Approaches for Use of Digital Health Technologies in Clinical Trials

Digital Health Technologies Defined

The term digital health technologies (DHT) continues to be defined in different ways, but for the purposes of this paper, they are defined as systems that use computing platforms, connectivity, software, and/or sensors for healthcare and related uses in patient-centered clinical outcomes in the review and assessment of new drugs, including clinical outcome assessments (COAs), but excluding electronic diaries (e.g., eDiaries).

Questions remain as to how the DHT field will continue to develop over time, and what methods are most effective in developing qualified DHT-based clinical outcome assessments and generalizable approaches to utilizing DHTs to advance their use in clinical trials. With multiple stakeholders in government, medicine, and patient advocacy, current literature and FDA guidance relevant to DHTs and to patient-centered clinical trials indicates which directions may prove effective in pursuing optimal clinical trial design for DHT usage, with topics of interest including symptom mapping, patient data access, and pre-competitive initiatives.

FDA Guidance and Initiatives

Public FDA initiatives and released guidance documents also play a critical role in the progress of the DHT field in regards to DHT use in clinical trials. The Digital Health Center of Excellence was created to serve as a central location to facilitate DHT knowledge and communication within FDA, both for internal and external stakeholders.

Of the guidance currently published, the Digital Health Technologies for Remote Data Acquisition in Clinical Investigations[1] and the Patient-Focused Drug Development (PFDD) Guidance series (particularly guidance 3[2] and 4[3]) appear to be the most relevant for considerations in reference to DHT design and implementation in clinical trials at the current time.

V3+ Framework

Of recent note for those involved in DHT work, in February 2024 the Digital Medicine Society (DiMe) released an expansion to its original V3 framework published in 2020. This expansion, titled the V3+

framework[4], emphasizes usability validation as a component of equal importance alongside analytical and clinical validation for determining whether a DHT is fit-for-purpose.

The enhanced focus on usability validation for DHTs as seen in the V3+ framework reflects the ongoing shift in industry and regulatory perspectives towards recognizing the importance of patient-centeredness in clinical trials. The framework begins with verification and proceeds stepwise through each successive phase as seen below. If any changes in the DHT or in trial design occur that could impact the steps of V3, the relevant steps should be repeated. For example, a change in patient population during or after clinical validation may require additional usability validation.

- Usability validation: Are there any changes to the context of use?
- Analytical validation: Are there any changes to software/algorithms?
- Clinical validation: Are there new patient populations involved?

Usability validation for DHTs assesses whether a given DHT can be used effectively by diverse users within the intended population and evaluates whether a DHT can achieve the specific goals enumerated in a clinical trial with "ease, efficiency, and user-satisfaction" within the intended context of use. By performing usability validation, a DHT can be selected that is most fit-for-purpose given the needs of study participants and patients. The applicability is broad, pertaining to both under development (pre-market) and commercially available (post-market) DHTs.

Symptom Mapping

The process of symptom mapping was used in WATCH-PD research under the Critical Path for Parkinson's (CPP) initiative to identify condition-specific DHT-based measures.[5] Collections of quantitative and qualitative data aided the identification of meaningful symptoms and permitted an analysis of the relevance of DHT-derived measures to symptoms.

Novel DHT-based measures were developed for relevance testing with early-onset PD patients because standard clinical assessments are insufficient for patients with early-onset disease. Surveys and interviews were conducted to identify symptoms meaningful to patients, assess content validity of digital measures, and connect those digital measures to the identified symptoms to assess relevance. The process included the four steps outlined below.

1. **Mapping** the DHT-based measures to known and hypothesized meaningful symptoms.
2. **Analyzing** symptom maps for types, frequencies, bothersomeness, and the importance of symptoms and impacts, along with their association with DHT-based measures.
3. **Assigning** each symptom to a Patient Reported Symptom Score (PRSS) based on the highest bothersomeness level. For example, if a participant placed the Tremor digital

measure next to the symptom "Tremor" at the "most bothersome" position in the symptom map, it would be associated with a PRSS of 4.

4. **Calculating** relevance of DHT-based measures by their association with symptoms through the PRSS. If digital measures were associated with more than one symptom, they were valued at the highest PRSS within a symptom map and counted once per participant.

Symptom mapping was an overall success. In addition to increasing data granularity and rigor, which allowed for precise quantification of qualitative data, the process demonstrated an enhanced ability of meaningfully relating symptoms to digital measures

- Nine of the ten WATCH-PD digital measures rated as relevant by study participants
- 95% of participants enjoyed the mapping process, stating that it improved their ability to conceptualize and communicate their symptoms to others.

Ultimately, symptom mapping allows a clearer understanding of the importance and bothersomeness of specific symptoms for patients. The research team is then sufficiently empowered to create meaningful and specific endpoints that are comprehensible to patients and useful for a clinical trial and can use patient feedback to assist in identifying potential anchors. The main drawback in this investigation is often a small study population (with an n of approximately 40). In future research with this population, it is recommended to apply the symptom mapping method within a larger study population and within different conditions of interest in order to determine if the observed patient benefits are scalable, repeatable, and generalizable in regard to determining meaningfulness of DHT-derived measures.

Patient Data Access

DHTs uniquely have the possibility of allowing patient access to data in real-time or near real-time. Whether this qualifies as unblinding can vary, but blinding remains the baseline FDA expectation for clinical trials. Although providing patients with access to their DHT-derived data may be beneficial in certain contexts, such as motivating patient compliance, doing so requires justification from the sponsor to be allowed from a regulatory standpoint.

Unblinding is not the only concern present in allowing data access as even if access does not qualify as unblinding there is still a need to avoid biasing the data generated (e.g., target setting, placebo effect). Ultimately allowing patient access to DHT-derived data does not necessarily mean that a clinical trial would then be unblinded to treatment effect, but reviewers should be aware of the implications of patient access and proceed accordingly when communicating with sponsors in this area.

Pre-Competitive Initiatives and Other Approaches

Pre-competitive initiatives that emphasize industry collaboration regarding DHTs and development of DHT-derived measures are one method to combat the expense of verification and validation that normally one sponsor company would undertake alone. The rise of independent non-profits that study various diseases independent of pharmaceutical companies has also supported verification and validation efforts within the DHT field for clinical trials.

Finally, pharmaceutical companies with sufficient resources have started their own departments focusing on development of digital health technologies for utilization in clinical trials. For companies that possess the requisite amounts of staff, money, and time, considering the creation of a DHT department could be a recommended course of action.

Conclusion

The DHT field is expected to continue evolving over time, and both regulatory and sponsor perspectives are expected to shift as various aspects, such as usability validation, are emphasized and techniques such as symptom mapping become more widely used. Pre-competitive initiatives, among other approaches, may assist pharmaceutical companies in regard to development and utilization of DHTs and derived measures for use in clinical trials.

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Disclosure Shabas Solutions LLC was engaged by the FDA to conduct the Digital Health Technologies Guidance Project for CDER.

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All references were last checked and/or verified on 3 October 2024.

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