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Digital Therapeutic Clinical Evidence Quality & Timing Recommendations

Clinical Evidence Quality Recommendations

Table 1 provides product manufacturers and healthcare decision makers (HCDM) with recommendations for demonstrating and assessing the quality of clinical evidence developed for DTx products related to the five clinical outcome domains of (1) safety, (2) benefit, (3) durability and duration of response, (4) usability and accessibility, and (5) user engagement within the regulatory, payment, and clinical use and acceptance ecosystems.

TABLE 1. QUALITY OF EVIDENCE RECOMMENDATIONS

Domain	Regulatory Pathway	Payment Pathway	Clinical Use and Acceptance
Safety	» Short-term safety data, collected during a patient's use of the DTx or within a clinical trial, are essential for pursuing the regulatory pathway. » Long-term safety data, whose collection extends beyond the time period of a clinical trial, may be important for specific therapeutic areas. » Objective and subjective endpoints are used for collecting safety data to support DTx regulatory approval. » Interventional clinical trials and real-world data (RWD)/real-world evidence (RWE) clinical studies are performed for collecting safety data to support DTx regulatory approval.	» Safety data could be important to demonstrate that a DTx can reduce healthcare system burden and support payor goals of cost avoidance, as applicable. » Cost-analysis of supplemental safety data, such as a reduction in a certain type of adverse event, can be useful to support financial claims that payors desire.	» Publishing clinical trial results in peer-reviewed journals that include appropriate safety data is important for gaining clinician acceptance.

Domain	Regulatory Pathway	Payment Pathway	Clinical Use and Acceptance
Benefit	» Efficacy data are essential for pursuing the regulatory pathway. » Effectiveness data are beneficial but may not be required by regulators for approval. » Engaging with regulators early in the process of study design to ensure data will be sufficient is highly recommended. » Regulators expect well-controlled investigations to support effectiveness claims, and in certain instances, other study designs may be sufficient. » If quality of life (QoL) claims are to be made, then it is required to collect QoL measures. » Validated QoL patient-reported outcomes (PRO) are expected to provide the most reliable and acceptable level of evidence.	» Aligning clinical trial eligibility criteria with the target patient population is crucial in meeting payor requirements for the coverage of appropriate patients. » The ability to make strong clinical claims backed by robust evidence generated using high-quality study designs is important. The study design needs to include endpoints that are relevant to payors. » Demonstrating that a DTx can replace or delay the use of a more costly therapy is often attractive to payors. » Payors are concerned with issues related to relevance, quality, and interpretability of PROs when evaluating data from these instruments.	» Clinicians will understand and accept benefit claims when it comes from a trial with a rigorous study design, providing evidence of comparative effectiveness, and gold standard outcome measures. » Demonstrating a meaningful QoL measure is important for gaining clinician acceptance.
Durability and Duration of Response	» Long-term efficacy and effectiveness data may be requested by regulators. It is important to engage regulators early in the design process to determine what durability evidence they may request.	» Payors prefer DTx products that have a durable treatment effect, as opposed to creating a blanket requirement for continued product use. Therefore, demonstrating the enduring effects of the DTx seeking a pathway to reimbursement. » The potential exists for negotiating with payors to provide incentives based on the results of prospectively designed RWD/RWE studies that demonstrate outcomes such as an overall reduction in healthcare costs over a period of time.	» Clinician uptake is more likely when therapies are supported with RWE that demonstrate duration of therapy response**.**

Domain	Regulatory Pathway	Payment Pathway	Clinical Use and Acceptance
Usability & Accessibility	» Evidence must meet acceptable levels of compliance and adherence to support claims. » Some regulatory pathways may require explicit usability testing (i.e., summative (validation) testing required by the FDA for software as a medical device (SaMD) products).	» Dependent on robust RWE being available to support DTx product claims and demonstrate value.	» Demonstrating the ability for the DTx to fit within the existing clinician workflows is key to acceptance within the clinical community. This may include evidence to support how clinicians can easily access and interpret data generated by the DTx.
User Engagement	» Evidence must meet acceptable levels of compliance and adherence to support claims. » It is recommended to involve end users in the trial design process, since involving patients could lead to higher levels of user engagement and better quality of evidence across categories.[1]	» Demonstrating patient engagement and interest in using the DTx is crucial, as this is often stated as a primary concern by payors (i.e., that even if the DTx works, patients might not use it as intended). Generating evidence to support patient engagement may be done as part of an interventional clinical trial (i.e., randomized control trial (RCT)), or gathered in the form of RWD and analyzed to produce RWE. » Evidence supporting high treatment persistence rates may be beneficial, particularly if the therapeutic contains components known to have barriers to behavioral activation (i.e., cognitive behavioral therapy (CBT)).	» Clinician uptake is more likely when DTx therapies are supported with RWE that demonstrate appropriate user engagement.

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-engagement-design-and-conduct-medical-device-clinical-studies

Clinical Evidence Timing Recommendations

DTx clinical evidence dossiers are developed in phases, with studies often conducted during specific periods of the product development, launch, and post-market life cycle. Table 2 identifies the types, timing, and target outcomes of clinical evidence generation during four product development phases: pre-development, early development, late phase development, and post-marketing.

TABLE 2. TYPES, TIMING, AND TARGET OUTCOMES OF CLINICAL EVIDENCE GENERATION

Development Phase	Purpose	Types of Study Designs	Evidence Collected	Pathway Relevance (in order of relevance)	
Pre-Development (exploratory, discovery phases)	The main driver of this phase is identifying and improving understanding of the product's mechanism of actions (MoA) or active principles.	» Review of existing clinical trial data and systematic reviews » Experimental clinical trials	» Behavior change » Safety (short-term) » Benefit (efficacy)	Regulatory	Can support clinical evaluation (for regulatory and clinical association); early evidence of safety and performance
				Clinical Practice Acceptance	Supports building trust in the product and an understanding of the product MoA
				Payment Pathway	Builds an early evidence base for product claims
Early Development (early feasibility, proof of concept phases)	This phase moves from basic science into productization: this will include validation of concepts, early safety and effectiveness data, as well as refining the therapeutic protocol (i.e., dosing, frequency of administration). It typically leverages shorter duration studies than late phase/pivotal studies. Product design is also initially tested in this phase (i.e., usability, human factors), as well as generating initial evidence of value beyond clinical outcomes (i.e., operational, experiential).	» Experimental clinical trials » Product analysis » Non-experimental trials	» Behavior change » Safety (short-term) » Benefit (efficacy, effectiveness) » Usability and accessibility » User engagement » Compliance and adherence	Clinical Practice Acceptance	Ecosystem acceptance and adoption, by increasing market confidence on the effectiveness of the product Supports wider adoption by building users' trust
				Regulatory	Informs future regulatory pathways
				Payment Pathway	Builds early evidence for product claims (i.e., safety, clinical utility)

Development Phase	Purpose	Types of Study Designs	Evidence Collected	Pathway Relevance (in order of relevance)	
Late Phase Development (pivotal, validation phases)	This phase includes developing core evidence for the product's regulatory submission. It is also of critical importance to consider the product's level of evidence of value and clinical utility to drive initial adoption and payor support immediately following regulatory approval.	» Experimental clinical trials » Product analysis » Non-experimental trials	» Safety (short- and mid-term) » Benefit (efficacy, effectiveness) » Usability and accessibility » User engagement » Compliance and adherence » Behavior change	Regulatory	Core evidence collected for product safety, effectiveness, and performance
				Payment Pathway	Main body of evidence developed for early conversations with payors
				Clinical Practice Acceptance	Evidence developed here will help drive adoption; regulatory approval contributes to this goal
Post-Marketing (intended use, real-world use phases)	In this phase, data are continuously collected from real-world use and studies to further expand the body of evidence that supports product claims and commercialization strategies. This includes gathering insight into durability and long-term safety, engagement, and impact.	» RWD » RWE » Experimental clinical trials » Product analysis » Non-experimental trials	» Safety (long-term) » Benefit (efficacy, effectiveness) » Usability and accessibility » User engagement » Compliance and adherence » Behavior change » Durability	Payment Pathway	Pivotal evidence to expand to market access and revenue generation (i.e., HEOR studies)
				Clinical Practice Acceptance	Expands on evidence of utility and value to further expand adoption
				Regulatory	Support for validation of new commercial claims

DTx Evaluation Considerations

Digital therapeutics can be used as standalone therapies, in conjunction with, or in place of other clinically validated therapies. Based on their proximity to existing therapies, HCDMs therefore frequently evaluate DTx products using the same criteria and requirements as pharmaceuticals and other similar treatments. This perceived expectation for DTx products to meet the same requirements, in terms of types, quality, and volume of clinical evidence as pharmaceuticals ignores DTx's agile development processes, mechanisms of action, ability to generate real-time outcomes, ongoing iterative nature, lower potential risk profiles, and place in therapy.

DTx products therefore require a fit-for-purpose evaluation approach that incorporates aspects of existing pharmaceutical and medical device evaluation frameworks, but are designed to evaluate the safety, efficacy, and impact of DTx therapies more appropriately. Notably, a fit-for-purpose DTx

product evidence evaluation framework, as initially proposed in this publication, does not weaken evidentiary requirements, but rather provides greater evidentiary strength and robustness that reflects how DTx products are designed and used in real-world settings.

Pharmaceuticals are recognized as an "embodied technology" for which the efficacy relates solely to the correct dose of the drug, which chemically interacts with the body's physiological systems. DTx products, on the other hand, use software-driven technologies to deliver their behavioral and physical impacts on end users, thus carrying different types and levels of risk than chemical-based products. For example, a counterfeit or low-quality DTx that relies on or disseminates incorrect, incomplete, or inconsistent therapeutic impact may be harmful to end users by delivering inadequate or inappropriate clinical interventions[2] (i.e., incorrect insulin dosing, inaccurate medical directions, insufficient infrastructure for mental health risk management). Although DTx products are not risk-free, they do carry different risks than pharmaceuticals, and should thus be evaluated appropriately.

Additionally, unlike pharmaceuticals, DTx products undergo incremental product modifications during the post-marketing phase. These product changes, or iterations, may impact many things, ranging from product functionality and bug fixes, to clinical and usability improvements that may impact the therapy's efficacy. Thus, DTx evaluation approaches that rely on RCTs and prospective studies often need to be paired with additional studies during the product's life cycle to account for the iterative nature of technological product design.[3] Where applicable, HCDMs should accept study designs that account for specific DTx characteristics, such as multi-phasic optimization strategies, sequential multiple assignment randomized trials, and micro-randomized trials developed with an adaptive design.[4]

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4576443/

[3] https://www.tandfonline.com/doi/full/10.1080/14737167.2021.1891883

[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4732571/; https://mhealth.jmir.org/2016/3/e107

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