Title

Tepid Uptake of Digital Health Technologies in Clinical Trials by Pharmaceutical and Medical Device Firms

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Conflict of Interest statement

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Abstract

Digital health technologies (DHTs) can enable more patient-centric therapeutic development by generating evidence that captures how patients feel and function, enabling decentralized trial designs that increase participant inclusivity and convenience, and collecting and structuring patient-generated data for regulators to use in approval decisions alongside traditional clinical outcomes. Though a growing body of evidence has documented increasing use of DHTs in clinical trials overall, the use of DHTs in clinical trials supporting medical product development is unclear; we quantify the use of DHTs in clinical trials sponsored by pharmaceutical and medical device firms. Despite interest from pharmaceutical and medical device manufacturers in DHTs, we find tepid uptake of DHTs in trials by these sponsor types over time. Further, to date, these sponsors have most frequently used conventional, hardware-based technologies that have been available for many years (e.g., Holter monitors, glucose meters) rather than newer activity monitors, mobile apps, and other online-based tools that are frequently used by non-industry sponsors. Considering the recent and evolving nature of regulatory guidance around DHT use in clinical trials, our findings suggest that organizations pursuing product development still appear hesitant to incorporate DHTs in trials that provide the most critical evidence for regulatory review and impact how new products are used. This suggests there are likely additional opportunities for sponsors of regulated trials to incorporate (more) DHTs and patient-centric endpoints into product development clinical trials. However, additional regulatory clarity and efforts to reduce operational barriers may be needed in order to more fully capture these opportunities.

Introduction

The U.S. Food & Drug Administration (FDA) defines digital health technologies (DHTs) as systems that use computing platforms, connectivity, software, and/or sensors for healthcare and related uses.[1] DHTs are comprised of either sensor-based hardware, software applications that run on general-use computing platforms, or a combination of both. Examples include wearable sensors that record biological or behavioral data and mobile applications that administer assessments.

In recent years, a growing body of evidence has documented the increasing use of DHTs in clinical trials, both overall and in studies of specific conditions, such as neurological diseases.[2,3] Simultaneously, the emergence of several pre-competitive groups advancing DHT use in trials, such as the Digital Medicine Society (DiMe), the Clinical Trials Transformation Initiative (CTTI), and the Scripps Research Digital Trials Center, has piqued the interest of pharmaceutical and medical device firms in using DHTs in product development, as evidenced by reported participation from industry in these initiatives.[4,5,6]

The incorporation of DHTs into clinical trials represents an important step toward achieving more patient-centric therapeutic development. DHTs can be used to capture changes in meaningful aspects of health for patients with chronic conditions (e.g. Parkinson's Disease)[3], which has become increasingly important to the FDA in evaluating treatment effects.[7,8] DHTs can also increase participant convenience by enabling decentralized trial designs[9] and relatedly, can improve the diversity of trial participants by limiting the number of required site visits, reducing the costs of participation, and improving patient satisfaction.[10,11]

The use of DHTs in clinical trials can also provide evidence for regulatory decision-making that improves understanding of new product effectiveness. For example, study endpoints that are important to patients but difficult to capture in traditional clinical settings, such as changes in sleep and physical activity, can be measured in clinical trials using DHTs. Additionally, DHTs that collect patient-reported outcomes assessing the impact of treatment on health-related quality of life can be used to support product labelling claims.[12]

Despite aggregate growth in DHT use for medical research, it is unclear whether the promise of these tools for product development is being realized, because studies have yet to quantify DHT use in clinical trials intended to generate evidence for new therapeutics. We present data on the use of DHTs in clinical trials most likely conducted in support of product development – namely those sponsored by pharmaceutical and medical device firms.

Methods

Following methodology from prior work, we downloaded ClinicalTrials.gov records with start dates from 2000-2022 on Apr 2, 2023, and searched all relevant text fields for over 1100 terms that indicate DHT use.[2] We manually reviewed 25% (175/703) of flagged trials to confirm search algorithm accuracy. Three false positives (0.017) were documented.

Within the set of trials where a DHT was used, we categorized the sponsor as either "pharma" (pharmaceutical or biotechnology), "medtech" (medical device), or "other". Though ClinicalTrials.gov includes a field for sponsors to self-identify as "industry", the entities reflected in this field include for-profit research centers, consulting firms, and medical labs, rendering this indicator insufficient for our purposes. Therefore, we compiled a comprehensive list of

pharmaceutical and device firm names from publicly available lists and ran a text search algorithm in the "sponsors" field. We also performed keyword searches for the strings "pharma" and "therapeutics" to look for any additional companies that were not otherwise included.

Using our dataset of DHT clinical trials, we analyzed trends in DHT use over time by sponsor type. We report data from 2000-2022, inclusive, however due to known reporting delays in registration on Clinicaltrials.gov, the data from 2021 and 2022 are likely incomplete. We also documented the type of DHT used in each trial and reported on differences by sponsor type. All analysis code is available for download at github.com/arieldora/[insertprojectdirectory].

Results

Consistent with prior studies, we documented continued growth in the use of DHTs since 2000. However, we found no evidence that this growth was driven by pharma- and medtech-sponsored trials, which remained relatively consistent over the most recent 5 years for which we expect data entry is near complete (2016-2020), ranging from 44 to 67 new trials per year. Additionally, pharma and medtech-sponsored trials accounted for only 67 of the 2,416 trials (<3%) started in 2020 that involved use of a DHT and only 703 of the 20,184 trials (<3.5%) identified over our entire period, 2000-2022 [Figure 1]. Further, over the past 23 years, only 318 pharma- and medtech-sponsored trials using DHTs (45.2%) were designated as Phase 1-4—i.e., those that typically submit data for regulatory purposes. These included 96 trials designated as Phase 1, 92 as Phase 2, 80 as Phase 3, and 50 as Phase 4. The remaining 385 (54.8%) pharma- and medtech-led DHT trials were not designated with any phase.

When pharma and medtech sponsors did use DHTs, they were most likely to use conventional, sensor-enabled hardware previously used in product development. For example, the top two categories of DHTs used by these sponsors were Holter monitors (19.9% of trials) and glucose monitors (15.2% of trials) respectively. In contrast, Holter monitors were not even among the top ten categories of DHTs used by other sponsor types and glucose monitors were used in only 2.8% of other trials. Instead, "other" sponsor types, which included individual investigators, medical centers, and government organizations, deployed newer DHTs that primarily focus on capturing the patient experience, including activity & movement monitors (16.4% of trials) and mobile apps (14.8% of trials) [Figure 2].

Discussion

Though there have been notable examples of pharma using DHTs to collect endpoints in product development trials, such as Bellerophon's use of Actigraph® to measure physical activity and Sage Therapeutics' use of the Kinesia ONE™ to measure tremors, our findings confirm that these examples remain sparse.[13,14] While non-industry sponsors continue to increase DHT use, take-up by regulated product manufacturers remains tepid and evidence of DHT use in trials most likely intended for product development research (e.g., trials designated as Phase 1-4) is even more limited.

Low adoption by product manufacturers may be fueled by a hesitation to use these tools in the high-cost, high-stakes context of therapeutic development. Our findings suggest that pharma and medtech sponsors rely primarily on conventional, hardware based DHTs that have

regulatory precedent because these technologies, such as Holter monitors and glucose meters, have been used in clinical trials to support product development for several decades.

Though FDA has expressed enthusiasm for the use of a broader set of DHTs in clinical trials, including software applications and novel sensors, by issuing guidance on DHT use for product development and the conduct of decentralized trials that rely on DHTs, final guidance on DHT use was only issued in December of 2023 and guidance on decentralized trial conduct remains in draft form.[15,16] Additionally, the FDA's recently announced (March 2023) Framework for the Use of DHTs in Drug and Biological Product Development is largely a planning initiative, rather than a formal set of recommendations for DHT implementation, suggesting the regulatory perspective is still evolving.[17] It also remains unclear to what extent the evaluation approaches used by other, non-US regulatory agencies and the FDA will be harmonized. For example, the European Medicines Agency (EMA) qualified a measure collected by wearable DHTs, "stride velocity 95th centile" as a secondary endpoint for use in product development clinical trials months before the FDA.[18] Further, since development programs are planned years in advance, the full impact of recent regulatory support for the use of DHTs in product development may not be observed for several more years.

Several operational barriers may also contribute to pharma and medtech hesitation around the use of DHTs in product development trials. First, many DHTs are currently manufactured by organizations other than those sponsoring the clinical trial, so technical modifications to the device can occur without regard for a given clinical trial protocol. In particular, the possibility of a DHT undergoing a software update, hardware upgrade, or product discontinuation during the clinical study period creates additional risk for trial sponsors.

Secondly, sponsors must take responsibility for navigating the process of selecting, and potentially sourcing, the most appropriate DHT for their study, which can be challenging in categories where several different brands and models exist, such as wearable activity trackers. Further adding to sponsor responsibility, sponsors must also ensure trial participants are trained and supported in their use of the selected technology and that risk mitigation and safety monitoring plans are put into place. Indeed, the December 2023 guidance document on DHT use in clinical investigations explicitly states that "the sponsor should explain how the DHT is fit-for-purpose for use in the clinical investigation" and "ensure training for trial personnel and participants", putting the burden on the study sponsor to not only select an appropriate tool, but also justify its use to regulators and provide technical assistance related to the technology (although as the FDA guidance notes, for many commercially available DHTs at least the product descriptions and technical specifications are likely to be publicly available).[15]

Thirdly, when DHTs are used to collect sensor-derived data for digital measures, the measure must undergo substantial verification, analytical validation, and clinical validation before it can be accepted by regulators as an endpoint in clinical trials,[15,19] a responsibility that could create additional data generation requirements for the trial sponsor during a period of product development that is already subject to substantial evidence generation criteria. Finally, while the use of DHTs to facilitate decentralized Phase 2 and 3 clinical trials has the potential to generate substantial value over the course of a product's development program,[20] the initial cost to implement DHTs in large sample size trials could be prohibitive for some pharma and medtech sponsors, particularly if use of the DHT is not expected to result in operational efficiencies, such as shorter trial durations or reduction in the number of study sites needed.

In this analysis, we attempted to take a comprehensive view of DHT use in product development trials. While the FDA requires registration on ClinicalTrials.gov for trials that are conducted under an investigational new drug application and in pursuit of product development,[21] products that are not being developed in expectation of US market entry may not be represented. It is therefore possible that some product development trials that used a DHT are not represented in our dataset. Additionally, though we searched all available data fields, including primary, secondary, and other outcomes, as well as detailed descriptions, because there is not yet a requirement to report use of a DHT in ClinicalTrials.gov, our text-based search algorithm could only detect cases where DHT use was explicitly mentioned by sponsors.[15] Finally, we assumed that all pharma and medtech-sponsored trials were related to product development and that trials sponsored by other organizations were for other evidence generation purposes, such as scientific exploration or advancement of care guidelines; however medical products can be developed by entities other than pharma and medtech firms, and in such rare cases, DHT use would not have been captured in this study.

To bring both the patient-centric and regulatory decision-making benefits associated with DHT use to fruition, DHTs will need to be used in more than just exploratory research; they will also need to be used in a fit-for-purpose manner in trials that generate evidence for product development. Our findings suggest there are likely additional opportunities for pharma and medtech manufacturers to incorporate DHTs into clinical trials. While hesitation may dissipate as DHTs are increasingly validated for use in regulatory-grade clinical trials and their benefits are increasingly quantified, to spur adoption of DHTs in product development, both additional regulatory clarity and efforts to reduce operational and technical barriers may be needed.

Study Highlights

What is current knowledge on the topic?

Digital health technologies (DHTs) can enable more patient-centric therapeutic development by increasing trial inclusiveness, lowering participation burden, and capturing aspects of health that are meaningful to patients but cannot be easily measured using traditional data collection methods. Though DHT use in clinical trials overall has grown, uncertainty remains about how often DHTs are used in product development trials in particular.

What question did the study address?

How much of the growing DHT use in clinical trials has been driven by sponsors pursuing product development, namely pharmaceutical and medical device firms?

What does this study add to our knowledge?

We show that the adoption of DHTs in trials sponsored by pharmaceutical and medical device firms remains tepid.

How might this change clinical pharmacology or translational science?

Despite increasing regulatory support for the use of DHTs in clinical trials, product development firms remain hesitant to increase DHT use. Efforts to reduce operational barriers and additional regulatory clarity may be needed to realize the patient-centric benefits of DHTs in product development.

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Author Contributions

CM & ADS wrote the manuscript, designed and performed the research, and analyzed the data.

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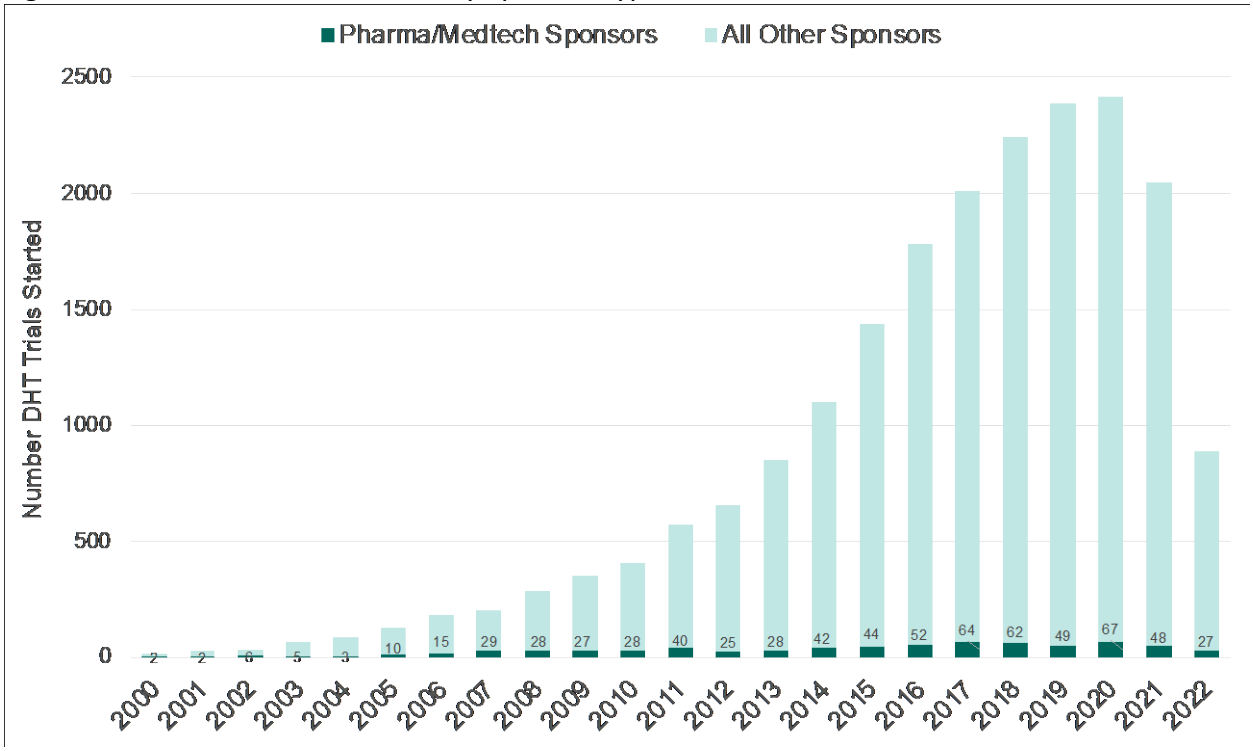
Figures

Figure 1. DHT Use in Clinical Trials by Sponsor Type, 2000-2022



Caption: Figure 1 illustrates growth in the number of clinical trials using DHTs started each year. Data labels are intended to show the number of DHT trials sponsored by pharmaceutical ("pharma") & medical device ("medtech") firms. NB: due to delays in trial registration, 2021 and 2022 data are likely incomplete. Source: Authors analysis of ClinicalTrials.gov records.

Figure 2. Most Common Types of DHTs Used by Pharmaceutical/Medical Device Firms and Non-Industry Sponsors

	Pharma & MedTech Sponsored (n=703)		Non-Industry Sponsored (n=19,481)	
Rank	*DHT Type*[a]	*No. (%) Trials*[b]	*DHT Type*[a]	*No. (%) Trials*[b]
1	**Holter monitors**	140 (19.9%)	**Activity & movement monitors**	3199 (16.4%)
2	**Glucose monitors & meters**	107 (15.2%)	**Smartphones**	2883 (14.8%)
3	**Activity & movement monitors**	71 (10.1%)	**Mobile apps**	2349 (12.1%)
4	**Smartphones**	68 (9.7%)	**Online surveys**	2153 (11.1%)
5	**Vitals sensors**	59 (8.4%)	**Text messages**	1342 (6.9%)
6	**Mobile apps**	50 (7.1%)	**Virtual reality**	1292 (6.6%)
7	**Online surveys**	38 (5.4%)	**Social media forums**	1257 (6.5%)
8	**iPads**	12 (1.7%)	**Video consultations**	1047 (5.4%)
9	**Sleep monitors**	12 (1.7%)	**Vitals sensors**	676 (3.5%)
10	**Handheld spirometers**	10 (1.4%)	**Glucose monitors & meters**	551 (2.8%)

[a] Glucose monitors & meters include continuous glucose monitors and connected glucose meters. Activity & movement monitors include smartwatches, wearable activity trackers, wearable and non-wearable movement detectors, and fitness trackers. Vitals sensors include smart cardiac and respiratory monitors. Social media forums include digital platforms (e.g., Facebook) and digital group chat services (e.g., WhatsApp).
[b] Only the ten most common DHT types are reported in this table; percentages do not sum to 100%.

Caption: Figure 2 depicts the most common types of DHTs used by sponsor type. To describe the type of DHT used, we grouped search terms into categories that represented DHTs with similar intended measurement objectives. For example, “fitbit” and “actigraph” were categorized as “activity & movement monitors”. Source: Authors analysis of ClinicalTrials.gov records.