ConnectedHealthInitiative

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Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Advancing the Use of Digital Health Technologies in Clinical Investigations for Drugs and Biological Products; Request for Information and Comments [Docket No. FDA-2026-N-2476; 91 FR 16006]

The Connected Health Initiative (CHI) appreciates the opportunity to provide input on the Food and Drug Administration's (FDA or the Agency) Request for Information regarding the use of digital health technologies (DHTs) in clinical investigations of drugs and biological products. CHI strongly supports FDA's ongoing commitment under PDUFA VII to establish a clear, science-based framework for the use of DHT-derived data in regulatory decision-making, and we welcome the Centers for Drug Evaluation and Research (CDER) and Biologics Evaluation and Research (CBER) initiative to update that framework in light of the rapid technological advances that have occurred since the December 2023 DHT Guidance.

DHTs, including wearable, implantable, ingestible, and contactless sensors, as well as smartphone-based applications, screen-based functional assessments, and machine-learning-derived digital biomarkers, are reshaping how clinical evidence is generated. They enable continuous, ecologically valid measurement of patient function in real-world settings; expand the populations that can meaningfully participate in clinical research, including pediatric, rare disease, rural, and mobility-limited patients; and create new opportunities for objective, sensitive endpoints that better reflect how patients feel and function. Realizing these benefits at scale, however, requires regulatory clarity that is risk-proportionate, technologically neutral, and aligned with the broader digital health framework FDA has built in recent years.

I. Statement of Interest and General Views

CHI is the leading multistakeholder policy and legal advocacy effort dedicated to improving health outcomes through digital and connected health technologies while reducing costs. CHI is driven by the consensus of stakeholders from across the connected health ecosystem, including digital health innovators, sensor and wearable developers, clinicians and health systems, sponsors of clinical investigations, patient advocates, and developers of AI-enabled clinical and life sciences technologies. CHI advocates before Congress, U.S. federal agencies, and state legislatures and agencies, and we work to promote responsible pro-digital health policies and laws in areas including reimbursement and payment, privacy and security, effectiveness and quality assurance, FDA regulation of digital health, health data interoperability, and the rising role of AI across the healthcare and life sciences value chain. For more information, see www.connectedhi.com.

CHI members have substantial experience designing, developing, validating, and deploying DHTs in clinical investigations of drugs and biological products. Our members include companies whose products span the full range of sensor modalities referenced in the RFI, such as accelerometers and inertial measurement units used to assess motor function and balance, continuous physiological sensors (heart rate, ECG, oxygenation, glucose, respiration, sleep architecture), screen-based assessments of cognition, reaction time, vision, and hearing, ingestible sensors, contactless and ambient sensing platforms, and mobile applications that orchestrate DHT-based interactive clinical tests. Our members' perspectives inform the recommendations below.

II. Response to RFI Questions

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?

CHI members report that the most significant regulatory challenges fall into seven categories. These challenges are not unique to the drug and biologic context, but they are amplified there because DHT-derived data must support regulatory decisions about products that operate on long development timelines and high evidentiary thresholds.

A. Lack of clarity on the regulatory status of the DHT itself

Sponsors and DHT manufacturers frequently face uncertainty about whether a given DHT used to collect data in a clinical investigation is itself a regulated medical device, an investigational device used solely for research purposes, or an unregulated general-wellness or fit-for-purpose research tool. This uncertainty is most acute when commercially available wearables or mobile applications are repurposed or customized for clinical research. The 2023 DHT Guidance helpfully addressed many of these distinctions, but the proliferation of new sensor modalities, app-based interactive tests, and AI-derived endpoints since 2023 has outpaced the guidance. CHI urges FDA to clarify that, consistent with the 21st Century Cures Act and CHI's longstanding support for a risk-based approach, DHTs used in clinical investigations should be regulated proportionate to risk and intended use, and that the appropriate evidentiary focus is on fitness-for-purpose for the specific clinical investigation context of use.

B. Verification, validation, and usability expectations are not risk-proportionate or technology-neutral

The 2023 DHT Guidance set out a sensible framework for verification, validation, and usability assessment, but in practice sponsors report that review divisions apply that framework inconsistently and often default to expectations calibrated to high-risk diagnostic or therapeutic devices rather than to the actual risk of the DHT's use in the investigation. CHI urges FDA to issue follow-on guidance and review-staff training that:

- Explicitly tie verification and validation expectations to the role of the DHT in the investigation (whether the DHT supports a primary endpoint, a secondary endpoint, an exploratory endpoint, or pharmacodynamic and safety monitoring), rather than to the DHT's consumer or device classification;

- Recognize that commercially available DHTs are often appropriate for fit-for-purpose use in clinical research and that requiring de novo analytical validation for sensors whose performance characteristics are already extensively characterized in the published literature creates unnecessary burden;
- Allow reasonable reliance on the DHT manufacturer's analytical performance data, post-market data, and conformance to recognized consensus standards, with sponsor-specific validation focused on the incremental questions raised by the investigation's context of use; and
- Apply usability and human-factors expectations proportionate to the population and burden of the assessment, with particular attention to the lower-burden, higher-frequency measurement that is one of the principal advantages of DHTs over episodic in-clinic assessment.

C. Endpoint qualification and the path from novel digital measure to regulatory-grade endpoint remain opaque

The single most consequential barrier identified by CHI members is the absence of a transparent, predictable, and resourced pathway for qualifying novel DHT-derived endpoints, including digital biomarkers and digitally derived clinical outcome assessments (COAs). The Drug Development Tool Qualification Program is an important pathway but is under-resourced relative to demand, slow, and largely inaccessible to small and medium-sized digital health developers. The Clinical Outcome Assessment Compendium provides limited insight into FDA's evolving thinking on digital measures, and individual investigational-new-drug application (IND) decisions on DHT-derived endpoints are inconsistently reasoned across review divisions and difficult to use as precedent. CHI urges FDA to:

- Publish a clear roadmap, including expected timelines and required deliverables, for qualification of DHT-derived endpoints under the COA Qualification Program, the Biomarker Qualification Program, and the Drug Development Tool Qualification Program more broadly;
- Establish a dedicated, transparent docket of qualified, in-review, and de-prioritized DHT-derived endpoint submissions, including a plain-language explanation of disposition, so that the broader community can learn from FDA's reasoning;
- Expand staffing and methodological capacity in CDER, CBER, and CDRH dedicated to DHT-derived endpoints, including digitally derived measures of neuropsychiatric function, sleep, mobility, and patient-reported burden; and
- Recognize fit-for-purpose qualification, in which a DHT-derived endpoint is qualified for a specific context of use, disease area, and patient population, rather than requiring sponsors to clear a single universal evidentiary bar before any regulatory acceptance is possible.

D. Inconsistent treatment across review divisions and across the FDA digital health portfolio

Sponsors report that two structurally similar DHT-derived endpoints can receive materially different treatment in different therapeutic areas, and that DHT-related expectations articulated in CDRH guidance documents do not always translate predictably to drug and biologic reviews in

CDER and CBER. The cross-Center DHT Steering Committee established under the PDUFA VII framework was a welcome development. CHI urges FDA to use this RFI as an opportunity to publicly report on the Steering Committee's output, document cross-Center alignment on recurring DHT issues (including AI-derived endpoints, predetermined change-control plans for DHT software, and acceptable analytical-validation approaches), and harmonize expectations across CDER, CBER, and CDRH so that sponsors can plan multi-year development programs around stable regulatory expectations.

E. Data quality, governance, and 21 CFR Part 11 application to DHT-collected data

Sponsors face substantial practical uncertainty in applying Part 11 expectations and the Agency's broader data integrity guidance to data collected continuously from patient-owned or sponsor-provided DHTs, often in the home environment, frequently transmitted through third-party platforms, and not infrequently incorporating proprietary AI-derived processing. CHI urges FDA to:

- Issue plain-language, scenario-based guidance on how Part 11 and predicate-rule data integrity expectations apply to DHT-collected data, including continuous sensor data, derived features, and AI-generated outputs;
- Clarify acceptable approaches to audit trails, source-data definition, and metadata for DHT-collected data, recognizing that the traditional CRF-centric model does not map cleanly onto continuous, high-volume DHT data streams;
- Recognize the legitimate roles of DHT manufacturers, cloud service providers, and data-management vendors in the data lifecycle, and provide guidance on sponsor oversight responsibilities without inadvertently consolidating the entire data lifecycle on the sponsor; and
- Confirm that risk-based monitoring and risk-based source data verification are appropriate, and indeed often preferable, for DHT-collected data.

F. AI- and machine-learning-derived endpoints and signal processing

Increasingly, DHTs incorporate AI- and machine-learning-derived signal processing, either embedded in the DHT itself or applied to its raw data, to generate the clinical features used as endpoints (for example, AI-derived gait parameters from accelerometer data, AI-derived sleep architecture from contactless sensing, AI-derived speech biomarkers, AI-derived cognitive scores from screen-based tests). The 2023 DHT Guidance was largely silent on this issue. CHI urges FDA to draw on its broader work on AI-enabled medical devices and AI-enabled clinical trials, including the AI-Enabled Device Software Functions guidance and the predetermined change-control plan framework, to provide DHT-specific guidance addressing:

- Transparency and documentation expectations for AI-derived DHT outputs used as endpoints or covariates;
- Subgroup performance evaluation and representativeness of training data;
- Drift monitoring and predetermined change control for DHT-embedded AI models updated during or across investigations; and

- Alignment with the NIST AI Risk Management Framework and its forthcoming healthcare profile, which CHI has consistently endorsed as the foundation for trustworthy AI in healthcare.

G. Privacy, security, and cross-jurisdictional data flows

DHTs used in clinical investigations frequently collect highly granular behavioral and physiological data (continuous activity, sleep, voice, and physiological signals), which is richer and more longitudinal than the data typically collected in episodic in-clinic visits. Sponsors and DHT manufacturers must navigate HIPAA, the Common Rule, state biometric and health privacy laws, the FTC Health Breach Notification Rule, and an increasingly fragmented international privacy landscape. CHI urges FDA to coordinate with the HHS Office for Civil Rights, the Federal Trade Commission, and the Office of Human Research Protections to issue aligned guidance on privacy-respecting use of DHTs in clinical investigations, and to clarify that meaningful research benefits should not be foreclosed by overlapping or unaligned privacy requirements.

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?

CHI sees significant opportunities for CDER and CBER, often in coordination with CDRH and other Agency components, to accelerate trustworthy adoption of DHTs. We organize our recommendations under five headings.

A. Operationalize a transparent, accessible DHT-derived endpoint qualification pathway

FDA's most impactful near-term action would be to expand and operationalize a transparent qualification pathway for DHT-derived endpoints. This should include published submission templates tailored to digital measures, dedicated review staff with measurement-science expertise, defined service-level commitments for letters of intent and qualification plans, and an active public docket of qualified, in-progress, and de-prioritized digital endpoints with the Agency's reasoning. Particular priority should go to therapeutic areas where conventional endpoints are known to be insensitive, burdensome, or poorly correlated with patient-meaningful function, such as mobility-affecting conditions, sleep disorders, neuropsychiatric conditions, rare diseases, and pediatric indications.

B. Establish and resource a DHT precompetitive collaboration

CHI urges CDER and CBER to convene, fund, or formally recognize a precompetitive collaboration among DHT manufacturers, sponsors, patient organizations, academic measurement scientists, and the Agency, modeled in part on existing public-private partnerships such as the Critical Path Institute consortia. Such a collaboration could pool data and expertise to qualify shared digital endpoints, develop reference datasets for analytical validation, generate normative data across demographic and clinical subgroups, and develop open methods for assessing fit-for-purpose performance. Small and medium-sized digital health developers face particular barriers to standalone qualification submissions and benefit disproportionately from precompetitive infrastructure.

C. Expand demonstration projects and structured pilots

The PDUFA VII commitment to DHT demonstration projects is important and should be expanded, with results published transparently. CHI recommends that demonstration projects deliberately span:

- Multiple sensor modalities (wearable, implantable, ingestible, contactless, screen-based);
- Multiple endpoint roles (primary, secondary, exploratory, safety monitoring, pharmacodynamic);
- Multiple population types, including pediatric populations, rare disease populations, and populations historically underrepresented in clinical research;
- Decentralized and hybrid trial designs, where DHTs are foundational to the operational model; and
- AI-derived endpoints and DHT-embedded AI signal processing.

CHI further recommends that demonstration projects be paired with rigorous evidence generation about the conditions under which DHT-derived endpoints are more sensitive, more ecologically valid, or less burdensome than traditional endpoints, and the conditions under which they are not. Demonstration projects should not be merely confirmatory of DHT promise; they should be designed to surface limitations and failure modes that will inform future guidance.

D. Provide structured early-engagement mechanisms for DHT-enabled programs

Sponsors and DHT manufacturers consistently identify the lack of timely, substantive early-engagement opportunities as a barrier to DHT adoption. CHI recommends that CDER and CBER establish or expand structured early-engagement mechanisms specifically for DHT-enabled programs, including pre-IND DHT consultation, dedicated Type B and Type C meeting tracks for DHT-related issues, and standing technical office hours staffed by measurement scientists. Early engagement is especially valuable for small and medium-sized digital health developers who cannot absorb the cost of redoing studies because of mid-program regulatory recalibration.

E. Harmonize internationally

DHT-enabled clinical investigations are increasingly multi-regional, and DHT manufacturers operate in global markets. CHI urges FDA to continue its leadership in ICH and IMDRF work streams relevant to DHTs, to seek convergence with the European Medicines Agency, the UK Medicines and Healthcare products Regulatory Agency, Japan's PMDA, and other counterpart regulators on analytical validation expectations, predetermined change control for DHT software, and the use of DHT-derived endpoints, and to publish bilateral and multilateral alignment documents where they exist.

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

CHI recommends that FDA develop or update guidance in the following areas. These recommendations build on the 2023 DHT Guidance rather than replacing it, and they are sequenced to address the issues that CHI members identify as most likely to delay or de-risk DHT-enabled programs.

A. Risk-proportionate verification and validation of DHTs for fit-for-purpose use

Updated guidance should provide concrete, scenario-based examples of how verification and validation expectations scale with the role of the DHT in the investigation and the risk to patients if the DHT performs poorly. Examples should include continuous physiological monitoring used for safety endpoints, accelerometer-derived motor endpoints, screen-based cognitive assessments, AI-derived speech and gait biomarkers, and contactless sleep monitoring. Guidance should explicitly recognize that commercially available DHTs are often appropriate for fit-for-purpose research use and that sponsors should not be required to duplicate analytical validation that has already been established in the published literature or in the DHT manufacturer's own regulatory submissions.

B. AI- and machine-learning-derived endpoints and DHT-embedded AI

Dedicated guidance is needed on the use of AI- and machine-learning-derived processing in DHT-derived endpoints, including transparency and documentation expectations, predetermined change-control planning for DHT-embedded models, subgroup performance evaluation, drift monitoring, and integration with FDA's broader AI-Enabled Device Software Functions framework. This guidance should reference the NIST AI Risk Management Framework and its forthcoming healthcare profile, and should align with the recommendations CHI has made in our December 2025 comments on FDA's framework for measuring and evaluating AI-enabled medical device performance in the real world and in our May 2026 comments on the AI-Enabled Optimization of Early-Phase Clinical Trials Pilot Program.

C. DHT-derived endpoint qualification: process and content

Guidance should address the process and content expectations for qualification submissions involving DHT-derived endpoints, including digital biomarkers and digitally derived clinical outcome assessments. Particular attention should be given to fit-for-purpose qualification, evidentiary expectations that scale with intended regulatory use, statistical methods for analytical validation against reference standards, methods for establishing clinical meaningfulness and patient-meaningfulness, and methods for evaluating equivalence between digital and legacy in-clinic measures.

D. Pediatric DHT use

The RFI rightly identifies pediatric DHT use as a high-priority topic. CHI recommends dedicated guidance addressing developmental appropriateness of sensor modalities and tasks across pediatric age bands; design considerations for engagement and adherence, including the role of gamification; analytical and clinical validation in pediatric populations, with attention to growth and development as a source of variability; ethical and assent considerations specific to continuous monitoring of children in the home environment; and the role of parents, caregivers, and schools in DHT deployment.

E. DHTs in decentralized and hybrid trial designs

DHTs are foundational to decentralized and hybrid trial designs. While FDA has issued guidance on decentralized clinical trials, CHI recommends an addendum or companion document specifically

addressing DHT operational considerations in decentralized contexts, including remote consent and assent for DHT use, remote setup and ongoing usability support, sponsor oversight of DHT-collected data flowing through patient-owned devices and third-party platforms, and approaches to participant burden and study fatigue in long-duration DHT deployments.

F. Data quality, governance, and 21 CFR Part 11 application to DHTs

As noted in Question 1, plain-language and scenario-based guidance is needed on the application of Part 11 and broader data integrity expectations to continuous, high-volume DHT data streams, including expectations for audit trails, source data, metadata, and the role of third-party platforms in the data lifecycle.

G. DHT-derived safety monitoring

DHTs offer significant promise for continuous safety monitoring during drug and biologic development, including continuous cardiac monitoring, fall detection, sleep and activity-based detection of clinical deterioration, and AI-supported review of continuous physiological signals. CHI recommends guidance addressing the use of DHT-derived signals as primary or supportive safety endpoints, integration with adverse-event ascertainment and reporting, signal-detection thresholds, and the interaction between DHT-derived safety signals and clinical adjudication.

H. Interoperability and data standards

DHT-collected data is most useful when it can be integrated with EHR data and other sources of evidence. CHI urges FDA to coordinate with the Assistant Secretary for Technology Policy (ASTP/ONC) and the National Library of Medicine to support the use of HL7 FHIR, the SMART on FHIR application framework, and recognized terminologies (LOINC, SNOMED CT, UCUM, RxNorm) for DHT-derived data. This is consistent with CHI's longstanding advocacy for FHIR-based interoperability across the digital health ecosystem and with our June 2025 comments to FDA on the role of FHIR in real-world evidence generation.

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

CHI strongly supports a sustained cadence of public workshops on DHT-specific topics. Workshops are particularly valuable for surfacing measurement-science issues, generating shared methodological resources, and aligning expectations across sponsors, DHT manufacturers, academic measurement scientists, patient advocates, and the Agency. We recommend the following priority workshop topics.

A. Disease-area workshops on digitally derived endpoints

Disease-area workshops allow the community to develop shared endpoints and reference datasets where they are most likely to be reused across sponsors. CHI recommends prioritizing the following disease areas:

- Neurodegenerative and movement disorders (e.g., Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, multiple sclerosis), where wearable-derived motor

measures, AI-derived speech and gait biomarkers, and screen-based cognitive assessments have the greatest near-term promise;

- Neuropsychiatric conditions, including major depressive disorder, anxiety disorders, post-traumatic stress disorder, and schizophrenia, where screen-based behavioral and cognitive assessments, passive sensing, and AI-derived speech and behavioral biomarkers are advancing rapidly;
- Pediatric and rare disease indications, with attention to developmental neurology, neuromuscular disease, autism, and metabolic disease, where small populations and limited historical control data place a particular premium on DHT-enabled endpoints;
- Cardiovascular and cardiometabolic disease, including continuous monitoring of arrhythmia, blood pressure, and glucose, and DHT-derived measures of activity, exercise tolerance, and sleep;
- Sleep disorders, where DHTs enable longitudinal, ecologically valid measurement that is difficult to obtain through in-laboratory polysomnography; and
- Oncology, particularly DHT-derived measures of functional status, symptomatic burden, and patient-reported outcomes that complement traditional response and survival endpoints.

B. Cross-cutting methodological workshops

CHI also recommends cross-cutting workshops on topics that recur across disease areas:

- Fit-for-purpose qualification of DHT-derived endpoints, including evidentiary expectations and statistical methods for analytical and clinical validation;
- AI- and machine-learning-derived DHT outputs, including transparency expectations, predetermined change-control plans, subgroup performance evaluation, and drift monitoring;
- Pediatric DHT use, including developmental appropriateness, gamification, and assent;
- Data quality and 21 CFR Part 11 application to DHT-collected data, including continuous sensor data and AI-derived features;
- Patient and caregiver perspectives on DHT burden, acceptability, and value, including approaches to incorporating patient-meaningfulness into endpoint selection; and
- DHT use in decentralized and hybrid trials, including remote setup, ongoing usability support, and sponsor oversight of third-party platforms.

C. Workshop design considerations

CHI urges FDA to design workshops in ways that maximize the generation of shared, durable resources rather than one-time exchanges. This includes publishing structured pre-reads and post-workshop summaries, committing to follow-on guidance or qualification activities where the workshop surfaces actionable issues, and ensuring meaningful participation by small and medium-sized digital health developers, patient organizations, and academic measurement scientists alongside large sponsors and DHT manufacturers.

III. Closing

CHI commends CDER and CBER for the deliberate, evidence-driven approach the Centers have taken to building the regulatory framework for DHT use in clinical investigations, and we appreciate the Agency's continued engagement with the digital health community on these issues. The recommendations above are intended to help FDA accelerate the responsible use of DHTs in drug and biological product development while preserving the rigor and patient-protective focus that is central to the Agency's mission. CHI and its members stand ready to support FDA in the development of guidance, qualification pathways, workshops, and demonstration projects, and we welcome the opportunity to meet with FDA staff to discuss these recommendations in greater detail.

Sincerely,

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