

# Digital Therapeutic Clinical Evidence Basics

Digital therapeutic (DTx) products generate multiple evidence types during their life cycle, including clinical evidence, real-world evidence (RWE), health economic and outcomes research (HEOR), and context-specific implementation pilots. Although this publication focuses primarily on clinical evidence requirements, comprehensive DTx evidence dossiers should provide healthcare decision makers (HCDM) with sufficient insights necessary to assess the value and effect of DTx interventions at the individual patient and population health levels of care.

**“In general, it is not possible to set a blanket threshold for all types of statistical assessments of clinical validation, as these will differ depending on the clinical measurement, patient population, and context of use.”**

Source: Goldsack, J.C., Coravos, A., Bakker, J.P. *et al.* (2020). Verification, analytical validation, and clinical validation (V3): The foundation of determining fit-for-purpose for Biometric Monitoring Technologies (BioMeTs). *npj Digital Medicine* 3, 55.<sup>1</sup>

A fit-for-purpose DTx evidentiary standard—applying both to products provided via prescription and non-prescription routes—must include the types, quality, timing, and levels of clinical evidence considered to be sufficient for DTx product regulatory, reimbursement, and clinical use purposes.

***As a first step, the following considerations should factor into developing a fit-for-purpose evidentiary standard framework:***

DTx  
Intervention  
Classifications

Clinical  
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Domains

Clinical Study  
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DTx Clinical  
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## DTx Intervention Classifications

The International Classification of Health Interventions (ICHI) defines a health intervention as “an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote, or modify health, functioning, or health conditions” (WHO, 2019).<sup>2</sup> Flowing from that definition, the classification encompasses interventions across all sectors of the health system and is built around three axes:

- » **Target.** The entity on which the action is carried out
- » **Action.** The deed done by an actor to the target
- » **Means.** The processes and methods by which the action is carried out

This publication provides guidelines for clinical evidence generation to demonstrate the value and effect of DTx interventions to treat, manage, or prevent medical conditions. It does not provide guidance for products primarily responsible for diagnosis, monitoring, screening, or general education of medical conditions.

## Clinical Outcome Domains

DTx treatment developers and manufacturers primarily focus on six domains when undertaking clinical evidence evaluations. These domains form the foundation of DTx clinical evidence dossiers and a guide for HCDMs as they assess the sufficiency of available DTx evidence.

Primary clinical outcome domains include:

1. **Safety.** The Code of Federal Regulations (CFR) Title 21 defines safety outcomes as the valid scientific evidence to adequately demonstrate the absence of unreasonable risk of illness or injury associated with the intended use of the device and condition of its use.<sup>3</sup>

This publication does not focus on product cybersecurity as a subset of safety. Cybersecurity is most often evaluated via other mechanisms (i.e., alignment with regional or national requirements, certifications) instead of clinical trials.

2. **Benefit.** Efficacy trials determine whether an intervention produces the expected result under controlled circumstances.<sup>4</sup>

Effectiveness studies measure the degree of beneficial effect under “real-world” settings.<sup>5</sup>

3. **Durability and duration of response.** Durability of an intervention may be defined as its ability to postpone or delay progression of disease in a safe and well-tolerated manner.<sup>6</sup>

Duration of response is the period of time the treatment effects persist after treatment is completed or discontinued.<sup>7</sup>

4. **Usability and accessibility.** Usability is the characteristic of the product that establishes effectiveness, efficiency, ease of user learning, and user satisfaction.<sup>8</sup>

Accessibility refers to how a technological product can be used by people from a population with the widest range of characteristics and capabilities to achieve a specified goal in a specified context of use.<sup>9</sup>

- 5. User engagement.** User engagement with technological aspects refers to how, how frequently, and for what duration a user makes use of the DTx system, including software, hardware, and any other components necessary for the DTx to function.<sup>10</sup>

User engagement, however, reflects a complex set of factors that go beyond standard adoption and utilization measures (i.e., attrition), and extends into the quality of patients' interaction with the intervention (i.e., task success, user satisfaction, net promoter score).

- 6. Behavior change.** Any alteration or adjustment of behavior that affects a patient's functioning brought about by psychotherapeutic, other interventions, or occurring spontaneously.<sup>11</sup>

## Clinical Study Participant Selection

Equitable participant selection is fundamental for enhancing the social value of DTx products and promoting their clinical effectiveness. Individuals selected for a study should reflect the population for whom the product is intended. The target population is represented by enrolling participants who meet specific enrollment criteria that match the key characteristics of the intended target population.

Insufficient participation from some groups within a population can result in inadequate information pertaining to the safety and effectiveness of the DTx product in important subpopulations.

Although outside the scope of this publication, additional insights about product appropriateness and usability by target populations and subpopulations may be generated through real-world data (RWD) and RWE evaluations. These real-world insights may be used to provide greater context to clinical evidence outcomes and influence the development of future product iterations.

## DTx Clinical Evidence Endpoints

HCDMs assessing the quality of DTx evidence outcomes may rely on the following considerations related to the use of endpoints in data generation, assessment, and analysis.

### *Selection and Assessment of Endpoints<sup>12</sup>*

A clinical endpoint is a measure of the benefit or reduced harm of an intervention and should therefore be a key symptom or sign of a disease, a valid measure of clinical benefit due to treatment, clinically relevant, responsive to change, and accepted by clinicians. Clinical endpoints should be reproducible, facilitate comparisons across studies, valid, and quantify what was intended to be measured. Protocols should clearly define endpoints and pre-specify clinically relevant effects based on published standards or consensus among independent clinicians and/or patients. In some cases, authoritative organizations have developed standards or guidance documents specifying how to define and implement specific types of digital health clinical endpoints in clinical trials (i.e., FDA, Consumer Technology Association, Digital Medicine Society).

Clinical endpoints are intended to measure the impact of an intervention on how a patient feels, functions, or survives. Because most interventions affect more than one disease characteristic, most trials measure multiple endpoints to document the benefits of the intervention. To illustrate the issue of multiple endpoints in clinical trials and studies, consider the example of efficacy measures. As described above, efficacy endpoints are measures intended to reflect the effects of an intervention. Efficacy spans several domains including clinical events, patient symptoms, measures, or functions. Most diseases have impacts on multiple domains and often on multiple organ systems. Therefore, it is often necessary to evaluate the effect of an intervention on several different endpoints.

Testing multiple endpoints increases the risk that any statistical significance observed in the analysis may be the result of chance and drive a false conclusion about the intervention's effects. To mitigate this risk, study protocols must pre-specify an outcome hierarchy and make a prospective determination of outcome classification according to their type—primary, secondary, and exploratory. For an efficacy study, the set of primary endpoints are the outcomes or outcomes that establish the effectiveness of the intervention. Power calculations should be part of study protocols and the sample size must be based on the desired power level and significance level to detect an expected effect size for the primary endpoint. Statistical analysis plans must specify approaches to adjust for multiple comparisons.

Designating primary endpoints is based on clinical importance and the likelihood of demonstrating an effect. Secondary endpoints are outcomes selected to demonstrate additional effects of the intervention after success on the primary endpoint or outcomes that provide evidence of the mechanism of action underlying the demonstrated clinical effect. The study may be powered to explore secondary endpoints; however, positive results on the secondary endpoints can be interpreted only if a treatment effect on the primary endpoint family is demonstrated first. Exploratory endpoints may include clinically important events that are expected to occur too infrequently to show a treatment effect or endpoints that for other reasons are thought to be less likely to show an effect but are included to explore new hypotheses.

### DTx Endpoint Types

Types of endpoints that DTx products use include:

- » **Objective endpoints.** Objective endpoints are those that can be measured without being influenced by the beliefs or expectations of the user. They tend to be quantitative, well-defined, and reliable regardless of the observer. Examples include wearables for measuring heart rate variability, sleep, or gait.
- » **Subjective endpoints.** Subjective endpoints can be influenced by the perceptions and beliefs of the users. These could be tested and validated tools such as questionnaires but nonetheless be impacted or influenced by individual interpretation or perception. Examples include assessments of depression or anxiety questionnaires or assessments of pain, and patient reported outcome surveys.
- » **Composite endpoints.** Composite endpoints combine numerous endpoints into a single outcome.<sup>13</sup> Such endpoints may be useful for providing a more multifaceted view of effects and can potentially help reduce bias. An example is the European Medicines Agency qualified PROActive composite measure, which combines patient-reported questionnaire data with activity monitor data in chronic obstructive pulmonary disorder (COPD) patients.
- » **Intermediate clinical endpoints.** An intermediate clinical endpoint is defined as “a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of an intervention, such as an effect on irreversible morbidity and mortality.”<sup>14</sup> An example is tracking heart rate and body movement during sleep as a proxy for sleep disturbance or nightmares.
- » **Surrogate endpoints.** Surrogate endpoints are measures that can be used as a substitute for a clinically meaningful endpoint. Although surrogate endpoints may predict a clinical benefit, they are not themselves clinical benefits.<sup>15</sup> Surrogate endpoints may take a shorter time to observe or may be easier to observe when the clinical endpoint may be too difficult, expensive, or unethical to measure. These must be validated. Examples include HbA1c for diabetic complications.

## Clinical Outcome Categories

Clinical outcomes are measures of mortality and morbidity, complications, symptom reduction, and functional status improvements for the disease of interest. The domains of health that a digital therapeutic study may assess include:<sup>16</sup>

- » **Survival outcomes.** Survival outcomes span all-cause survival and cause-specific survival.
- » **Physiological and clinical outcomes.** Physiological and clinical outcomes that measure signs and symptoms of disease, laboratory and other clinical test parameters, and anthropometric measurements.
- » **Life impact or functioning outcomes.** Life impact or functioning outcomes that measure the impact of the intervention on the following subdomains: physical functioning (i.e., the ability to perform physical activities of daily living); social functioning (i.e., the ability to participate in social activities and to operate within society); role functioning (i.e., the ability to fulfill the requirements of an individual's role such as caregiver or employee); emotional functioning (i.e., the impact of the disease on well-being and psychological status); cognitive functioning (i.e., the impact of the disease on cognitive domains such as memory and attention); and quality of life (i.e., perception of an individual's position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns).
- » **Adverse events.** Adverse events are defined by the FDA as any untoward medical occurrence associated with the use of a drug/intervention in humans, whether or not considered drug/intervention related. Tolerability is defined as “the degree to which overt adverse effects can be tolerated by the subject” by the International Conference on Harmonization (ICH) and measured as withdrawal from intervention.

## Process Variables

Apart from the health domains listed above, studies of digital interventions may also evaluate the delivery of care and how the participant interacts with the intervention. Such aspects of process may include the following:

- » **Adherence and compliance.** Although the two terms are often used interchangeably, an implicit difference exists between them. *Compliance* is defined as “the extent to which the patient's behavior matches the prescriber's recommendations,” whereas *adherence* is defined as the “active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result.”<sup>17</sup> The main distinction is that the adherence metric emphasizes patient participation in the choice of treatment goals and regimen.

Adherence consists of two components: compliance and persistence. Compliance, measured as a proportion, refers to using the digital therapeutic per the recommended time period (i.e., twice daily sessions for four weeks), whereas persistence refers to the accumulation of time from initiation to discontinuation of therapy (i.e., four weeks).<sup>18</sup> Although conceptually similar, compliance refers to the intensity of exposure to the intervention during the duration of therapy, whereas persistence, often measured as patient retention, refers to the overall duration of therapy.

- » **User engagement.** User engagement is a concept that goes beyond whether the individual adheres to and persists with the intervention, but instead evaluates the quality of their interaction with the intervention. Although the definition of engagement is still evolving—especially as it pertains to clinically informed, data-driven measurement processes—current metrics include capturing users’ level of attention, task success, and interactivity with the digital intervention, as well as the particular sections and elements of the intervention the individual engages with.<sup>19</sup> Beyond “generic” measures of engagement (i.e., number of sessions, weekly active usage, or program completion), *measures of meaningful engagement* may refer to “a clinically informed and data-driven approach to identify specific engagement metrics that uniquely predict the long-term value for a digital therapeutic.”<sup>20</sup>
- » **User satisfaction and preference.** Treatment satisfaction is defined as a patient’s perception of the extent to which all aspects of the intervention (i.e., mode of delivery, duration, and benefit) meets their health needs.<sup>21</sup>

User preference endpoints aim to capture the value that patients place on aspects of the intervention. The FDA defines patient preference endpoints as “qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions.”<sup>22</sup>

Note that while process variables are valuable endpoints and measure metrics that may contribute to the effectiveness of the intervention, they must be accompanied by and correlated with a meaningful clinical outcome demonstrating treatment benefit.

### Biomarkers

The Biomarkers, EndpointS, and other Tools (BEST) glossary defines a *biomarker* as “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.”<sup>23</sup> Biomarkers may have molecular, histologic, radiographic, physiologic, or behavioral characteristics.

Highly relevant to the evaluation of digital interventions are digital biomarkers defined as a characteristic or set of characteristics, collected from digital health technologies, that are measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.<sup>24</sup> Digital biomarkers may represent digitization of measurement of previously established traditional biomarkers, (i.e., gait or heart rate), or may be novel in that they provide an entirely new domain of measurement (i.e., vocal biomarkers).<sup>25</sup> As with any biomarker, digital biomarkers require rigorous testing and validation.

### Reported Outcomes

Reported outcomes, also referred to as clinical outcome assessments,<sup>26</sup> may also be defined based on the source of the assessment. Examples include:

- » **Clinician-reported outcomes.** *Clinician-reported outcome* (ClinRO) is defined as “a measurement based on a report that comes from a trained health-care professional after observation of a patient’s health condition.” Most ClinRO measures involve a clinical judgment or interpretation of the observable signs, behaviors, or other manifestations related to a disease or condition. ClinRO

measures cannot directly assess symptoms that are known only to the patient. ClinRO measures can include reports of particular clinical findings (i.e., presence of a skin lesion or swollen lymph nodes), clinical events (stroke, heart attack, death, hospitalization for a particular cause), or rating scales, such as the Hamilton Depression Rating Scale (HAM-D) for assessment of depression.<sup>27</sup> ClinROs reflect the clinician's assessment of the patient's symptoms. Depending on the purpose of the assessment, these may need to be conducted and contextualized appropriately (i.e., clinician's assessment of depression symptom severity versus patient's self-report).

- » **Patient-reported outcomes.** *Patient-reported outcome* (PRO) is defined as “a measurement based on a report that comes directly from the patient (i.e., study participant) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.” A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others. PRO measures include rating scales (i.e., numeric rating scale of pain intensity or Minnesota Living with Heart Failure Questionnaire for assessing heart failure) and count of events (i.e., patient-completed log of emesis episodes or micturition episodes).<sup>28</sup> PROs reflect the patient's experience and perspective. Depending on the purpose of the assessment, these may need to be contextualized appropriately (i.e., asking a patient with Alzheimer's disease to rate their memory or functioning versus their clinician or caregiver).
- » **Observer-reported outcomes.** *Observer-reported outcome* (ObsRO, which includes caregiver) is defined as “a measurement based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than the patient or a health professional.” Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life and are particularly useful for patients who cannot report for themselves (i.e., infants or individuals who are cognitively impaired). An ObsRO measure does not include medical judgment or interpretation. ObsRO measures include rating scales, such as Acute Otitis Media Severity of Symptoms scale (AOM-SOS), and Face, Legs, Activity, Cry, Consolability scale (FLACC), or counts of events (i.e., observer-completed log of seizure episodes).<sup>29</sup> ObsROs reflect the observer's experience and perspective on the patient's condition. Depending on the purpose of the assessment, these may need to be conducted and contextualized appropriately (i.e., asking a parent about their child's aggressive behaviors at school).
- » **Performance outcomes.** *Performance outcome* (PerfO) is defined as “a measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions. A PerfO assessment may be administered by an appropriately trained individual or completed by the patient independently. PerfO assessments include measures of gait speed (i.e., timed 25 foot walk test using a stopwatch or using sensors on ankles), or measures of memory (i.e., word recall test).”<sup>30</sup>

## Control Arm Considerations

Designing appropriate control arms for clinical studies can be a complex process. Although this section is non-exhaustive, it provides high-level considerations for DTx products.

### Control Arm Design

For comparative clinical outcome studies, it is necessary to select or design a control arm. For DTx, this can be particularly challenging and requires careful consideration of the treatment delivery, its mechanism of action, and the type of evidence being collected, among other things.

Types of controls may include:

- » Placebo controls, such as sham applications that are designed to resemble an active therapy but do not possess a clinically active mechanism of action
- » Non-placebo controls, such as:
  - Waiting list
  - Active comparator (i.e., treatment as usual, the current standard of care, other digital application, an alternative treatment modality)
  - Historical control

An alternative study design that does not incorporate controls is a head-to-head trial, where the aim is to prove equivalence of two active interventions or a higher level of efficacy of one intervention over another.

### Blinding Clinical Studies

Blinding, the concept that a participant in a trial does not know which arm of a study they are assigned to, is another challenge for DTx when conducting comparative trials. Different types and levels of blinding exist and careful consideration should be put into selecting the appropriate blind for each study. When blinding is incorporated into the study design, it is important to clearly define who can and will be blinded (i.e., researcher, patient, caregiver) and to include a plan to demonstrate how the integrity of the blinding process was maintained throughout the study. DTx manufacturers and HCDMs must reference local regulatory guidance requirements when establishing and conducting blinding protocols.

When claiming that a trial has been blinded, clinical trial sponsors are recommended to abide by research reporting standards (i.e., [Consolidated Standards of Reporting Trials, CONSORT](#))<sup>31</sup> to ensure that all appropriate blinding checks are conducted during trials. Many DTx trials select a blind-to-hypothesis approach over a blind-to-assignment approach. When digital controls are deployed, they should only be referred to as a sham application if sponsors are able to guarantee that participants remain appropriately blinded.



# DTx Clinical Evidence Types

DTx evidence dossiers may cover a spectrum of domains, spanning from product feasibility, usability, accessibility, and user engagement to real-world impact and effectiveness. DTx products must therefore use various study designs to assess the appropriate endpoints during the appropriate phase of the product's life cycle.

Product manufacturers may utilize the following clinical evidence types as part of a DTx evidence dossier:

- » Non-experimental, observational studies
  - **Descriptive.** Case report, case series, cross-sectional (descriptive or prevalence)
  - **Analytical.** Cross-sectional survey, case-control, cohort (prospective or historical)
  - **Implementation pilot.** Assess site-specific implementation capacity and value
  - **Localization pilot.** Assess cultural adaptation, language translation, linguistic accuracy/validation, etc.
  - **Prospective.** Observational, cohort
- » Product analyses
  - **Retrospective analyses.** Chart reviews, medical/pharmacy claims, electronic medical records, other novel data sources
  - **Expert reviews.** Clinical practice guidelines, clinical pathways, health technology assessment agency evaluations, published systematic reviews
  - **Coverage decision assessments and formulary reviews.** External organization product evaluations, product indication reviews
  - **Patient perspectives.** Practical use of therapies, patient preference information (PPI)
  - **Consumer studies.** Medical affairs, marketing study

- » Experimental, interventional clinical studies
  - **Non-controlled studies.** Prospective single arm trial, open label trial, head-to-head comparative trial
  - **Controlled trials.** Non-randomized controlled trial, self-controlled study, crossover study
  - **RCT.** Unblinded/open-label, single-blind, double-blind, triple blind
- » RWD
  - Product performance and technical outputs
  - Patient-specific clinical and self-reported outcomes
  - End user and clinician engagement and satisfaction measures
- » RWE
  - Pragmatic clinical trials with real-world elements
  - RWE as a retrospective or prospective observational study
- » Systematic reviews of interventional, observational, or mixed methods studies
  - Meta analysis

The NICE evidence standards for digital health technologies recommends that “the choice of study design should be appropriate for the intended purpose of the DHT [digital health technology]. Randomized controlled trials would be preferable where this study design is appropriate. High quality, comparative real-world study designs may also be acceptable.”

Source: NICE. Evidence standards framework for digital health technologies. August 9, 2022.<sup>32</sup>

Additional forms of evidence generation that product manufacturers may utilize include HEOR studies (i.e., economic impact), implementation pilot studies (i.e., clinical workflow optimization), and localization pilot studies (i.e., linguistic validation, cultural adaptation).

## ENDNOTES

- 1 <https://www.nature.com/articles/s41746-020-0260-4#Sec25>
- 2 <https://www.tandfonline.com/doi/full/10.1080/14992027.2020.1736344#>
- 3 <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-860/subpart-A/section-860.7>
- 4 <https://www.ncbi.nlm.nih.gov/books/NBK44024/>; <https://www.fda.gov/media/99769/download>
- 5 <https://www.ncbi.nlm.nih.gov/books/NBK44024/>
- 6 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6785960>
- 7 <https://www.astrazeneca-us.com/media/astrazeneca-us-blog/2018/clinical-trial-endpoints-in-cancer-research-four-terms-you-should-know-09242018.html#modal-historic-confirmation>
- 8 [https://www.fda.gov/files/medical%20devices/published/FDA-Perspectives-on--Human-Factors-in-Device-Development-\(June-2012\).pdf](https://www.fda.gov/files/medical%20devices/published/FDA-Perspectives-on--Human-Factors-in-Device-Development-(June-2012).pdf)
- 9 [https://ris.utwente.nl/ws/portalfiles/portal/40147417/FedericiBorsci2010Usabilityevaluation\\_Modelsmethodsandapplications.pdf](https://ris.utwente.nl/ws/portalfiles/portal/40147417/FedericiBorsci2010Usabilityevaluation_Modelsmethodsandapplications.pdf)
- 10 <https://arxiv.org/pdf/2205.01851.pdf>
- 11 <https://dictionary.apa.org/behavior-change>
- 12 <https://www.eunetha.eu/wp-content/uploads/2018/01/Clinical-endpoints.pdf>; [www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf](https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf); [https://www.fda.gov/media/157635/download&sa=D&source=docs&ust=1665155156023336&usg=AOvVaw1bbusLm\\_OnMSiqZxVdUiz](https://www.fda.gov/media/157635/download&sa=D&source=docs&ust=1665155156023336&usg=AOvVaw1bbusLm_OnMSiqZxVdUiz)
- 13 <https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf>
- 14 <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval>
- 15 <https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development>
- 16 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5854263/>
- 17 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4087153/>; <https://www.ahajournals.org/doi/10.1161/circulationaha.108.768986#R1-768986>
- 18 <https://www.ahajournals.org/doi/10.1161/circulationaha.108.768986>
- 19 <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2768347#zoi200424r19>
- 20 <https://www.frontiersin.org/articles/10.3389/fdgth.2022.890081/full#B9>
- 21 <https://www.karger.com/Article/Fulltext/490413#ref20>
- 22 <https://www.frontiersin.org/articles/10.3389/fphar.2019.01395/full#B10>
- 23 <https://www.ncbi.nlm.nih.gov/books/NBK326791/>
- 24 <https://www.nature.com/articles/s41746-022-00583-z>
- 25 <https://www.frontiersin.org/articles/10.3389/fpsy.2021.640741/full>
- 26 <https://www.fda.gov/about-fda/clinical-outcome-assessment-coa-frequently-asked-questions#COADefinition>
- 27 <https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/glossary.clinicianreported-outcome/>
- 28 <https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/glossary.patientreported-outcome/>
- 29 <https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/glossary.observerreported-outcome/>
- 30 <https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/glossary.performance-outcome/>
- 31 [https://www.researchgate.net/publication/12030511\\_The\\_Revised\\_CONSORT\\_Statement\\_for\\_Reporting\\_Randomized\\_Trials\\_Explanation\\_and\\_Elaboration](https://www.researchgate.net/publication/12030511_The_Revised_CONSORT_Statement_for_Reporting_Randomized_Trials_Explanation_and_Elaboration)
- 32 <https://www.nice.org.uk/corporate/ecd7/resources/evidence-standards-framework-for-digital-health-technologies-pdf-1124017457605>



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For more information, please  
contact [info@dtxalliance.org](mailto:info@dtxalliance.org)

[www.dtxalliance.org](http://www.dtxalliance.org)

