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Food and Drug Administration

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To Whom it May Concern:

This letter represents comments submitted on behalf of the **Digital Medicine Society (DiMe)** for consideration by the U.S. Food and Drug Administration (FDA) regarding Docket No. [FDA-2021-D-1128](#) for "[Digital Health Technologies for Remote Data Acquisition in Clinical Investigations Draft Guidance for Industry, Investigators, and Other Stakeholders.](#)"

DiMe is a 501(c)(3) **non-profit organization** dedicated to **advancing digital medicine to optimize human health**. We do this by serving professionals at the intersection of the global healthcare and technology communities, supporting them in developing digital medicine through interdisciplinary collaboration, research, teaching, and the promotion of best practices.

Founded in 2019, DiMe is the first **professional organization** for experts from all disciplines comprising the diverse field of digital medicine. Together, we drive scientific progress and broad acceptance of **digital medicine to enhance public health**.

Many of our DiMe members conduct clinical trials of new medical products or develop digital health technologies for use in these trials. The following comment leverages the combined expertise of our members regarding the use of digital health technologies (DHTs) in clinical trials. We appreciate the opportunity to offer our comments on this draft guidance document.

We appreciate that this guidance was issued by multiple centers: Oncology Center of Excellence (OCE), The Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER). In particular, we are pleased to see there is a continuing trend in harmonizing guidance and hope this continues. Reduction in gray areas for those developing digital health technologies and those using them in clinical investigations will allow regulations to be more approachable and followable, lessening the burden for all involved.

We applaud FDA’s human-centered approach to this guidance. Recognizing that patients should be the beneficiary of the work done in drug, tool, and measure development, digital or otherwise, is critical to identifying problems and developing solutions that matter.

We note that the scope of this guidance allows for **generalized use of best practices across technologies** and appreciate FDA providing that flexibility.

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Comment Structure: Feedback and Resources From the Digital Medicine Community

Our comment is structured around feedback and questions that we have received from the digital medicine community. We do not presume to provide answers, that is the sole domain of the Agency. Rather, following each question we pose in this comment, we highlight resources that 1) the digital medicine community is currently referencing, and 2) that we believe are of high quality.

Definitions of and Surrounding Digital Health Technology

Lines 15-18 and 813-818 of the Glossary define digital health technology (DHT) as a “system that uses computing platforms, connectivity, software, and/or sensors, for healthcare and related uses.” We recognize the complexity of DHTs and appreciate the broad definition and

recommend the further inclusion of language that references a **modular stack of hardware and software components**¹ in this definition.

Line 23 references **hardware** and/or **software** that may comprise a DHT, pointing to a footnote defining the two terms, as well as **firmware**. There is opportunity to clarify these definitions to remove ambiguity.

FDA might consider aligning to definitions provided by ISO/IEEE:

- Hardware - an electronic or mechanical element, including its interface and documentation²
- Software - computer programs, procedures and possibly associated documentation and data pertaining to the operation of a computer system³
- Firmware - combination of a hardware device and computer instructions or computer data that reside as read-only software on the hardware device⁴

It is worth noting that ISO/IEEE considers the **firmware to be a part of the software**, as opposed to the guidance, which includes the firmware in the hardware. Aligning to ISO/IEEE standards may reduce the burden on manufacturers of DHTs as they work to comply with regulations.

FDA might also consider the addition of language regarding the **core operation of the hardware** and the specific role of the firmware, including the appropriate regulations for each.

Comments on *Regulatory Considerations and Engagement with the Agency*

The inclusion of language regarding the **optional qualification regulatory path** is welcome guidance. It provides clarity for the device manufacturer and sponsor. Additional information provided in the FDA's webinar covering this draft guidance made a clarifying note that qualification is advantageous when **using the same DHT in multiple clinical trials**. We recommend adding this additional language to the guidance as it creates clarity for following the qualification path.

¹ Coravos A, Doerr M, Goldsack J, Manta C, Shervey M, Woods B, William A. Wood WA. Modernizing and designing evaluation frameworks for connected sensor technologies in medicine. *npj Digital Medicine* (2020) 3:37 ; <https://www.nature.com/articles/s41746-020-0237-3>

² IEEE 1012-2012 IEEE Standard for System and Software Verification and Validation, 3.2

³ IEEE 828-2012 IEEE Standard for Configuration Management in Systems and Software Engineering, 2.1

⁴ ISO/IEC 12207:2008 Systems and software engineering — Software life cycle processes, 4.14

Lines 110-112 describe **devices used in clinical investigations as “exempt from most requirements applicable to devices.”** We request additional clarification on this terminology, who is able to make this distinction, and through what mechanism this distinction should be pursued. Specifically, whether a medical device clearance is preferred or irrelevant to the agency would assist our community.

There is an opportunity to define the **boundaries between exempt DHTs, DDT/MDDT, SaMD, and other qualification programs**, including specifics across different centers. Clarifying these boundaries could allow for harmony across guidances and centers to produce a guidance library that supports digital health innovation through a shared unifying language and understanding of processes.

Comments on *Considerations When Using Digital Health Technologies in Clinical Investigations*

We recognize that it is challenging to create **one guidance that meets the needs of a diverse audience of readers** (manufacturers, sponsors, quality teams, etc.) and appreciate the care taken to be as broad as possible in this draft guidance.

The DiMe Society and our community have developed relevant resources, such as **The Playbook**⁵ that builds a shared foundation for developing and deploying digital clinical measures using a step-wise approach and **Digital Measures that Matter to Patients: A Framework to Guide the Selection and Development of Digital Measures of Health**⁶ that may be useful to FDA.



The Playbook’s step-wise approach for developing and deploying clinical measures⁵

⁵ <https://playbook.dimesociety.org/>

⁶ Manta C, Patrick-Lake B, Goldsack J, C. Digital Measures That Matter to Patients: A Framework to Guide the Selection and Development of Digital Measures of Health. Digit Biomark 2020;4:69-77. <https://www.karger.com/Article/Fulltext/509725#>

Through our and our collective digital medicine community's experiences, we deem **measure development as a precursor to technology selection**. We recognize the discussion of endpoints in *Section IV. D* and recommend the addition of a section describing measure development (inclusive of *Section IV. D*), prior to *Section IV. A. Selection of a Digital Health Technology and Rationale for use in a Clinical Investigation*.

Measures collected with DHTs during clinical investigations may be collected to determine study eligibility, assess efficacy, safety, and/or adherence to protocol.

Digital measures also vary by the type of underlying software/technology. To evaluate the quality of the digital measurement product, it is valuable to **distinguish between** those tools that rely upon **sensor-generated** data and those that rely on **reported, survey data**.

We use the term, "**biometric monitoring technology**" (**BioMeT**) to describe measurement tools that process data captured **by mobile sensors using algorithms to generate measures of behavioral and/or physiological function**. We suggest that this may be useful language for the Agency to adopt in future guidance.

Evaluation of a digital measurement product that collects patient-generated data digitally should be based on the context of use and should consider the type of technology:

- **Survey-derived measures** (e.g., an ePRO): The evaluation process is already well described by prior FDA guidelines (e.g., construct, context and content validation)
- **Sensor-derived measures** (e.g., using a wearable): Evaluation should be based on the verification, analytical validation, and clinical validation (V3)⁷ process detailed further on page 6 of this comment

As the recently released guidance on *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders* deals largely with identifying meaningful aspects of health relevant to patients, citing that guidance would be beneficial to the readers.

As related to the selection of the DHT, we echo the **fit-for-purpose** definition (Line 150-152 and *Glossary* 824-824) of a conclusion that the level of validation associated with a DHT is sufficient to support its context of use. Our digital medicine community recognizes the need for clarification when considering the **potential for a mixed technical capability of the target study population**, or at least the need to urge sponsors and investigators to consider such a perspective when selecting a DHT.

⁷ Goldsack JC, Coravos A, Bakker JP, Bent B, Dowling AV, Fitzer-Attas C, Godfrey A, Godino JG, Gujar N, Izmailova E, Manta C. Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for biometric monitoring technologies (BioMeTs). *npj Digital Medicine*. 2020 Apr 14;3(1):1-5. <https://www.nature.com/articles/s41746-020-0260-4>

We appreciated the **flexibility in DHT use** in clinical investigation during the COVID-19 pandemic and encourage maintaining a similar approach in the future. This flexibility allows for participants to have choice when enrolling in a trial and can **encourage subject participation and retention**.

Lines 257-258 describe the **use of technical specifications and descriptions provided by the DHT manufacturer**. While these lines indicate that these manufacturer specifications and descriptions may be “sufficient,” further guidance is requested to define the exact materials needed to meet this sufficiency and limit the variety of interpretations possible by DHT manufacturers and sponsors. Additionally, we suggest the inclusion of clarifying language on using a DHT in an alternate manner to the DHT manufacturer’s intended use.

In regards to the *Verification, Validation, and Usability of Digital Health Technologies*, we champion the efforts to properly evaluate and document a digital measure and the DHTs used to measure it. Our community has developed extensive, high-quality resources to this end that have been adopted by nearly 100 companies and the European Medicines Agency.

We offer an overview of the resource here.

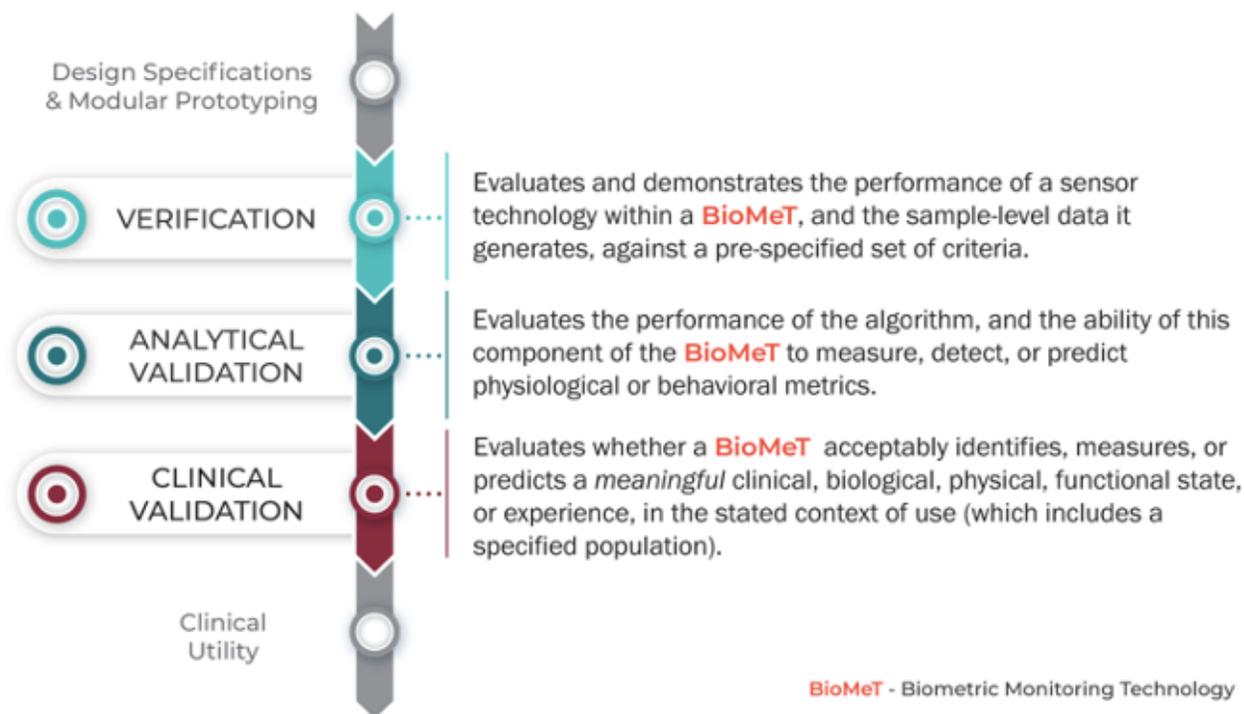
The **evaluation framework for sensor-derived digital measures should encompass both the product’s components (e.g., hardware, firmware, and software, including algorithms) and the intended use of the product**. Existing frameworks for new biotechnologies are not sufficiently adaptable, but they can provide meaningful insight for developing new evaluation frameworks for BioMeTs.

We propose a three-component framework to unite the different disciplinary experts who should participate in the foundational evaluation of sensor-derived digital measures. This **V3 framework includes (1) verification, (2) analytical validation, and (3) clinical validation**.

V3 are foundational to determine whether a digital medicine tool is fit-for-purpose. An evaluation of the usefulness and utility is only applicable after gaining evidence and assurance that the underlying data and predictions are “valid” to answer a given question.

The V3 process is summarized in the figure below and described in detail in the manuscript, “Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for Biometric Monitoring Technologies (BioMeTs)”. This manuscript was developed by a **multi-disciplinary group of experts** with the goal of identifying considerations for **evaluating and documenting measurement performance of technologies that generate sensor-derived digital measures**. We hope it may be a useful resource for the Agency.

Utilizing the definitions shown in the figure below provides increased flexibility to use parts of the modular stack of a DHT and not others while maintaining necessary rigor.



The stages of the V3 framework for biometric monitoring technologies⁸

In addition to the offer of this resource, our digital medicine community requests specifics about what to include in the verification and validation plan, including the level of evidence that is acceptable. We recognize that the variations in studies, measures, and technologies makes for a particularly challenging request. Guidance around the general categories that should be included in the verification and validation plan, whether there is an expectation to reference a gold standard, and what makes for a good reference measure (or examples of such) are, perhaps, specific enough to be actionable. We also would encourage providing examples of the evidence required when a DHT is software alone and when it is a software/hardware/firmware combination.

We are pleased that usability is referenced, along with the *Applying Human Factors and Usability Engineering to Medical Devices* guidance. We suggest the inclusion of additional guidance regarding the critical factors that should be included in usability testing for DHTs,

⁸ Goldsack JC, Coravos A, Bakker JP, Bent B, Dowling AV, Fitzer-Attas C, Godfrey A, Godino JG, Gujar N, Izmailova E, Manta C. Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for biometric monitoring technologies (BioMeTs). *npj Digital Medicine*. 2020 Apr 14;3(1):1-5. <https://www.nature.com/articles/s41746-020-0260-4>

such as environmental variables on the sensor performance or human biocompatibility of the hardware.

We appreciate the inclusion of a section focused on *Evaluation of Clinical Endpoints From Data Collected Using Digital Health Technologies*. As mentioned above, we recommend this section to be **moved prior** to *Selection of a Digital Health Technology and Rationale for Use in a Clinical Investigation* and including guidance on **determining a meaningful aspect of health, identification of concept of interest, followed by the development of the digital endpoint**.

We appreciate the approach the Agency takes in the draft guidance and agree that **digital medical product development tools should be no different than non-digital** and request clarification about how we justify use, specifically whether using existing biomarker and COA guidance is sufficient. Should they be sufficient, a reference to these guidances would be beneficial.

Perhaps out of scope for this guidance, DiMe's community notes that efforts to develop new digital clinical measures should return value over and above existing assessments, for example reduction of participant burden, higher quality data, cost savings, participant adherence, new information, and appeal to a more diverse population.

As we explore *Risk Considerations When Using Digital Health Technologies*, we encourage a **risk-based approach**, similar to that used by the FDA in other guidances. for other endpoints.

We suggest the inclusion of language around **risks to equity** or, if appropriate, references to other guidances addressing equity and inclusion. The use of DHTs in clinical investigations is at high risk of excluding populations based on socio-economic status. DiMe has convened a **Digital Health Measurement Collaborative Community (DATAcc)** to develop and demonstrate best practices and advance harmonized approaches to speed the use of digital health measurement to improve health outcomes, health economics, and health equity.⁹ We hope the resources developed and pending release are useful to the readers of this guidance.

Lines 458-486 discuss *Statistical Analysis*. There is an opportunity to conform the **method of defining endpoints to those of standard industry guidance**. We recognize that the diversity of sensors, algorithms, and methods make guidance difficult, yet realize the need for specifics on the requirements and optional supporting elements for defining an endpoint. For instance, defining **meaningful change**, particularly **when access to the patient population is not available**, and indicating whether the **change in a referenced traditional**

⁹ <http://datacc.dimesociety.org/>

endpoint could be used as a benchmark would provide valuable insight to the audience of this guidance.

We recommend the inclusion of guidance related to **missing or changing data due to software upgrades or technical failures within the *Statistical Analysis* section**. Included in the required statistical analysis plan should be documentation regarding these missing or changing data, such as **missing timestamps, duplicate timestamps** (i.e., during daylight savings), **short and long-term gaps in data**, and even **partially uploaded files** due to technical trouble or connectivity issues.

We are pleased to see specific guidance, such as those around providing instructions to participants for **cleaning the DHT** (lines 506-508). Based on our interactions with individuals who have participated in trials using DHTs, we want to make a note that cleaning procedures should take into consideration the **burden on the trial participants**. Cumbersome, lengthy, or frequent cleaning procedures can result in non-compliance by the participant, leading to a lack of or altered data collection. DHT manufacturers, sponsors, and investigators should take this into account and consider evaluating the cleaning protocol as a part of usability testing.

Lines 515-518 note **cybersecurity risks** as a part of the *Clinical Risks* section. FDA may wish to consider either a separate risks section dedicated to cybersecurity or **highlighting the impact of cybersecurity in each risk category** to clarify the extensive reach of cybersecurity threats.

Lines 536-539, 567-569, and 582-589 discuss important points related to **data privacy, data access, and end-user license agreements**. We agree that participants must be made aware of all entities with access to the data, measures to keep data safe, and that sponsors and investigators should attempt to work with DHT manufacturers to navigate this process. We encourage the inclusion of guidance that recommends **starting as early as possible (long before preparing informed consent documents) when working with DHT manufacturers** in understanding the end-user license agreements and their impact on data privacy and security. We also recommend that **relevant highlights from the end-user license agreements be included in the informed consent document using understandable language for the participants**.

In the *Record Protection and Retention* section, the guidance states the **requirement of record retention in clinical investigation** and emphasizes the need for source data retention "to reconstruct and evaluate the clinical investigation, and the data should be available for inspection." There is an opportunity to clarify the **definition of source data in the context of continuous sensor-based DHT**. To derive digital measures from continuous time series of sensor data, a pipeline composed of signal processing and/or machine

learning steps is typically deployed to transform the raw sensor data to the discrete data features so that they can be used as endpoints in statistical models for efficacy and safety analysis. We believe that **the retention of the raw sensor data, or its least processed form, is essential to the use of sensor-based DHT in clinical investigation.** This processing pipeline, or algorithm, is not currently standardized for most sensor-based DHTs and continues to iterate to keep pace with the rapidly evolving data science and technology landscape. **Processing pipelines can also be proprietary/black box and change during firmware and software updates, imposing further challenges to data consistency.**

As an example, sensors that use accelerometer data capture gravity (G) changes on multiple axes. These micro-G measurements are captured many times per second and are the basis for the resulting endpoints. **The micro-G data would be considered the source data, not the post-processed unit of measurement or calculated endpoint.**

There is an opportunity to further clarify the definition of **source data** in the context of such sensor-based DHT and recognize the **importance of retaining minimally processed data**, as this offers the ability to **investigate missing data, improve data consistency**, and potentially **re-evaluate the clinical data** when more accurate algorithms become available in the future.

Lines 616-624 discuss details around **data outputs for the DHT.** With a lack of standardization around how source data is generated, we recommend that data with the **highest granularity, or least amount of processing, should be the default “source.”** This mitigates the most risk when manufacturers are generating data utilizing different non-standard methods. The capture of the raw data or least processed data **allows for all other aspects of the data processing to be revisited or audited at any time.**

In the *DHT Updates and Other Changes* section, lines 753-755 discuss the **assessment of updates to a DHT** to ensure no significant impact on the measurements performed and data collected. Our digital medicine community requests clarification on **evidence needed around the impact of updates** when assessing for consistency. For instance, is documentation from the software manufacturer stating backward and/or forward compatibility sufficient or is additional evidence needed? Further clarification regarding the difference between a **manufacturer’s software update** for something like a security patch and an **update impacting the use of the DHT for the trial purposes** is requested in terms of the evidence needed to support the “no significant impact” conclusion. Our community follows the National Academy of Medicine definition of **high quality data**, which is **data that**

leads to the same conclusion.¹⁰ We wonder if this aligns to your classification of “no significant impact” and, if this language might provide clarity to readers.

Lines 762-772 discuss software and operating systems updates. **Dedicated solutions are preferred during active data collection of a DHT.** Clear guidance on the **types of updates** a manufacturer can push to production will allow sponsors to accept or decline these types of updates. Certain updates that might be a **"feature enhancement" could be opted out by the sponsor to mitigate risk.** While any **updates on Security, Data Integrity, and Privacy are clearly documented and approved by sponsors for "live" clinical trials using a DHT.**

Conclusion

We recognize the effort on this draft guidance regarding DHT use in clinical investigations as an impactful, helpful guidance that instructs and assists DHT manufacturers, sponsors, investigators, and regulators alike. It is no small feat to provide clarity to a young industry with a wealth of unknowns. We desire to assist the field of digital medicine by providing **quality resources, best practices and use cases, and forums for valuable connections** that can drive the field forward **productively and with patients always in mind.**

We appreciate the efforts to create a broadly applicable guidance that does not overburden the industry with regulations and we hope our comments are helpful in improving this guidance. At DiMe, we are committed to the **safe, effective, ethical, and equitable** use of digital technologies in clinical investigations and see through this guidance and our interactions with FDA that the Agency shares this commitment.

Thank you,



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CEO



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Program Lead

¹⁰ Institute of Medicine (US) Roundtable on Research and Development of Drugs, Biologics, and Medical Devices; Davis JR, Nolan VP, Woodcock J, et al., editors. Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making: Workshop Report. Washington (DC): National Academies Press (US); 1999. Executive Summary. <https://www.ncbi.nlm.nih.gov/books/NBK224572/>