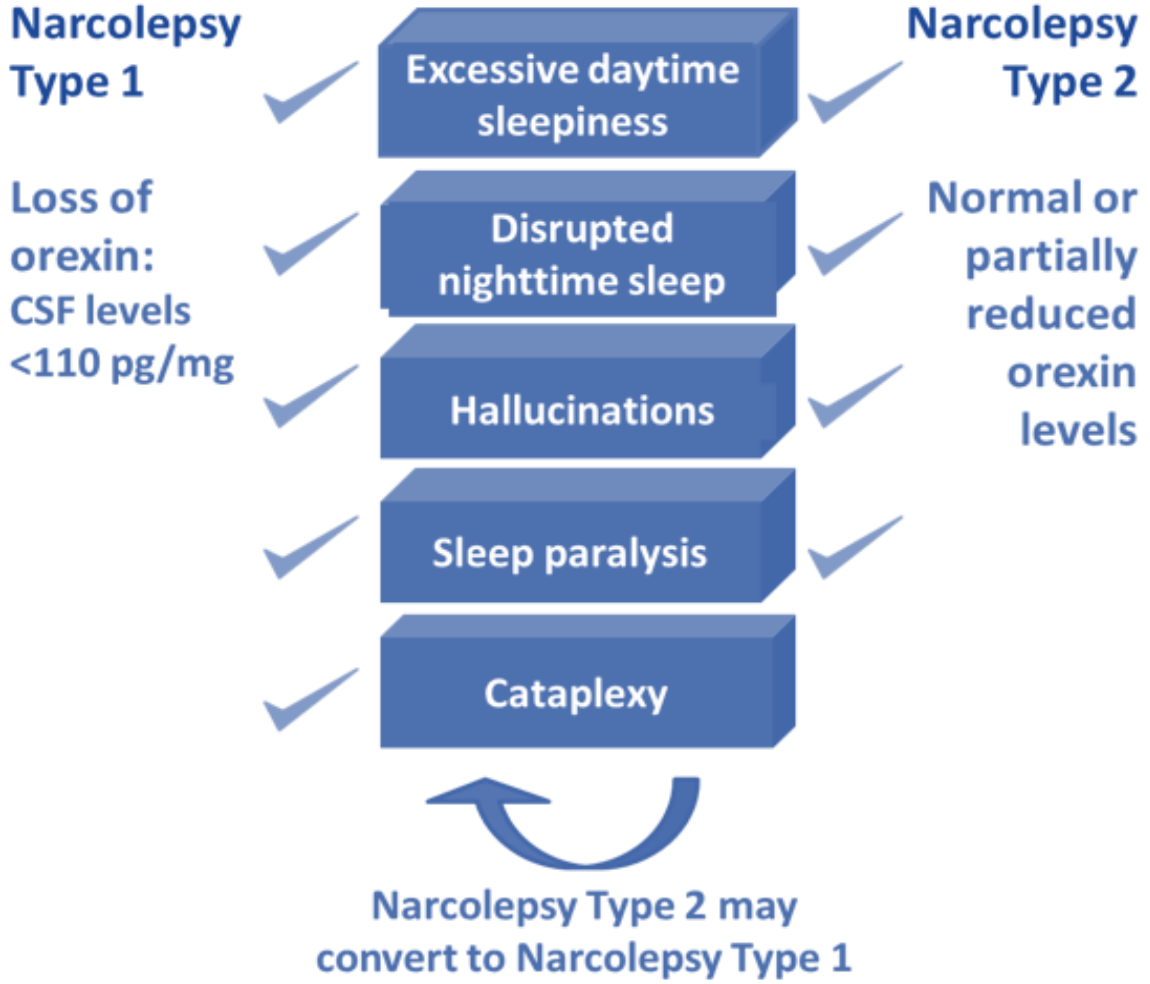
- Example from sleep medicine
- Device selection
- Regulatory Perspective
- Q&A

This presentation does not include any data or results from Takeda drug trials

Case study outline: Narcolepsy

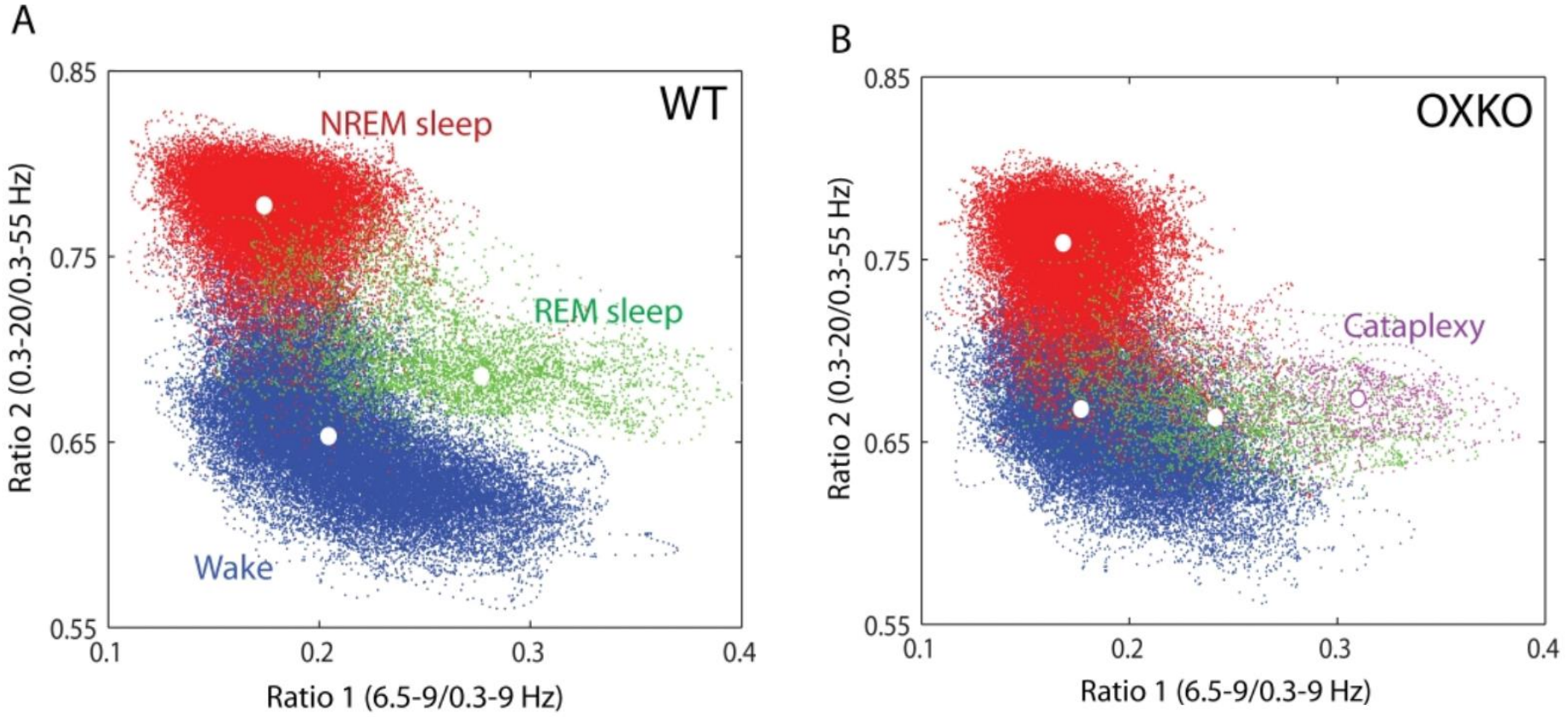
- NT1 caused by severe loss of neurons that produce the orexin (hypocretin) neurotransmitters in the hypothalamus.
- Longitudinal objective measures of symptoms are limited making it difficult to evaluate therapies.

- **Cataplexy is assessed by Weekly Cataplexy Rate (WCR) recorded in patient diaries.**
- **NT is assessed via polysomnography (PSG); overnight clinical multi-parametric analysis including electroencephalography (EEG).**



Scammell, T. E. (2015). Narcolepsy. *New England Journal of Medicine*, *373*(27), 2654-2662.

Translational Murine models of NT show narcoleptic mice have less distinct and more labile states of sleep and wakefulness



Diniz Behn, C. G., Klerman, E. B., Mochizuki, T., Shih-Chieh, L., & E. Scammell, T. (2010). Abnormal sleep/wake dynamics in orexin knockout mice. *Sleep*, *33*(3), 297-306.

Deep learning based analysis of sleep & wakefulness signatures

Rapid transition to REM at start of night vs control

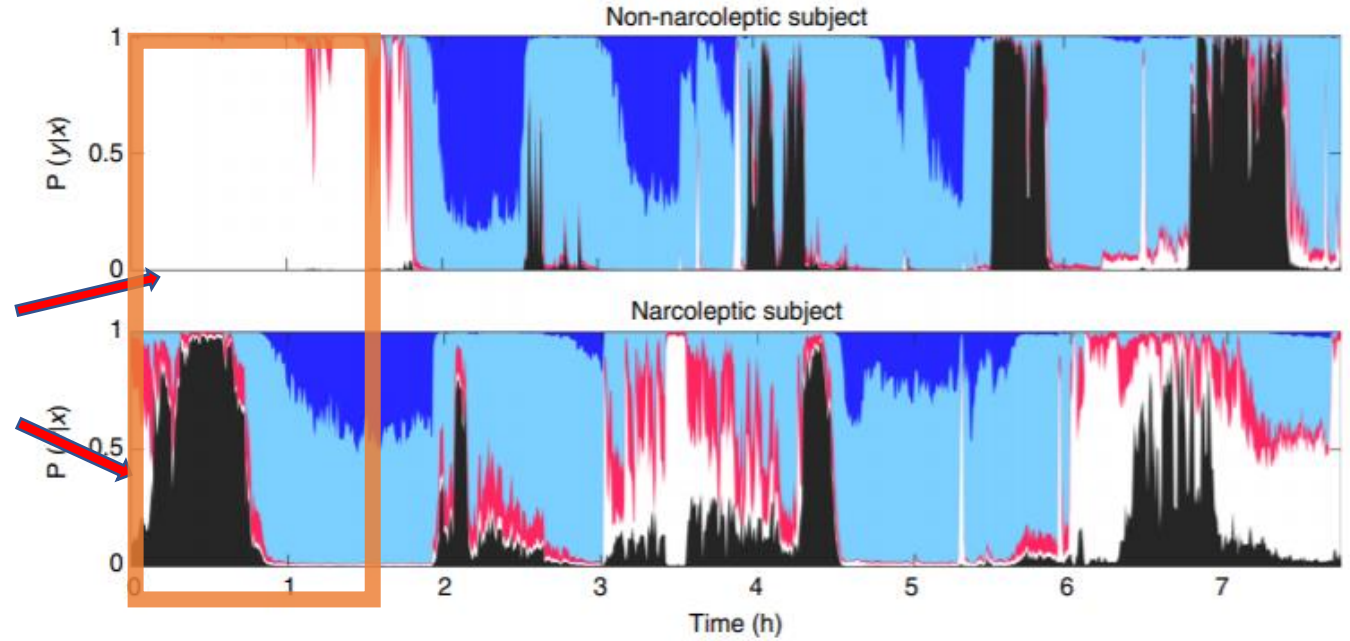


Fig. 3 Examples of hypnodensity graph in subjects with and without narcolepsy. Hypnodensity, i.e., probability distribution per stage of sleep for a subject without narcolepsy (top) and a subject with narcolepsy (Bottom). Color codes: white, wake; red, N1; light blue, N2; dark blue, N3; black, REM

Stephansen, J. B., Olesen, A. N., Olsen, M., Ambati, A., Leary, E. B., Moore, H. E., ... & Mignot, E. (2018). Neural network analysis of sleep stages enables efficient diagnosis of narcolepsy. *Nature communications*, *9*(1), 1-15.

Key Features of article:

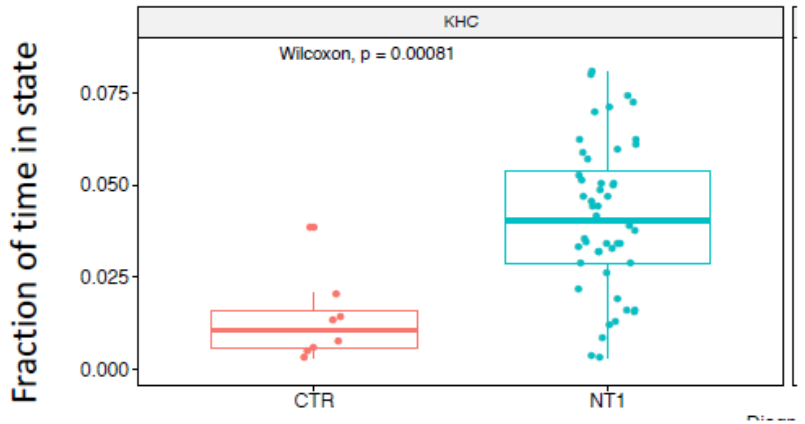
- **Novel scoring output: probability in a given stage.**
- **Accurate automated sleep scoring.**
- **State-of-the art NT1 detection based on unusual sleep stages + genetics.**
- **Long-term potential for fast sleep staging, at home NT1 diagnosis**

Novel Exploration of Alternative Definitions of Sleep States

Clustering hynodensity data yields candidate novel sleep states

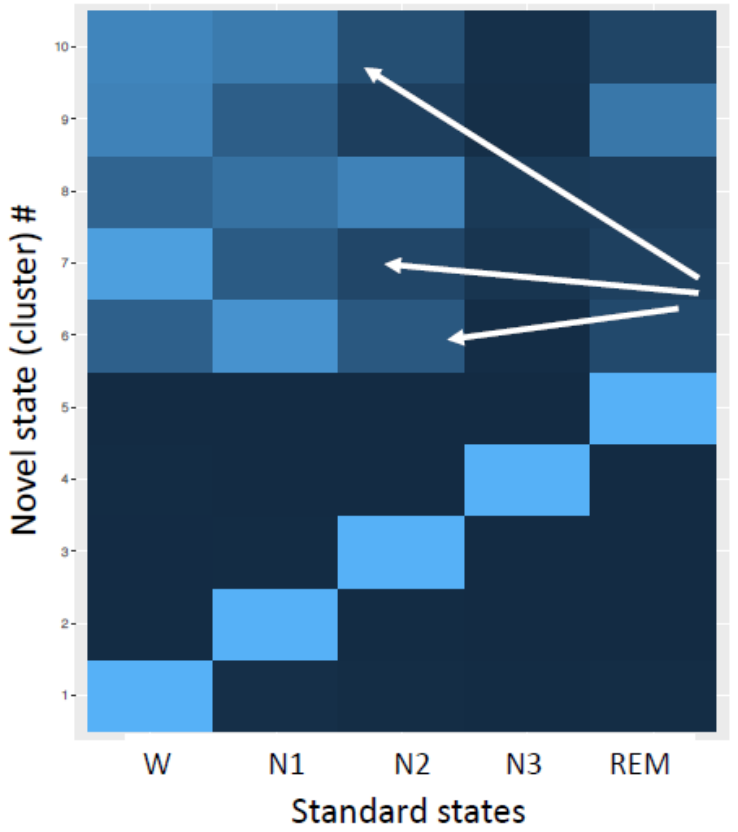
Approach

- Developed classification-guided clustering techniques to identify key time periods
- Training data: 362 subjects (114 NT1)
- Cluster the hypnodensities in these periods
  - Currently using k-means clustering, k = 10
  - Use data weighting to enforce standard states are found as the first five states



Time spent in mixed REM/Wake state discriminates NT1 from non-NT1

Clustering -> mixtures involving REM, Wake + N1



REM-wake mix (!)

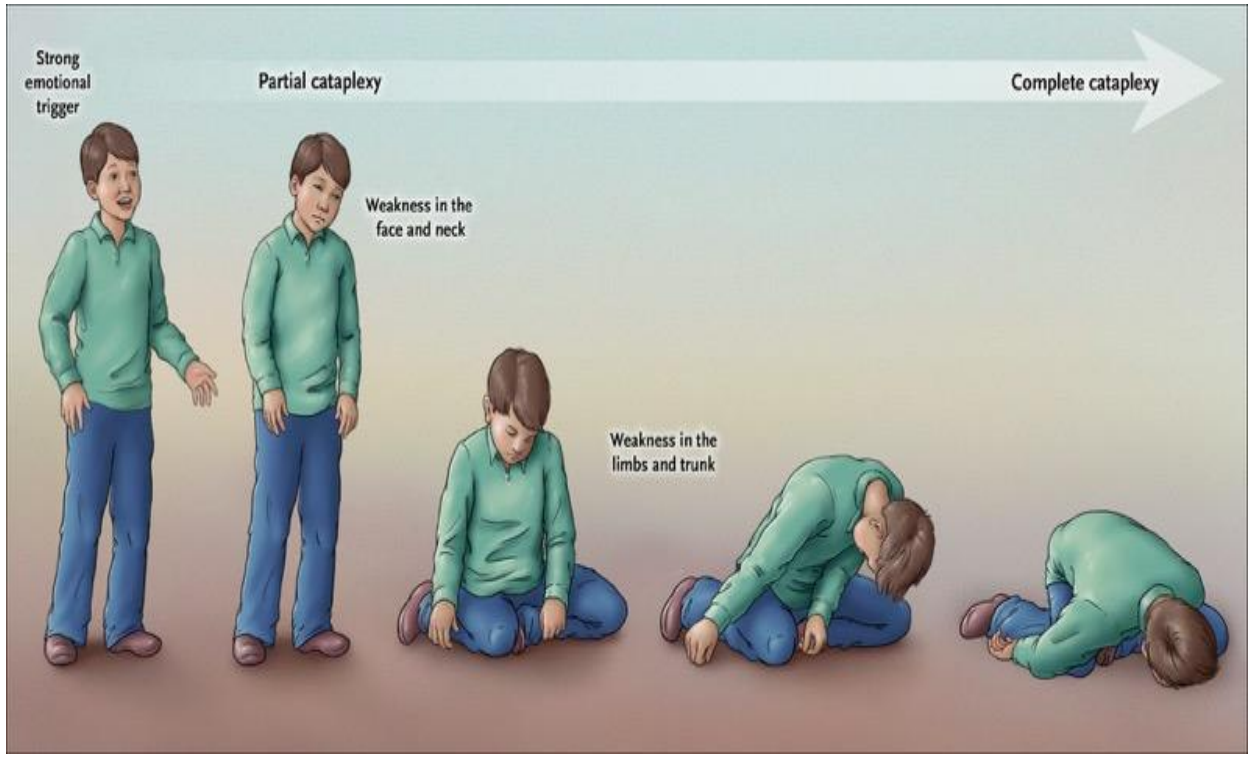
N2+N1

Wake+N1, with some REM and N2

plotting sqrt(weight) to highlight weaker contributions

B. Tracey 'Machine Learning to Study Narcolepsy' Sleep 2020

Physiological Markers of Cataplexy



Scammell, T. E. (2015). Narcolepsy. *New England Journal of Medicine*, *373*(27), 2654-2662.

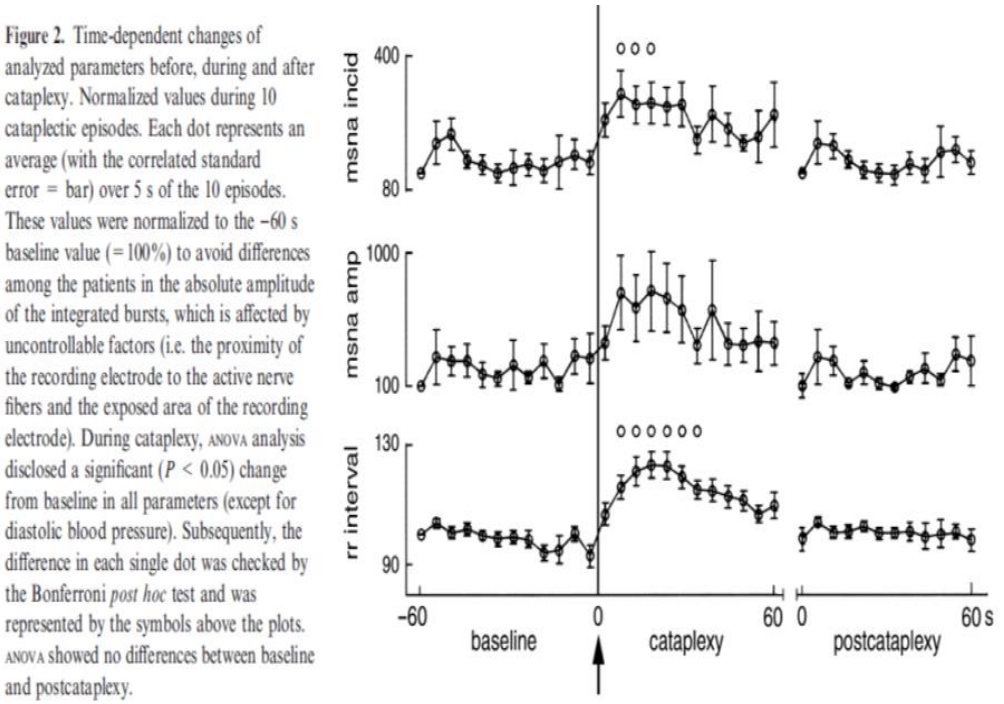


Figure 2. Time-dependent changes of analyzed parameters before, during and after cataplexy. Normalized values during 10 cataplectic episodes. Each dot represents an average (with the correlated standard error = bar) over 5 s of the 10 episodes. These values were normalized to the −60 s baseline value (= 100%) to avoid differences among the patients in the absolute amplitude of the integrated bursts, which is affected by uncontrollable factors (i.e. the proximity of the recording electrode to the active nerve fibers and the exposed area of the recording electrode). During cataplexy, ANOVA analysis disclosed a significant ($P < 0.05$) change from baseline in all parameters (except for diastolic blood pressure). Subsequently, the difference in each single dot was checked by the Bonferroni *post hoc* test and was represented by the symbols above the plots. ANOVA showed no differences between baseline and postcataplexy.

Donadio, V., Plazzi, G., Vandi, S., Franceschini, C., Karlsson, T., Montagna, P., ... & Liguori, R. (2008). Sympathetic and cardiovascular activity during cataplexy in narcolepsy. Journal of sleep research, 17(4), 458-463.

- Sudden, emotionally triggered episodes of muscle weakness with preserved consciousness.
- Typically begin with weakness of the muscles of the face and neck.
- Spreads to involve the muscles of the limbs and trunk.
- Cardiovascular activity changes pre-during-post cataplexy to monitor episode

Portable Devices for EEG, Accelerometry, and EGG for scalable approaches in clinical trials

Internal example of NT1 standard nPSG[1]

Portable devices to be included in the study:

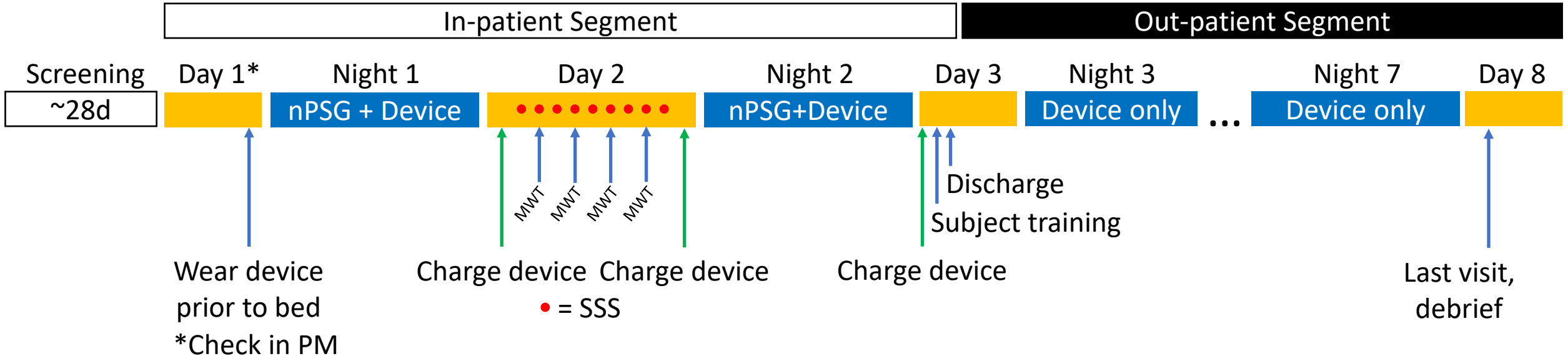
- EEG device: DREEM headband
- ECG device: Body Guardian heart/mini
- Accelerometer: Actigraph Centrepoint
- ePRO for patient diary

Goal is to have all devices working off of one handheld for data upload.

1. Based on algorithms developed by Stephansen et al, 2018

*A. Dowling, SCOPE SUMMIT, Miami, 2021

Study: Wake and Sleep State Transitions on a Portable Electroencephalogram (EEG) Device in Narcolepsy Patients and Healthy Participants*



1. Study includes 16 people with narcolepsy and 16 age/gender matched healthy controls
2. Digital devices include night-time EEG, 24/7 accelerometry and ECG monitoring, and ePRO diary
3. 2 nights of in-patient testing to enable testing EEG device against gold-standard nPSG
4. 5 nights of out-patient testing for at-home use of digital devices
5. Subjects kept an ePRO diary for sleep quality as well as narcolepsy symptoms

*A. Dowling, SCOPE SUMMIT, Miami, 2021

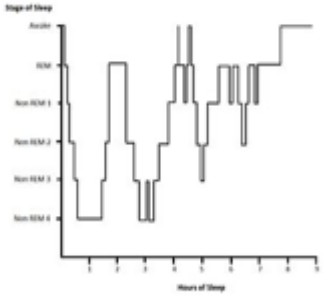
Clinical Validation of Portable EEG

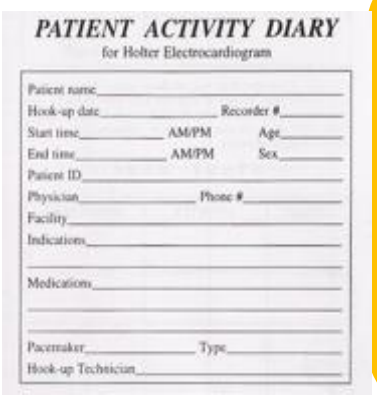
Study: Wake and Sleep State Transitions on a Portable Electroencephalogram (EEG) Device in Narcolepsy Patients and Healthy Participants

- Validation
  - Concordance of sleep state scoring
  - Correlation of sleep transitions
  - *In-clinic comparison to gold standard PSG*
- Digital Biomarker
  - Night to night variability in sleep patterns
    - Sleep transitions
    - Healthy vs Narcolepsy
  - *At-home data*

From subjective measurements → **Continuous quantification of sleep structure in clinic and at home to better capture disease phenotype**

Hand-scored PSG




PATIENT ACTIVITY DIARY
for Holter Electrocardiogram

Patient name
Hook-up date Recorder #
Start time AM/PM Age
End time AM/PM Sex
Patient ID
Physician Phone #
Facility
Indications
Medications
Pacemaker Type
Hook-up Technician

- **Expand knowledge of narcolepsy and other sleep disorders**
- **Better patient stratification**
- **Provide objective sensitive and reproducible endpoints for dose-response relationship**

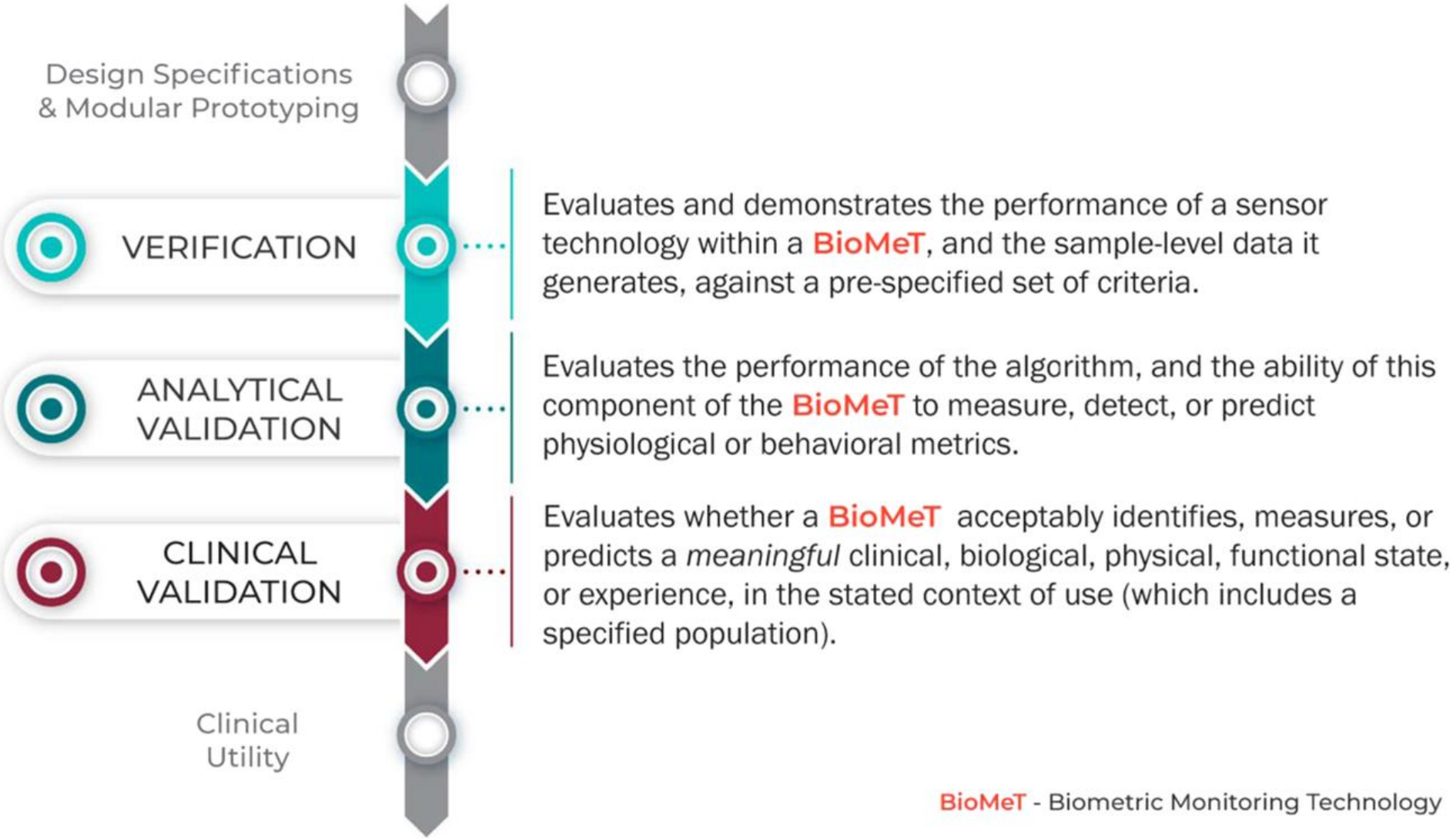
- ✓ **Overcome the limitations of static snapshots of clinical visits**
- ✓ **Establish novel efficacy endpoints linked to primary clinical measures**
- ✓ **Ultimately enable Phase III with quantifiable, extended outpatient measures that correlate with established clinical endpoints**

*A. Dowling, SCOPE SUMMIT, Miami, 2021

Device Considerations

- Target Population
- Target Markets
- Intended Use
- Use Environment
- Safety
- Approval dates
- Regulatory requirements (US/EU)
- Access to device
- Cost
- Supply chain and Distribution Strategy
- Manufacturing Capacity
- Subject compliance
- Site compliance
- Device storage at site
- Kitting
- Training
- Device Service and maintenance
- User – Device interface
- Quality and Reliability
- Life of Device (years)
- Battery
- Portability
- Data storage and accessibility (CRO and Sponsor)
- Software
- Study design
- Licensing & contracts

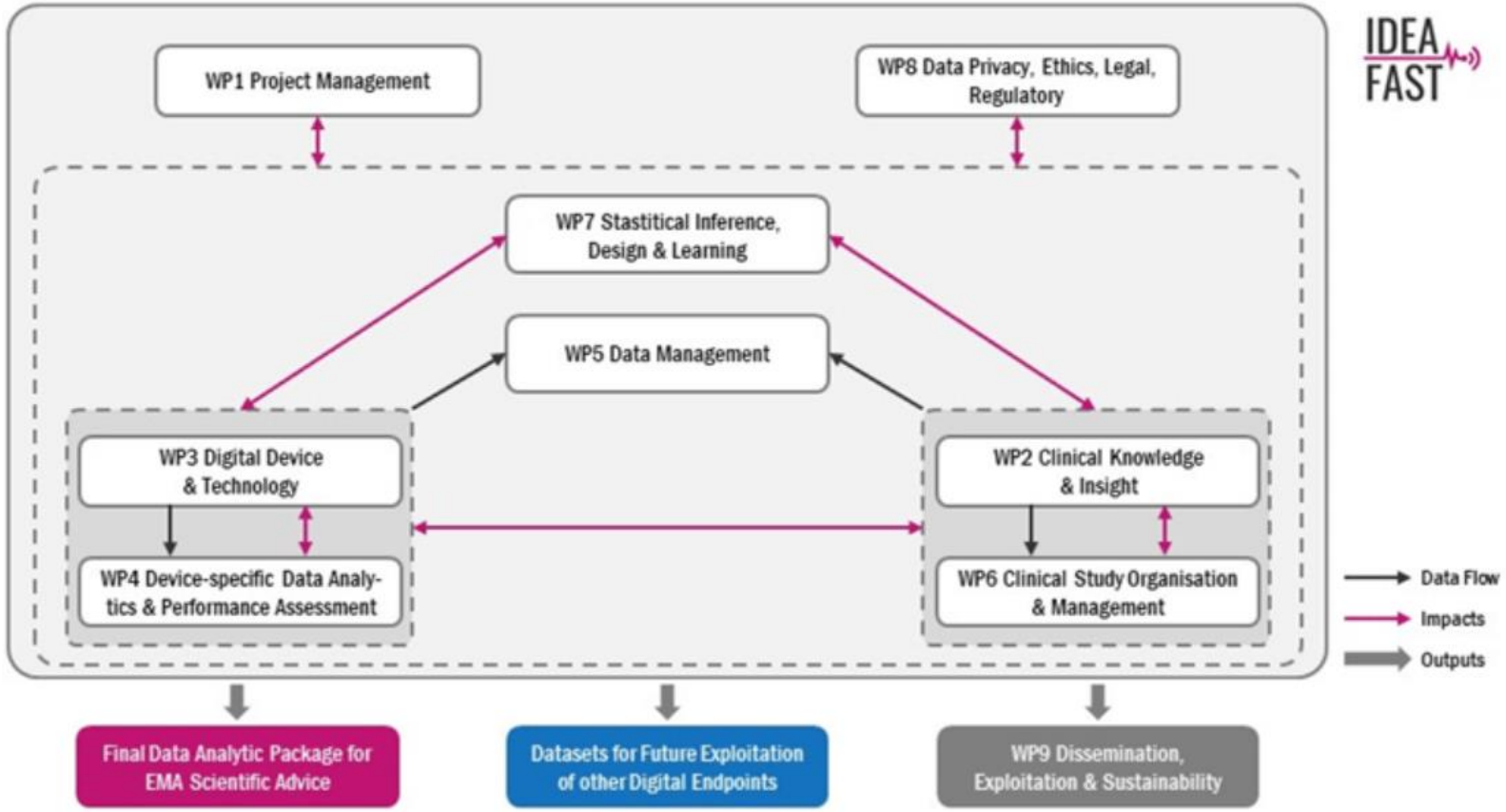
Clinical Validation: Meaningful Metric to Specific Population



Goldsack, J.C., Coravos, A., Bakker, J.P. *et al.* Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for Biometric Monitoring Technologies (BioMeTs). *npj Digit. Med.* 3, 55 (2020).

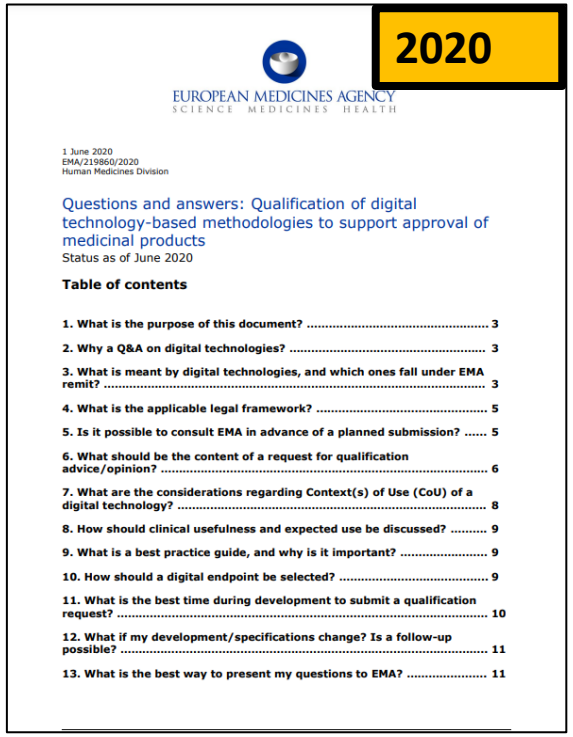
Public-Private Collaboration IMI: Sleep & Fatigue

https://idea-fast.eu/



Schematic illustration of the relationship between the IDEA-FAST WPs

Guidelines and Frameworks for Developing Digital Endpoints



2020

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 June 2020
EMA/219860/2020
Human Medicines Division

Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products
Status as of June 2020

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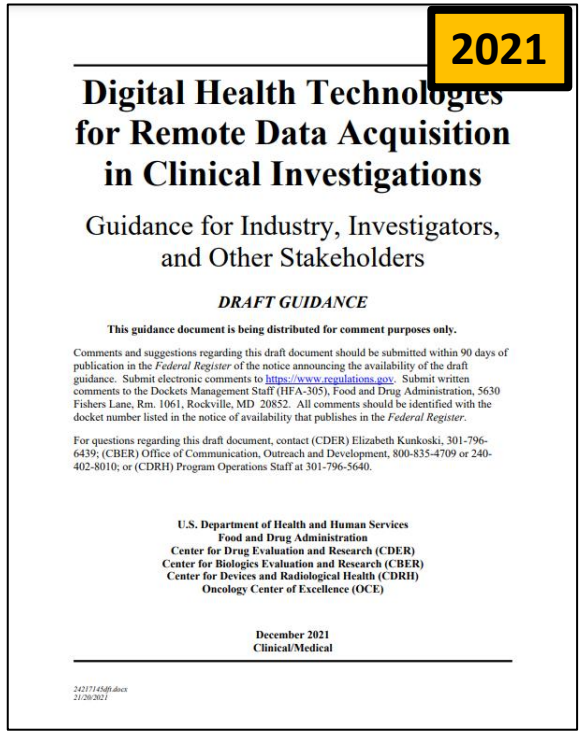


2021

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Elizabeth Kunkoski, 301-796-6439; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Program Operations Staff at 301-796-5640.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

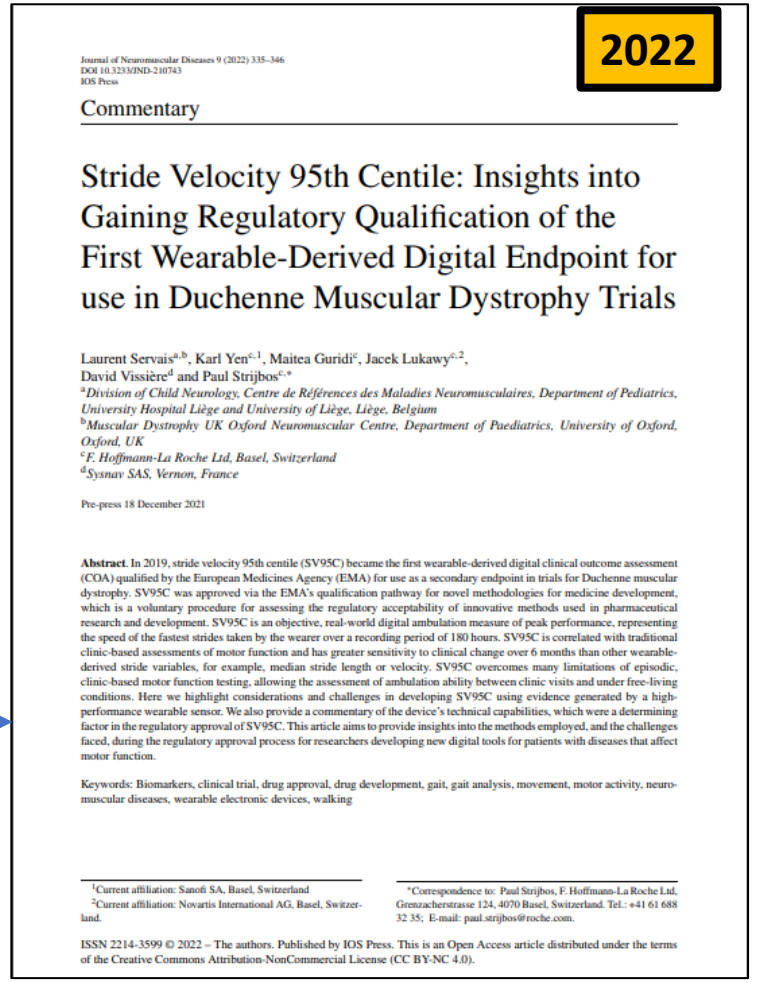
December 2021
Clinical/Medical

2121714Sfft.docx
21/20/2021

EMA approved stride velocity 95th centile as an acceptable secondary efficacy endpoint in clinical trials of ambulant DMD patients > 5yrs.

Quantifies patient ambulatory ability as the minimal velocity of 5% of the most rapid strides taken by the patient.

Only device currently validated for the assessment of this endpoint is the Actimyo device



2022

Journal of Neuromuscular Diseases 9 (2022) 335–346
DOI 10.3233/JND-210743
IOS Press

Commentary

Stride Velocity 95th Centile: Insights into Gaining Regulatory Qualification of the First Wearable-Derived Digital Endpoint for use in Duchenne Muscular Dystrophy Trials

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[b]*Muscular Dystrophy UK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, UK*
[c]*F. Hoffmann-La Roche Ltd, Basel, Switzerland*
[d]*Sysnav SAS, Vernon, France*

Pre-press 18 December 2021

Abstract. In 2019, stride velocity 95th centile (SV95C) became the first wearable-derived digital clinical outcome assessment (COA) qualified by the European Medicines Agency (EMA) for use as a secondary endpoint in trials for Duchenne muscular dystrophy. SV95C was approved via the EMA's qualification pathway for novel methodologies for medicine development, which is a voluntary procedure for assessing the regulatory acceptability of innovative methods used in pharmaceutical research and development. SV95C is an objective, real-world digital ambulation measure of peak performance, representing the speed of the fastest strides taken by the wearer over a recording period of 180 hours. SV95C is correlated with traditional clinic-based assessments of motor function and has greater sensitivity to clinical change over 6 months than other wearable-derived stride variables, for example, median stride length or velocity. SV95C overcomes many limitations of episodic, clinic-based motor function testing, allowing the assessment of ambulation ability between clinic visits and under free-living conditions. Here we highlight considerations and challenges in developing SV95C using evidence generated by a high-performance wearable sensor. We also provide a commentary of the device's technical capabilities, which were a determining factor in the regulatory approval of SV95C. This article aims to provide insights into the methods employed, and the challenges faced, during the regulatory approval process for researchers developing new digital tools for patients with diseases that affect motor function.

Keywords: Biomarkers, clinical trial, drug approval, drug development, gait, gait analysis, movement, motor activity, neuromuscular diseases, wearable electronic devices, walking

[1]Current affiliation: Sanofi SA, Basel, Switzerland
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*Correspondence to: Paul Strijbos, F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, 4070 Basel, Switzerland. Tel.: +41 61 688 32 35; E-mail: paul.strijbos@roche.com.

Key Messages

Measurements

Novel digital end-points or biomarkers

Taking measurements away from clinic to home

Delivering higher-resolution, faster, or cheaper measurements

Clinical validation requires extensive resources and multi-disciplinary collaboration

Analytical Tools

Advanced analytics of existing data streams (AI/ML)

New insights from existing datasets

Novel analytics / algorithms for clinical decision making

Pre-competitive collaboration

Patient-centricity

Patient Input needed at each stage of development

Patient education and support during clinical trials

Patient engagement and compliance tools

Digital data collection tools: Understanding symptom burden

Questions and Comments