27 May 2026

To: Food and Drug Administration, HHS

Re: Docket No. FDA-2026-N-2476

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to respond to the FDA request for information and comments regarding *Advancing the Use of Digital Health Technologies in Clinical Investigations for Drugs and Biological Products*.

The ISCTM offers these comments for consideration based on our experience and expertise in human CNS research. The ISCTM is an independent organization focused on advancing the development of improved treatments for CNS disorders. No member of this Working Group, comprised of scientists, clinicians, trialists, former regulatory, and drug developers from both industry and academia, received compensation for comments provided. Comments represent individual opinions and not that of the institution, agency, or company affiliation of group members.

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INFORMATION AND COMMENTS ON ADVANCING THE USE OF DIGITAL HEALTH TECHNOLOGIES IN CLINICAL INVESTIGATIONS FOR DRUGS AND BIOLOGICAL PRODUCTS:

General comments

ISCTM welcomes the FDA's call for comment on digital health technologies (DHTs). We believe that DHTs play a pivotal role in the advancement of clinical trials, particularly for CNS conditions. Below, we share sentiments frequently voiced among our membership and during our semi-annual conferences.

Question 1: What regulatory challenges do DHT manufacturers, sponsors or other interested parties face regarding the use of DHTs in clinical investigations of drugs and biological products?

With respect to regulatory challenges that DHT stakeholder groups face in clinical investigations of new drugs, we would like to highlight two categories which we believe are most important for the agency to consider:

Validation standards: Existing guidance does not outline a clear pathway to develop fit-for-purpose DHT devices, measures, and subsequent biomarkers or endpoints.

- Uncertainty surrounding what constitutes sufficient analytical and clinical validation introduces additional risk and costs to clinical development programs when considering the use of DHTs as endpoints in clinical trials.
- DHTs seeking to complement or replace traditional scales face an evidentiary bar that is higher than what the established gold standard scales faced, leaving sponsors to navigate these complex requirements without a reliable roadmap.

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- This is particularly acute in CNS drug development, where DHTs are frequently being explored as more sensitive tools to capture treatment-related signals. This uncertainty around DHT validation further incentivizes the use of familiar, previously validated measures which have known psychometric limitations and are frequently cited as contributing factors to the high failure rates observed in modern CNS clinical trials.

Regulatory pathway ambiguity: Presently, there are multiple engagement and qualification options available to review DHTs and their measures. Sponsors and other stakeholders need clarity on the intent of each pathway, and which should be followed for a given intended use case.

- Existing qualification routes, most notably the Drug Development Tool (DDT) Qualification Program, have not served sponsors and DHT developers well in practice: the pathway is slow, the success rate is low, and outcomes are limited to exploratory-use qualification of Clinical Outcome Assessments (COAs). This does not substantially alter the risk profile when seeking to use DHT data as a primary or key secondary endpoint in a clinical trial.
- Developers recognize that the IND pathway has become the most efficient route for DHT endpoint development. The working group believes that providing clear, formal guidance on building a robust DHT validation case within the IND framework and an alternative low cost, risk-based framework that allows DHT developers to incrementally and iteratively de-risk their measures would significantly improve adoption.

Question 2: What opportunities are there for CDER and CBER to support and facilitate the adoption of DHTs in clinical investigations of drugs and biological products?

With respect to opportunities, we believe there are three broad opportunity categories that CDER and CBER should consider to further facilitate DHT adoption:

Risk-based, tiered validation framework: Establish a validation framework that formally differentiates requirements according to their associated regulatory risk and intended role within a given measurement hierarchy.

- This would provide sponsors with a clear and proportionate roadmap: exploratory DHTs would face a lower validation burden, while those intended as primary endpoints would be held to a correspondingly higher standard.
- Critically, this approach would directly address the sunk cost risk by allowing sponsors to de-risk early-stage DHT investment before committing to more demanding validation requirements.
- ISCTM would welcome the opportunity to contribute to the development of such a framework through its working group structure and membership.

A review of existing programs to foster more proactive and transparent regulatory engagement.

- Creating a more proactive and transparent engagement approach with CDER and CBER throughout the development process. This could be achieved through a re-scoping of existing engagement pathways (e.g. CPIM, ISTAND, DDT) or establishing novel ones to facilitate more dynamic discussions during DHT measure and endpoint development.

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- Publication of anonymized case studies illustrating what an acceptable DHT evidence package looks like across different contexts of use would significantly reduce the uncertainty which puts downward pressure on adoption.

The agency could consider what options are available to incentivize DHT adoption.

- The working group would like to pose the following to the agency: given FDA's repeated public commitment to driving DHT adoption, what concrete incentives could be established to support that goal?
- Options might include expedited review pathways for DHT-derived endpoints, formal recognition of validated DHT measures across programs, dedicated advisory support for precompetitive consortia, or defined consultation mechanisms for sponsors navigating novel DHT-based endpoint development.
- The field is committed to advancing the use of novel measurement strategies, including DHTs; a clear signal from the agency on how it may incentivize first movers could make a substantial difference.

Question 3: What areas of guidance would support the use of DHTs in clinical investigations?

Related to our previous comments to both questions 1 and 2, we believe the FDA could meaningfully supplement existing guidance for the use of DHTs within drug development in a number of ways:

Consider additional categorical definitions beyond the existing positioning of digital measures as endpoints and biomarkers.

- The current guidance aligns DHTs to the existing definitions of biomarkers (measuring a pathological disease process) and endpoints (measuring a patient-relevant disease concept).
- In practice, DHTs can occupy a third categorical space, where digital measures capture meaningful variance in the disease that is not explicitly mapping to a biological process, and where patients may possess limited insight. An example could be specific neurophysiological, biometric functions and gait parameters in neurodegenerative disease. Patients align to the importance of mobility but during qualitative interviews have shown less insight into the differential value of the specific digital measures tied to the concept such as step counts, distance walked or cadence.
- Further, we would ask the agency to consider a qualification path for a digital biomarker or endpoint that would qualify the measurement approach at the concept of interest level, in a non-proprietary manner.
- As an example, the recent EMA qualified use of Stride Velocity 95th percentile (SV95c) in Duchenne's was not specific to a device or algorithm provider.
- Concept-level qualification would help practically reduce the number of sponsor-DHT provider groups interacting with the agency to qualify similar measures within individual programs and would increase the likelihood of pre-competitive standardization of DHT-related measures such as moderate to vigorous physical activity (MVPA).

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Providing further clarity on the language of "appropriate" performance and the required evidence to support validation and use of a digital endpoint.

- More specific definitions would clarify expectations for both DHT developers and sponsors who intend to use the technologies in clinical trials.
- Inclusion of practical or theoretical examples of DHTs and digital measures proceeding through endpoint qualification within the guidance itself would further reduce ambiguity.
- Guidance on acceptable levels of correlation between digital measures and established anchors would further improve clarity. DHTs are often measuring novel disease variance and frequently have limited correlations to existing gold standard COAs. A high degree of correlation to a measure, which assesses omnibus symptom burden and not specific concepts of interest captured by a DHT, should not be an expectation.
- Guidance is also needed on the role of supportive validation data for novel measures; including case-control discrimination, pre-post differences to known interventions and other population level data that can provide additional evidence of the novel measure's alignment to disease.
- Specific guidance to support a tiered validation approach as outlined in *Question 2* above, with guidelines on expected evidentiary thresholds for DHTs and digital measures depending on the intended position within the measurement hierarchy.
- Further insight into how and where the newly released series of guidelines on Generative AI, Machine Learning algorithms and advanced adaptive systems should be leveraged within DHT device and measure development.

Question 4: What specific DHT related topics, such as digitally derived endpoints in certain disease areas, would benefit from discussion in a public workshop?

We believe that there are a number of topics that would benefit from a public workshop. We, as a society, would welcome the opportunity to collaborate with the agency and other scientific organizations such as C-Path on these workshops and participate in shared publication and dissemination of the findings. Specific recommendations for workshop topics include:

Review of the utility of DHTs and digital measures within CNS (Psychiatry and Neurology) clinical trials.

- Within CNS, DHTs are currently being explored as novel endpoints providing contextual support to other COAs, internal decision-making aids (particularly in early Phase trials) and cohort enrichment or stratification tools.
- A workshop discussing use cases, within the context of CNS, and the FDA's perspective on how DHTs may be best leveraged within each use case would be valuable.

A workshop for "what good looks like" DHT validation case studies.

- In line with comments in *Question 2 and Question 3* above, a workshop containing a detailed walk through of digital measure validation and endpoint development with concrete examples would help support a reproducible roadmap for DHT sponsors and developers to leverage.
- DHTs themselves produce data that are different than data from other COAs. It is highly dimensional in nature, very high frequency (at times continuous) and can be very specific.

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- A workshop reviewing the differences between DHT and COA derived data and what these differences mean in the context of endpoint development would be very valuable. Specific agency perspective on data aggregation methods, appropriate observation windows and methods of combining several specific digital measures in multi-component endpoints would be helpful.

A workshop discussing how to approach standardization to speed adoption.

- Facilitating a discussion about setting definitional standards for specific digital measures, including establishing a common validation dataset, protocols for cross device compatibility and standard measurement definitions.
- This would allow DHT and digital measurement developers to work towards validating a comment set of measures and would speed adoption and subsequent review.

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