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FOUNDER & CEO

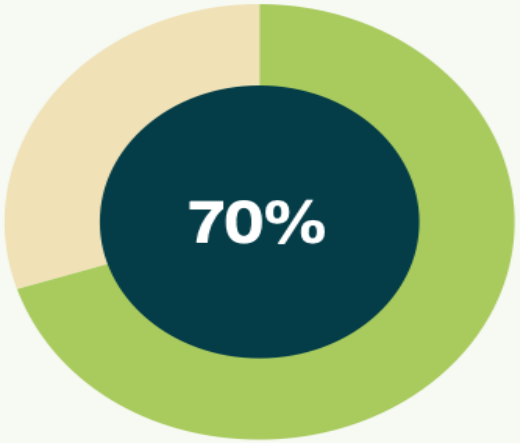
CSD Partners

Digital Innovation in Drug Development - Is Your Strategy Aligned?

Agenda

- **Current landscape**
  - Why and why now?
  - Regulatory perspectives
- **Four cases - digital endpoints and AI tools**
  - FDA approval of digital endpoint as Primary Endpoint in Pivotal Cardiopulmonary Study
  - Unlocking Voice as Sensitive ALS Endpoint in Phase 1b
  - Redefining ALS Progression and Phenotyping through DHT and AI
  - FDA Accepts the First Innovative AI Tool for Depression Into ISTAND Pilot
- **Summary**
- **Q&A**

Clinical trials in 2025



Research by Intel predicts that 70% of clinical trials will incorporate digital sensors by 2025.[4]

Why shall we care?

https://www.clinicalleader.com/doc/wearables-big-data-in-clinical-trials-where-do-we-stand-0001

Why NOW?

- External driving forces:
  - **Technology:** AI/tech elevating health augmentation
  - **Pandemic acceleration** of virtual models
  - **Stakeholder** interests:
    - Patient demand for convenience
    - Congressional/stakeholder interest
    - FDA prioritizing modernization of clinical trials
- Internal driving forces:
  - **Innovation**: require more sensitive tools in earlier lines and/or new targeted population
  - **Reduce Cost**: Need smaller and faster trials
  - **Increase Access & Rev:** Evidence continuity for value justification; consumer driven market share gain

Guidance Signals Commitment to Responsible Progress

DHTs for Drug Development Webpage

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

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 2023
Clinical/Medical

Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 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, elizabeth.kunkoski@fda.hhs.gov or 301-796-6439; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; (CDRH) Office of Clinical Evidence and Analysis, CDRHClinicalEvidence@fda.hhs.gov; (CFSAN) yuguang.wang@fda.hhs.gov or 240-402-1757; (CTP) ctp-bimo@fda.hhs.gov; or (CVM) Eric Nelson eric.nelson@fda.hhs.gov or 240-402-5642.

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)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Tobacco Products (CTP)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)
Office of Clinical Policy (OCLiP)

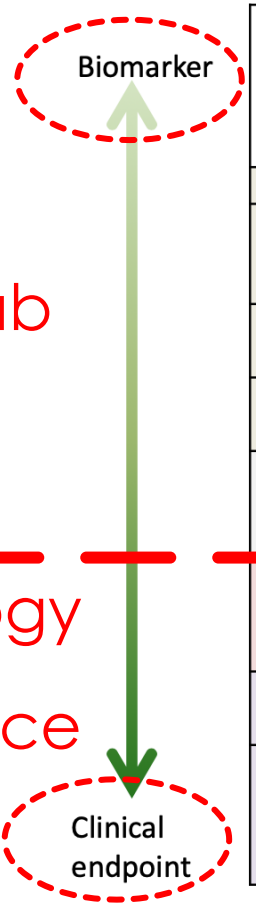
March 2023
Procedural
Revision 1

What are DHTs?

A digital health technology (DHT) is a system that uses computing platforms, connectivity, software, and/or sensors, for healthcare and related uses. Examples include but are not limited to portable sensors and/or mobile applications (mobile apps) such as activity trackers and smart watches.

- Our focus today is on a subset of these which are portable instruments that can be worn by patients or placed in their environments
- More specifically we will be discussing those that involve the use of sensors to measure clinical features

Digital Biomarker vs Digital endpoint



Type of endpoint	NDAs N=218	Examples of endpoints measured
Chemistry	30%	HBA1c, pregnancy test, GFR
Hematology		Severe neutropenia
Pathology		Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells
Microbiology		Sustained virological response, plasma viral load, conversion to negative sputum
Imaging +/- (survival, clinical signs)	22%	Bone mineral density; vertebral fractures, spleen volume, progression free survival
Physiological/ functional measurement	7%	6 minute walk, normal sinus rhythm, FEV1, sleep studies
Clinical event /clinical sign	22%	Death, hospitalization, MACE, MS relapse
CRO/PRO	32%	Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score

Endpoints used in registrational studies in 2015-2020

Method of Measurement vs Endpoint

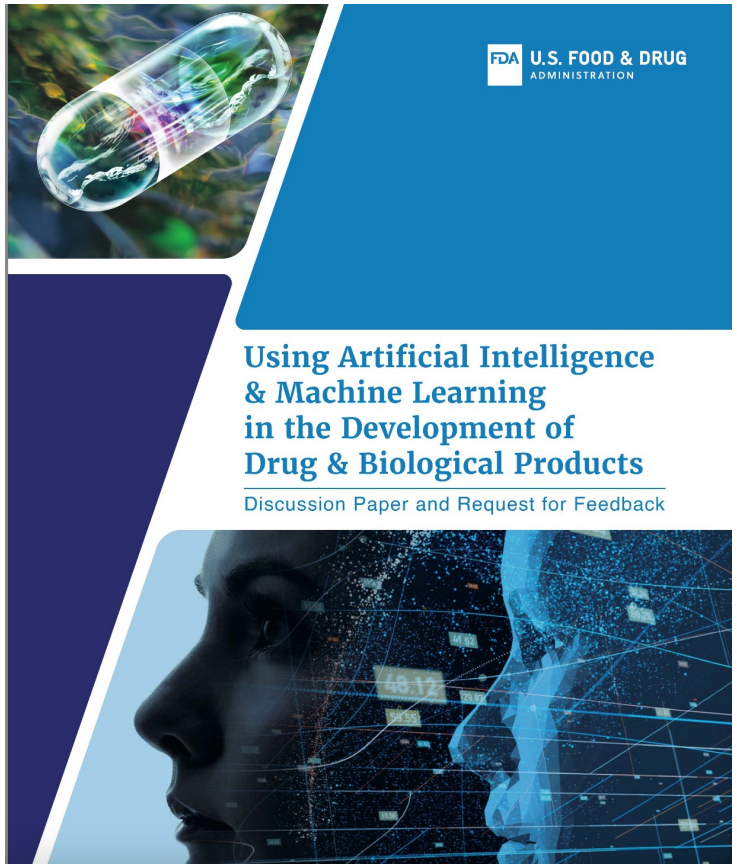
- Validation and verification are technological assessments. They address how well the **technology** measures the clinical feature of interest.

- Justification of an endpoint (or a clinical outcome assessment) is a clinical issue. It addresses how well the **clinical feature** of interest represents a meaningful response to treatment (nothing to do with the DHT).

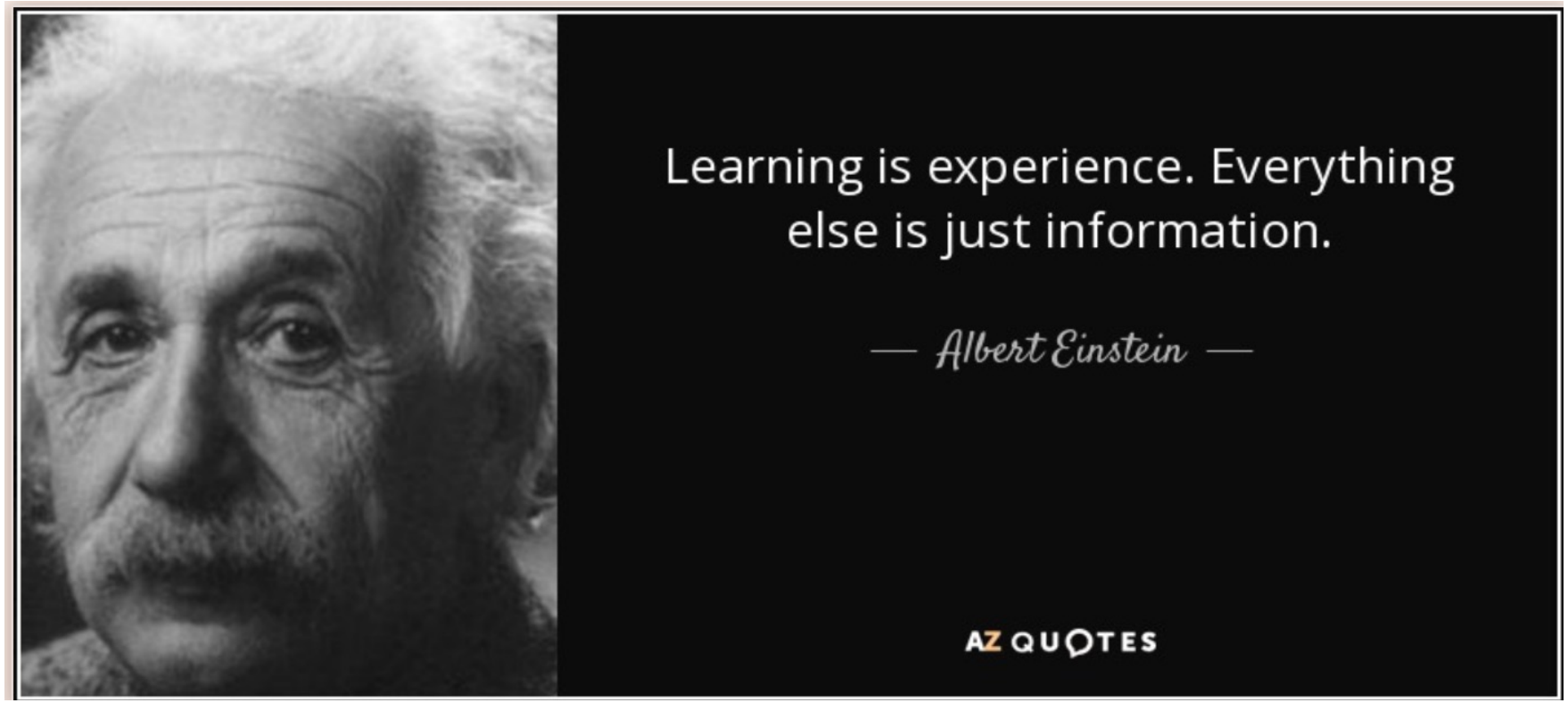
Opportunities for Digital Endpoints - Regulatory Lens

- Limitations of Current Standards:
  - Subjective CRO/PROs inadequately capture real-world health status
  - Patients who cannot report, e.g. infants, dementia pts
  - Snapshots missing on-off/rare events or dosing effects
- Opportunities from Digital Endpoints:
  - More objective measurement in real-world living
  - More DE&I potential
  - Richer & continuous data with multiple validating potentials

How does AI/ML fit into the picture?



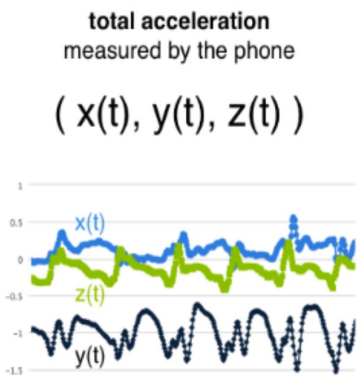
C. Clinical Research .....
1. Recruitment .....
2. Selection of Trial Participants .....
3. Dose/Dosing Regimen Optimization .....
4. Adherence .....
5. Retention .....
6. Site Selection.....
7. Clinical Trial Data Collection, Management, and Analy
8. Clinical Endpoint Assessment.....
D. Postmarket Safety Surveillance .....
1. Case Processing.....
2. Case Evaluation.....
3. Case Submission.....
E. Advanced Pharmaceutical Manufacturing.....
1. Optimization of Process Design.....
2. Advanced Process Control .....
3. Smart Monitoring and Maintenance .....
4. Trend Monitoring.....



CASE STUDIES

Case 1: Digital Outcome Measures of Physical Activity Approved as Primary Endpoint in Pivotal Cardiopulmonary Study

Actigraphy



- **"Poster Child" of DHT from FDA for digital endpoint**
  - **broad applicability** across many disease areas (e.g. neuromuscular, cardiorespiratory, rheumatologic diseases, oncology) where functionality assessments are important clinical endpoints
  - **addresses limitations of existing methods** like the 6-minute walk test (6MWT) which can be confounded by patient anxiety, enthusiasm, pain levels
  - Accelerometer technology used in actigraphy is already **widely adopted in consumer** wearables and cell phones, demonstrating market acceptance and understanding

Case 1: Digital Outcome Measures of Physical Activity Approved as Primary Endpoint in Pivotal Cardiopulmonary Study

- Bellerophon's Ph 2b primary endpoints (6MWT, SpO2) showed clinical improvements but lacked statistical significance
- Included **Moderate-to-Vigorous-Physical Activity (MVPA) from wearables** as an exploratory endpoint in Ph 2b
- MVPA demonstrated strong clinical and statistical significance in Ph2b

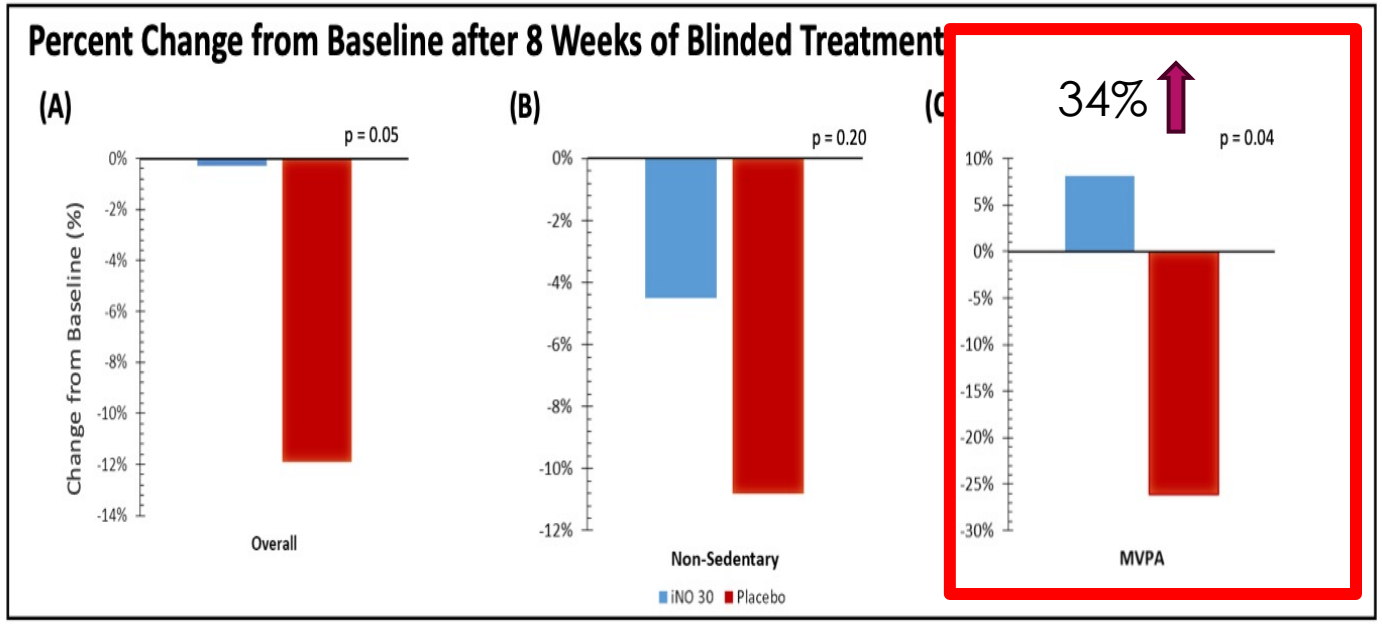


Figure 2: Subjects on pulsed inhaled nitric oxide (iNO) demonstrated a placebo corrected improvement of **(A)** 12% in overall activity, **(B)** 6% in non-sedentary activity and **(C)** 34% in MVPA. Percent change is calculated as absolute change/baseline, e.g. Δ MVPA (minutes)/Baseline MVPA (minutes). Statistical analysis was conducted for active vs. placebo via student t.test at week 8 on available data.

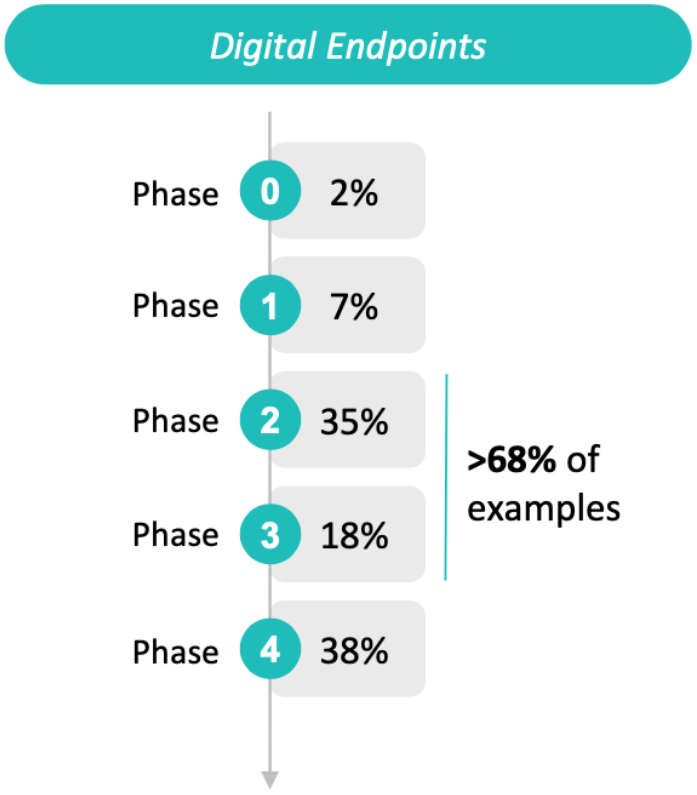
https://investors.bellerophon.com/static-files/df769f34-1caa-4c67-a17d-27a63bda13ac

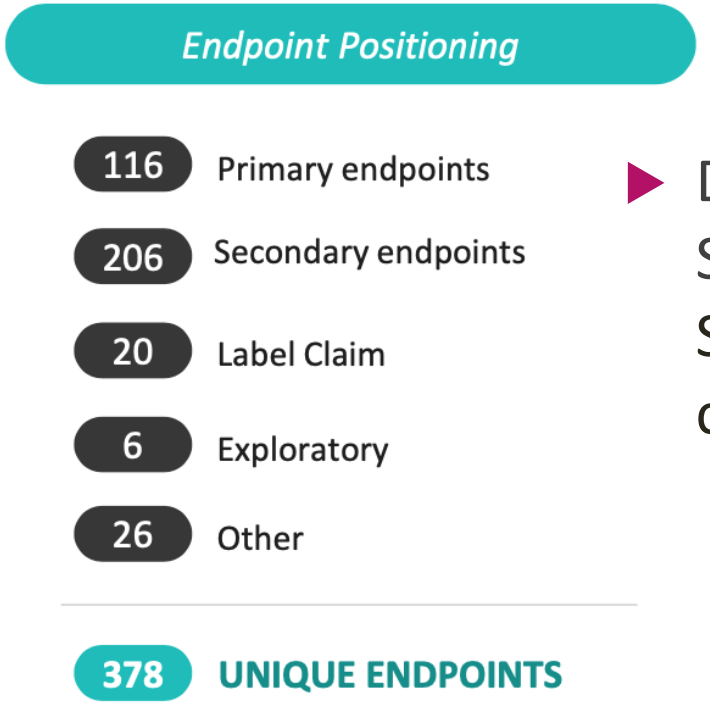
Case 1: Digital Outcome Measures of Physical Activity Approved as Primary Endpoint in Pivotal Cardiopulmonary Study

- FDA approved **MVPA as primary endpoint for phase 3 registrational REBUILD study** – first case
- Enabled **55% trial sample size reduction** – from 300 to ~140
- While ultimate phase 3 missed statistical significance, **fail fast** strategy was served
- The **consistency of digital and traditional endpoints** in this Ph3 trial reinforces the confidence stakeholders can place in digital endpoints

Similarly, on August 8th, 2023, EMA approved Sysnav's stride velocity 95th centile (SV95C) to replace 6MWT as a primary digital endpoint for Duchenne Muscular Dystrophy registrational study, enabling sample size reduction from 100+ down to just 30 patients

Companies do start thinking about DHT early…





- DiMe (Digital Medicine Society) data from 104 Sponsors who have collected digital endpoints

Source: https://www.dimesociety.org/index.php/knowledge-center/library-of-digital-endpoints

Last updated January 31, 2023

Case 2: Unlocking Voice as Sensitive ALS Endpoint in Phase 1b

- **Speech deterioration** is one of the functionally limiting issues in ALS progression
- Traditional verbal function measures can be subjective and lack sensitivity
- **Verge genomics** VRG50635 targets abnormal protein aggregation implicated in **ALS progression**

- Ph1:
  - placebo-controlled, blinded trial in healthy volunteers and ALS patients
  - 3 parts: single dose, multiple ascending doses, and crossover cohort **looks for preliminary activity indicators**

Case 2: Unlocking Voice as Sensitive ALS Endpoint in Phase 1b

- Ph1b: **POC** for speech analytics as a pragmatic and **meaningful ALS endpoint**
- Modality.AI's platform analyzes vocal decline patterns from home audio recordings

modality.ai

Remote Assessment for ALS using Multimodal Dialog Agents: Data Quality, Feasibility and Task Compliance

Vanessa Richter, Michael Neumann*, Jordan R. Green*, Brian Richburg*, Oliver Roesler*, Hardik Kothare* and Vikram Ramanarayanan*†*

Responsiveness, Sensitivity and Clinical Utility of Timing-Related Speech Biomarkers for Remote Monitoring of ALS Disease Progression

Hardik Kothare[1], Michael Neumann[1], Jackson Liscombe[1], Jordan Green[2], and Vikram Ramanarayanan[1,3]

Combining Multiple Multimodal Speech Features into an Interpretable Index Score for Capturing Disease Progression in Amyotrophic Lateral Sclerosis

Michael Neumann[1], Hardik Kothare[1], and Vikram Ramanarayanan[1]

[1] Modality.AI, Inc., San Francisco, USA

vikram.ramanarayanan@modality.ai

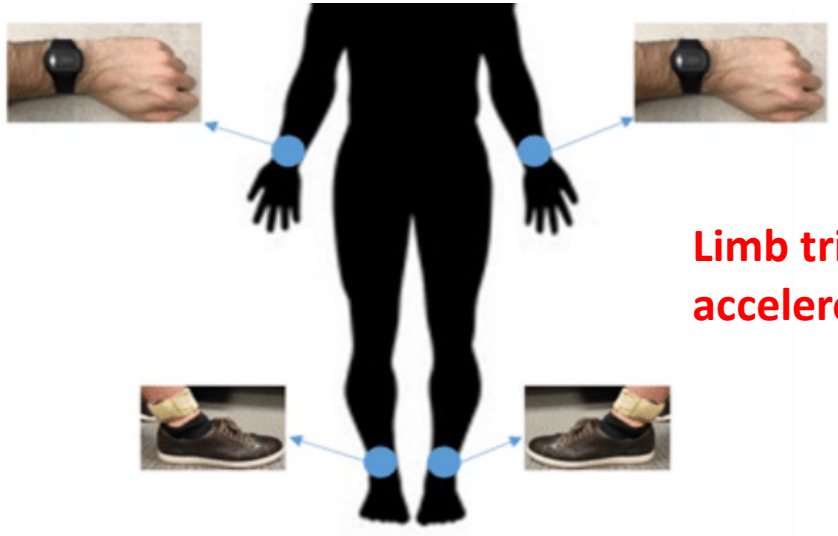
Case 3: Redefining ALS Progression and Phenotyping through DHT and AI

ALSFR-R

ALS Functional Rating Scale–Revised (ALSFRS-R)[5]

BULBAR	FINE MOTOR	GROSS MOTOR	RESPIRATORY
Speech 4 Normal 3 Detectable speech disturbance 2 Intelligible with repeating 1 Speech combined with nonvocal communication 0 Loss of useful speech	**Handwriting** 4 Normal 3 Slow or sloppy; all words are legible 2 Not all words are legible 1 Able to grip pen but unable to write 0 Unable to grip pen	**Turning in Bed** 4 Normal 3 Somewhat slow and clumsy, but no help needed 2 Can turn alone or adjust sheets, but with great difficulty 1 Can initiate, but not turn or adjust sheets alone 0 Helpless	**Dyspnea** 4 None 3 Occurs when walking 2 Occurs with one or more of the following: eating, bathing, dressing (ADL) 1 Occurs at rest, difficulty breathing when either sitting or lying 0 Significant difficulty, considering using mechanical respiratory support
Salivation 4 Normal 3 Slight but definite excess of saliva in mouth; may have nighttime drooling 2 Moderately excessive saliva; may have minimal drooling 1 Marked excess of saliva with some drooling 0 Marked drooling; requires constant tissue or handkerchief	**Cutting Food*** 4 Normal 3 Somewhat slow and clumsy, but no help needed 2 Can cut most foods, although clumsy and slow; some help needed 1 Food must be cut by someone, but can still feed slowly 0 Needs to be fed	**Walking** 4 Normal 3 Early ambulation difficulties 2 Walks with assistance 1 Non-ambulatory functional movement only 0 No purposeful leg movement	**Orthopnea** 4 None 3 Some difficulty sleeping at night due to shortness of breath. Does not routinely use more than two pillows 2 Needs extra pillow in order to sleep (more than two) 1 Can only sleep sitting up 0 Unable to sleep
Swallowing 4 Normal 3 Early eating problems—occasional choking 2 Dietary consistency changes 1 Needs supplemental tube feeding 0 NPO (exclusively parenteral or enteral feeding)	**Dressing and Hygiene** 4 Normal 3 Independent and complete self-care with effort or decreased efficiency 2 Intermittent assistance or substitute methods 1 Needs attendant for self-care 0 Total dependence	**Climbing Stairs** 4 Normal 3 Slow 2 Mild unsteadiness or fatigue 1 Needs assistance 0 Cannot do	**Respiratory Insufficiency** 4 None 3 Intermittent use of BiPAP 2 Continuous use of BiPAP 1 Continuous use of BiPAP during the night and day 0 Invasive mechanical ventilation by intubation or tracheostomy

*There are different assessments for cutting food with gastrostomy.

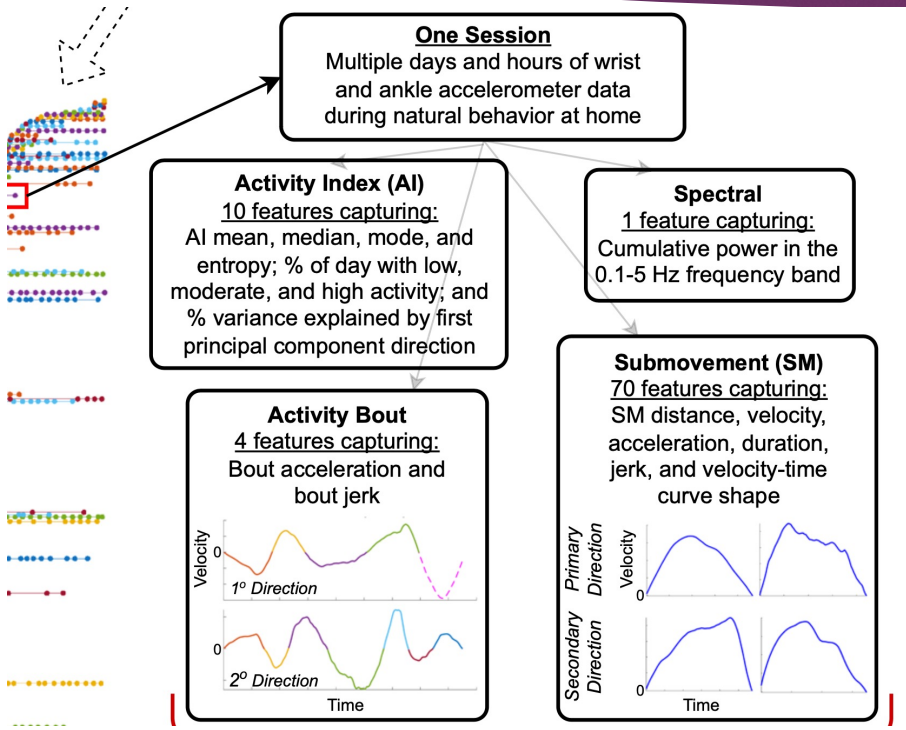


Limb triaxial accelerometer

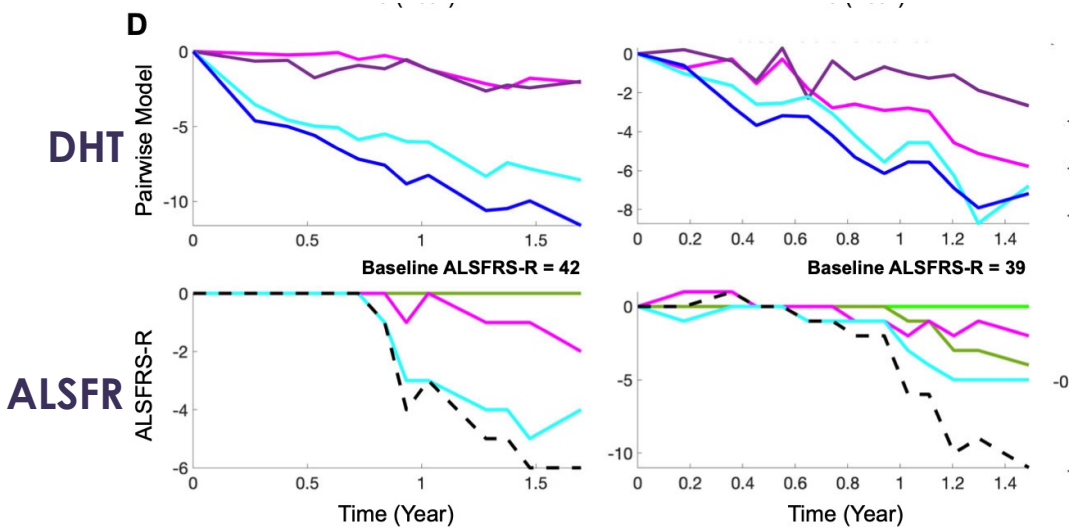
- Episodic: miss short-term motor fluctuations
- Subjective: interrater variability
- Task-based: increase patient burden
- Population based progression metrics

- Continuous: granular limb sub-movement
- Objective: no need for special rater
- Ecological validity: minimum patient burden
- AI/ML derives personalized vectors of decline

Case 3: Redefining ALS Progression and Phenotyping through DHT and AI



- 85-dimensional feature vector for 1 session -> overall severity



- Disease progression detected much earlier with limb accelerometer
- Personalized progression pattern allows more accurate phenotyping subgroups

https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/37604821/

Case 3: Redefining ALS Progression and Phenotyping through DHT and AI

- Potential opportunities for drug developers
  - **Earlier** patient identification: years before function loss
  - **Faster** response detection: mons to years earlier
  - **Personalized** progression signatures: accurate targeting & stratification
  - **Sample size reduc**tions: ~42%

- Business Impact
  - **Lowers clinical trial costs**: smaller, faster trials
  - **Expedites time-to-approval**: higher sensitivity tools
  - Enhances product **differentiation**: personalized response profiling
  - Strengthens **value evidence**: pricing, access, and reimbursement
  - May increase **market share**: patient facing dashboards driving adherence

FDA's ISTAND Pilot Program accepts submission of first artificial intelligence-based and digital health technology for neuroscience

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[1/23/2024] FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) recently accepted a new submission into the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program. This submission is the first artificial intelligence-based and digital health technology-based project and the first project in neuroscience to be accepted into ISTAND.

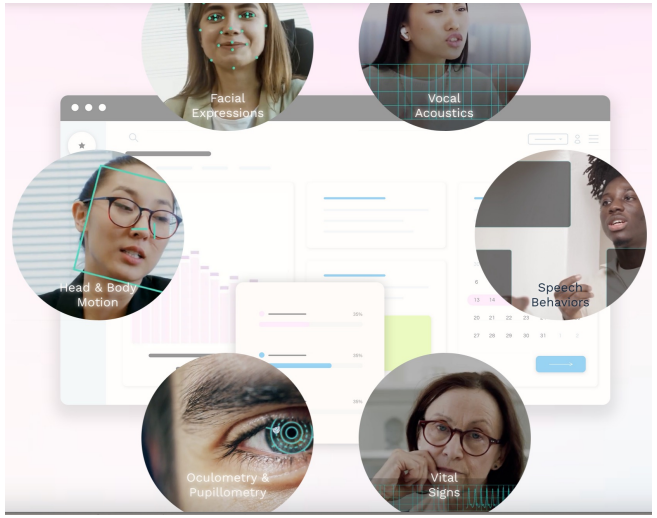
"This marks a pioneering step for the ISTAND program as the first artificial intelligence-based, digital health technology project in neuroscience to be accepted into the pilot

FDA describe this tool as "an automated depression and anxiety severity measurement product utilizing multiple behavioral and physiological indices of depression in a machine learning (ML) model to infer ClinROs for depression and anxiety: the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) scores with a performance equivalent to a trained clinician. "

Case 4: FDA Accepts the First Innovative AI Tool for Depression Into ISTAND Pilot

COA

AI-COA



- Clinician conducts interview, assigns symptom scores using HAM-D/HAM-A questionnaires
- Requires trained rater, subject to inter-rater variability

- Multimodal AI integrates facial, vocal, verbal and physiological data to facilitate interview
- Automates ClinRO questionnaires leveraging machine learning for score reliability

Case 4: FDA Accepts the First Innovative AI Tool for Depression Into ISTAND Pilot

- **Still long way to go:**
  - Letter of Intent (LOI) -> Qualification Plan -> Final Drug Development Tool (DDT) qualification package
  - 20 Questions to address: Context of Use (COU), Technical, Clinical, Statistical, eg:
    - "Does the algorithm for AI-COATM **continue to evolve** during the qualification review and after its qualification? How can you ensure that the specific interpretation and application of AI-COATM in drug development and regulatory review remain consistent after the qualification? "
    - "Explicitly state the percentage targets that you are aiming to reach for the **demographic composition** of the study population in respect to the intend to treat population. "
    - "In the intended use, AI-COATM is proposed to be initially used **alongside human** clinical rating interviews of the HAM-D or HAM-A, and regulatory approval is sought for combining both ratings to increase endpoint measure reliability and **reduce sample sizes**... Please provide the statistical analysis method with **pre-specified success criteria** that can address reduced variability of the combined rating from AI-COATM and human clinical rating interviews. "

Summary

- Digital Health Explosion – guidelines are out; act now or be left behind
- Registrational study: MVPA accepted as primary endpoint in pivotal trial; enabled 55% sample size reduction – regulatory precedence is here
- Early phase study: novel voice endpoint explored for registrational study and post-marketing use – Ph1 is the best stage to explore and validate novel endpoint
- Disease model: Limb sensors unlocking personalized ALS progression – true personalized medicine is coming, rethink your patient identification and stratification strategy
- AI augmented multi-modal clinical outcomes assessment – re-imagine the future COA with AI and co-create drug development tool (DDT) with the agency

Q & A

Questions

- **Could these innovations add value to payers to justify premium pricing or improve patient access?**
  - Evidence continuity, precision access, value-based arrangement, conditional reimbursement, continuous value adjustment etc
- **Which therapeutic areas currently have the most digital traction?**
  - Diseases that already use PRO and COA as key endpoints; current measurements have limitations; new targeted population that needs sensitive tools for differentiation (eg. AE for early oncology trial) or pt identification (eg neurodegenerative disease); sensors that have commonly used; Strong business case: reduce costs/risk, increase access & revenue
- **What are some key barriers and how to mitigate them?**
  - technological readiness, evidentiary and regulatory precedent building, trust enablement and collaborative mindset

THANK YOU!

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