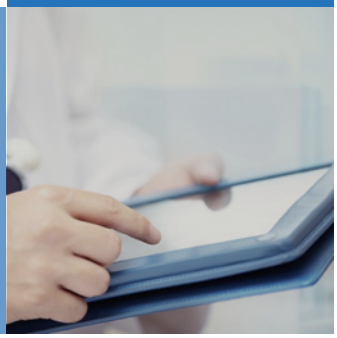

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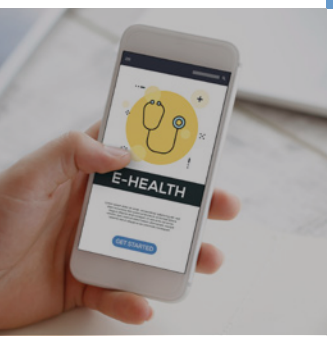


Transforming the Regulatory Landscape for Digital Health Technologies in Drug Development

HEALTH ADVANCES

Executive Summary

As tools that harness data to develop solutions for health applications, digital health technologies (DHTs) hold tremendous promise to transform the lives of patients and the management of diseases. In drug and medicinal product development, DHTs can improve the standards of practice in three main ways:

- Generate novel measures to improve understanding of the impact of an intervention on a disease or improve existing measures to better reflect the patient and caregiver experience.
- Enable decentralized clinical trials to broaden access, reduce trial costs, and improve the representativeness of clinical trials.
- Support trial implementation (e.g., patient identification and enrollment) to increase efficiency, patient convenience, and probability of success in late stage development.

The promise of DHTs to unlock these possibilities rests on distinct features of these technologies, which we refer to as value drivers. These value drivers benefit patients both directly and indirectly, by creating efficiencies in the drug development process. The five identified value drivers are rapid innovation, broad stakeholder engagement, data proliferation, autonomy, and flexible models. These characteristics fundamentally distinguish DHTs from traditional drugs and medical devices rendering their regulation inherently complex. Without an evolution of regulatory frameworks to recognize this paradigm shift, the benefits of DHT innovations in global drug development will be delayed.

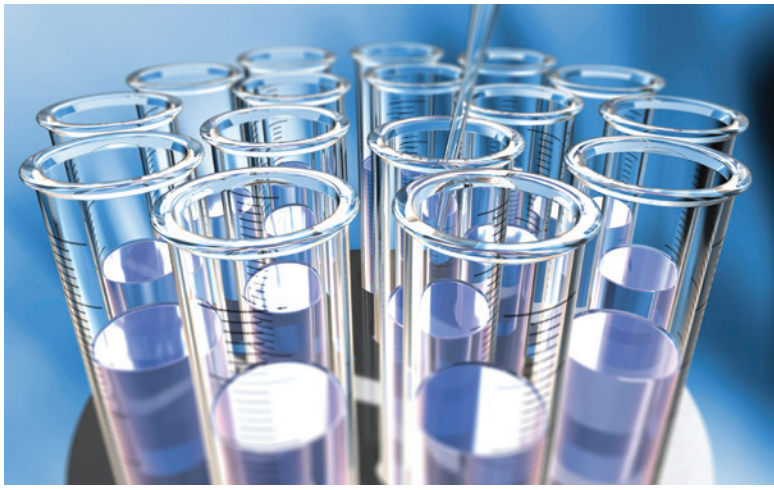
This paper summarizes the value of DHTs in drug development and highlights the inherent challenges of the current regulatory paradigm. We propose solutions to achieving a modernized regulatory approach that harnesses the full potential of these innovative technologies.

KEY FINDINGS

- The Food and Drug Administration (FDA) and European Medicines Agency (EMA) have existing guidances and qualification programs that provide a strong foundation for a DHT regulatory framework in drug development. However, these frameworks largely mirror traditional drug and device value drivers that do not fully address the regulatory needs of DHTs.
- Four primary gaps persist in the US and EU that limit the potential value of DHTs in drug development:
    1. The scope of regulatory requirements for DHTs in drug development is not sufficiently clear. For example, whether certain DHTs are defined as medical devices and in which situations medical device regulations apply to DHTs (e.g. use in interventional clinical trials) remain unclear.
    2. There is a lack of coordination between drug and device regulators. Formal guidance on the use of DHTs in drug development has primarily been developed by drug regulators without a clear connection to existing medical device guidance.
    3. Technical standards and operational processes are open to interpretation by manufacturers and regulators. Regulatory expectations for data storage, management, and sharing, and criteria for adoption of DHTs in clinical trials is minimally defined.
    4. Acceptability of DHT-generated data as clinical evidence is ambiguous with limited precedent to clarify the regulatory decision-making process. An evidence framework with clear requirements for pre- and post-market use has yet to be developed.
- Increased adoption of remote patient monitoring due to COVID-19 is an opportunity to gain collaborative experience and accelerate regulatory progress in the use of DHTs in clinical trials.

RECOMMENDATIONS

- To unlock the full potential of DHTs, an agile regulatory framework is needed. We propose four recommendations tailored to the unique value drivers of DHTs in drug development:
    1. **Collaborative models** to advance the development of a DHT regulatory framework with input from regulators, patients, health care providers, industry sponsors, technology developers, health technology bodies, and others.
    2. **Shared guidance** jointly developed by drug and medical device regulators with a focus on consistent technical standards for international development across geographies.
    3. **Evidence framework** that outlines model use cases of DHT-generated data throughout the drug development lifecycle and clarifies the evidence requirements for each stage.
    4. **Agile regulatory approaches** that allow flexibility for future innovations and adaptability for the unique characteristics and applications of DHTs.



The Unique Value of Digital Health Technologies

Digital health technologies (DHTs) refer to solutions that collect or analyze data, and then transform those data into applications.[1] In the biopharmaceutical ecosystem, DHTs span two main use cases:

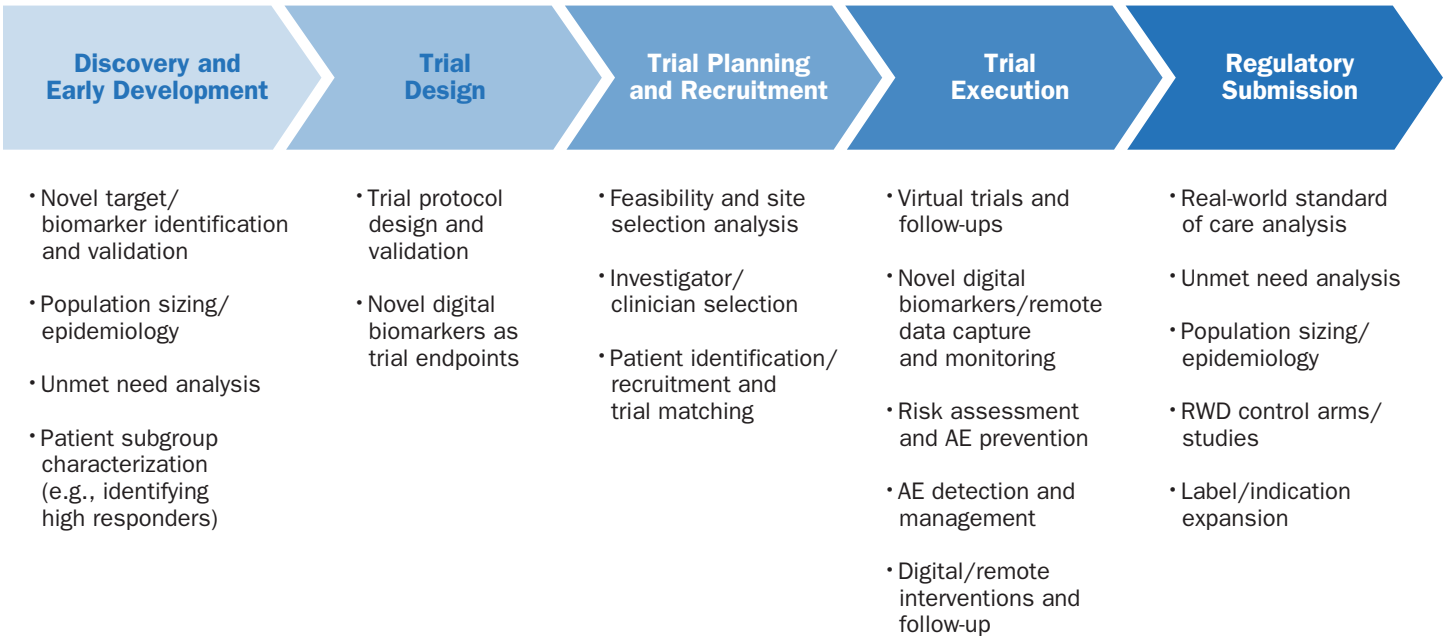
- In drug development, DHTs can accelerate R&D by generating novel insights, enabling novel digital measures, supporting decentralized clinical trials, and optimizing study implementation.
- In commercial settings, DHTs can be used as stand-alone or drug-companion solutions, catalyzing better access and delivery of care and potentially even improved clinical outcomes.

DHT APPLICATIONS ACROSS DRUG DEVELOPMENT

This paper focuses on the use of DHTs in drug development where applications of DHTs increasingly offer ways to generate, integrate, and analyze data to reveal novel insights and enable new research approaches (Figure 1).

Digital health technologies offer a range of potential applications in the drug development lifecycle. Novel endpoints captured by DHTs may be more objective or sensitive than current assessment tools. Decentralized clinical trials could reduce patient commuting and travel requirements for study participation, mitigating trial drop-out, reducing logistics and labor costs, and expanding and expediting access and recruitment. Remote monitoring can provide a more holistic view of the patient experience through continuous data collection, generate earlier evidence about treatment performance in the real-world settings, and enable early detection of adverse events for timely intervention. Regulators and other stakeholders can gain valuable insights from data collected by connected devices and mobile applications in trials and post-market studies.

Figure 1 | Applications for DHTs in Drug Development



Applications of digital health technologies have the potential to improve the R&D process in terms of efficiency, time to market, development costs, and success rate.

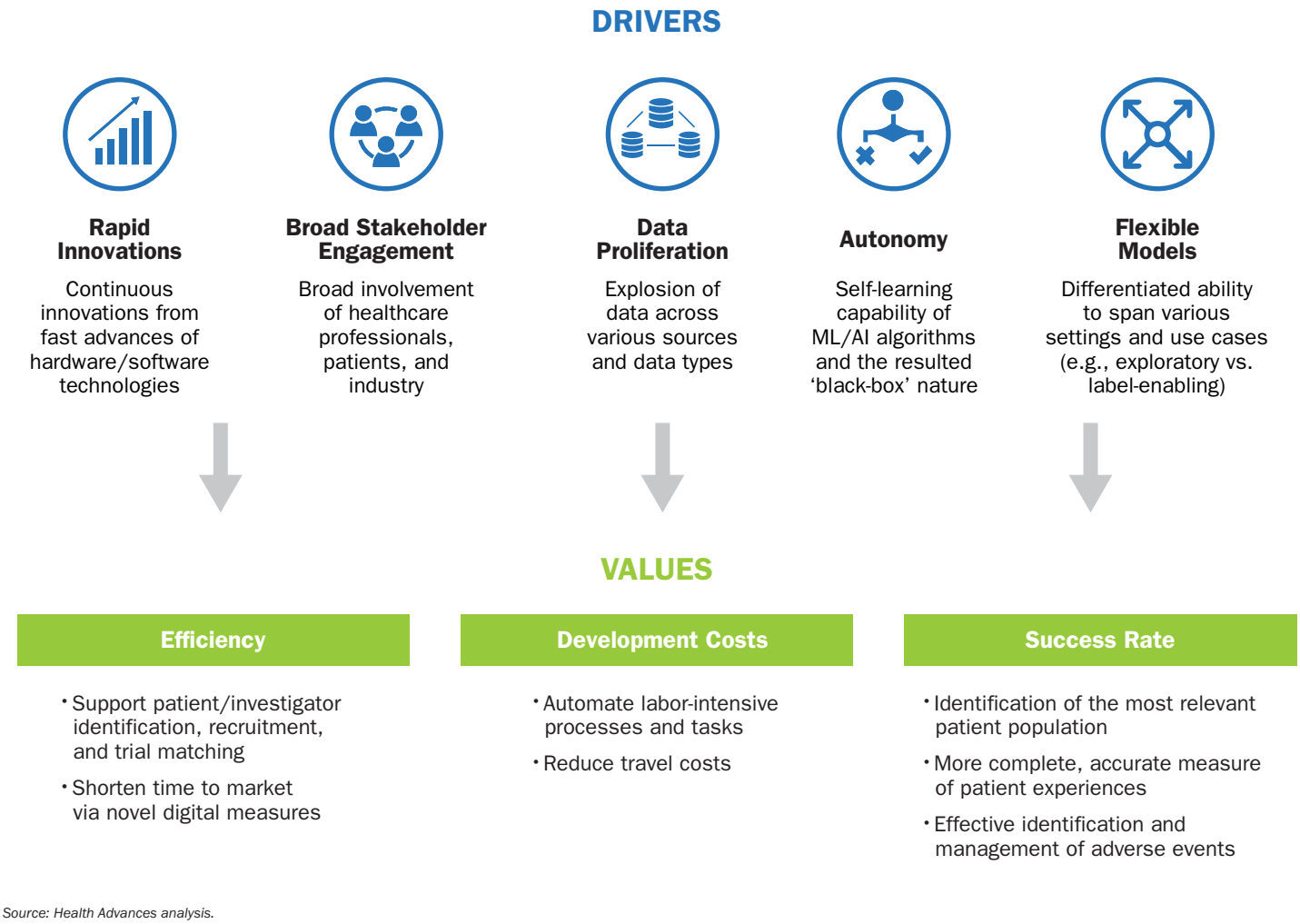
Source: Health Advances analysis.

VALUE DRIVERS OF DIGITAL HEALTH TECHNOLOGIES

A unique set of characteristics fuel the full value of DHTs in drug development (Figure 2).

1. Compared to the development cycles of drugs and traditional medical devices, innovations in DHTs occur more rapidly. This is driven by continuous advances in hardware (e.g., computing power, cloud capability, biometric sensors) and the shortened development lifecycle of software and algorithm-based technologies such as machine learning (ML) and artificial intelligence (AI).
2. By providing new value, DHTs keep health care stakeholders engaged and foster collaboration between groups with limited connection in the traditional health care paradigm.
3. DHTs can collect greater quantities of information from the real-world environment. As these data proliferate, they are likely to reveal new insights that were previously difficult to detect.
4. The self-learning capabilities associated with advanced analytics like ML and AI can unlock new insights from the evolving data with minimal human supervision. These autonomous capabilities mean that underlying algorithms can continuously improve as data becomes available.
5. The capabilities of DHTs span many different settings and applications, which means the same tools can be applied flexibly in different scenarios depending on the use case.

Figure 2 | Value Drivers of DHTs in Drug Development



Source: Health Advances analysis.

The Current Regulatory Environment for DHTs in Drug Development

US LANDSCAPE

In the US, the FDA Center for Devices and Radiological Health (CDRH) regulates the use of novel DHTs that meet the definition of a medical device when in drug development, while the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) review DHT-generated data for drug development.

A DHT for use in clinical trials does not need to be approved or cleared as a medical device. Rather, the FDA requires proper verification and validation of the DHT per existing investigational regulations. Applicable regulations may include Investigational New Drug (IND) or Investigation Device Exemption (IDE), and Investigational Review Board (IRB) approved protocol studying a Nonsignificant-Risk (NSR) medical device.

DHT-generated data, intended for use as a clinical outcome or a biomarker measure, can be reviewed through three overlapping pathways: the Drug Approval Process (i.e. IND pathway), the Scientific Community Consensus route, or through the Drug Development Tool (DDT) Qualification Programs.[3] Drug sponsors may pursue one or a combination of pathways to advance development programs, although each have advantages and disadvantages (e.g. time horizon, cost, feasibility).

DDT Qualification Program

The DDT Qualification Program consists of two programs relevant to DHT-generated data, the Clinical Outcome Assessment Qualification Program (COAQP) and the Biomarker Qualification Program (BQP).[2]

Drug development tools are qualified within a specific context of use (COU), which identifies the specific use of the DDT in drug development or regulatory review. Qualified DDTs may be used to support or obtain approval for any drug. While qualification is a voluntary process, it allows for integration of innovative approaches to conditions or diseases that may create opportunities in new areas of drug development as knowledge of disease and pathogenesis advances.

To better define the regulatory framework for drug development tools, FDA has released Guidances with open dockets for public input:

- The "Qualification Process for Drug Development Tools (DDTs)" Draft Guidance in 2014 first proposed qualification programs for DDTs including biomarkers.[4]
- The FDA-NIH Biomarker Working Group published the "BEST (Biomarkers, EndpointS, and other Tools) Resource" in 2018, a glossary for key definitions of biomarkers, endpoints, and other tools.[5]
- The "Qualification Process for DDTs" revised Draft Guidance in 2019 to implement new statutory processes and add transparency provisions for qualification submissions.[6]

FDA Examples

Recognizing the value of DHTs in drug development, FDA has been working with drug manufacturers to explore the use of novel digital measures as exploratory and even label-enabling endpoints. For example, the FDA approved Galaxy S3, a finger taping device to measure intra-tap variability, for use by Roche as an exploratory measure in its Phase Ib study for Parkinson's Disease.[7]

EU LANDSCAPE

The EMA oversees the review of new drugs through the centralized procedure and is primarily responsible for regulating the use of DHTs in drug development. In Europe, existing Guidance is generally consistent with the FDA Guidance. Despite these similarities, the DHT regulatory framework in Europe is unique in several ways.

- Unlike the FDA which regulates both drugs and medical devices, EMA exclusively focuses on drug regulation. Medical devices however are currently governed by national laws of the EU Member States with regulatory oversight by the National competent authorities (NCAs). This division of governance oversight creates an opportunity for regulatory divergence due to differing interpretation of DHT policies at the Member State level.
- Additionally, the new Medical Device Regulation (MDR, 2017/745), which assigns additional responsibilities for medical devices to the EMA and NCAs, and the General Data Protection Regulation (GDPR) impact DHTs classified as medical devices or used within clinical trials to collect, analyze, or store patient data.

Since 2009, EMA has released several guidance and qualification opinions on the use of DHTs in clinical trials:

- The "Qualification of Novel Methodologies for Drug Development" guideline in 2009 outlines the process for obtaining a qualification opinion on a novel clinical trial methodology including biomarkers.[8]
- The "Essential considerations for Novel Methodologies" 2017 document provides a checklist for the development of a novel trial methodology including context of use, endpoint selection, and clinical utility and analytical validation.[9]
- The 2019 "Qualification opinion on eSource Direct Data Capture" is a public example of EMA thinking on the use of DHTs in clinical trials.[10]
- The 2020 "Questions and Answers: Qualification of digital technology-based methodologies to support approval of medicinal products" highlights key considerations for successful qualification of digital technology-based methodologies.[11]

Digital Health Technologies are central to expanding EMA's role as a leading health authority. The "Regulatory Science Strategy to 2025" developed by EMA[12] sets out three strategic goals directly relevant to DHTs:

- Emphasis on the integration of science and technology includes biomarkers, genomics, and precision medicine.
- Focus on collaborative evidence generation fosters innovations such as novel data and endpoints in clinical trials.
- Enabling and leveraging research and innovation in regulatory science encourages the use of novel technologies and cross-stakeholder collaborations.

In addition, EMA has assembled a group of digital experts, with a subgroup exclusively focused on mHealth.[13] Coalescing the appropriate talent with strong digital expertise will serve as a vital foundation for EMA to advance the European DHT regulatory framework.

EMA Examples

In accordance with the regulatory framework EMA has actively explored the use of digital measures in specific drug development situations. For example, in 2019 the EMA qualified stride velocity 95th centile, a device-agnostic secondary endpoint used to quantify ambulation in Duchenne Muscular Dystrophy (DMD) patients.[14]

KEY GAPS

- Existing FDA and EMA Guidance and programs provide a strong foundation for the regulation of DHTs in drug development. Recognizing the complex issues and shortage of professionals with digital expertise, there are four areas that require further refinement (Figure 3).

1. **Clarification of the DHT regulatory scope.** There is a lack of clarity on the regulations that apply to the use of DHTs in clinical trials, whether they are marketed as medical devices or not, and how data generated from such DHTs can be used in a regulatory submission to drug regulators. It is also unclear what the regulatory implications of using DHTs in clinical trials are for pharmacovigilance (e.g. signal identification/duplicate reporting in high volume datasets, AE reporting for continuous data monitoring), remote monitoring (e.g. validation of data for biometric sensors), and for novel clinical measurement (e.g., expectations for developing a novel digital drug development tool).
2. **Coordination between drug and medical device regulators.** To properly harness the appropriate regulatory experience and expertise, there must be closer coordination between drug and device regulators within a given jurisdiction, particularly in the context of drug development. Cross-organizational collaboration remains limited today, particularly in Europe where drug and device authorities may be different. Recognizing this there is a growing desire to address this challenge by industry and regulators alike.
3. **Ambiguity in the technical application of DHT use in drug trials.** Regulatory expectations in key areas such as data security, privacy, and data management and sharing have yet to be clearly defined. As technical standards remain open to interpretation by manufacturers and regulators alike, proper implementation of DHTs in trials is taken on at-risk creating additional resource strain for all parties. This is particularly true in Europe where the General Data Protection Regulation (GDPR) imposes additional requirements on the access to and transfer of patient data.
4. **Guidance on the use of DHT-generated data focused on "concepts of interest."** Beyond digitalization of existing drug development tools (e.g. ePRO, eCOA), the precedent for implementation of DHTs to measure new concepts of interest in clinical trials is limited. For a variety of reasons, drug developers interested in using DHTs to measure a novel concept of interest largely rely on individual product pathways to advance these strategies today. The challenge for the industry is how to move beyond these case-by-case experiences to a more efficient, predictable regulatory pathway.

Figure 3 | Key Gaps in DHT Regulation for Drug Development (US and EU)

1. **Ambiguity in regulatory scope of DHTs**
2. **Insufficient coordination between drug and medical device regulators**
3. **Undefined technical standards and implementation of DHTs**
4. **Unclear acceptability of DHT-Generated Data**

An Agile Regulatory Approach for DHTs

To embrace the potential of DHTs, regulatory frameworks must evolve to address the five main DHT value drivers. We offer four recommendations to make progress on the regulatory gaps identified earlier including specific next steps to unlock the promise of DHTs in drug development (Figure 4).

REGULATORY RECOMMENDATIONS TO EMBRACE DHTS IN DRUG DEVELOPMENT

1 **Establish Collaborative Models** to advance DHT regulation with input from regulators, patients, health care providers, industry sponsors, technology developers, and others.

- **Collaborative regulatory projects**
- **Consortium-led data collaboratives**
- **Assessment of new regulatory pathways for DHTs**
- **Creation of open source protocols and standards**
- **Explore industry self-regulation**

DHTs serve a range of end users and can catalyze new connections. This makes broad stakeholder feedback critical in an updated regulatory environment. Regulators have the drug and medical device expertise, but feedback from a wider set of stakeholders is necessary. Health care providers can provide important perspectives about how to better integrate DHTs into existing workflows. Patients can share important insights about what matters most to them, and the experience they seek from DHTs. Biopharma companies and DHT developers can provide valuable feedback about how DHTs create value for drug development, where existing regulatory frameworks impede practical use of DHTs, and how proposed solutions align with real-world experiences and objectives. Given the nascent nature of DHTs, it is imperative for industry sponsors to collaborate with each other, and with regulatory and other stakeholders, to advance our experiences with DHTs and the associated regulatory needs.

Collaborative Models: Parkinson's Disease Case Study

The benefit of such collaboration is evident in the Digital Drug Development Tools (3DT) team, a group of leading biopharma companies, academic centers, and patient advocacy groups launched by the Critical Path for Parkinson's Consortium (CPP).[15] Members of the 3DT team will be working together to analyze digital data collected in early Parkinson's Disease (PD) patient populations, with the goal of facilitating discussion and alignment with regulatory agencies. On a wider scale, this kind of direct engagement and collaboration between and among stakeholders and regulatory agencies could facilitate effective, efficient, and necessary communication and the exchange of information and insights in a fast-moving digital landscape. It can also serve to quickly resolve discrepancies between regulatory expectations and real-world DHT challenges and help to catalyze the development of a new regulatory framework.

2 **Develop Shared Guidance** jointly between drug and medical device regulators with a focus on consistent technical standards for international development across geographies.

- **Guidance on verification and validation for DHT-generated data**
- **Guidance on post-approval data collection and review**
- **Standards for data privacy, management and sharing**
- **International harmonization on technical guidance**
- **Consensus expectations for autonomous technology**

Intersection of Drug and Device Regulation

Using combination products as an analog, unique, stand-alone decisions made by either one set of experts or another can create inconsistencies across applications. For example, a combination product with a drug primary mode of action (PMOA) typically has a much longer review cycle and approval process than combination products with a device PMOA. Experts should ensure that decisions about PMOA are consistently administered across DHTs.

When it comes to DHTs used in conjunction with drugs, existing Guidance is frequently siloed to either the drug or the device regulatory authority within a given jurisdiction. This is in part because DHTs intended for commercialization are regulated as medical devices by CDRH in the US and member state national competent authorities in Europe. However, drug regulators at CDER, CBER, EMA, and EU national competent authorities have oversight of the clinical review of DHT-generated data for drugs. As each of these authorities have valuable expertise at the intersection of DHTs and drug development, more seamless collaboration across FDA Centers and European health authorities would improve efficiency and consistency in the regulatory review of DHTs in drug development.

3 **Create an Evidence Framework** that outlines model use cases of DHT-generated data throughout the drug development cycle and clarifies the evidence requirements for each stage.

- **Use case guidance for process implementation and evidence requirements**
- **Evaluation of existing regulatory framework**
- **Best practices for deployment of DHTs in trials**
- **Verification and validation standards for AI/ML products**
- **Decision-tree of questions to address across drug lifecycle**

Joint Guidance from drug and device regulators is needed to clarify expectations for data (privacy, management, sharing), regulatory considerations for deploying DHTs in traditional and decentralized clinical trials (e.g. site and investigator qualification criteria, modification of trial processes), and clarification on how existing drug development tool guidance applies to DHTs. Given both technology advances and drug development are global enterprises, international convergence on technical standards and Guidance in global forums is critical to avoid regional requirements that limit adoption.

Since DHTs have a broad range of applications across drug R&D, there is no "one-size-fits-all" evidence framework. A modernized regulatory approach should provide guidance that covers implementation processes and evidence requirements across clearly defined use cases (see Figure 1). These use cases should span data intended to support drug labeling claims to those collected for exploratory purposes with an emphasis on the quality and quantity of data expected. To encourage broad adoption, the DHT evidence standards in early-stage, proof-of-concept (POC) studies should be feasible and realistic with an emphasis on proper follow-up studies building on early stage

Figure 4 | Proposed Solutions for Regulatory Recommendations

DHT VALUE DRIVERS	Collaborative Models	Shared Guidance	Evidence Framework	Agile Regulation
Rapid Innovations	• Cross-sector exploration of new regulatory pathways for DHTs and DHT-generated data	• Guidance on post-approval data collection and criteria for changes that necessitate post-market regulatory review	• Open evaluation of existing regulatory framework, as applied to DHTs, to identify gaps for modernization	• Assessment of the role of private regulators (standards bodies, consortium, alliances) in defining technical standards
Broad Stakeholder Engagement	• Defined regulatory collaborative spaces and projects	• Cross-expert Guidance outlining clear standards for data privacy, management, and sharing	• Consensus best practices for on deployment of DHTs in traditional and decentralized clinical trials	• Formation of FDA and EMA DHT Policy Labs to involve multi-disciplinary groups in across the stages of policy development
Data Proliferation	• Establishment of consortium-led data collaboratives to promote data sharing including IT infrastructure and analytics expertise	• Formal Guidance on verification and validation of DHT-generated data endorsed by drug regulators	• Development of decision-tree tool of regulatory questions to be answer at difference stages of drug development (e.g., feasibility, POC, pivotal)	• Adoption of emerging technologies like blockchain to encourage public and private data sharing
Autonomy	• Creation of pre-competitive open source protocols and IT standards to establish transparency and trust	• Consensus expectations for autonomous technologies in drug development from drug and device regulators	• Standards for verification and validation process for AI and ML based products	• Creation of regulatory sandboxes to test innovative product ideas without normal regulatory and financial hurdles
Flexible Models	• Explore appropriate use cases for industry self-regulation (e.g., FDA Pre-Cert pilot)	• International harmonization on technical Guidance from drug and device regulators	• Define use cases with guidance that covers implementation processes and evidence requirements	• Inclusion of more diverse stakeholders' input in policy setting forums, like the International Medical Device Regulators Forum (IMDRF)

findings. To best reflect patient needs, evidence requirements in late-stage, label-enabling studies must be clinically robust, but should center on the impacts considered most important to patients and caregivers.

While not within the scope of this paper, a robust evidence framework should expand into post-approval data collection and address the adaptive nature of DHTs (e.g., software updates, ML and AI-based tools). Defined evidence requirements will enable industry sponsors to study approved drugs efficiently in the real-world setting and to provide the most valuable insights to regulators.

As technology continues to advance, DHTs will evolve beyond our current concept. This exponential rate of change is revealing that current policy making cycles are inadequate and that now is the time to rethink and redesign our regulatory processes. As a prerequisite, a regulatory framework for DHTs must be highly adaptive to rapidly advancing technologies, sensitive to future innovations, and able to address frequent product updates.

4 **Design Agile Regulatory Approaches** that allow flexibility for future innovations and adaptability for the unique characteristics and applications of DHTs.

- **Inclusion of more diverse stakeholders in policy setting forums**
- **Regulatory sandboxes to test innovative products**
- **Formation of Regulator-sponsored Policy Labs**
- **Use of private regulators to defined technical standards**
- **Adoption of emerging technology for data sharing**

The concept of an agile regulatory framework is to evolve how regulatory policies and guidance are created, tested, and applied. In reimagining DHT regulation, two useful approaches are systems thinking and design thinking. Systems thinking moves beyond immediate problems to recognize underlying connections and patterns that drive complex issues. Design thinking is a process of creative problem solving that focuses on iterative, human-centered solutions. Together these processes can expand the range of stakeholders engaged in the development and implementation of new regulatory policies with built in feedback loops that enable timely evaluation and adjustments.[16]

While policymakers remain the central actor by defining parameters for governance and setting the standard for outcomes, an added benefit of this approach is that it encourages innovators to work proactively with and provide feedback directly to regulators. Early examples of this co-creation concept in the regulation of drug development include EMA's Regulatory Science Strategy for 2025[12] and the FDA's Technology Modernization Action Plan and Digital Health Software Precertification Program.[17, 18]

A Call to Action

The immense potential of Digital Health Technologies cannot be realized without appropriate regulatory leadership. The COVID-19 pandemic has made it clear that the ability to leverage technology to support clinical trials is paramount. Given the gap between the current regulatory state and what is necessary, the case for a modernized regulatory approach for DHTs in drug development is compelling.

Due to the complex, dynamic nature of Digital Health Technologies explored throughout this paper, regulators cannot be expected to address all challenges alone. Instead, the path to a modernized regulatory framework must be informed by a range of stakeholders. As a starting point, the learnings from implementation of remote monitoring in response to COVID-19 can serve as a case study for collaborative dialogue and policy development.

Digital Health Technologies can benefit many stakeholders in the health care ecosystem, but only if their promise is achieved safely and effectively. We hope this paper serves as a framework to the timely development of agile regulatory approaches for Digital Health Technologies in drug development.

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