MEDINFO 2025 — Healthcare Smart × Medicine Deep
M.S. Househ et al. (Eds.)

doi:10.3233/SHTI250868

Trend of Digital Biomarkers (dBM) as Endpoints in Clinical Trials: Secondary Analysis of Open Data

Mizuki MORITA[a,b,1] Mina HONJOH[b] and Takahiro YAMANE[a]
[a] *Department of Biomedical Informatics, Faculty of Interdisciplinary Science and Engineering in Health Systems, Okayama University*
[b] *Faculty of Health Sciences, Okayama University Medical School*
ORCiD ID: Mizuki Morita https://orcid.org/0000-0001-8592-5499, Takahiro Yamane https://orcid.org/0000-0003-3251-384X

Abstract. This study examined clinical trial trends to guide digital biomarker (dBM) guideline development. Analysis of 2005-2023 data was conducted to assess the frequency and types of dBM used as endpoints (dEP) in these trials and the associated target diseases. Clinical trials using dEP increased from 0-7 per year (2005-2019) to 15-20 annually from 2020. Endocrine and metabolic conditions were the most common targets, showing a distinct disease distribution compared to overall trials. Most measurements used actigraphy devices or blood glucose sensors, with glucose sensors focusing on metabolic conditions while actigraphy covered broader applications. Additionally, 42.4% of trials used dEP as primary endpoints. While dEP use is growing, it remains limited in disease scope and device variety. Expanding both would enhance their utility in clinical research.

Keywords. Clinical endpoint, clinical outcomes, wearable devices

1. Introduction

Accurately understanding a patient's condition is essential for effective treatment. Medical institutions rely on examinations and tests, while clinical trials often use self-reported quality of life (QOL) indicators to evaluate patients between visits. However, QOL indicators lack objectivity, and clinical tests require in-person visits.

The emergence of wearable devices has enabled continuous health monitoring outside of medical institutions, paving the way for dBM [1,2]. Unlike traditional biomarkers or self-reported QOL indicators, dBM provides new ways to assess health conditions, offering complementary insights. Despite their potential, dBM usage remains limited, with uncertainty about optimal device and indicator selection for specific conditions. To promote dBM adoption, analyzing past clinical trials using dBM as endpoints (digital endpoints, dEP) is essential.

This study examined dBM endpoint trends in clinical trials through analysis of open data, investigating usage patterns, target diseases, devices, and measured indicators to identify development opportunities and clinical needs.

[1] Corresponding Author: Mizuki Morita, email: mizuki@okayama-u.ac.jp

2. Methods

Data from 2005 to 2023 was obtained from the Digital Medicine Society (DiME)'s Library of Digital Endpoints [3], which compiles clinical trials from ClinicalTrials.gov using digital biomarkers as endpoints (dEP). Note that the number of trials may differ from total dEP count, as multiple endpoints can exist within a single trial. Multiple researchers conducted the analysis, and all data processing steps were double-checked to ensure accuracy and reliability.

Our analysis focused on three categories: sensor/device (measurement device type), condition category (disease classification, e.g., sleep disorder for chronic insomnia), and health concept (measured aspect, e.g., sleep or physical activity via actigraphy).

The following research questions guided our analysis:

1. How many clinical trials used dEP, and what was the trend over time?
2. For which diseases were dEP used?
3. What devices were commonly used to measure dBM?
4. What relationships emerged between diseases, devices, and measurement data?
5. Which diseases and devices were most frequently used as primary endpoints?

3. Results

3.1. Overall trend

Between 2005 and 2023, 131,128 industry-sponsored clinical trials were registered on ClinicalTrials.gov. Of these, 99 trials (0.075%) used dBM as endpoints.

The number of trials using dEP remained below 10 per year from 2005 to 2019. However, from 2020 onward, the number increased, with more than 14 trials conducted annually between 2020 and 2023 (Figure 1). The highest number of trials was recorded in 2021, with 20, while the highest percentage was in 2020, at 0.216% (17/7,881).

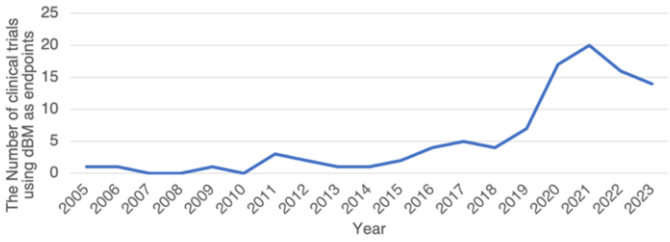

Figure 1. Trend of the number of clinical trials using dBM as endpoints.

3.2. Condition category

The most common condition categories in trials using dEP were endocrine or metabolic conditions (31 trials) and neurological (25 trials). Other categories included cardiovascular/cerebrovascular (12 trials), respiratory (11 trials), mental/behavioral/neurodevelopmental disorders (10 trials), and sleep/wake (9 trials). Remaining categories had between 1 and 4 trials each.

Compared to overall clinical trial trends [4], there was a noticeable bias in condition categories for dEP trials. Notably, oncology trials were underrepresented, while endocrine or metabolic conditions and neurological disorders were overrepresented.

3.3. Sensor/device

The most frequently used devices for dBM measurement were actigraphy (62 trials) and blood glucose sensors (25 trials). Other devices included digital recording devices (2 trials), cough monitors (1 trial), ECG wearable patches (1 trial), skintronics (1 trial), and HRV monitors (1 trial).

3.4. Relationship of between condition category, health concept, and sensor/device

The schematic diagram of the relationship between the condition category, health concept, and sensor/device is shown in Figure 2.

Actigraphy primarily evaluated health concepts such as physical activity (52 dEPs), sleep (30 dEPs), and neurological or sensory functions (10 dEPs). Other health concepts included neurocognitive functions (4 dEPs), blood (2 dEPs), respiratory (2 dEPs), cardiovascular (1 dEP), nocturnal scratch (1 dEP), skin (1 dEP), and other (1 dEP).

The condition categories associated with actigraphy were diverse for both physical activity and sleep. However, for neurological or sensory functions, only neurological disorders were represented.

Blood glucose sensors primarily measured blood-related health concepts, with most trials falling under the endocrine or metabolic conditions category.

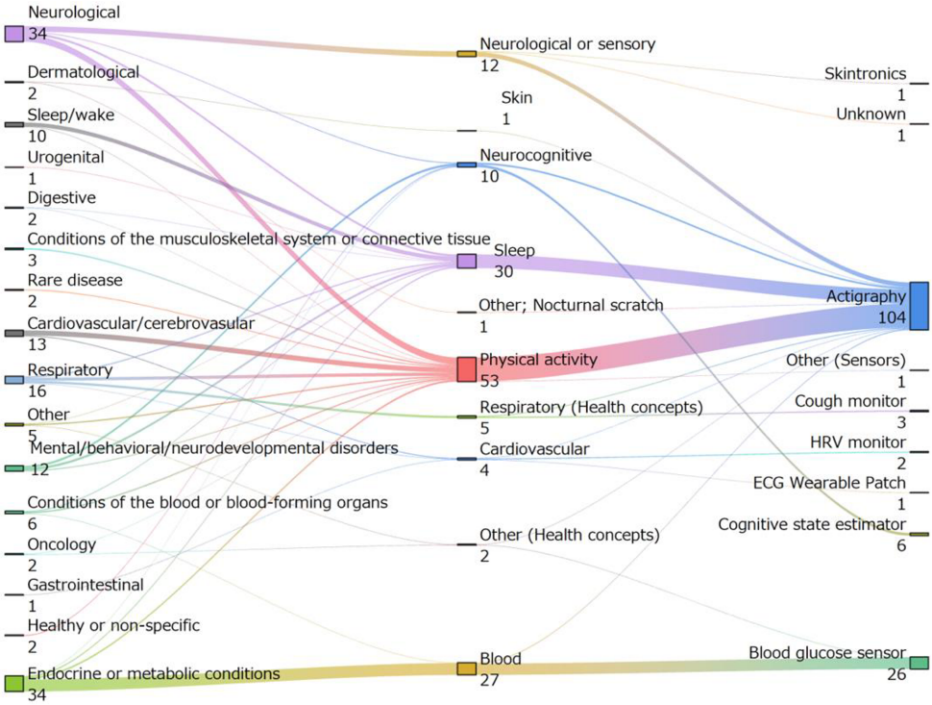

Figure 2. Relationship of between condition category, health concept, and sensor/device.

3.5. Primary endpoint or not

Of the clinical trials that used dBM as an endpoint, 42.4% employed it as a primary endpoint. This proportion varied over time but remained between about 30% and 60% from 2020 onward.

By condition category, dBM was frequently used as a primary endpoint in endocrine or metabolic conditions (19 trials), followed by neurological (8 trials), sleep/wake (6 trials), cardiovascular/cerebrovascular (5 trials), and respiratory (5 trials).

Regarding sensor/device, actigraphy (27 trials) and blood glucose sensor (17 trials) were the most common devices used for primary endpoint measurements. Other devices were not yet widely used for primary endpoints.

4. Discussion

4.1. Overall trend

The number and percentage of clinical trials using dBM as endpoints have generally increased over time, despite some fluctuations. Notably, a significant rise was observed in 2020. However, despite this growth, the overall adoption of dEP remains limited. It is important to note that our dataset included only industry-sponsored clinical trials and excluded those using dBM for adverse event detection. As a result, the actual numbers and proportion of clinical trials incorporating dEP are likely much higher.

4.2. Condition category

While dBM endpoints have been applied across a broad range of condition categories, their distribution shows noticeable bias. Comparing the overall distribution of clinical trials to those involving dBM endpoints reveals that some disorders are more suitable for dBM applications than others.

4.3. Sensor/device

Although many sensors and devices can be used to measure dBM [5], the types used as endpoints in clinical trials were highly skewed. This distribution does not reflect the broader availability of sensors and devices.

4.4. Relationship of between condition category, health concept, and sensor/device

Actigraphy is a versatile device capable of measuring both daytime physical activity and nighttime sleep patterns. Given its relevance to multiple diseases, it is the most commonly used device for dBM measurement in clinical trials. In contrast, blood glucose sensors are more limited in their application, primarily used for monitoring blood glucose levels in diabetes-related trials. The prevalence of these trials likely explains the frequent use of blood glucose sensors as endpoints.

Considering the versatility of actigraphy, its use in dBM development is expected to continue expanding across a wider range of diseases. Additionally, there is potential for the adoption of other sensors and devices in future trials.

4.5. Primary endpoint or not

In neurological disorders and sleep-related conditions, treatment effects are often reflected in patients' daily and nightly movements, making these areas well-suited for actigraphy-based evaluations [6].

In diabetes research, traditional primary endpoints such as fasting blood glucose and HbA1c levels are being supplemented by continuous glucose monitoring (CGM). For example, some trials now evaluate the proportion of time blood glucose levels remain within a standard range (ClinicalTrials.gov ID: NCT04409587) [7]. This shift highlights the growing importance of dBM in assessing treatment outcomes.

5. Conclusion

This study analyzed data from 2005 to 2023 to examine the use of dBM as endpoints (dEP) in clinical trials, including the types of dBM employed and the diseases targeted. While the number of clinical trials using dEP has been increasing, they still represent only a small proportion of all trials. There is a notable bias in the disease categories that utilize dEP compared to overall clinical trial trends. Additionally, the range of devices used for dBM remains limited. The frequent use of actigraphy highlights its high versatility, but there is a need for broader adoption of other devices to expand the application of dBM in future clinical trials.

Acknowledgements

The authors gratefully acknowledge Manami Tetsutani and Moe Tanuma for their crucial contributions to data quality assurance and validation procedures.

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