Paper ST10

Digging Deep into Digital Biomarkers: Empowering Clinical Trials

Vijay Pasapula (Cerus), Unnat Patel (AnalysisMate), Gianna Huang (Gilead), Mike Hamidi (Pfizer), Jing Su (Merck), Sudeepa Dutta (ICON), Teckla Akinyi (J&J), Lavanya Sundaram (Sanofi), Nimita Limaye (IDC), SathishKumar Chitta (Veranex)

ABSTRACT

Digital biomarkers are consumer-generated physiological and behavioral measures collected through connected digital tools (portables, wearables, implantables, digestables, etc.,) without interference to a patient's daily lifestyle. Data becomes a digital biomarker when a relationship is drawn to a health-related outcome. As a part of PHUSE "Emerging Trends & Technologies" working group, project "Digital Biomarkers in Clinical Submissions" exploring the current state of digital biomarkers in clinical trials and its future impact. In this paper we are digging deep into milestones in digital biomarker ecosystem, classification of digital biomarkers, verification and validation, data flow, evolving FHIR landscape, submission, data privacy and integrity, role of digital biomarker to digital therapeutics, benefits and challenges, statistical modeling considerations.

INTRODUCTION

Digital biomarkers are a type of biomarker that utilizes technology such as sensors, wearables, and mobile devices to measure physiological or behavioral data. They are becoming increasingly popular in healthcare research and clinical applications as they allow for continuous monitoring of an individual's health status, providing real-time or near real-time data. This information can be used to track biological processes in the body, evaluate the effectiveness of treatments, and aid in disease diagnosis and treatment monitoring.

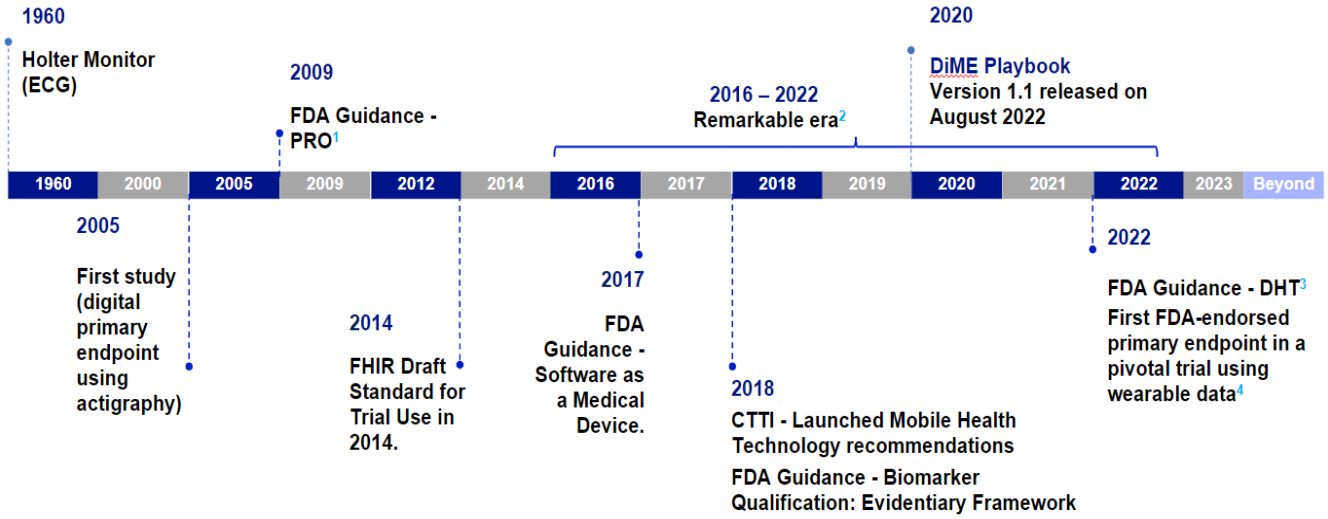
Digital biomarkers can be non-invasive or minimally invasive, making them more convenient for patients and less disruptive to daily life. They can also be collected remotely, which increases the feasibility of large-scale studies and improves accessibility for people in remote locations.

While digital biomarkers are still in the early stage of development and require further validation, they have the potential to revolutionize healthcare by providing more detailed and personalized information about an individual's health status.

Digital biomarkers are used in different therapeutic areas, including but not limited to Cardiovascular disease, Diabetes, Oncology, Sleep, Respiratory, Neurological and Neuropsychiatric diseases. (Özdoğan, 2019) Currently, the Cardiovascular segment holds a dominant position in the market (Anon., 2022).

Digital biomarkers technology built to record data such as blood pressure, activity tracking, skin conductance, mobility, posture, oxygen levels, glucose monitoring, tremors, sleep, pain, temperature, heart rate, etc.

Digital biomarkers provide high-quality insights from real-world data collected in home settings, enabling measurement of new endpoints, gathering rich patient data remotely and reducing patient burden, while being low cost. They can be used for post-licensure safety monitoring, personalized medicine, early disease detection and real-time monitoring, and when combined with traditional biomarkers can enhance diagnostic, prognostic, and predictive capabilities (de Jong, 2022).



[1] Patient Reported Outcomes
[2] Out of 366 studies mentioned in DiME Library of digital endpoint; 341 are listed between this timeframe.
[3] Digital Health Technologies for Remote Data Acquisition in Clinical Investigations - Guidance for Industry, Investigators, and Other Stakeholders. First Draft Guidance released on 21Jan2022
[4] Case study- Link

Figure1: Milestones in Digital Biomarkers Ecosystem

DIGITAL vs. TRADITIONAL

Similarities:
- Both digital and traditional biomarkers measure indicators of normal biological or pathogenic processes or responses to exposures or interventions.
- Both types of biomarkers can be categorized based on their clinical goal.
- Both digital and traditional biomarkers can provide quantitative and qualitative results.
- Both types of biomarkers aim to be accurate and reproducible.

Differences:
- Digital biomarkers allow for continuous monitoring of physiological or behavioral data, while traditional biomarkers measure singular, distinct events.
- Significantly more investment has been made in the validation of traditional biomarkers.

CLASSIFICATION

There is a large ambiguity in the semantics used within digital biomarkers, including the classification (Babrak, et al., 2019). This is especially highlighted as the field is emerging and with a large variety of digital biomarkers measured across a myriad of hardware and software. Additionally, the development of digital biomarkers in clinical trials is a highly collaborative requiring input from several fields (healthcare, engineering, analytics, technology companies and users), who use the terms differently (Babrak, et al., 2019) (Motahari-Nezhad, et al., 2022). In the pursuit of harmonization several classification strategies have been suggested with the integral starting point of understanding the definition of a digital biomarker. The **B**iomarkers, **E**ndpoint**S** and other **T**ools (BEST) group, developed by FDA and NIH, defines biomarkers: *as a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions* (FDA-NIH Biomarker Working Group, 2016). Digital biomarkers fall within this definition; however, they do include behavioral measures (Babrak, et al., 2019).

Several classification strategies have been suggested that focus on one or several parts of the definition. These include: (i) classification based on BEST categories (Coravos, et al., 2019), which focuses on the clinical utility of the biomarker; (ii) classification based on clinical status/outcome, which looks at the novelty of the measurement or device in a clinical context (Wang, et al., 2016); (iii) classification based on patient interaction, which focuses on the combination of how the device works and how the patient uses it (Walton, et al., 2020) (Babrak, et al., 2019), and (iv)

classification based on FDA device clearance, which considers the risk classification from CDRH of the digital tool in use (Coravos, et al., 2019).

Of note to classification strategies is the publication of a guidance document by the FDA in December 2021 (U.S. Food and Drug Administration, 2021) which contains comments on how information should be structured when clinical investigations use digital data collected remotely. This document offers a promising spring board and identifies the need for harmonization as the field matures.

VERIFICATION and VALIDATION

Verification refers to the process of ensuring that a product, service, or system meets the specified requirements and design specifications. This includes activities such as testing, inspection, and demonstration. In the context of digital health technology, verification can include functional testing of software, usability testing of interfaces, and performance testing of devices. The goal of verification is to ensure that the technology is fit for its intended purpose.

Analytical validation is the process of evaluating the performance of analytical methods used in digital health technology. This includes determining the accuracy, precision, and repeatability of the methods used in the technology. Analytical validation is critical for ensuring that the technology produces accurate and reliable results. In digital health technology, analytical validation can include testing the performance of diagnostic algorithms, evaluating the accuracy of sensor-based measurements, and assessing the reliability of data analysis methods.

Clinical validation is the process of evaluating the safety and effectiveness of digital health technology in real-world clinical settings. This includes testing the technology in patients, assessing its impact on patient outcomes, and evaluating its performance under real-world conditions. Clinical validation is critical for ensuring that the technology is safe and effective for use in patients. In digital health technology, clinical validation can include testing the technology in clinical trials, conducting observational studies, and evaluating the impact of the technology on patient outcomes.

Together, verification, analytical validation, and clinical validation are critical steps in the development of digital health technology. They are needed to ensure that the technology is safe, effective, and fit for its intended purpose. Verification and analytical validation focus on the technical and laboratory aspects of the technology, while clinical validation focuses on the real-world performance and safety of the technology in patients. All of these steps are necessary to ensure that digital health technology is reliable, accurate, and beneficial for patients (Goldsack, et al., 2020).

DATA FLOW

The data flow for a digital biomarker used in regulatory submission typically involves the following steps:

Data Collection: Digital biomarkers are collected using sensors or other methods on digital devices. Data collection can be either active (requiring patient input) or passive (automatically collected), with the choice between the two depending on the study's goals. A combination of both active and passive data collection may provide a more complete picture.

- **Active Data Collection:** In active data collection, patients are required to actively participate in the data collection process by entering information into a device or app. This might include self-reported symptoms, medication usage, or physical activity levels. Active data collection can be useful for collecting specific information about the patient's condition or behavior, but it relies on the patient's cooperation and ability to accurately report the information.
- **Passive Data Collection**: In passive data collection, data is automatically collected by a device without any active involvement from the patient. This might include continuous monitoring of physiological signals, such as heart rate or sleep patterns, using wearable sensors. Passive data collection can provide a continuous stream of information about the patient's health and behavior, but it may not capture specific information about the patient's condition or environment that can be obtained through active data collection.

Data Compression: In order to minimize the amount of data being transmitted, the collected data may be compressed, or reduced in size, before transmission. This can improve the efficiency of the transmission process and reduce the risk of data loss or corruption during transit.

Data Transmission: The data is transmitted over a secure network, such as the internet, using a variety of protocols, such as Bluetooth, Wi-Fi, or cellular data. The method of transmission will depend on the type of device being used and the specific requirements of the study or treatment program.

Data Standardization: The data is mapped to CDISC SDTM standards. There are initiatives to automate data

mapping by using Health Level 7 (HL7) Fast Healthcare Interoperability Resources (FHIR).

Data Analysis: The data is analyzed to identify patterns or trends that may be relevant to the person's health status and analyzed data is stored as per CDISC ADaM standards.

Data Tabulation and Visualization: The analyzed data is presented in tabular and a visual format, such as a table or graph or chart, to make it easy to understand and interpret.

Data Storage and Sharing: The processed and analyzed data is stored in a secure location, and can be shared with healthcare providers or other authorized parties for further analysis or use in treatment decisions.

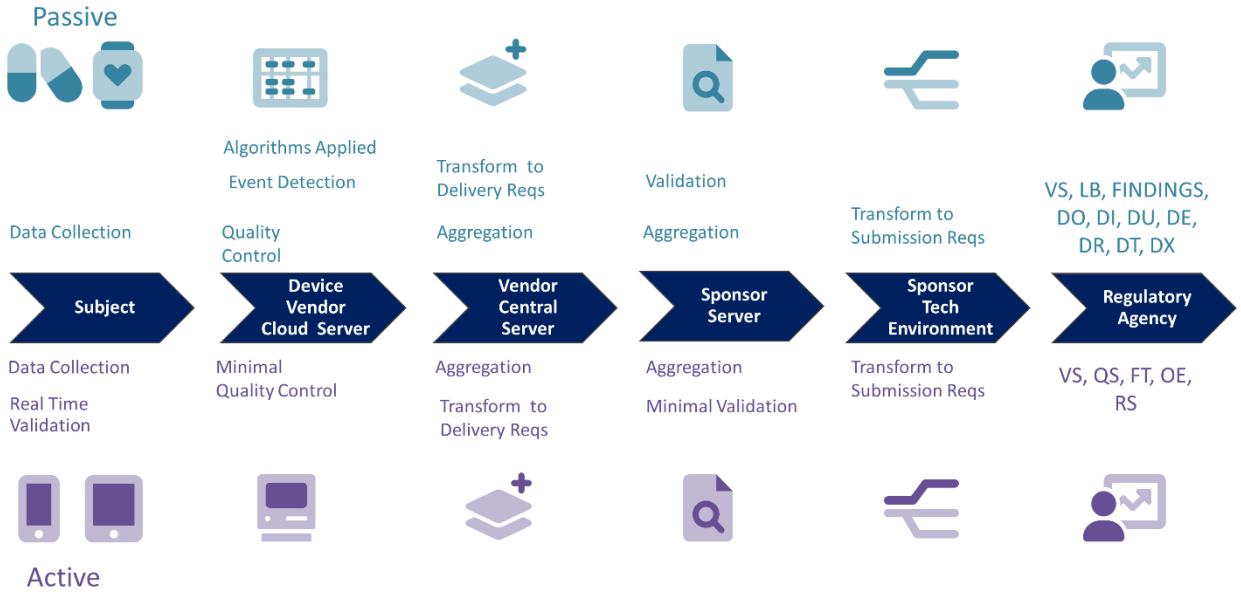


Figure 2: Data Flow

EVOLVING FHIR LANDSCAPE

Digital biomarkers and endpoints can help patients and enable more innovative clinical trials in the future (e.g., real-time data generation for clinical decision outcomes). However, we must first step back and understand how to use an interoperable and modernized digital health infrastructure to collect and exchange data from digital health technology (DHT) solutions. The future of DHTs can use the Health Level 7 (HL7) Fast Healthcare Interoperability Resources (FHIR, pronounced "fire"), which are a set of standards resources built to use RESTful API to exchange health care data (Health Level Seven International, n.d.).

Since the 21st Century Cures Act (Cures Act) was signed into law on December 13, 2016, the focus has been on fostering an age of innovation and advancements to help patients get medical products fast and efficiently (21st Century Cures Act. , 2016). In turn, the U.S. FDA produced its Technology Modernization Action Plan (TMAP) on September18, 2019 and a corresponding Data Standards Program Action Plan (DSPAP) on January 29, 2021 (U.S. Food and Drug Administration, 2021) (U.S. Food and Drug Administration, 2019). The TMAP action plans describe the use of APIs for data exchange, interoperability, and its cloud infrastructure, among other technologies, to help advance and establish modernization capabilities of the future. In addition, the DSPAP describes the 21 CFR 11 compliance using HL7 FHIR, using sources like Electronic Health Records (EHRs), etc. Lastly, concerning the use of DHTs, the FDA's Digital Health Center of Excellence has begun to establish guidelines, policies, and resources. It's important to note that the FDA is not the only regulator evaluating FHIR (e.g., EMA, Health Canada, PMDA, etc.) (U.S. Food and Drug Administration, n.d.).

There are many different areas of health care that FHIR exists to help drive innovation and interoperable efficiency of data exchange (Lehne, et al., 2019). For example, the FHIR US Core Profiles (Health Level Seven International, n.d.) for healthcare data exchange within the U.S. realm was initially developed and published as part of the Office of the National Coordinator for Health Information Technology (ONC) (Office of the National Coordinator for Health Information Technology, n.d.). The objective of the U.S. Core Profiles is to create a standard set of FHIR resources and terminology to enable interoperable healthcare data exchange (e.g., actors such as payers, providers, researchers, vendors, and patients) (Domnisch, 2022). Furthermore, SMART-on-FHIR (SMART Health I.T., n.d.) was launched to provide an open and free standards-based API framework. For example, there are SMART on FHIR

Genomics projects to create a standards-based approach supporting clinical decision-making using the API framework (SMART Health I.T., n.d.).

FHIR can also help facilitate the same strategy for DHTs by using a consistent standards method for data exchange, but one that can enable interoperability from the outset (Careem, 2022). Some of this work is already happening with Apple Health (Apple, n.d.), Google Healthcare (Google, n.d.), Microsoft Azure Health Data Services (Microsoft, 2022), FHIR Works on AWS (Amazon Web Services, 2020), and many other vendor-based service solutions. FHIR's strengths are around the flexibility of resources (e.g., the 80/20 rule) to accommodate different use cases, semantically structured, built using modern web technologies, internationally used, and making continued advances with each release.

Nevertheless, there's a lot more R&D and cross-industry collaboration that is required in this space to achieve maturity. Still, the FHIR standard provides the necessary solutions to support the future of DHTs (e.g., wearables, Digital Therapeutics – DTx) and the proactive identification of digital biomarkers. Moreover, FHIR can enable the standardization of these digital biomarkers at the originating state (i.e., by design), which helps accomplish some of the outcomes set forth by the Cures Act. Therefore, in the short-term, FHIR versions of R4 and R5 may require further profiling until standardized content is normalized in future versions. Figure 3 illustrates a conceptual vision using FHIR for DHTs and its relevance to the digital biomarker process flow.

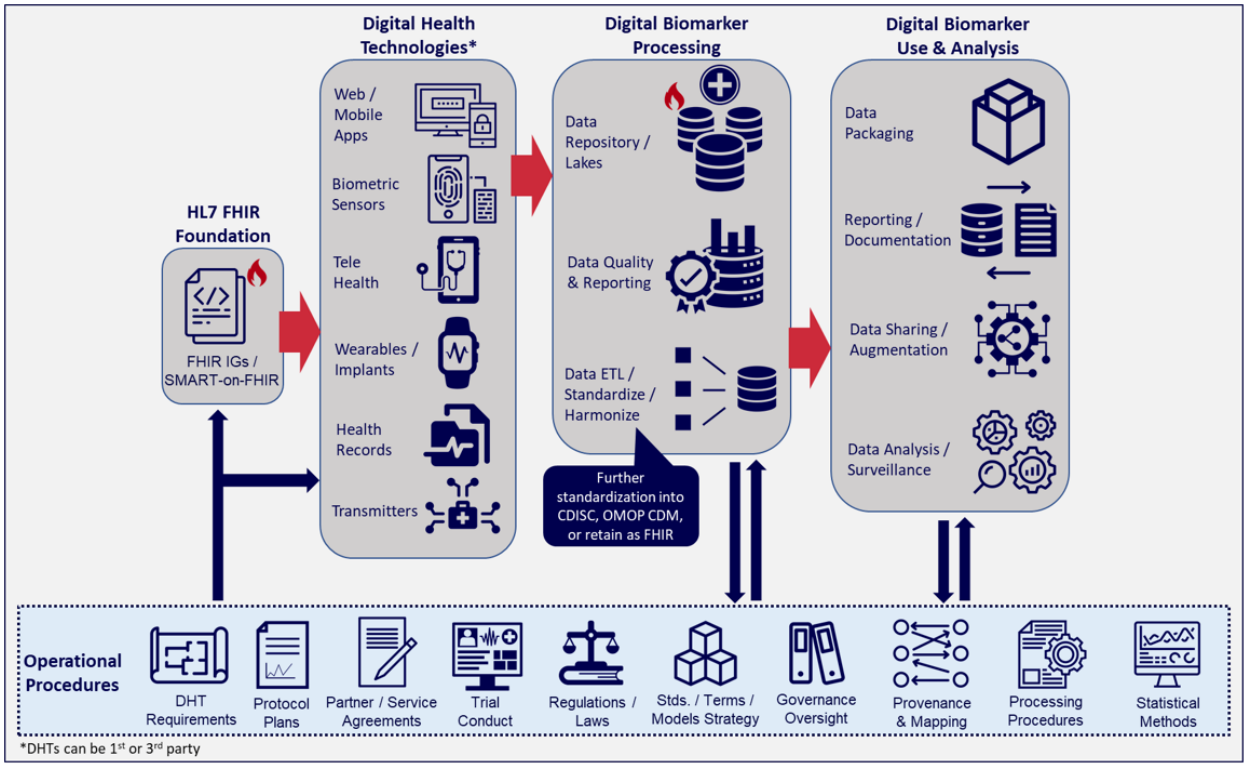


Figure 3: FHIR-enabled DHTs for Digital Biomarker Conceptual Data Flow

SUBMISSION

In the submission documentation, sponsor should provide the supporting documentation on the verification and validation of the digital biomarker/DHT used in the study. V3, a three-component framework demonstrating Verification, Analytical Validation, Clinical Validation should be helpful for regulatory reviewers on how the digital measure is evolved and utilized in the studies.

According to FDA guidelines on DHT, Sponsor should provide fit-for-purpose for use of DHT in the clinical investigation. For commercially available DHTs, the technical specifications and user manuals provided by the manufacturer may cover this requirement. Regarding data integrity, sponsors should include information about data management aspects covering how the data is collected, stored, transmitted and archived ensuring privacy and security (U.S. Food and Drug Administration, 2021) (Goldsack, et al., 2020).

Submission related Key take aways from Digital Medicine Society Playbook:

- Sponsors are responsible for ensuring that clinical trials conducted using connected sensor technologies can be “readily reconstructed”
- Source documents will be required during inspection by regulatory authorities. Source documents are the earliest practically retainable record of the data. sponsors should define source data as the first level of data that is both clinically relevant to the trial and interpretable
- Sponsors should ensure that audit trails are implemented to track the data (including any modifications made to the data) from the point of creation by the sensor in the connected sensor product through to the first practically retainable record of the data (durable media) (DiMe Society, n.d.).

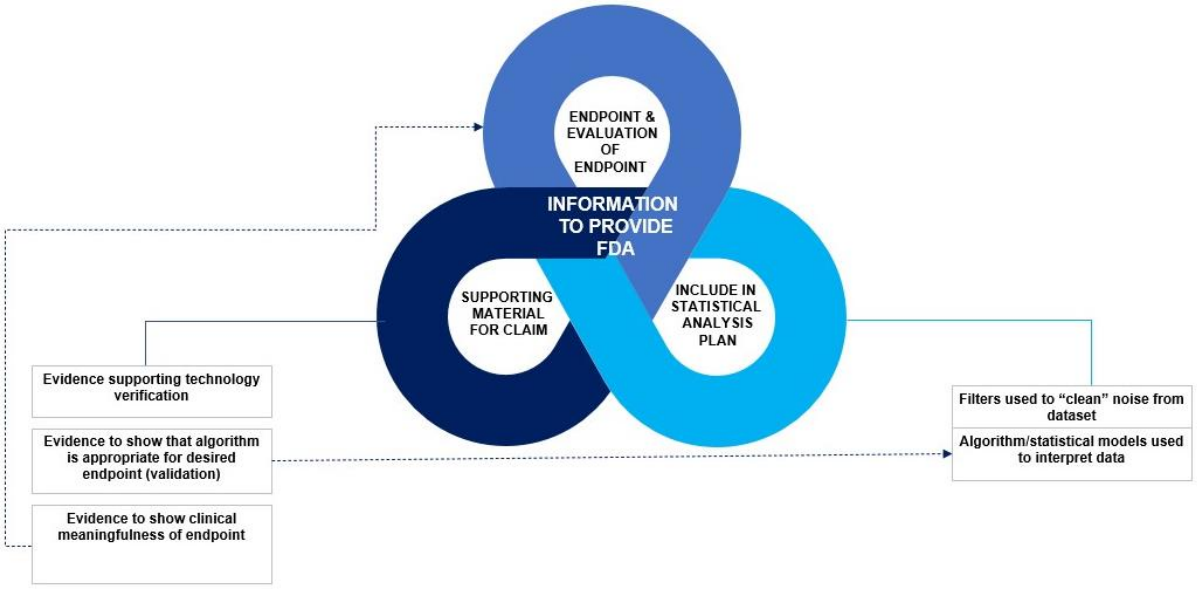


Figure 4: Information to provide FDA. Source: (CTTI, 2021)

DATA PRIVACY and DATA INTEGRITY

There are several unique data privacy challenges that digital biomarker data presents, including the speed and volume of extremely personal and sensitive Protected Health Information (PHI) that is gathered. This increases the risk of potential data breaches and calls for enhanced cybersecurity measures. This becomes even more relevant when data is gathered around sensitive topics such as mental health issues across multiple stakeholders within the healthcare ecosystem. Should this data be accessed by payers or employers, this could have a significant impact on reimbursement decisions or may even impact an individual’s employment. Thus, one must ensure the access to data is regulated and that the misuse of data is not allowed. Blockchain technologies and data deidentification can be used to address some of these concerns.

Dynamic patient consent plays a key role in protecting the patient’s data. Dynamic patient consent is an interactive online e-consenting process by which provides patients with ongoing touch points, enabling ease of reconsenting through their clinical trial journey, and the ability to consent to some parts of the consent request and or change their decision to consent within the trial, thus improving the patient experience and driving retention. Questions around data ownership need to be addressed and data governance models need to be established to drive transparency and build trust. Thus, one needs to implement robust data governance models, with clear policies around data acquisition, storage, sharing and use. As data sovereignty gains increasing importance, compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the General Data Protection Regulation (GDPR) regulations is critical.

With an increasing focus on ethical A.I., when ML models are developed to predict treatment response, it is important to select the right data to eliminate bias, and have adequately large training datasets and long enough training periods to improve the model’s performance. Transparency is critical as regulators do not like black-box technologies and regulatory agencies require algorithms to be fixed, so that the algorithm does not change when new data comes in. While this may not allow one to fully leverage the ‘learning’ potential of ML models, these are measures that regulators are taking to manage risk.

ROLE OF DIGITAL BIOMARKER to DIGITAL THERAPEUTICS (DTx)

Digital therapeutics (DTx) are a type of medical treatment that uses digital technology, such as software, mobile apps, or wearable devices, to improve health outcomes. They are designed to provide evidence-based therapeutic interventions to prevent, manage, or treat a medical condition (Digital Therapeutics Alliance, n.d.).

By using digital biomarkers to track the effectiveness of a digital therapeutic, drug developers can make adjustments to improve the therapeutic's efficacy and personalize treatment for individual patients. Additionally, digital biomarkers can also be used to validate the effectiveness of digital therapeutics in clinical trials, which is important for getting them approved by regulatory bodies.

Let's say a company is developing a digital therapeutic for people with diabetes. The digital therapeutic is a smartphone app that provides education on diabetes management and tracks the user's glucose levels, physical activity, and dietary intake. To create the digital therapeutic, the company uses digital biomarkers such as glucose levels, step count, and calorie intake to measure the effectiveness of the app in improving diabetes management. The company can then use this data to make adjustments to the app, such as providing personalized suggestions for physical activity or modifying the educational content to better meet the needs of individual users.

In a clinical trial, the company can use digital biomarkers to demonstrate that the app is effective in improving diabetes management. For example, they can show that users who used the app had better glucose control, as indicated by digital biomarkers such as glucose levels, compared to a control group who did not use the app. This evidence of effectiveness can be used to support the regulatory approval process.

It is worth noting that digital therapeutics are a relatively new field and regulatory authorities are still in the process of creating guidelines for the approval process.

BENEFITS

The pandemic has accelerated our path towards an inevitable conclusion – a digitally connected healthcare future that empowers both patients and caregivers alike. Digital biomarkers have proven its capability to take the health industry onto a next level. A few benefits have been listed below.

- Measure a whole new range of endpoints which were impossible to measure before, including early detection of disease and progression **(U.S. Food and Drug Administration, 2021) (Rosa, et al., 2021)**
- Enable personalized medicine; leveraging digital biomarkers, providers can essentially run a "trial" for each individual patient, continuing to generate evidence for care protocols **(RockHealth, 2016)**
- Digital biomarkers can help gather rich data about patients, passively and remotely, reducing patient burden and provide high quality insights **(RockHealth, 2016)**
- Improving data quality, reproducibility, privacy and sharing when including Blockchain technology algorithms that facilitate data accuracy and security improving analysis of big data when using A.I. and ML algorithms **(Rosa, et al., 2021)**
- Real-time monitoring creates opportunities to be proactive in preventing data loss or retrospective data entry, data errors by real-time 'reactivity', improving intervention fidelity when using smart apps and A.I. algorithms (i.e., Clinical Decision Support or CDS) **(ActiGraph, n.d.) (Rosa, et al., 2021)**
- Combining panels of digital & traditional biomarkers with validated digital phenotype signatures promises to directly enhance diagnostic, prognostic, and predictive capabilities **(RockHealth, 2016)**
- Post licensure safety monitoring **(Garcia-Gancedo & A, 2022)**
- Low cost **(HealthXL, 2022)**

Note: This does not intend to be an exhaustive list.

CHALLENGES

Digital biomarkers present a number of challenges that need to be addressed to ensure their accurate and effective use. Some of these challenges include:

Categories	Challenges
Scientific and	➢ Validation and verification of digital device for the disease and population

clinical	➢ Selection of endpoints collected using digital device ➢ Algorithm validation (Ceesay & Svetnik, 2022)
Technical	➢ Capabilities for long-term deployment such as battery life and remote capture mechanisms ➢ Cybersecurity risks that may impact digital biomarker collection (U.S. Food and Drug Administration, 2021) ➢ Digital devices updates and changes
Operational	➢ Privacy concerns ➢ Regional regulatory hurdles (Forbes, 2022) (ActiGraph, n.d.) ➢ Uncertainties around stakeholder incentives ➢ Uncertainties around workflow integration (RockHealth, 2016) ➢ Recruitment of a skewed (tech-savvy, younger) population ➢ Training and equipping sites and study participants (ActiGraph, n.d.) ➢ Subject device compliance (Ceesay & Svetnik, 2022)
Statistical	➢ Missing data (Ceesay & Svetnik, 2022) ➢ Difficulty in interpreting large data (ActiGraph, n.d.)
Regulatory Submission	➢ Lack of data standards

STATISTICAL MODELING CONSIDERATIONS

Digital biomarker data analysis typically involves a variety of statistical methods, including descriptive statistics, inferential statistics, and machine learning techniques. Descriptive statistics are used to summarize and describe the data, such as calculating mean, median, and standard deviation. Inferential statistics are used to make inferences about a population based on a sample of data, such as performing hypothesis tests or estimating population parameters. Machine learning techniques, such as linear regression, decision trees, and neural networks, are used to model complex relationships between the digital biomarker data and other relevant variables, such as disease progression or treatment response.

Statistical modeling for digital biomarker data is the need to account for the temporal and longitudinal nature of the data. Many digital biomarkers are collected continuously over time, and the data may have a complex structure with multiple correlated measurements at different time points. Below are few aspects to consider

Missing data - Digital biomarkers are often collected via mobile devices, and participants may not always be able to provide data, due to technical issues or lack of access to the device. Therefore, statistical methods for handling missing data, such as multiple imputation or inverse probability weighting, are needed to ensure that the missing data does not introduce bias or affect the conclusions.
Computational methods - large data sets and computational requirements for digital biomarker data analysis. Digital biomarkers generate a large amount of data, and conventional computation methods may not be efficient enough to handle the large data sets. Therefore, specialized software and parallel computing techniques, such as distributed computing or cloud computing, may be needed to perform the analysis in a timely and efficient manner.
Bias - The use of digital biomarkers in clinical trials can introduce bias that can influence the outcome of the study (Holko, et al., 2022). Factors such as age, gender, internet accessibility, psychological barriers, ethnic groups, education, and income can lead to sampling bias, as shown in a study by Ruth (2021) that found differences in the impact of digital health technology (DHT) use and results (Tappen, et al., 2022). According to Janet D. (2022), who conducted a review of 20 studies available on PubMed, the main sources of bias in digital biomarker studies are related to data collection, management, and skewed training data. Additionally, algorithm bias, which is an inherent challenge in digital biomarkers, can lead to unreliable predictions and conclusions for underrepresented groups. Kristine G. (2022) emphasizes the importance of recognizing and preventing bias throughout the decision-making process, from data collection to algorithm interference. To address these issues, population stratification and multivariate modeling can be used in the analysis stage. It is important to consider user accessibility, social factors, and the intended population when using digital biomarkers in clinical trials. The FDA's Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan, released in 2021 (FDA, 2021), acknowledges the need to evaluate and address algorithmic bias, with future regulatory actions aimed at improving and identifying robust and resilient algorithms.

FORWARD LOOKING

Looking ahead, the future of healthcare looks promising with the continued advancement of digital health technology. The ability to collect more real-time and longitudinal data through wearable devices and mobile apps is expected to drive demand for digital biomarkers in various disease areas, including diabetes, respiratory diseases, cardiovascular diseases, and sleep disorders. With government and corporate investments in healthcare digitalization and smart hospitals, the market for digital health technology is projected to grow significantly, reaching USD 27.17 billion by

2030 (Straits Research, 2022). By working together to develop and implement standards and best practices, clinical research professionals, technology companies, and government regulators can fully realize the potential of digital health technology and improve healthcare for patients around the world. The use of smartwatches and other consumer wearables for monitoring multiple physiological factors of the human body, including the accurate detection of heart conditions such as Atrial Fibrillation, is expected to become more widespread, reducing mortality risks and improving overall patient outcomes.

In the future, digital biomarkers have the potential to solve a range of complex drug development scenarios, including:

- Personalized medicine: Digital biomarkers can help tailor drug treatment to individual patients based on their unique biology and disease state.
- Clinical trial design: Digital biomarkers can streamline the drug development process by allowing for smaller, more efficient clinical trials that rely on real-world data.
- Early detection of drug efficacy: Digital biomarkers can provide real-time feedback on drug efficacy, enabling earlier detection of positive or negative results and reducing the need for larger, longer trials.
- Improved safety monitoring: Digital biomarkers can provide continuous monitoring of a drug's safety profile, reducing the risk of adverse events and allowing for more informed decision-making.
- Development of new novel digital medicinal products
- Development of combination therapies: Digital biomarkers can help identify patients who are most likely to benefit from combination therapies, allowing for more effective treatment strategies.
- Better understanding of disease progression: Digital biomarkers can provide a continuous, real-world view of disease progression, helping to identify new targets for drug development and improving our understanding of complex diseases.
- Reduced time to market: By streamlining the drug development process and reducing the need for large, time-consuming clinical trials, digital biomarkers have the potential to significantly shorten the time it takes for new drugs to reach the market.

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CONTACT INFORMATION

Vijay Pasapula
Sr Director, Stat Programming, Cerus Corporation
Email: Vpasapula@cerus.com

Unnat Patel
Founder & President, AnalysisMate LLC
Email: unnat.patel@analysismate.com