**Joint FDA / FNIH Workshop for Digital Measures:**
**Navigating the Development of a Digitally Derived Endpoint**
Bethesda Marriott, Bethesda, MD
June 24-25, 2024.

# Roundtable Discussion: Development of a Digitally Derived Endpoint – What is "Good" to Whom?


**Charmaine Demanuele, PhD**
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Global Biometrics & Data Management
Pfizer Research & Development

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Head of Clinical Research
Biomeasures, Endpoints & Study Technologies
Translational Clinical Sciences
Pfizer Research & Development


June 25th, 2024

# Examples of Digital Endpoints as Primary Endpoints in Clinical Trials

## FDA accepted Moderate-to-vigorous physical activity (MVPA) as a primary endpoint for PH-ILD

REBUILD Trial: NCT03267108

*MVPA represents the **time spent performing physical activity of moderate to high intensity**, such as brisk walking or jogging*

- *Phase-2 results showed significant difference in treatment group from baseline to week 16*
- *Helped to expedite study completion by significant reduction of study size*

*April 2017*

*Change in MVPA included as primary endpoint (along with change in 6MWD time)*

*September 2022*

***FDA approved decrease in study size from 300 to 140** (maintaining study power of >90%), given the treatment effect observed in MVPA*


Actigraph

## EMA accepted 95th percentile of stride velocity (SV95C) as a primary endpoints for DMD

ActiLiége Next Trial: NCT05982119

*SV95C represents the **top 5% fastest steps taken during normal daily living***

- *Reflects intense activity level, sensitive to treatment effect*
- *Less sensitive to external factors, such as weather*
- *Moderate correlation with ambulation measures, e.g., 6MWT*
- *Can discriminate DMD patients from age-matched controls* [1]

*April 2019*

*EMA qualified SV95C as a secondary endpoint for DMD studies in patients aged at least 5 years*

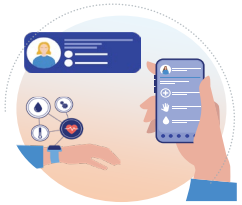
*February 2023*

***EMA qualified SV95C as a primary endpoint for DMD trials***

ActiMyo

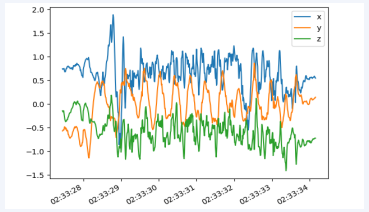
1 Servais et al. (2023); https://doi.org/10.1038/s41591-023-02459-5

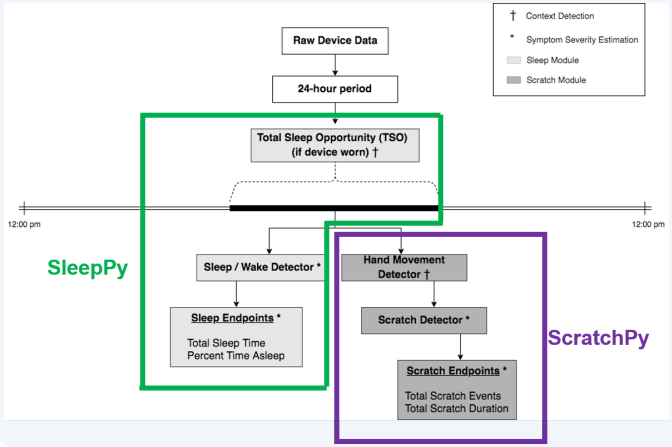
# Using Digital Health Technologies (DHT) to Improve Patients Lives with Atopic Dermatitis



- Novel biosensors & digital technologies offer **incredible opportunities** in healthcare
  - Important that they are validated and usable in a clinical and health care setting

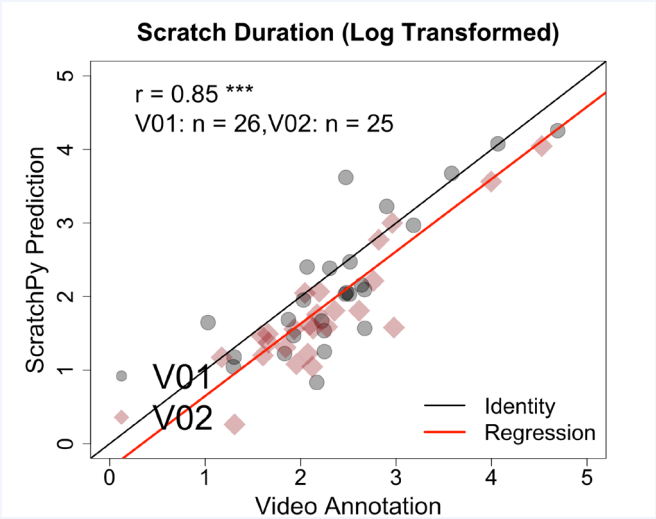
## Development of Novel Digital Measures






## Validation Digital Endpoints (NDE)

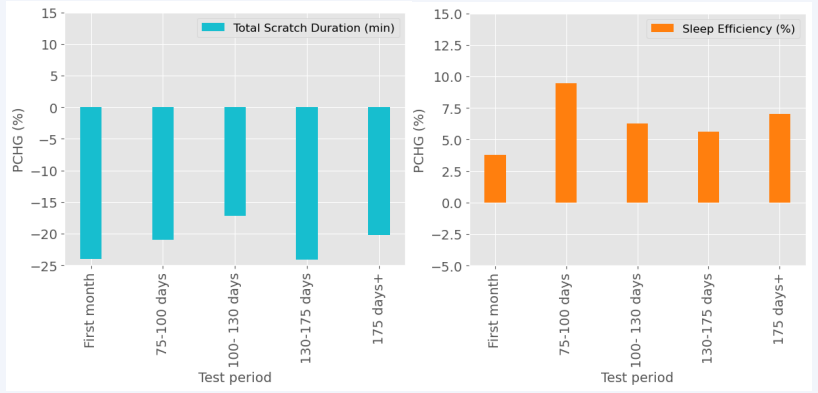
- Pfizer developed nocturnal sleep and scratch algorithms/NDE; DHT can be used to **accurately quantify** nocturnal scratch and sleep **passively over time at home, as well as in a clinical settings.**




Christakis et al. Journal of Open Source Software, 2019.
Mahadevan et al, *Nature Digital Medicine*, 2021

## Therapy-mediated changes

- Developed statistical methods to evaluate the continual measures of nocturnal scratch and sleep
- Clinical studies have demonstrated that therapeutic agents can generally reduce scratch duration and improved sleep in patients with Atopic Dermatitis.

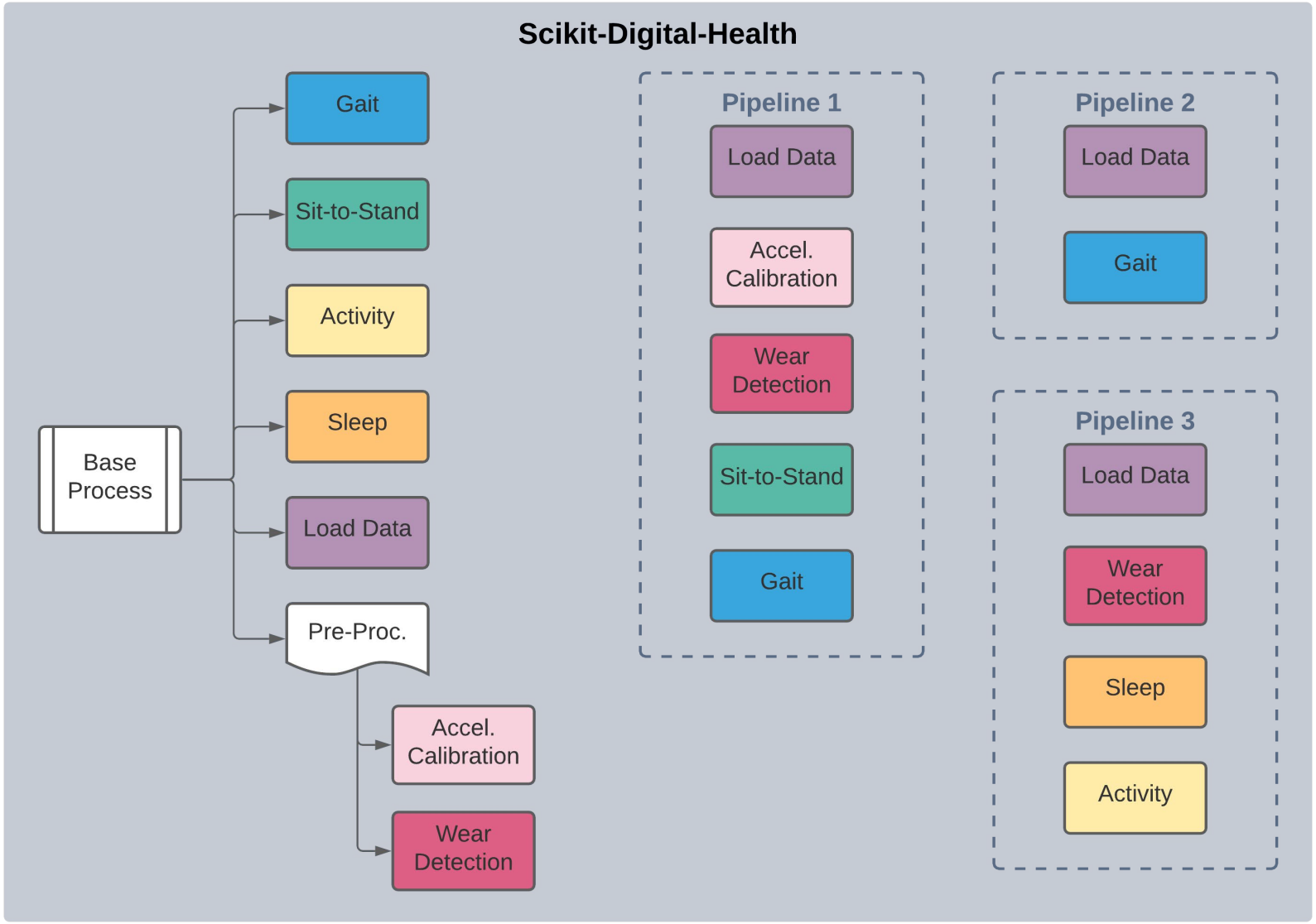



Pfizer

# Enable Large-Scale Deployment in Clinical Trials

- ✓ Patients:
  - Meaningfulness of endpoint, usability of technology
- ✓ Operational Aspects:
  - Site burden, battery life, software, failure rate, QC, monitoring of wear, distribution, data transfer, internet/broadband
- ✓ Non-performance Related specifications:
  - Cost, scalability, training of sites, country acceptance, software compliance, data storage, contracting
- ✓ Data
  - Vast amounts of data; defining compliance thresholds; handling missing data from continuous recordings (Di et al., Contemp Clin Trials, 2022)
- ✓ Regulatory:
  - Is the technology fit for purpose for the COU
  - Qualification pathway, COA development/anchoring to established measures

# Enable Large-Scale Deployment in Clinical Trials

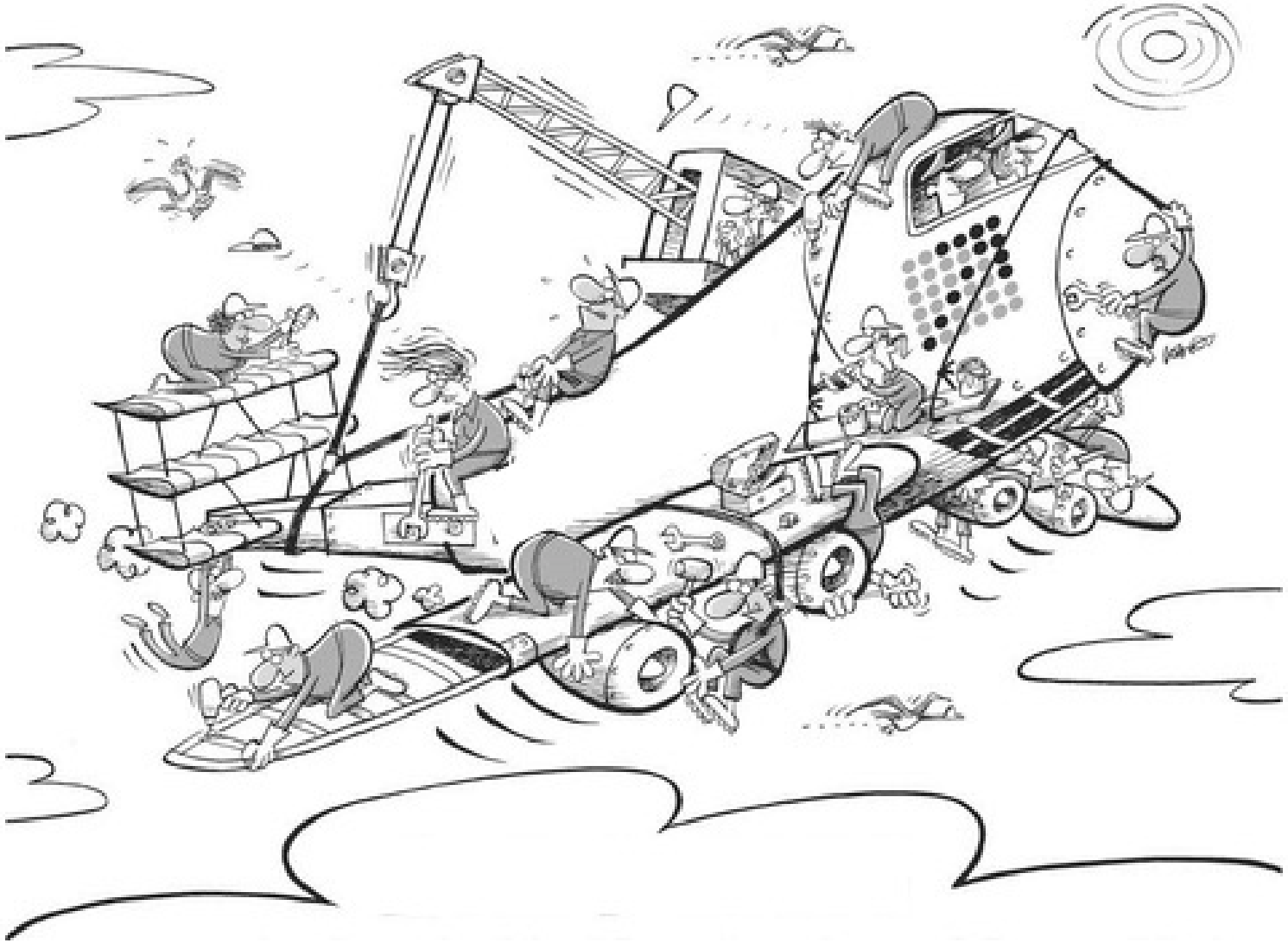



**Scikit Digital Health (SKDH) framework enables automatic, efficient, and robust data processing in the cloud**
Adamowicz *et al.*, JMIR Mhealth Uhealth, 2022

# Bridging from Clinical Trials to Clinical Care

- What information is important to patients and providers
- How will that information be shared/integrated as part of the EHR
- How will reimbursement work to ensure broad access to technology
- How will safety concerns be addressed
- Who or what will analyze data and at what frequency, will there be quality controls/calibration/verification?

# There is still a lot of work to do



# Roundtable Discussion: **Development of a Digitally Derived Endpoint – What is "Good" to Whom?**

- ***What's the problem you are hoping that digital measures are going to solve for you?***
- ***What are the pitfalls we've experienced; how do we avoid them?***
- ***What would "good" or success look like?***

*Moderator:* Leonard Sacks, CDER (15min each panel with 5 min Q&A; 2:20 – 4:00pm)

*Panelists:*

- ***Patient perspective****:* Jennifer Handt, DMD Parent WLE; Nick Elliott, Watch PD; David Shulman, ALS PWLE
- ***Human factors research and technologies****:* Katarzyna Wac, QoLife Technologies; Scooter, Plowman, Verily; Mark Hyer, Clarivate
- ***Drug development and clinical trial implementation****:* Xuemei Cai, Pfizer; Victoria Bangieva, DiME; Charmaine Demanuele, Pfizer and Szczepan Baran, VeriSim Life
- ***Regulatory perspective****:* Cheryl Coon, C-Path; Thorsten Vetter, EMA; Francesca Cerreta, EMA;
- ***Moving from clinical trials to clinical care:*** Indu Navar, Everything ALS; Tara McMmullen, CMS

# Development of a Digitally Derived Endpoint – What is "Good" to Whom?

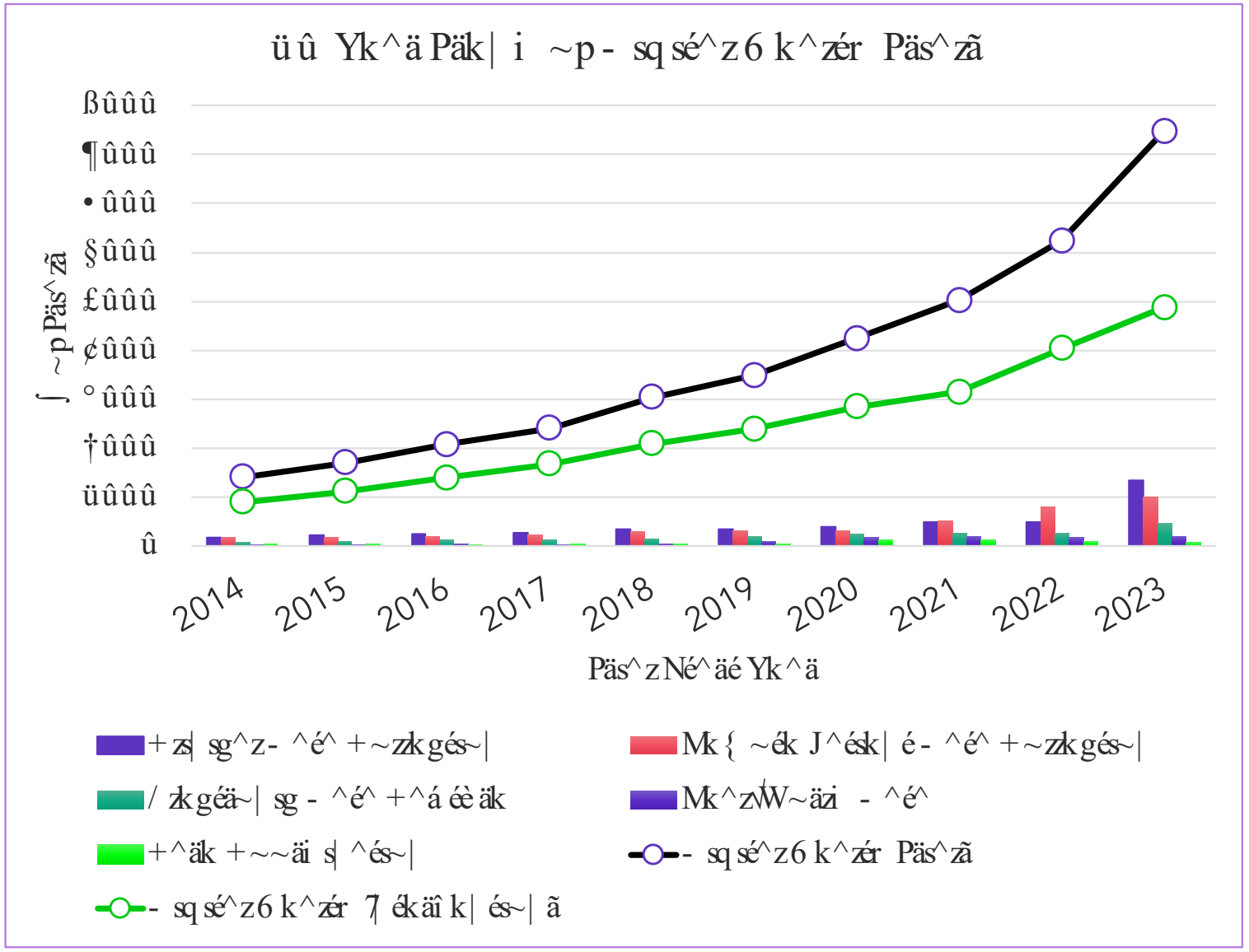
Support Slides for Panel Discussion

What diseases are of greatest importance?

Mark Hyer, Clarivate

June 2024

Clarivate™

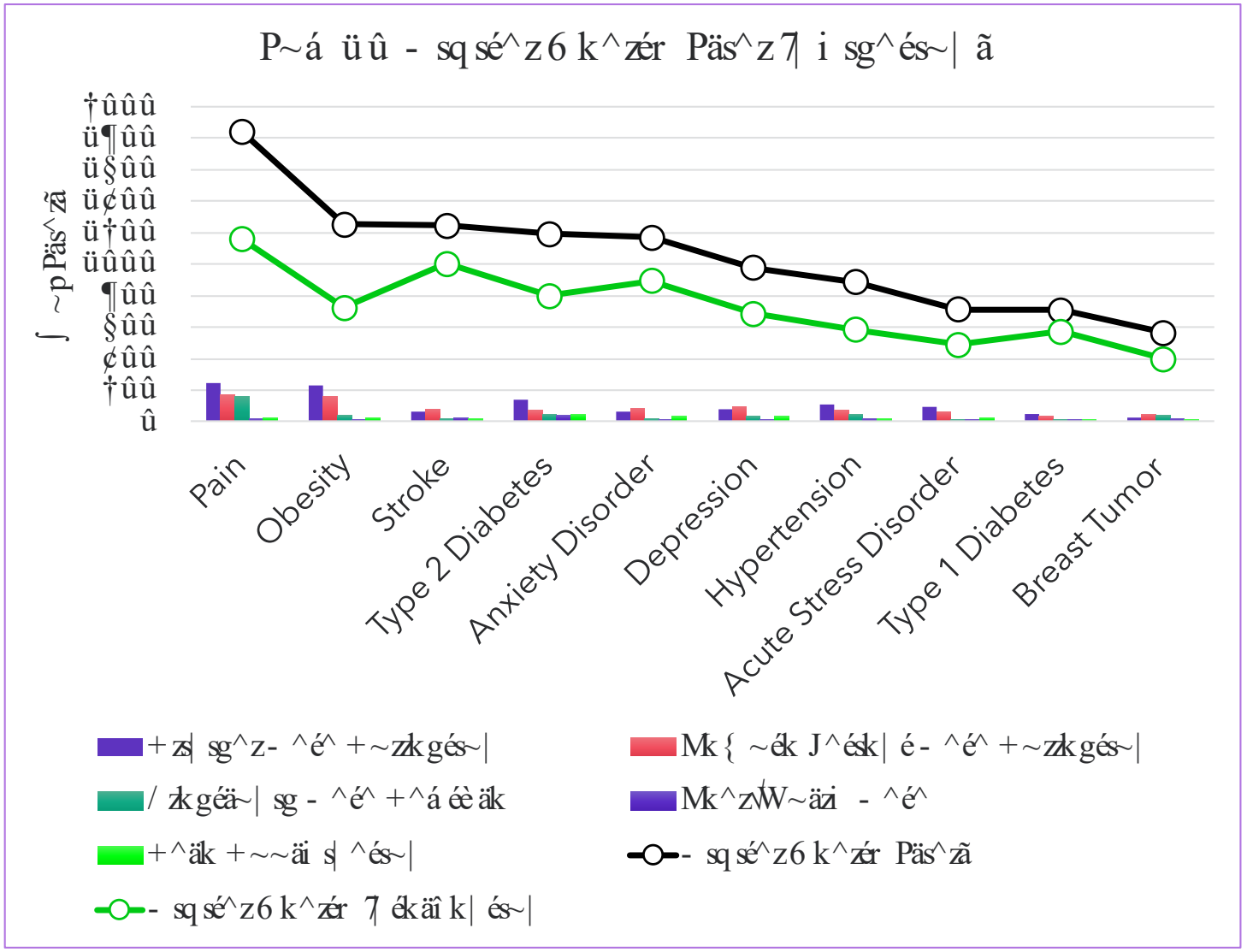



Number of digital health trials over a span of 10 years. Total digital health trials is represented by the black line.

The number of trials testing digital health interventions is represented by the green line.

The number of trials making use of other digital health technologies in the trial are represented by the bar chart, each trial may use multiple digital health technologies.

Source: Cortellis Digital Health Intelligence




Analysis of top 10 indications digital health trials over a span of 10 years.

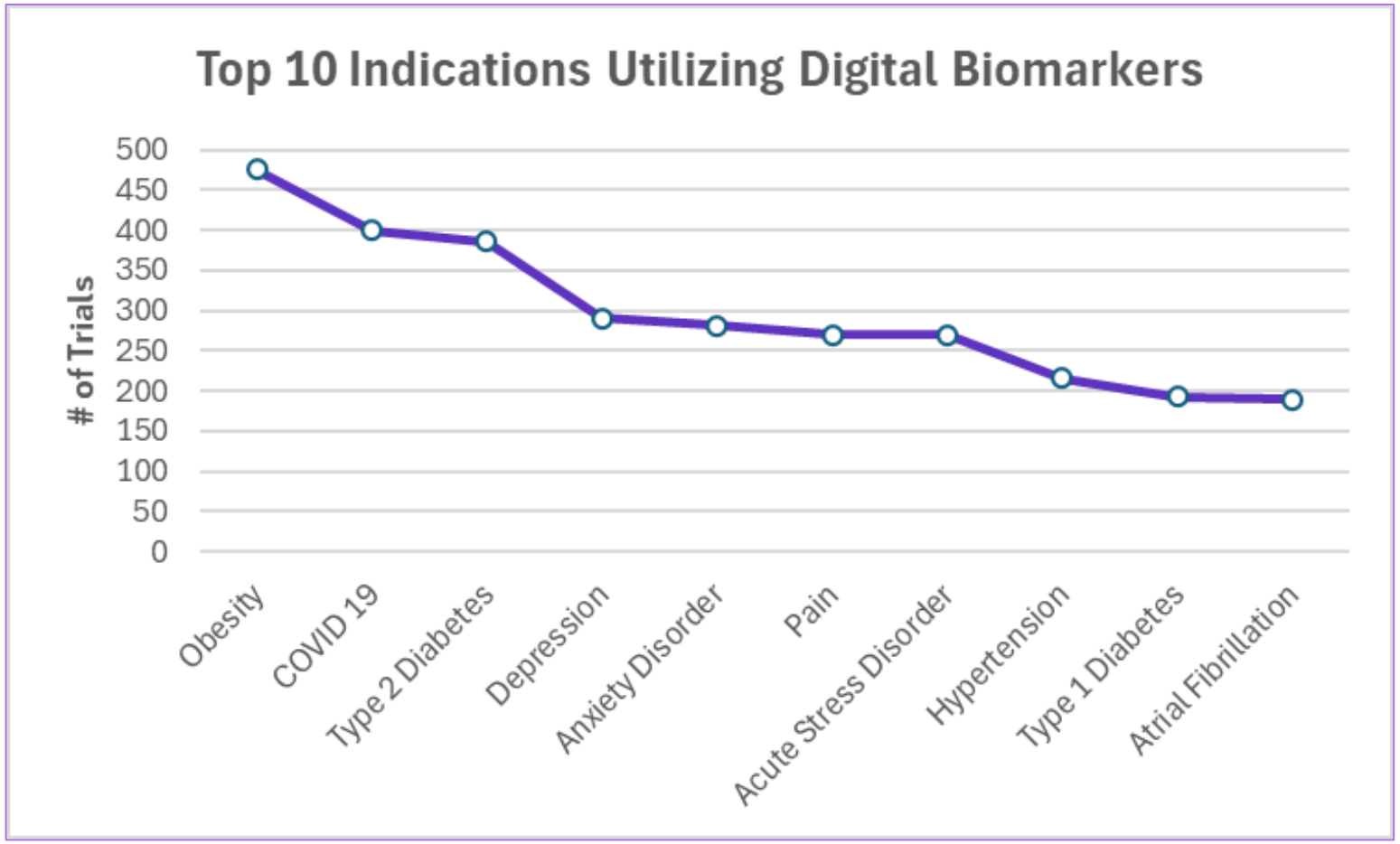
Total digital health trials per indication is represented by the black line.

The number of trials per indication that are testing digital health interventions is represented by the green line.

The number of trials making use of other digital health technologies in the trial are represented by the bar chart, each trial may use multiple digital health technologies.

Source: Cortellis Digital Health Intelligence

"From Dreams to Implementation: The Realities of Incorporating GenAI in Life Sciences and Healthcare"
Clarivate Poster Session #108747 Drug Information Association (DIA) Global Meeting
16 –20 June 2024, San Diego, CA, USA. Presenter Matt Wampole




Analysis of top 10 indications utilizing digital biomarkers over a span of 10 years.

The majority of these trials are located in the United States but additional countries include:

- Canada
- China
- Germany
- Japan
- Netherlands
- Spain
- South Korea
- Turkey
- United States

Analysis from Angela Weidner, Senior Product Manager

Source: Cortellis Digital Health Intelligence

# Convergence of AI and Digital Measures for Seamless Preclinical to Clinical Translation

**Szczepan Baran, VDM MS**
Chief Scientific Officer
VeriSIM Life

***Roundtable Discussion: Development of a Digitally Derived Endpoint – What is "Good" to Whom?***
*Joint FDA / FNIH Workshop for Digital Measures: Navigating the Development of a Digitally Derived Endpoint*
*Location: Bethesda Marriott, Bethesda, MD*
*Date: June 24-25, 2024.*

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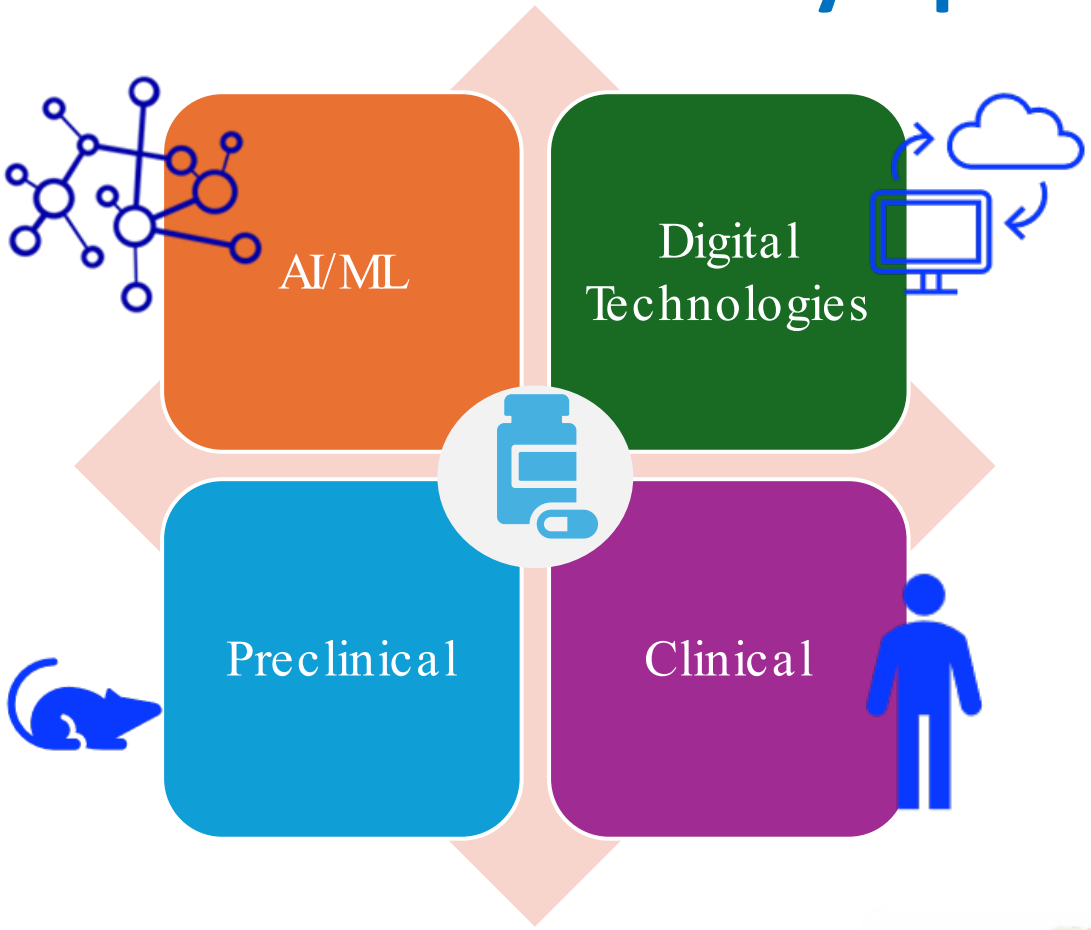
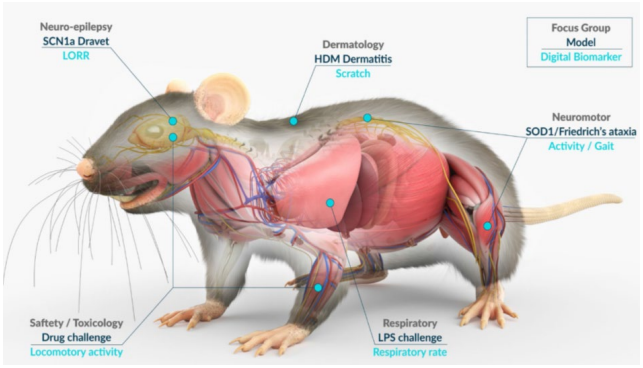
# Symposium Goals




**To enable**

- **Increased translational relevance** of preclinical models
- Faster **go-no/go decisions** → reduce rate of late-stage failures
- **Improved safety and efficacy of treatments** especially in areas of significant unmet need
- More **patient-centric** clinical trials




# Digital Technologies & AI/ML in Drug Development

## THE OPPORTUNITY

AI for **target identification**, virtual screening and optimization of compounds

**Characterize** toxicology and pharmacological responses

Move from **snap-shot observed assessments** in the clinic to **continuous monitoring** of behavior and function in the home

AI for **toxicology and efficacy predictions**

AI/ML has potential to **automate analysis and reporting**

Multimodal data collection and analysis provide tremendous opportunity to map the **patient journey**


Video and sensor technologies enable **real time monitoring** of animal physiology, behavior & health

Potential to **improve animal welfare** by reducing invasive monitoring

**Predictive analytics** to predict human responses based on animal models

Characterize treatment impact on **disease progression** and **symptom fluctuations**

Capture **early signs of efficacy** of disease modifying treatments

**Reduce sample size of** clinical trials through objective endpoints that are meaningful to patients

**Reduce burden** on patients and caregivers

Potential to make clinical trials more **patient centric** through decentralized and BYOD approaches

Goldsack et al., 2020; Manta et al., 2020; Callego et al., 2021; Quresh et al., 2023; Izmailova et al., 2023;

# Timing is Everything

## Strong Interdisciplinary Communities And Pre-competitive Initiatives

DIGITAL MEDICINE SOCIETY

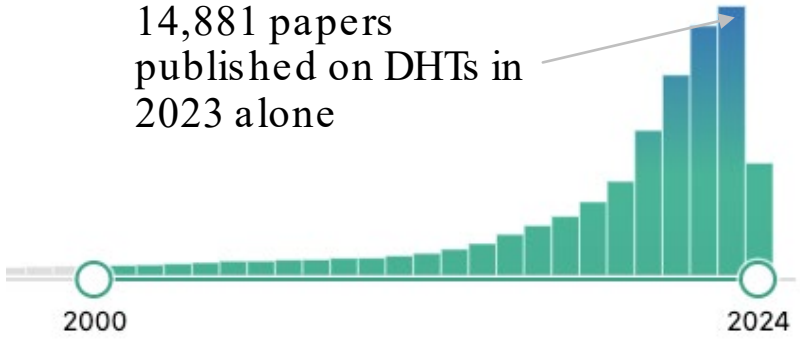
DIGITAL IN VIVO ALLIANCE

The 3Rs Collaborative

Mobilise-D

IDEA FAST

14,881 papers published on DHTs in 2023 alone

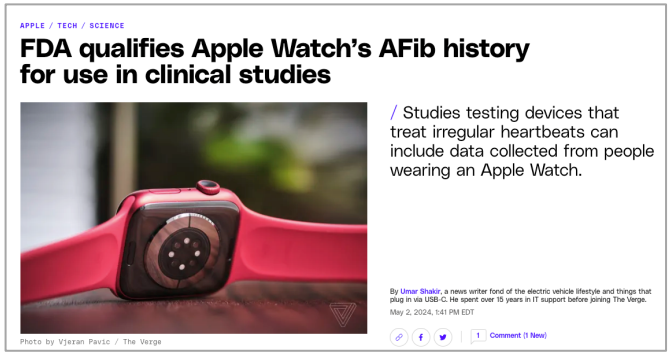



https://www.efpia.eu/news-events/the-efpia-view/blog-articles/digital-endpoints-for-patient-focused-health-management/

## Strong Interest from Regulators

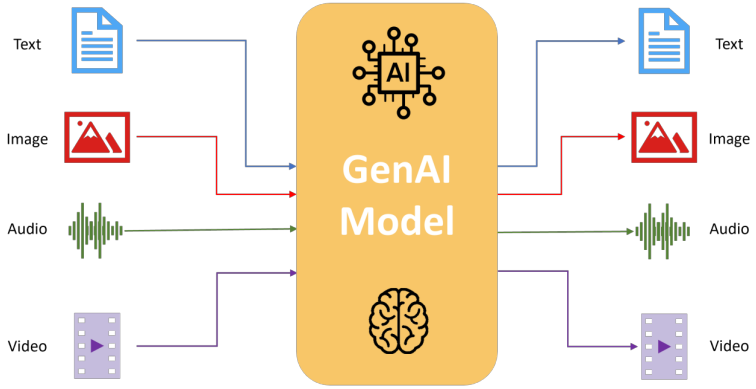

**Digital Health Technologies for Remote Data Acquisition in Clinical Investigations**

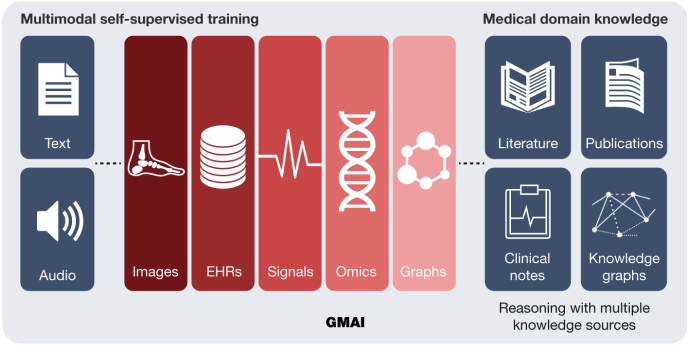
Guidance for Industry, Investigators, and Other Stakeholders




First DHT qualified under FDA's Medical Device Development Tools program

## Strong advances in AI/ML models &infrastructure




Moor, Michael, et al. "Foundation models for generalist medical artificial intelligence." *Nature*

https://blog.petrieflom.law.harvard.edu/2023/03/20/how-artificial-intelligence-is-revolutionizing-drug-discovery/

# Agenda at a Glance

| Time | Session Type | Speakers |
|---|---|---|
| 9:15-9:40 am | Welcoming Remarks from Pfizer LT<br><br>Introductory Talk | Nasir Khan & Brian Corrigan<br><br>Jo Varshney & Szczepan Baran |
| 9:40-10:25am | 1. Prelude to Preclinical AI/ML and Digital Biomarkers | Ben Vandendriessche<br>Brian Berridge |
| 10:40-11:40 am | 2. Technical Challenges & Innovations | Anand Giddabasapp, Elias Oziolor and Larsson Omberg |
| 11:40-12:10pm | 3. Preclinical and Clinical Uses of Digital Measures | Brian Berridge & Carrie Northcott |
| 12:30–2pm | Breakout Session #1 | All |
| 2:10-3:10pm | 4. Case Studies | Pradeep Babburi, Michael Ellis, Matt Czech, Ariel Dowling, Pietro Artoni |
| 3:15-4:45pm | Breakout Session #2 | All |
| 4:45-5pm | Concluding Remarks | Charmaine D. and Szczepan Baran |

SOCIAL 5-6 pm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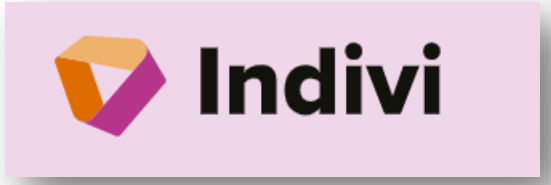
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Ventures


VERTEX

# Breakout Sessions

**Breakout Session 1: Identify strategies for integrating digital measurements and AI/ML to enhance preclinical to clinical translation.**

- Addressing the Challenge of bridging the preclinical to clinical gap
- Confidence in Digital Measures
- Increased adoption of digital technologies and AI/ML in the drug development life cycle

**Breakout Session 2: Outline a framework for adopting preclinical digital biomarkers to complement those emerging in the clinical space.**

- Outline main components of a development framework for pre-clinical to clinical measures
- Relative merits of reverse translation vs forward translation in digital biomarker development
- Regulatory considerations for qualification of preclinical digital biomarkers
- Changes in current regulatory framework to facilitate wider implementation of digital measures and AI/ML in clinical trials

# Key Take-aways

- Video and sensor technologies facilitate real-time &objective monitoring in preclinical research
- Wearable and mobile technologies are revolutionizing clinical trials
- Growing acceptance and integration of digital measures in the regulatory framework
- Symposium served as a springboard for actionable strategies
- Laid the groundwork for a peer-reviewed manuscript and a forthcoming workshop with the FDA in White Oak Campus (October 28th, 2024)

# Preclinical Executive Summary

| | Identified Strengths | Challenges/Opportunities |
|---|---|---|
| **Digital Measures/AI/ML** | ➢ Preclinical is using digital technology/AI/ML way before these methods started the Gartner Hyper cycle in clinical devt (eg; CV space/QTc)<br>➢ Good examples in telemetry, hERG, S7A/E14, open source algorithms available | ➢ Scientific dialog, collaboration and mutualization of resources (data storage, tech infrastructure) across companies barely exist in PC/C continuum<br>➢ DIVA/DIME coming together demonstrated benefit of convergence. Can they join forces to materialize from a scientific question standpoint?<br>➢ Technology can double the workload and difficult to see value—Developing use case critical |
| **Forward and Reverse Translation** | ➢ Not everything need to translate and digital tools can be for internal decision making; no need to qualify<br>➢ Leverage learnings from use cases which are already available across companies | ➢ Pre-competitive efforts are needed to foster data sharing initiatives especially when animals models and digital endpoints are fairly standardized--critical for AI/ML iterations<br>➢ Use clinical results as the reference when a 'gold standard' does not exist; reverse translation has greater opportunities than forward translation! |
| **Implementation** | ➢ Several Preclinical case examples and precedence shared from DIVA, Pfizer (breathing, motion speed, USV, PN); AbbVie (PN, Pain, activity), Takeda (GLS in mice)<br>➢ Much experience is available within biomarker qualification framework (similar to V3+) that can be leveraged to qualify digital tools | ➢ Volume of data, sensitivity, cost/value ratio and keeping up with the technological pace is challenging<br>➢ Terminology mapping/ontologies/frameworks for preclinical and clinical critical; Standardization of measuring digital measures across companies and devices is challenging<br>➢ SOPs need sign off from both preclinical and clinical; design PC studies with clinical in mind |
| **Case Examples** | ➢ Telemetry is well adapted but can be further developed<br>➢ Learn and expand knowledge from neuro endpoints (PN, Alzheimer's, AD, seizures) | ➢ Seizure detection, activity monitoring is a gap; pharma companies not ready for expensive, scalable digital cages<br>➢ Positive POCs in clinics can be a substrate to evaluate the relatedness between digital measures that could detect early Rx effect in human vs in an appropriate rodent model (eg; ALS SOD1 hypothesis) |

GLS=Global longitudinal strain; USV=Ultrasonic vocalization; PN=Peripheral neuropathy; POC=Proof of concept

# Clinical Executive Summary

| | Identified Strengths | Opportunities |
|---|---|---|
| Digital Measures | ➢ Tremendous opportunity in developing more patient centric endpoints to holistically measure symptoms and function in patient's naturalistic environment<br>➢ Opportunity to make clinical trials a care option for all<br>➢ Emerging examples of regulatory acceptance as primary endpoints in interventional trials (e.g. 95$^{th}$ percentile stride velocity for DMD) | ➢ Differing terminologies: NDEs can be seen as COAs or digital biomarkers → require different validation pathways<br>➢ Establishing meaningful change in these NDEs using anchor-based, distribution-based or qualitative approaches<br>➢ Operational considerations: device type, location and form factor, battery life, tolerability, compliance, data transfer capabilities, etc<br>➢ More focus is needed on the context of use of NDEs |
| **AI/ML** | ➢ Strong advances in AI/ML models and infrastructure (e.g. cloud-based processing) enable us to process vast amounts of multimodal data efficiently & robustly<br>➢ AI/ML can potentially enhance the utility, reliability, and patient-centricity | ➢ Need for robust data collection including a rigorous data monitoring strategies (as outlined in DIME's playbook)<br>➢ Need to conduct studies to validate these novel AI-enabled NDEs against "gold" standard measures |
| Implementation | ➢ DIME's V3 framework that discusses the verification, analytical and clinical validation of novel endpoints is being adapted across preclinical and clinical domains<br>➢ DIME's DATAcc is a collaborative community with CDRH aimed at advancing digital health measurements.<br>➢ Multidisciplinary initiatives focused on assessing the net financial benefits of employing NDEs in clinical trials | ➢ Hardware/OS-agnostic digital endpoints are crucial to long drug development cycles for reliable and future-proof digital endpoints. Cross-device reliability is paramount.<br>➢ Opportunity to standardize derivation of digital measures across companies and across technologies<br>➢ Opportunity to take some of the learnings and successes in the clinical space to advance preclinical innovation |
| Case Examples | ➢ Showcased how Abbvie is using NDEs across the portfolio highlighting one example in Axial Spondyloarthritis<br>➢ Takeda showcased an example of cardiac strain and sweat biomarkers in Fabry Disease | ➢ Despite the increased adoption, there are limited examples where NDEs are being used to make go/no decisions<br>➢ Need to continue the investment in strategy and data collection during clinical trials to achieve more success stories |

NDE = Novel Digital Endpoints; DIME = Digital Medicine Society; CDRH = Center for Devices and Radiological Health,
DATAcc= Digital Health Measurement Collaborative Community

# Organizing Committee

**Szczepan Baran**
Chief Scientific Officer,
VeriSIM Life

**Charmaine Demanuele**
Exec Dir Biostats
GBDM, Pfizer

**Kirsty J Kerin**
Exec Assistant
GBDM, Pfizer

**Ravi Shankar Singh**
Sr. Director, ClinPharm,
TCS, Pfizer

**Shashi Ramaiah**
VP, Global Head of
Investigative labs,
Drug Safety R&D, Pfizer

**Terry R Van Vleet**
Head of Investigative Toxicology
& Pathology, AbbVie

**Weida Tong**
Director Division of
Bioinformatics &
Biostatistics; FDA/NCTR

**Natalie Bratcher-Petersen**
Head of Partnerships, TLR Ventures
Manager, Digital In Vivo Alliance

**Larsson Omberg**
EVP Data Science
Koneksa Health

**Dave Hurry**
Chief Data Officer
Koneksa Health

# Thank you to all the presenters, moderators, organizers and invited participants




# Question 1

- Introduce yourself and describe your affiliation

- What would **good** look like?
  - What DHT?
  - What disease?
  - What population?
  - Why?

# Question 2

- What two principles would you address as part of **change management** to support the use of DHTs in clinical trials?
  - A pitfall to avoid
  - An incentive to promote