MANUFACTURER SUBMISSION PACKET

DTx Value Assessment & Integration Guide

VERSION 2.0

DIGITAL THERAPEUTICS ALLIANCE

What Is a Digital Therapeutic?

Digital therapeutics (DTx) deliver to patients evidence-based therapeutic interventions that are driven by high-quality software programs to treat, manage, or prevent a disease or disorder. They are used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes.

DTx products incorporate advanced technology best practices relating to design, clinical evaluation, usability, and data security. They are certified or cleared by regulatory bodies as required to support product claims regarding risk, efficacy, and intended use.

Digital therapeutics empower patients, clinicians, and payors with intelligent and accessible tools for addressing a wide range of conditions through high-quality, safe, and effective data-driven interventions.

How Are DTx Products Different From Wellness Apps?

Per industry standards, digital therapeutic products should adhere to these foundational principles:

1. Treat, manage, or prevent a disease or disorder.
2. Produce a medical intervention that is driven by software.
3. Incorporate design, manufacturing, and quality best practices.
4. Engage end users in product development and usability processes.
5. Incorporate patient privacy and security protections.
6. Apply product deployment, management, and maintenance best practices.
7. Publish trial results inclusive of clinically meaningful outcomes in peer-reviewed journals.
8. Be reviewed and cleared or certified by regulatory bodies as required to support product claims of risk, efficacy, and intended use.
9. Make claims appropriate to clinical evaluation and regulatory status.
10. Collect, analyze, and apply real-world evidence and/or product performance data.

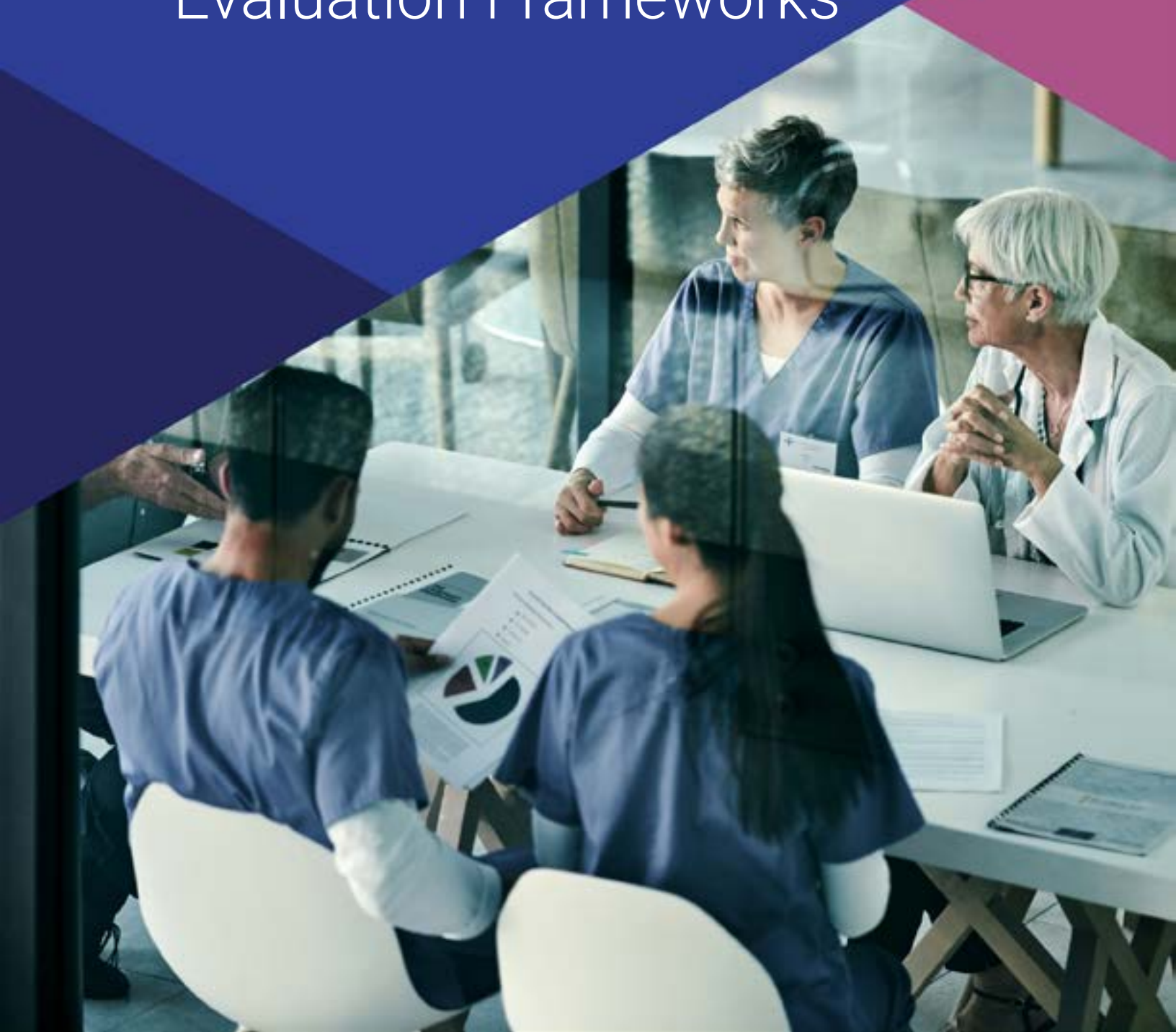
Revised: May 2022

Contents

This resource is for educational purposes only and is not intended as legal advice to individual companies. Payors have differing coverage, coding, and reimbursement policies. Laws, regulations, and payor policies concerning coverage, coding, and reimbursement are complex and are evolving rapidly. For legal advice, please consult with legal counsel.

Digital Therapeutics Alliance makes no warranty or representation regarding the completeness, accuracy, or timeliness of the information provided and makes no guarantee of coverage or reimbursement for any digital therapeutic product. Contact the applicable payor for specific guidance regarding coverage, coding, and reimbursement guidelines.

Harmonizing DTx Evaluation Frameworks



Why Is This Guide Necessary?

Increased Patchwork of Frameworks

Healthcare decision makers (HCDM) play a critical role in providing patients with access to high-quality, clinically validated digital therapeutic (DTx) products.

HCDMs already use consistent frameworks to evaluate other evidence-based clinical therapies such as pharmaceuticals. However, given the recent growth of the DTx industry and lack of frameworks defining what "good" looks like, many HCDMs have needed to develop their own methods to evaluate DTx products. As a result, a patchwork of HCDM requirements and frameworks are emerging for DTx manufacturers at the local, national, and regional levels.

Harmonizing DTx Requirements

As more HCDMs across the world review, assess, approve, and implement DTx products, it is important for these clinicians, policy makers, and payors to have access to reliable frameworks that enable more consistent evaluation of DTx products across local, national, and regional settings.

DTA developed the DTx Value Assessment & Integration Guide to provide a common language and process for HCDMs and DTx manufacturers to jointly use throughout DTx product evaluation processes. By providing the building blocks of DTx product review and economic assessment pathways, this Guide serves as a tool for HCDMs and DTx manufacturers to use in assessing baseline information about DTx products, their value, and their impact in real-world settings.

This Guide serves as a critical step in product access and contracting discussions. It addresses a wide spectrum of HCDM considerations across various settings—ranging from individual health systems and employers, to single-payor government systems, and multi-payor public/private settings—and will continue to be updated to ensure ongoing relevance in this quickly evolving ecosystem.

Developing a Dynamic Framework

DTA compiled this Guide with input generated by DTA member organizations dedicated to manufacturing, evaluating, supporting, and utilizing DTx products.

To encourage Guide applicability across HCDM settings, DTA conducted a series of workshops for Guide version 1.0 with payors, clinicians, and members in June–August 2021. Workshop participants reviewed the Guide and made recommendations for optimization. A neutral third-party facilitated each workshop and developed a formal manuscript that summarizes the process and outcomes.

As part of the launch of Guide version 2.0, HCDMs and industry stakeholders are asked to provide DTA with insights related to the Guide's utility, implementability, and ongoing development at https://www.surveymonkey.com/r/DTxValueGuideFeedback.

Who Will Benefit?

This Guide is designed to assist HCDMs in assessing and integrating DTx products into clinical use settings. HCDMs include payors, employers, governments, evaluators, health system administrators, clinical leaders, patients, and other individuals responsible for:

- Developing product access policies at the patient and population levels
- Identifying and evaluating new medical therapies and technologies
- Conducting formal product reviews (i.e., Pharmacy & Therapeutics [P&T] review, Health Technology Assessment [HTA] review)
- Developing patient coverage benefit design
- Authorizing DTx product coverage, funding, or reimbursement
- Undertaking product contracting processes
- Enabling patient, caregiver, and clinician DTx product authorization, access, and adoption
- Conducting ongoing clinical and economic product evaluations in real-world settings

TARGET AUDIENCES FOR THIS GUIDE

ADVISORY TEAM	AUTHORIZING CLINICIAN	CLINICAL SUPPORT TEAM
Patient advisory boards, caregivers, and practicing care team members	Clinicians qualified to authorize patient use of the product	Administrative representatives and clinical practice implementation teams
COMPLIANCE TEAM	**END USER**	**PAYOR ENTITY**
Legal, regulatory, privacy, and security teams	Patients, caregivers, clinicians, and care teams	Payors, employers, health plan strategy and budgetary approval teams
POLICY MAKERS	**PRODUCT ACCESS TEAM**	**PRODUCT EVALUATION TEAM**
Government entities, HTA bodies, and public payors	Technical infrastructure, implementation, and support teams	P&T committees, formulary developers, and innovation divisions

This Guide provides the following entities with:

HEALTHCARE DECISION MAKERS

- A consistent set of criteria to rely on when evaluating DTx products
- A baseline framework to use when seeking information from DTx manufacturers
- A guide that can serve as a starter evaluation process for healthcare systems
- A process that can be used in parallel with, or to refine, existing evaluation systems
- An initial benchmarking system to compare various DTx products to each other

CLINICIANS

- A framework to assess the legitimacy and impact of DTx products for patient care
- A process to determine how to best implement DTx products in practice
- A tool to assess DTx appropriateness for individual patient use
- A guide to determine how to leverage real-world outcomes in patient care

DTx MANUFACTURERS

- A rubric to pre-populate and distribute to appropriate entities (DTx Manufacturer version of this Guide, currently reserved for DTA member companies)
- A framework that provides HCDMs, policy makers, and clinicians with information on product design, impact, and utilization
- A more consistent set of expectations to meet across all clinical use environments

THIS GUIDE:

- Does not provide a definitive decision for HCDMs on whether or not to use a specific product in practice.
  - Although the considerations provided in this Guide assist in the product evaluation process, it leaves the final determination decision to the individual evaluators.
- Does not imply that a product has met all necessary qualifications for clinical use only on the basis that it may have responded to the considerations provided here.
  - Every DTx product is different and must be evaluated carefully based on the intended patient population, target condition, and desired outcomes.
- Does not provide a static framework.
  - At the individual product level, digital therapeutics rely on real-world data (RWD) and outcomes to continually optimize product offerings. Therefore, it is important that evaluation processes are dynamic to account for this important principle.
  - At the industry level, this Guide and framework will evolve as the DTx industry continues to grow and increasingly impact patient care provision across the world.

Industry Overview: Digital Health & Therapeutic Landscape

Industry Overview: Digital Health & Therapeutic Landscape

Differentiating Between Digital Health Products

The digital health landscape encompasses a broad range of technologies, with each serving a specific purpose. Although some digital health technologies are used for wellness, medication adherence, monitoring, or patient diagnosis, others use software to directly treat, manage, or prevent a disease or disorder. It is important for HCDMs to identify which digital health technologies (DHT) will best meet end users' needs and expectations.

A commonly recognized category of patient-facing digital health technologies are loosely referred to as digital health apps. These products are typically available in traditional app stores for immediate download and use, address a wide range of wellness issues, and have significantly varying degrees of patient privacy protections and clinical evidence support.

Digital health apps, however, represent only one type of software-based product in the broader patient-facing digital health continuum.

Given the significant differences between the digital health technology product types, it is critical for HCDMs and end users to distinguish between digital products that serve distinct purposes. For example:

PATIENTS NEED TO KNOW

- What am I using?
- Why am I using it?
- How will it help?
- Has someone verified it is safe and effective?
- Will it protect my data?
- Is it affordable?

CLINICIANS NEED TO KNOW

- What should I expect?
- How does it relate to other treatments?
- Does it provide actionable data or insights?
- Is it necessary for me to authorize or prescribe this product?
- Is this product covered by insurance?
- Will my patient be able to afford it?

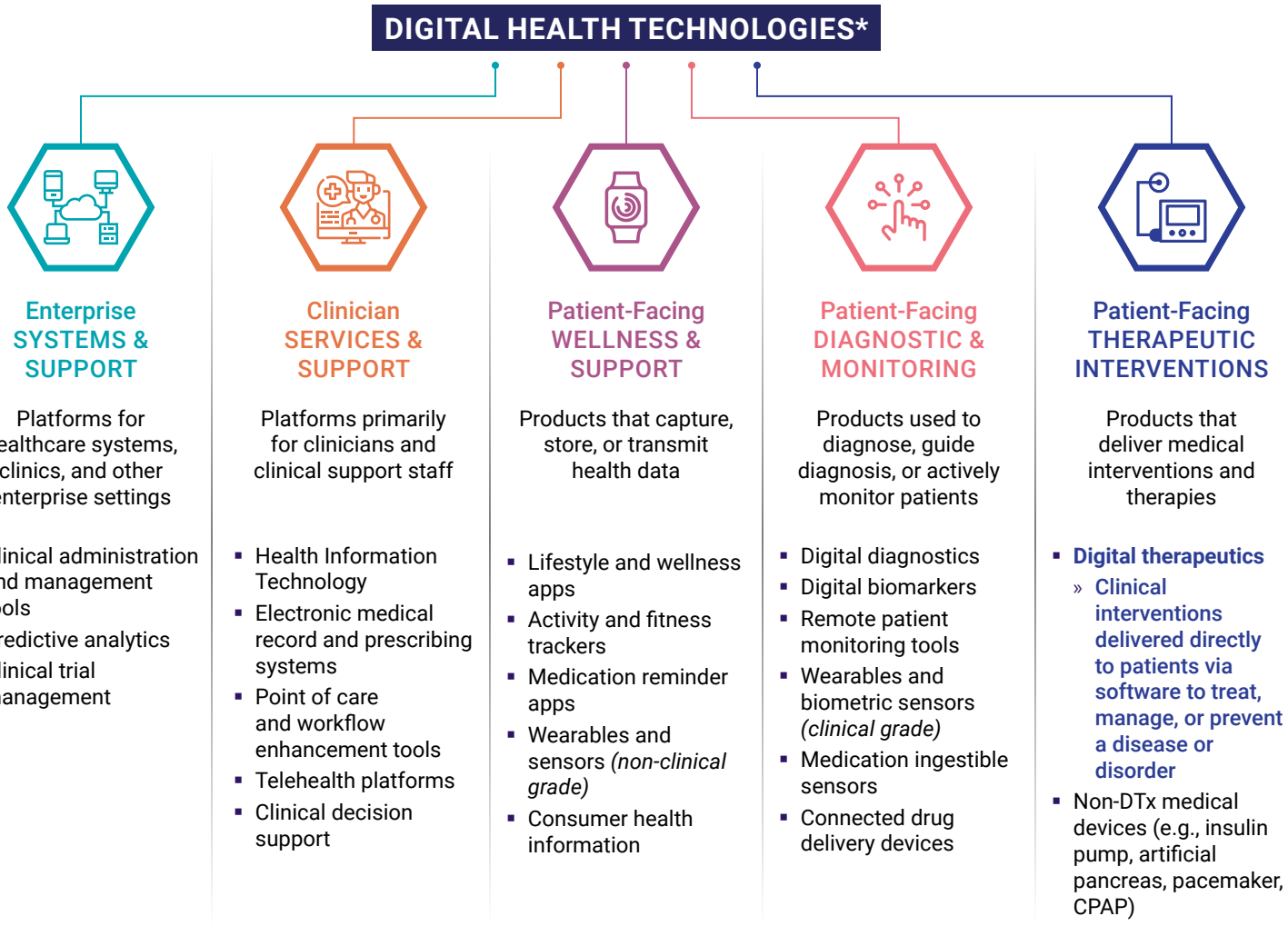
HEALTHCARE PAYORS NEED TO KNOW

- What type of product are we covering?
- How will it benefit patients at the individual and population levels?
- What types of clinical and economic outcomes should we expect?

POLICY MAKERS NEED TO KNOW

- What level of risk does each product pose to patients?
- What is the appropriate level of regulatory oversight?

The following figure provides a high-level overview of the types of DHTs that are currently used across the healthcare ecosystem.



**Categorizations of the digital health technology ecosystem will continue to evolve. This is a select representation of a broad, diverse ecosystem.*

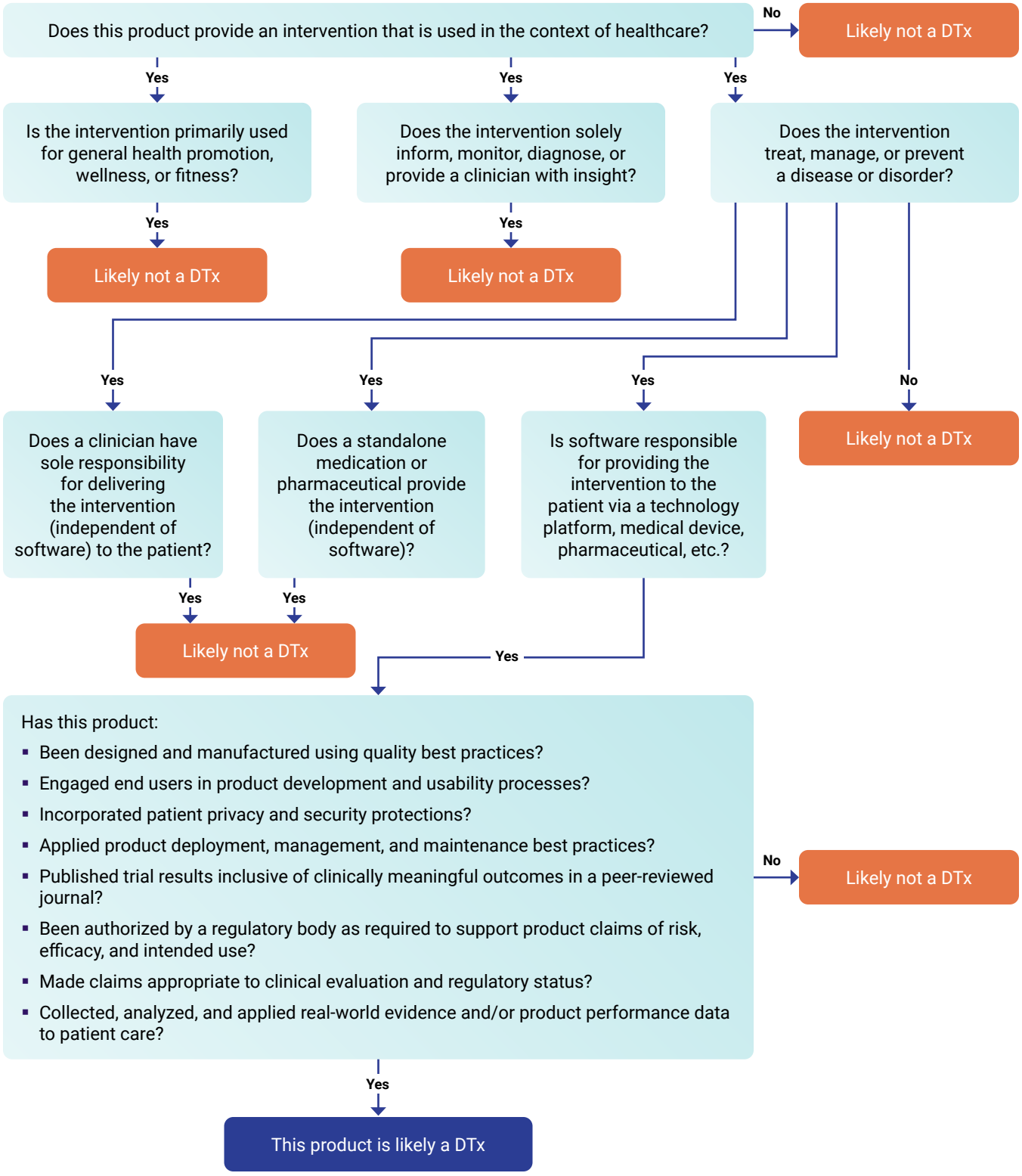
Even though this Guide focuses on digital therapeutics—products that deliver clinical interventions directly to patients via software to treat, manage, or prevent a disease or disorder—DTx products may also integrate a variety of other digital capabilities into their product offerings, such as wearables and biometric sensors, diagnostic capabilities, the delivery of health information to patients, and clinical decision support features for clinicians.

As clinicians, healthcare systems, employers, and payors continue integrating these products into patient care, digital therapeutics will increasingly influence the delivery and consumption of healthcare globally.

Is This Product a DTx?

Given the proliferation of products available to patients, caregivers, and clinicians for use in healthcare, it can be difficult for end users to determine which products are digital therapeutics vs. other types of DHTs.

This flow chart helps HCDMs and end users understand which products qualify as a digital therapeutic and therefore are best suited to be evaluated using this Guide.



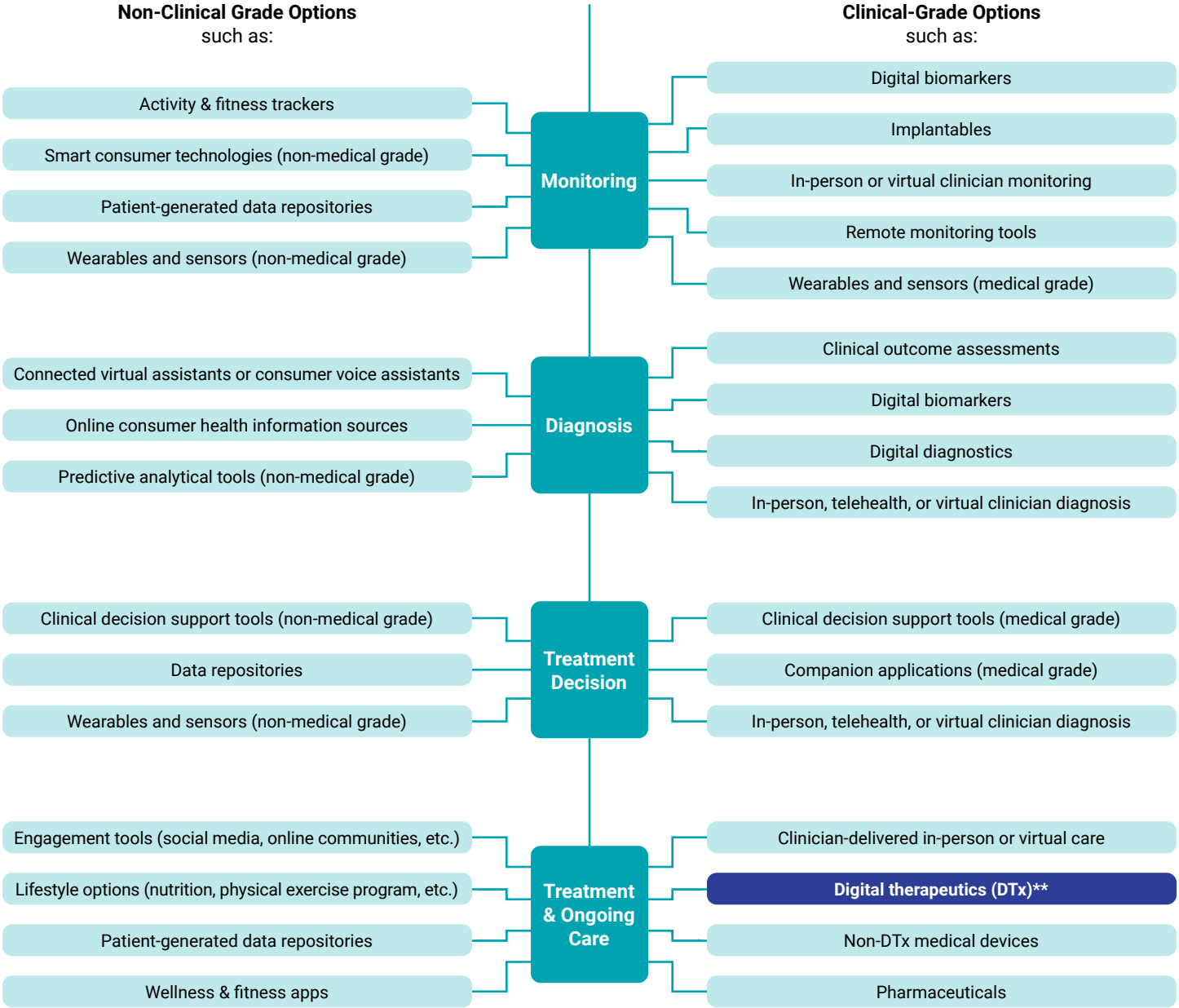
Where Do Digital Therapeutics Fit into Healthcare?

Digital therapeutics play an important role in the healthcare ecosystem alongside clinician-delivered care, pharmaceuticals, and other non-DTx medical devices.

The following overview lists various types of interventions available for patient monitoring, diagnosis, treatment decisions, and ongoing care. This non-comprehensive diagram provides a snapshot of a complex ecosystem and will continue to evolve as new offerings are made available to patients, caregivers, and clinicians.

PATIENT NEED ARISES DUE TO A SPECIFIC DISEASE OR DISORDER

Care options may include:*



Categorizations of the healthcare ecosystem will continue to evolve. This is a select representation of a broad, diverse ecosystem.
***As described on page 9, DTx products may also integrate a variety of other digital capabilities into their product offerings.*

DTx Manufacturer Submission Packet

DTx Manufacturer Contact Information & Attestation

DTx Manufacturer Contact Information

Company:

Address line 1:

Address line 2:

Address line 3:

Primary contact:

Email:

Phone:

Preferred method of contact:

DTx Product Information

Product name:

Product website:

Brief product description:

DTx Manufacturer Attestation

Date of submission:

Name of submitter:

☐ All information provided in this Guide is accurate to the best of my knowledge.

Checklist for DTx Manufacturers

In submitting this Guide to a HCDM, the DTx manufacturer indicates which steps are:

Step	Completed	Accompanied by supplementary information (i.e., clinical, health economic data)	Requires further authorization prior to submission (i.e., NDA)	Not currently applicable for this product
DTx Product Benchmark Questions	☐	☐	☐	☐
DTx Product Evaluation: Clinical Impact & Intended Use				
Step 1: DTx Product Basics	☐	☐	☐	☐
Step 2: Clinical Impact	☐	☐	☐	☐
Step 3: DTx Product Authorization and Distribution	☐	☐	☐	☐
Step 4: Patient-Facing Technical Considerations	☐	☐	☐	☐
Step 5: Product Usability	☐	☐	☐	☐
Step 6: Patient Centricity	☐	☐	☐	☐
Step 7: DTx Product Technical Considerations	☐	☐	☐	☐
Step 8: DTx Manufacturer Evaluation	☐	☐	☐	☐
DTx Product Evaluation: Regulatory & Security				
Step 9: Regulatory Oversight	☐	☐	☐	☐
Step 10: Security Best Practices	☐	☐	☐	☐
Step 11: Data Privacy and Governance	☐	☐	☐	☐
Step 12: Intellectual Property Considerations	☐	☐	☐	☐
DTx Product Evaluation: Clinical Evidence				
Step 13: DTx Product Evaluation Types	☐	☐	☐	☐
Step 14: Assessing Clinical Evidence Types	☐	☐	☐	☐

Step	Completed	Accompanied by supplementary information (i.e., clinical, health economic data)	Requires further authorization prior to submission (i.e., NDA)	Not currently applicable for this product
Step 15: Assessing Quality of Clinical Evidence	☐	☐	☐	☐
Step 16: Types of Real-World Data (RWD) Generated by DTx Products	☐	☐	☐	☐
Step 17: Utilizing DTx-Generated RWD	☐	☐	☐	☐
Step 18: Development and Impact of Real-World Evidence (RWE)	☐	☐	☐	☐
DTx Product Evaluation: Economic Assessment				
Step 19: Preparing for a DTx Economic Analysis	☐	☐	☐	☐
Step 20: Undertaking a Formal Economic Analysis	☐	☐	☐	☐
Step 21: Key Considerations for a DTx Economic Impact Evaluation	☐	☐	☐	☐
Step 22: Factors That Affect DTx Therapy Economic Impact	☐	☐	☐	☐
Step 23: Health Technology Assessment (HTA) Considerations	☐	☐	☐	☐
Implementing Digital Therapeutics in Practice				
Step 24: DTx Product Implementation and Engagement	☐	☐	☐	☐
Step 25: Determining Full-Scale Launch vs. an Implementation Pilot Study	☐	☐	☐	☐
Step 26: Clinical Team Engagement	☐	☐	☐	☐
Step 27: Payment Codes	☐	☐	☐	☐
Step 28: Ensuring Quality Data Sets	☐	☐	☐	☐
Step 29: Access to DTx Product Outcomes	☐	☐	☐	☐
Step 30: Product Integration	☐	☐	☐	☐

DTx Product Benchmark Questions

The following ten questions:

» Provide HCDMs with a high-level understanding of a DTx product's stage of development and real-world use

» Do not substitute for a full product evaluation, as outlined in the remainder of this Guide

» Enable HCDMs to more easily conduct a side-by-side comparison of multiple products

DTx manufacturers provide further insights related to these topics in subsequent steps of the Guide to provide HCDMs with a fuller understanding of the product's abilities and impact.

1. What is the DTx product's current stage of development?

- ☐ Product is in technical and pre-clinical development phase
- ☐ Product is in clinical development phase
- ☐ Product is undergoing regulatory review
- ☐ Product has met all necessary clinical and regulatory requirements in one or more jurisdictions

*Please see **Step 1** in the Guide for more detailed product evaluation criteria.*

2. What level of evidence has the product generated? *[select the most rigorous study design completed]*

- ☐ Product has completed one or more observational studies (i.e., real-world use)
- ☐ Product has completed a non-controlled experimental/interventional study (i.e., prospective single arm trial, open label trial, head-to-head comparative trial)
- ☐ Product has completed a non-randomized experimental/interventional study (i.e., non-randomized controlled trial, self-controlled study, crossover study)
- ☐ Product has completed one or more randomized controlled trials (RCTs)

*Please see **Step 13** in the Guide for more detailed product evaluation criteria.*

3. What is the product's clinical intended use?

- ☐ Product does not prevent, manage, or treat a disease or disorder (likely is not a DTx product)
- ☐ Product prevents a disease or disorder
- ☐ Product manages a disease or disorder
- ☐ Product treats a disease or disorder

*Please see **Step 2** in the Guide for more detailed product evaluation criteria.*

4. How is patient use of the product primarily authorized?

- ☐ Product access is provided to a patient without clinician, payor, employer, or third-party involvement
- ☐ Product access is provided via a clinically validated screening tool that patients use to determine qualification for therapy
- ☐ Product access is provided via an authorized clinical protocol that states criteria for automatic patient qualification
- ☐ Product access is provided via a non-prescription recommendation by a clinician, payor, employer, or other qualified entity
- ☐ Product access is provided via a formal prescription from a qualified clinician (in-person or virtually) or other qualified entity

*Please see **Step 3** in the Guide for more detailed product evaluation criteria.*

5. **What is the product's regulatory status in the target jurisdiction of use?**
   - ☐ Product has not determined its regulatory pathway yet
   - ☐ Product does not require regulatory review and is not required to list or register
   - ☐ Product does not require regulatory review, but is required to list or register and meets health authority requirements for software development
   - ☐ Product is undergoing regulatory and/or market authorization review
   - ☐ Product has completed regulatory review and received market authorization in at least one jurisdiction

   *Please see **Step 9** in the Guide for more detailed product evaluation criteria.*

6. **What is the product's current level of security?**
   - ☐ Product does not have an information security risk management and governance framework in place
   - ☐ Product has an information security risk management and governance framework in place
   - ☐ Product has self-attested cybersecurity credentials
   - ☐ Product actively holds a third-party security certification

   *Please see **Step 10** in the Guide for more detailed product evaluation criteria.*

7. **What is the product's current level of privacy?**
   - ☐ Product does not have a privacy protocol in place
   - ☐ Product provides end users with a privacy notice
   - ☐ Product enables end users to consent and authorize how data are stored, shared, saved, and used
   - ☐ Product fulfills the previous criteria and meets all national requirements for privacy (i.e., GDPR, HIPAA)

   *Please see **Step 11** in the Guide for more detailed product evaluation criteria.*

8. **What forms of economic assessment related to the target jurisdiction has the product undergone?**
   - ☐ Product has not undergone an economic analysis
   - ☐ Product has undergone a population- or setting-specific economic outcomes evaluation
   - ☐ Product has undergone an economic outcomes evaluation that accounts for multiple populations
   - ☐ Product has undergone a formal economic review process conducted by a third-party

   *Please see **Steps 19–23** in the Guide for more detailed product evaluation criteria.*

9. **What is the product's current stage of commercialization in the target jurisdiction of use?**
   - ☐ Product is not commercially available to patients
   - ☐ Product is available to select patients who are engaged in pre-market studies
   - ☐ Product is available to limited patient populations via pilot studies
   - ☐ Product is commercially available to patients

   *Please see **Step 1** in the Guide for more detailed product evaluation criteria.*

10. **What is the product's stage of reimbursement in this or other jurisdictions?**
    - ☐ Product is in pre-coverage phase
    - ☐ Product is undergoing initial coverage decision evaluations
    - ☐ Product is being paid for by patients and other end users
    - ☐ Product is covered by one or more payor entities

    *Please see **Step 1** in the Guide for more detailed product evaluation criteria.*

DTx Product Evaluation: Clinical Impact & Intended Use

Step 1: DTx Product Basics

Digital therapeutics provide patients with clinically validated, scalable disease treatment, management, and prevention options. The following questions provide HCDMs with a baseline framework to begin evaluating a digital therapeutic product.

Product Overview

Product name:

Target disease or disorder(s):

Intended use(s):

Target patient population(s):

Clinical issues addressed and/or gaps filled by product:

Product Use Considerations

Approved indication(s):

Directions for use:

Duration of therapy:

Dosing regimen:

Potential adverse events:

Risks or warnings:

Drug interaction(s):

Device interaction(s):

Check all that apply.

Intended environment of therapy delivery:

- ☐ Patient setting (i.e., home, work, school)
- ☐ Healthcare setting (i.e., clinic, hospital)
- ☐ Aged or disability residential care (i.e., nursing home, rehabilitation center)
- ☐ Other:

Intended environment of ongoing therapy use:

- ☐ Patient setting (i.e., home, work, school)
- ☐ Healthcare setting (i.e., clinic, hospital)
- ☐ Aged or disability residential care (i.e., nursing home, rehabilitation center)
- ☐ Other:

What stage of development is the product currently in?

- ☐ Technical and pre-clinical development phase
- ☐ Clinical development phase
- ☐ Product is undergoing initial regulatory review
- ☐ Product has cleared all necessary clinical and regulatory requirements in one or more jurisdictions
- ☐ Other:

Most recently released version of the DTx product:

In addition to the DTx product delivering a therapeutic intervention directly to a patient via software, the product also has the ability to:

- ☐ Monitor, predict, or react to the progression of a disease or disorder
- ☐ Deliver clinical insights (immediate or trends) to the patient and/or caregiver(s)
- ☐ Deliver actionable clinical insights to a clinician or HCDM
- ☐ Enable remote patient monitoring
- ☐ Collect patient-generated insights and outcomes
- ☐ Collect information on patient-reported outcomes (PROs), quality of life, etc.
- ☐ Assist in the diagnosis of a disease or disorder
- ☐ Monitor medication adherence/outcomes
- ☐ Track non-medication therapy adherence/outcomes
- ☐ Enable medication and/or overall therapy optimization
- ☐ Provide patient with general health insights
- ☐ Connect patient with a therapist or health coach
- ☐ Support meaningful interactions between a patient and clinician
- ☐ Other:

What is the product's current stage of commercialization in the target jurisdiction of use?

- ☐ Product is not commercially available to patients
- ☐ Product is available to select patients who are engaged in pre-market studies
- ☐ Product is available to limited patient populations via pilot studies
- ☐ Product is commercially available to patients
- ☐ Other:

What is the product's stage of reimbursement in this or other jurisdictions?

- ☐ Product is in pre-coverage phase
- ☐ Product is undergoing initial coverage decision evaluations
- ☐ Product is being paid for by patients and other end users
- ☐ Product is covered by one or more payor entities
- ☐ Other:

Step 2: Clinical Impact

DTx products provide patients, caregivers, and clinicians with new therapeutic options to support, improve, or replace the current standards of care for a wide range of diseases and disorders. For example, in certain care pathways, medications have long been the only therapeutic option available to patients. However, with the introduction of digital therapeutics, patients now have the opportunity to benefit from therapies that use software in addition to chemical or person-driven interventions to achieve their therapeutic goals.

Check all that apply.

To directly impact patient needs and clinical outcomes, this product:

- ☐ Provides a clinically validated therapeutic option for a disease or disorder (i.e., further optimizes therapy, addresses an unmet or under-addressed patient need)
- ☐ Delivers a personalized therapeutic intervention (i.e., intervention based on patients' needs, tailored to patient outcomes and abilities)
- ☐ Improves patient outcomes (i.e., increased cognitive performance, lower risk of cardiometabolic complications, reduced disease state comorbidities)
- ☐ Consistently demonstrates beneficial clinical outcomes (i.e., clinical trials, RWD, real-world evidence [RWE])
- ☐ Provides the patient with real-time results and insights (i.e., clinical outcomes, progress on personalized goals)
- ☐ Improves the patient experience (i.e., increased utilization, engagement, acceptance, enjoyment)
- ☐ Enables the analysis of patient- and population-level health outcomes (i.e., patient-specific outcomes, subpopulation analyses, population health trends)
- ☐ Makes therapies more accessible and scalable to patients (i.e., provided remotely, reaches underserved populations)

Types of clinical measures the DTx product uses:

DTx product's relationship to other therapies:

- ☐ DTx intervention is a standalone therapy
- ☐ DTx intervention indirectly supports another therapy:
- ☐ DTx intervention directly supports a concurrent treatment:
- ☐ DTx intervention complements a clinician-delivered therapy:
- ☐ DTx intervention can replace an existing therapy:
- ☐ Co-prescribed and/or concomitant therapies:
- ☐ Other:

Does the DTx have a comparator therapy?

- ☐ No
- ☐ Yes:

How does the DTx therapy relate to the current standard of care?

- ☐ There is no current standard of care for this condition
- ☐ DTx therapy supports current standard of care
- ☐ DTx therapy improves standard of care
- ☐ DTx therapy replaces standard of care
- ☐ Other:

How does the intervention align with evidence-based clinical guidelines?

- ☐ DTx therapy approach is reflected in an evidence-based clinical guideline(s):
- ☐ DTx therapy (i.e., product name) is specifically included in an evidence-based clinical guideline(s):
- ☐ DTx therapy is not currently represented in clinical guidelines:
- ☐ Other:

The following data sets may be used to determine patient progress in therapy:

- ☐ DTx-generated data (i.e., real-world outcomes, therapy trends)
- ☐ Standardized patient assessments (i.e., GAD-7, PHQ-9, PSS)
- ☐ Patient-reported outcomes (i.e., validated outcome measures, disease state triggers, pain perception)
- ☐ Therapy status (i.e., duration, stage, progression of therapy)
- ☐ Other:

Step 3: DTx Product Authorization and Distribution

Because DTx deliver clinical interventions to patients for a specific disease or disorder, these products should be used by the right patient, at the right time, and for the right purpose. As such, DTx products typically undergo some form of an authorization process prior to patient use to ensure that each therapy is used appropriately.

Check all that apply.

Product Authorization

Patient access to the product may be provided via:

- ☐ Formal prescription from a qualified clinician (in-person or virtual engagement)
- ☐ Clinician referral for a non-prescription DTx product (in-person or virtual engagement)
- ☐ Direct authorization by an employer for a non-prescription DTx product
- ☐ Direct authorization by a payor for a non-prescription DTx product
- ☐ "Authorized clinical protocol" established by a HCDM to authorize automatic patient access when necessary qualification requirements are met
- ☐ "Clinically validated screening tool" that patients use to determine whether they qualify for the therapy
- ☐ "Over-the-counter" model where no form of third-party authorization is necessary
- ☐ Other:

Ability and/or necessity of DTx therapy to be reauthorized or terminated following the first use cycle:

Product Distribution

Patients may access or download the DTx product shell (without access to the product's content until a patient-specific authorization code is used):

- ☐ On the following online app stores:
- ☐ On a dedicated device:
- ☐ Other:

Patients receive a product access code following authorization of a non-prescription or prescription product—and any necessary product components (i.e., hardware, wearables)—via:

- ☐ Remote delivery via SMS or email
- ☐ Remote delivery via mail
- ☐ In-person delivery at a clinic or hospital
- ☐ In-person delivery at a pharmacy
- ☐ Other:

Entities involved in product distribution may include:

- ☐ DTx product support center
- ☐ Clinician and/or clinical team
- ☐ Virtual health coach or provider
- ☐ Telehealth provider
- ☐ Pharmacy
- ☐ HCDM
- ☐ Other:

When appropriate, following the use of DTx hardware product components (i.e., sensors, wearables), these are:

- ☐ Retained by the patient
- ☐ Returned to the DTx manufacturer
- ☐ Other:

Commentary: This framework provides a high-level overview of the DTx product's ability to be authorized and/or reauthorized by HCDMs. DTx products may either be incorporated into traditional healthcare distribution processes or enable novel methods of therapy authorization and distribution.

Step 4: Patient-Facing Technical Considerations

DTx are software-based and can be hosted on multi-purpose or dedicated hardware platforms. DTx products may be used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes.

Check all that apply.

What component(s) are required for the software to deliver its therapeutic value?

- ☐ Multi-purpose computing device (i.e., smartphone, tablet, computer, virtual reality [VR] headset)
- ☐ Dedicated computing device (i.e., delivery device is specific to the DTx therapy)
- ☐ Hardware (i.e., wearable, sensor, scale)
- ☐ Medication
- ☐ Service (i.e., virtual or in-person care)
- ☐ Other:

DTx product may be used on the following host technology(ies):

- ☐ Smartphone
- ☐ Tablet
- ☐ Laptop or desktop computer
- ☐ Headset
- ☐ Wearable (i.e., smartwatch)
- ☐ Medical device
- ☐ Other:

Hardware components that may be required for, or to enhance, product use:

- ☐ Hardware or affiliated medical device; specifically:
- ☐ Wearable or sensor; specifically:
- ☐ Other:

Hardware components may be:

- ☐ Patient-owned; specifically:
- ☐ Provided to the patient; specifically:

Level of network connection required for product use:

- ☐ Does not require a sustained network connection (offline-capable)
- ☐ Requires ongoing basic network connection
- ☐ Requires ongoing broadband or high data connection
- ☐ Other:

Product software is compatible with:

- ☐ iOS
- ☐ Android
- ☐ Web
- ☐ Other:

Form(s) of technical assistance available to patients and clinicians:

- ☐ In-product support
- ☐ Product demonstrations, videos, on-demand content
- ☐ Dedicated product website (+/- chat functionality)
- ☐ Phone service line
- ☐ Virtual or video "in home" support
- ☐ Clinic or pharmacy in-person support
- ☐ Other:

Commentary: DTx products have varying levels of technical requirements depending on the disease state being addressed and the type of intervention delivered to the patient. Understanding the product's technical requirements will assist HCDMs and IT teams in enabling optimal use of the DTx therapy.

Step 5: Product Usability

Product appropriateness and usability are critical to ensuring that the DTx product's full therapeutic value is delivered to the patient. The following considerations can help HCDMs determine which end users may benefit from the specific DTx therapy. Correctly identifying patient populations who will benefit from a DTx therapy and ensuring that all necessary technical requirements are accounted for will increase the likelihood of successful clinical outcomes and reduce unnecessary costs.

Check all that apply.

DTx product accounts for the following:

- ☐ Language(s):
- ☐ Health literacy levels:
- ☐ Digital health literacy levels:
- ☐ Cultural considerations:
- ☐ Disability considerations:
- ☐ Special patient circumstances, abilities, and needs:
- ☐ Patient age considerations:
- ☐ Other:

Product Usability

DTx product includes the following:

- ☐ End user-centric design (i.e., understandable user interface and display)
- ☐ Patient-centric instructions (i.e., directions, time commitment)
- ☐ Clearly identified patient and clinician product access points (i.e., initial, ongoing)
- ☐ Technical considerations (i.e., hardware interoperability, battery drain)
- ☐ End user usability testing
- ☐ Other:

Patient Protection

DTx product includes the following:

- ☐ Product provides necessary device and information security [further insight provided in Step 10]
- ☐ Patient data is protected [further insight provided in Step 11]
- ☐ Other:

End User Support

DTx product includes the following:

- ☐ Reliable and consistent product performance
- ☐ End user-centric technical support (i.e., FAQs, call center, virtual, in-person)
- ☐ Regular software updates for ongoing user friendliness and patient applicability
- ☐ Other:

Product Design Process

DTx product includes the following:

- ☐ Human factors testing, physiological tracking methods
- ☐ Qualitative research (i.e., focus groups, observational sessions, user interviews)
- ☐ Other:

Step 6: Patient Centricity

Digital therapeutics exist for the benefit of patients and other end users. As such, they need to be designed to meet patient needs, address current gaps in care, and improve health outcomes. Given the diversity of patient experiences and needs, the following considerations provide HCDMs with a guide to optimize product appropriateness:

Check all that apply.

To use this product appropriately, individual patients should:

- ☐ Have access to host technologies (i.e., smartphone, tablet, headset)
- ☐ Have access to related product components (i.e., hardware, sensors, medications, in-person therapy)
- ☐ Have access to WiFi or cellular internet (i.e., sustained or intermittent connection, broadband)
- ☐ Display a sufficient level of literacy, digital health literacy, numeracy
- ☐ Be informed of available cost-sharing or product coverage options
- ☐ Other:

Patient financial considerations for this product include (varies by use setting, payor):

- ☐ This product may be fully covered by a health plan, in-network provider, payor, or employer, with no patient cost
- ☐ This product may be partially covered, with some patient out-of-pocket costs (i.e., deductible, co-insurance)
- ☐ This product may be patient-covered, with no third-party coverage
- ☐ Other:

Typical patient costs for this product may be:

This product may provide patients with the following clinical benefits:

- ☐ Reliable insights and resources as patients manage and navigate their care
- ☐ New treatment modality for patients if other therapy options are insufficient, inappropriate, or already exhausted
- ☐ Equitable access to high-quality therapies through the product's ability to scale
- ☐ Delivery of reliable clinical insights to relevant clinical care teams
- ☐ Other:

This product may provide patients with the following environmental and social benefits:

- ☐ Expanding patients' ability to receive active clinical care in and beyond traditional settings (i.e., in-home settings, asynchronous care, remote/digital care)
- ☐ Providing novel therapy options for patients in underserved settings (i.e., low-income, rural, urban settings)
- ☐ Providing technical support services for patients, caregivers, and other end users (i.e., in-product support, product support center, multilingual support)
- ☐ Addressing existing disparities (i.e., social determinants of health, accessibility, socioeconomic status)
- ☐ Other:

Additional consumer friction points this product may address include:

- ☐
- ☐

Step 7: DTx Product Technical Considerations

Digital therapeutics are recognized as medical devices and therefore are subject to a variety of internationally recognized standards, national, and local regulations. Understanding the product's technical requirements will assist HCDMs and IT teams in enabling optimal use of the DTx therapy.

Check all that apply.

Technical Considerations

DTx product typically functions:

- ☐ As a standalone product
- ☐ With built-in capacity to integrate data streams and outputs with other products
- ☐ As part of a multi-product platform
- ☐ Other:

To generate therapeutic interventions, the product uses:

- ☐ Static algorithms
- ☐ Artificial Intelligence (AI) functionalities
- ☐ Machine Learning (ML) functionalities
- ☐ Other:

DTx manufacturer has taken the following steps to prevent biases in therapeutic algorithms:

Product has notification, recovery, and resolution plans in the event of a(n):

- ☐ Software malfunction
- ☐ Hardware malfunction
- ☐ Integration malfunction
- ☐ Affiliated product malfunction
- ☐ Other:

Data Infrastructure and Storage

The following entities are typically responsible for:

- Data storage/hosting:
- Data access:
- Data ownership:
- Data upkeep/deletion:
- Other:

Typical frequency of:

- Software patches:
- Operating system updates:
- Cybersecurity improvements:
- Other:

Measures tracked for DTx product uptime availability:

Measures tracked for DTx product reliability:

Data storage is hosted on:

- ☐ Private cloud, in the following country(ies):
- ☐ Public cloud, in the following country(ies):
- ☐ Hybrid cloud, in the following country(ies):
- ☐ Multicloud, in the following country(ies):
- ☐ Other:

Step 8: DTx Manufacturer Evaluation

Equally important to ensuring DTx product quality is the confidence HCDMs must have in the manufacturers that develop and support each product. The following criteria provide HCDMs with a high-level overview of a manufacturer's reliability, governance, and services.

Check all that apply.

What is the company's approach to ensuring product quality?

The manufacturer:

- ☐ Ensures safe, effective, and secure products during all life cycle phases
- ☐ Uses good development practices that incorporate appropriate review activities such as code review, peer review, and self-review
- ☐ Conducts verification and validation processes to ensure conformity to requirements and confidence the software meets its intended use, user needs, and operational requirements
- ☐ Other:

Will the company have the ability to launch, scale, and maintain this product long-term?

The manufacturer:

- ☐ Has a history of strong internal leadership and organization tenure
- ☐ Is well-managed across key pillars
- ☐ Openly shares relevant information with stakeholders to build confidence in the organization and its products
- ☐ Has the appropriate resources necessary to ensure effectiveness across all life cycle processes and activities in meeting user requirements
- ☐ Demonstrates the ability to meet the scale required with a reproducible impact
- ☐ Possesses the ability to enable smooth product rollouts and provide ongoing maintenance
- ☐ Prioritizes a patient safety focus to monitor and manage risks
- ☐ Other:

How does the company approach data generation and management?

The manufacturer:

- ☐ Optimizes product use through real-world performance monitoring
- ☐ Provides patients with clear and concise information related to data access and use
- ☐ Protects and stores data according to local, national, and regional requirements
- ☐ Other:

How will the company support customers?

The manufacturer:

- Provides customer support services (i.e., health systems, employers, clinicians, patients)
- Has a history of pursuing partnerships with relevant stakeholders
- Demonstrated success with previous product lines, launches, or pre-market pilots
- Other:

Commentary: Companies that develop and manufacture DTx products must be dedicated to scientific, rigorous product development and maintenance processes that undergo clinical evaluations and are subject to regulatory oversight. These factors enable increased product trustworthiness and integrity.

DTx Product Evaluation: Regulatory & Security

Step 9: Regulatory Oversight

Digital therapeutics are reviewed and cleared by regulatory bodies as required to support product claims of risk, efficacy, and intended use. Regulatory bodies in different regions and jurisdictions may set forth different levels of regulatory and market authorization requirements for DTx based on the product's intended use and level of risk. DTx manufacturers are required to comply with all local, national, and regional regulatory frameworks and sets of requirements.

Check all that apply.

What form(s) of regulatory oversight does the product require?

☐ Product has completed regulatory reviews and/or received market authorization in:

	Regulatory Status #1	Regulatory Status #2	Regulatory Status #3
Jurisdiction (country or region)			
Regulatory or notified body			
Clearance, certification, or approval date			
Regulatory class* (product classification)			
Product indication			
Other regulatory designations, etc.			

* Regulatory classifications and definitions may differ between regions.

- [ ] Product is undergoing regulatory and/or market authorization review in the following jurisdiction(s) (including responsible oversight or notified body):

1.
2.
3.

- [ ] Product does not require regulatory review and is marketed in the following jurisdiction(s):

1.
2.
3.

- [ ] Product has not officially submitted for review in a regulatory jurisdiction yet
- [ ] Other:

Step 10: Security Best Practices

Digital therapeutics must comply with a variety of international and national security standards. DTx manufacturers and products that adhere to appropriate regulations and laws generally reduce the risk of security breaches, clinician and patient mistrust, and compromised electronic health data.

Check all that apply.

Does the manufacturer have an information security risk management and governance framework in place to account for information security controls, risk management, etc.?

- ☐ Yes, it is validated at the organization level
- ☐ Yes, it is validated at the product level
- ☐ The process is in progress
- ☐ No
- ☐ Other:

What cybersecurity certifications and/or accreditations does this manufacturer and/or product maintain?

- ☐ ISO/IEC 27001 (Third-party auditor):
- ☐ HITRUST (Number):
- ☐ SOC 2 (Number):
- ☐ Other:

The product has cybersecurity credentials that are: ☐ Self-attested ☐ Externally certified ☐ Neither

Is the scope of the certified company and/or product components appropriate to their purpose?

How does the DTx product verify:

Patient authentication (methods to ensure the appropriate patient is accessing the therapy):

Patient authorization (methods to determine if the patient has permission to use the therapy):

Encryption (methods to ensure data are unreadable by unauthorized individuals):

Data access (methods to ensure the appropriate individuals have access to product-generated data):

Therapy access (methods to ensure the appropriate individuals have access to product content and interventions in case of failed login/authentication):

Is a protocol in place to address a data breach or other privacy/data security crisis?

Does the manufacturer engage in vulnerability testing?

What other measures does the manufacturer use to ensure security?

Commentary: It is usually not necessary for DTx products to achieve more than a single cybersecurity certification to demonstrate alignment with security best practices. DTx products are also subject to country, region, or product-specific requirements, many of which may not be represented here.

Step 11: Data Privacy and Governance

Patient privacy, governance, and consent processes are critical to the use, trustworthiness, and safety of DTx products. Digital therapeutics must comply with all applicable regional and local electronic Protected Health Information (PHI) and sensitive data regulations.

Check all that apply.

DTx product provides end user with a privacy notice that describes:

- ☐ How the organization collects, uses, and retains end user data
- ☐ Types of data the product obtains
- ☐ Data protection mechanisms
- ☐ Length of data retention
- ☐ How and by whom information is used
- ☐ How relevant data are shared
- ☐ Enables patient opt-out, retraction of data, and/or revocation of consent
- ☐ Other:

Patient is able to consent and authorize how personal digital health data are:

- ☐ Stored
- ☐ Shared
- ☐ Saved
- ☐ Incorporated in digital health records
- ☐ Other:

What types of personally identifiable and sensitive data does the product gather?

What internal company policies and procedures determine how information is collected, protected, and used?

Data are/may be stored on a:

- ☐ Public cloud
- ☐ Private cloud
- ☐ Dedicated server
- ☐ Other:

Data are/may be stored in the following geographic location(s):

Does the product include insurance liability coverage?

- ☐ Yes
- ☐ No
- ☐ Other:

Other entities involved in DTx product deployment processes, particularly where patient data might be accessible, are held to same standards as the DTx manufacturer:

- ☐ Yes
- ☐ No
- ☐ Other:

Policies that govern third-party access and utilization of data:

The following types of data may be shared from the DTx product with third-parties:

DTx manufacturer procedures in case of a potential data privacy breach include:

Step 12: Intellectual Property Considerations

Although digital therapeutics are not traditionally granted market exclusivity, they are typically protected through a variety of pathways, including:

» **Patents:** Exclusive right and protection granted for an invention for a limited period. Patent protected products cannot be commercially made, used, distributed, or sold without the patent owner's consent. Products, designs, and methods that potentially infringe on and violate protected patents risk legal action.

» **Trademarks:** Trademark protection ensures that the owners of marks have the exclusive right to use them to identify goods or services, or to authorize others to use them in return for payment. The period of protection varies, but a trademark can be renewed indefinitely upon payment of the corresponding fees.

» **Copyrights:** Copyright laws grant authors, artists, and other creators protection for their literary and artistic creations.

» **Licensing agreements:** Agreement that is executed between two or more private parties.

Check all that apply.

This DTx product is protected by:

- ☐ Patent(s)
- ☐ Trademark(s)
- ☐ Copyright(s)
- ☐ Licensing agreement(s)
- ☐ Other:

Does this product require permissions prior to system use? ☐ Yes ☐ No

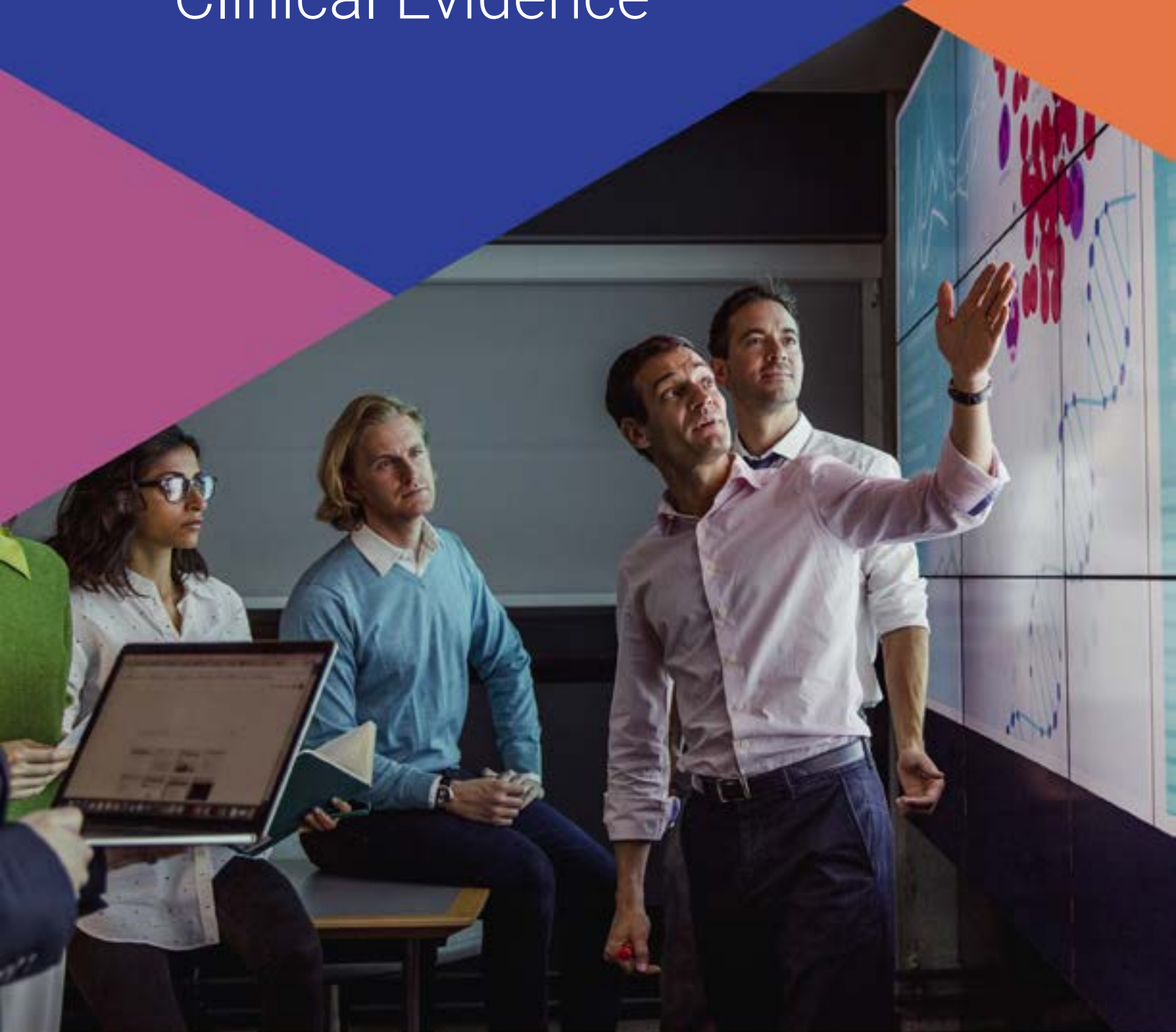
If yes:

Does this DTx product require a setting-specific licensing agreement to be used? ☐ Yes ☐ No

If yes, what types of considerations may be included in the licensing agreement?

- ☐ Product modifications
- ☐ White labeling opportunities
- ☐ Data access permissions
- ☐ Other:

DTx Product Evaluation: Clinical Evidence



Step 13: DTx Product Evaluation Types

Digital therapeutics undergo multiple evaluations throughout the product life cycle. These clinical and economic studies are used in the evaluation of product safety, effectiveness, real-world use, implementation, value assessment, and therapy optimization. In general:

» **Regulatory oversight:** Clinical pre-market evaluations are generally required to secure regulatory clearance and/or CE marking.

» **Coverage and reimbursement:** Clinical trials and economic evaluations are generally required for initial payor assessments.

» **Clinical practice:** Clinical trials and RWD are generally used to determine direct patient care and clinician decision making.

» **Clinical guidelines:** Clinical trials and RWE are generally used for DTx product incorporation into clinical guidelines.

The following overview provides the types of evaluations that a DTx product have undergone. HCDMs should conduct a thorough review of study design, outcomes, and quality of evidence.

Number completed	Number In progress	
		Experimental/Interventional Clinical Trials
		Randomized Controlled Trial (RCT)
		Other controlled trials: Non-randomized controlled trial, self-controlled study, crossover study
		Non-controlled studies: Prospective single arm trial, open label trial, head-to-head comparative trial
		Other:
		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.
		Other:

Number completed	Number In progress	
		Real-World Outcomes
		RWD generation:
		Product performance and technical outputs
		End user and clinician engagement and satisfaction measures
		Other:
		RWE generation:
		Pragmatic clinical trial using an RCT-type design, with real-world elements
		RWE as a retrospective or prospective observational study
		Other:
		Product Analyses
		Retrospective analyses: chart reviews, medical/pharmacy claims, electronic medical records, other novel data sources
		Expert reviews: clinical practice guidelines, clinical pathways, HTA agency evaluations, published systematic reviews
		Coverage decision assessments and formulary reviews: external organization product evaluations, product indication reviews
		Patient perspectives: insight into the practical use of therapies
		Other:
		Economic Evaluation
		Budget impact analysis
		Cost-benefit analysis
		Cost-effectiveness analysis

Number completed	Number In progress	
		Cost-utility analysis
		Cost-minimization analysis
		Other:
		Systematic Review
		Meta analysis
		Other:

Step 14: Assessing Clinical Evidence Types

Digital therapeutics undergo clinical evaluations to assess product safety and clinical efficacy. Outcomes may also be used to determine therapy effectiveness, how the therapy should be used in target settings, length of therapy duration, the types of patients who may benefit, and appropriate use in clinical practice. Strong outcomes in studies often correlate to higher performing, lower risk products; reliable clinical outcomes and performance; and increased overall value of investment.

In this DTx Manufacturer Submission Packet version, three copies of the clinical evidence study reviews are included.

Check all that apply.

Study Basics (First Study)

Study name:

Publication name and citation:

Trial registry number:

Was the study protocol modified after registering in clinicaltrials.gov or a similar registry? ☐ Yes ☐ No

If yes, describe how:

Study status:

- ☐ Study is currently underway
- ☐ Study is completed, but not published
- ☐ Study is completed and published
- ☐ Study forms the basis for regulatory clearance, CE marking, and/or product marketing claims
- ☐ Other:

Study partners (i.e., university, CRO):

Sponsor or funding source(s):

Has this study been peer-reviewed? ☐ Yes ☐ No ☐ Undergoing peer-review process

Study Design

Clinical study design used:

- ☐ RCT
- ☐ Non-randomized controlled trial
- ☐ Prospective, single arm trial
- ☐ Cohort study
- ☐ Case-control study
- ☐ Case study
- ☐ Pragmatic clinical trial
- ☐ RWE
- ☐ Other:

Study start and completion dates:

Study setting(s) and geographic location(s):

Trial design, randomization, and blinding procedures:

Study Population

Target population and subgroups:

Inclusion criteria:

Exclusion criteria:

Baseline patient characteristics and demographics:

Study population is representative of:

- ☐ General population
- ☐ Target population
- ☐ Other:

To mitigate bias, datasets are balanced across:

- ☐ Gender
- ☐ Ethnicity
- ☐ Age
- ☐ Other:

Clinical Outcomes

Key findings of the study:

Primary endpoint:

Secondary endpoints:

Comparator used:

Treatment and intervention used, dosing regimen:

Concomitant therapies, washout period:

Study Basics (Second Study)

Study name:

Publication name and citation:

Trial registry number:

Was the study protocol modified after registering in clinicaltrials.gov or a similar registry? ☐ Yes ☐ No

If yes, describe how:

Study status:

- ☐ Study is currently underway
- ☐ Study is completed, but not published
- ☐ Study is completed and published
- ☐ Study forms the basis for regulatory clearance, CE marking, and/or product marketing claims
- ☐ Other:

Study partners (i.e., university, CRO):

Sponsor or funding source(s):

Has this study been peer-reviewed? ☐ Yes ☐ No ☐ Undergoing peer-review process

Study Design

Clinical study design used:

- ☐ RCT
- ☐ Non-randomized controlled trial
- ☐ Prospective, single arm trial
- ☐ Cohort study
- ☐ Case-control study
- ☐ Case study
- ☐ Pragmatic clinical trial
- ☐ RWE
- ☐ Other:

Study start and completion dates:

Study setting(s) and geographic location(s):

Trial design, randomization, and blinding procedures:

Study Population

Target population and subgroups:

Inclusion criteria:

Exclusion criteria:

Baseline patient characteristics and demographics:

Study population is representative of:

- ☐ General population
- ☐ Target population
- ☐ Other:

To mitigate bias, datasets are balanced across:

- ☐ Gender
- ☐ Ethnicity
- ☐ Age
- ☐ Other:

Clinical Outcomes

Key findings of the study:

Primary endpoint:

Secondary endpoints:

Comparator used:

Treatment and intervention used, dosing regimen:

Concomitant therapies, washout period:

Study Basics (Third Study)

Study name:

Publication name and citation:

Trial registry number:

Was the study protocol modified after registering in clinicaltrials.gov or a similar registry? ☐ Yes ☐ No

If yes, describe how:

Study status:

- ☐ Study is currently underway
- ☐ Study is completed, but not published
- ☐ Study is completed and published
- ☐ Study forms the basis for regulatory clearance, CE marking, and/or product marketing claims
- ☐ Other:

Study partners (i.e., university, CRO):

Sponsor or funding source(s):

Has this study been peer-reviewed? ☐ Yes ☐ No ☐ Undergoing peer-review process

Study Design

Clinical study design used:

- ☐ RCT
- ☐ Non-randomized controlled trial
- ☐ Prospective, single arm trial
- ☐ Cohort study
- ☐ Case-control study
- ☐ Case study
- ☐ Pragmatic clinical trial
- ☐ RWE
- ☐ Other:

Study start and completion dates:

Study setting(s) and geographic location(s):

Trial design, randomization, and blinding procedures:

Study Population

Target population and subgroups:

Inclusion criteria:

Exclusion criteria:

Baseline patient characteristics and demographics:

Study population is representative of:

- ☐ General population
- ☐ Target population
- ☐ Other:

To mitigate bias, datasets are balanced across:

- ☐ Gender
- ☐ Ethnicity
- ☐ Age
- ☐ Other:

Clinical Outcomes

Key findings of the study:

Primary endpoint:

Secondary endpoints:

Comparator used:

Treatment and intervention used, dosing regimen:

Concomitant therapies, washout period:

Step 15: Assessing Quality of Clinical Evidence

Given the importance of clinical evidence in determining a DTx's clinical impact at the patient and population levels, HCDMs are encouraged to evaluate the quality of each study being submitted as part of the product's dossier.

Therefore, DTx manufacturers are asked to provide the following criteria based upon the tenets of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework per submitted clinical study.[1]

In this DTx Manufacturer Submission Packet version, three copies of the clinical evidence quality assessment reviews are included.

Check all that apply.

This Study Accounts for the Following Considerations (First Study):

Risk of bias

- ☐ Potential limitations in the design or conduct of the study identified
- ☐ Conflicts of interest among study contributors identified
- ☐ Other:

Imprecision

- ☐ Study outcomes are inside of the 95% confidence interval
- ☐ The "n" is appropriate (i.e., a sample size that is powered appropriately for intended outcomes)
- ☐ Study analysis accounts for patient populations who have enrolled in the product, in addition to those who have been included in the study but declined participation
- ☐ Analytic methods address potential skewed, missing, or censored data; approaches to study adjustments; or population heterogeneity and uncertainty
- ☐ Other:

Inconsistency

- ☐ Multiple studies suggest similar clinical outcomes and have consistent confidence intervals
- ☐ Similarity between statistical and clinical significance relative to sample size
- ☐ Large magnitude of effect
- ☐ Other:

[1] https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/

Indirectness

- ☐ Patients studied are similar to those for whom the clinical recommendation applies
- ☐ Interventions studied reflect actual practice
- ☐ Outcome studied is a surrogate for the appropriate outcome
- ☐ Other:

Publication bias

- ☐ Potential holes in evidence are accounted for
- ☐ Outcomes are generated from experimental/interventional data
- ☐ Published studies underwent a peer-review process
- ☐ Other:

This Study Accounts for the Following Considerations (Second Study):

Risk of bias

- ☐ Potential limitations in the design or conduct of the study identified
- ☐ Conflicts of interest among study contributors identified
- ☐ Other:

Imprecision

- ☐ Study outcomes are inside of the 95% confidence interval
- ☐ The "n" is appropriate (i.e., a sample size that is powered appropriately for intended outcomes)
- ☐ Study analysis accounts for patient populations who have enrolled in the product, in addition to those who have been included in the study but declined participation
- ☐ Analytic methods address potential skewed, missing, or censored data; approaches to study adjustments; or population heterogeneity and uncertainty
- ☐ Other:

Inconsistency

- ☐ Multiple studies suggest similar clinical outcomes and have consistent confidence intervals
- ☐ Similarity between statistical and clinical significance relative to sample size
- ☐ Large magnitude of effect
- ☐ Other:

Indirectness

- ☐ Patients studied are similar to those for whom the clinical recommendation applies
- ☐ Interventions studied reflect actual practice
- ☐ Outcome studied is a surrogate for the appropriate outcome
- ☐ Other:

Publication bias

- ☐ Potential holes in evidence are accounted for
- ☐ Outcomes are generated from experimental/interventional data
- ☐ Published studies underwent a peer-review process
- ☐ Other:

This Study Accounts for the Following Considerations (Third Study):

Risk of bias

- ☐ Potential limitations in the design or conduct of the study identified
- ☐ Conflicts of interest among study contributors identified
- ☐ Other:

Imprecision

- ☐ Study outcomes are inside of the 95% confidence interval
- ☐ The "n" is appropriate (i.e., a sample size that is powered appropriately for intended outcomes)
- ☐ Study analysis accounts for patient populations who have enrolled in the product, in addition to those who have been included in the study but declined participation
- ☐ Analytic methods address potential skewed, missing, or censored data; approaches to study adjustments; or population heterogeneity and uncertainty
- ☐ Other:

Inconsistency

- ☐ Multiple studies suggest similar clinical outcomes and have consistent confidence intervals
- ☐ Similarity between statistical and clinical significance relative to sample size
- ☐ Large magnitude of effect
- ☐ Other:

Indirectness

- ☐ Patients studied are similar to those for whom the clinical recommendation applies
- ☐ Interventions studied reflect actual practice
- ☐ Outcome studied is a surrogate for the appropriate outcome
- ☐ Other:

Publication bias

- ☐ Potential holes in evidence are accounted for
- ☐ Outcomes are generated from experimental/interventional data
- ☐ Published studies underwent a peer-review process
- ☐ Other:

Step 16: Types of Real-World Data (RWD) Generated by DTx Products

Through their ongoing use in patient care settings, DTx products generate a wide variety of RWD and outcomes that:

» Are made available to patients, caregivers, clinicians, and payors in line with patient privacy protections

» Form the foundation of decisions by clinicians and clinical teams

» Directly factor into RWE and economic analyses

With increasing frequency, DTx-generated outcomes and measures are replacing or supplementing outcomes generated through non-digital methods.

Check all that apply.

Digital therapeutics generate one or more types of RWD, outcomes, and insights depending on the product's purpose and functionality. Although this list is not comprehensive and will evolve, examples of RWD this product is able to produce include:

Clinical Measures

- ☐ Clinical outcomes (i.e., respiratory control, mobility, mental health status, FIM scores)
- ☐ State of medical condition (i.e., disease state severity, comorbidities)
- ☐ Digital endpoints (i.e., measures not previously available or assessed)
- ☐ Digital biomarkers (i.e., walking gait, joint mobility)
- ☐ Standardized patient assessments (i.e., GAD-7, PHQ-9, PSS)
- ☐ Patient-reported outcomes (PROs) (i.e., validated outcome measures, disease state triggers, pain perception)
- ☐ Physiologic data via associated sensors and hardware (i.e., pulse, breathing rates, blood pressure)
- ☐ Insight on related therapies (i.e., medication use and dosages, adherence patterns)
- ☐ Degree of disease state severity and change (i.e., condition improvement, deterioration)
- ☐ Other:

Product Functionality

- ☐ Product performance (i.e., product up/down time, functionality, internet connectivity)
- ☐ Analytics (i.e., system or product performance, efficiency)
- ☐ Quality measures (i.e., HEDIS, CAHPS measures)
- ☐ End user satisfaction measures (i.e., product acceptability, perceived helpfulness)
- ☐ Interoperability (i.e., EHR integration, performance related to connected or affiliated devices)
- ☐ Other:

Patient and Clinician Utilization

- ☐ User demographic data (i.e., age, gender, ethnicity)
- ☐ User geolocation (i.e., country, state, region)
- ☐ Utilization flow (i.e., gestural data, behavioral flow, performance data, utilization metrics)
- ☐ Patient engagement (i.e., time, frequency, duration of product utilization)
- ☐ Patient onboarding (i.e., consent documentation, patient/caregiver training, patient preferences)
- ☐ Patient utilization (i.e., registration, downloads, screen time usage, long-term retention)
- ☐ Patient adherence (i.e., completed vs. recommended modules, exercises, or lessons)
- ☐ Patient open-ended comments (i.e., patient preferences, satisfaction, surveys)
- ☐ Clinician inputs (i.e., prescribing parameters, authorization and discontinuation orders)
- ☐ Clinician engagement (i.e., registrations, initial and ongoing activity)
- ☐ Clinician implementation (i.e., utilization, frequency of use)
- ☐ Patient-clinician communications (i.e., scheduling, messaging)
- ☐ Patient, caregiver, clinician support service utilization (i.e., service type, frequency)
- ☐ Other:

Step 17: Utilizing DTx-Generated RWD

Compared to traditional medications, DTx products uniquely generate RWD, which includes a wide variety of data sets related to patient outcomes and product performance. RWD is generated on an ongoing basis by DTx products as a result of patient product use and is made available to patients and appropriate stakeholders in alignment with privacy and patient consent requirements.

Check all that apply.

How are DTx-generated RWD outcomes used in practice?

- ☐ Provide patients and caregivers with real-time insights on therapy progress and outcomes
- ☐ Generation of clinically actionable data to inform clinical decision making and optimize patient therapies
- ☐ Safety surveillance and adverse event identification
- ☐ Analysis of individual, subpopulation, and population trends and outcomes
- ☐ Payor-level de-identified data analysis for research purposes
- ☐ Short-term product functionality improvement and bug identification
- ☐ Long-term product improvement and iteration
- ☐ Other:

What additional data sources may be merged with DTx-generated RWD?

- ☐ Outputs from sensors, wearables, and other product plug-ins
- ☐ Validated patient assessment tools
- ☐ Electronic health record (EHR) and healthcare claims data
- ☐ Disease registry lists and outcomes
- ☐ Patient-generated insights
- ☐ Other:

Who is responsible for analyzing and delivering RWD outcomes?

- ☐ DTx manufacturer
- ☐ Health system
- ☐ Clinician
- ☐ HCDM/payor
- ☐ Other:

What level of the DTx-generated data source chain may reviewers and clinicians see?

- Raw data
- Processed data
- Data trends
- Other:

Commentary: RWD serves a vital role in the patient care continuum. Given the different purposes that RWD and RWE serve, when RWD is available, it may not be necessary to conduct a formal RWE study for direct patient care purposes. DTx-generated RWD is reliable and provides immediate and ongoing patient-specific insights.

Step 18: Development and Impact of Real-World Evidence (RWE)

Compared to RWD that is generated by DTx products on an ongoing basis and used by patients and clinicians in real time, RWE is developed through a formal clinical trial design process. RWE involves the formal analysis of RWD and other data sources to answer a specific clinical question related to the DTx product or related therapies, often conducted in the form of a prospective or retrospective observational study.

In this DTx Manufacturer Submission Packet version, two copies of the RWE study evaluation criteria are included.

Check all that apply.

Conducting an RWE Study

What situations are most appropriate to develop RWE for this product?

- ☐ Inform a population-level decision
- ☐ Assess long-term DTx product clinical impacts
- ☐ Demonstrate that treatment effects are reproduced in broader populations or new clinical use settings
- ☐ Provide insights beyond those gathered in RCTs and RWD
- ☐ Assess DTx product use in a health system workflow
- ☐ Conduct a formal economic impact analysis
- ☐ Demonstrate impact on costs by using RWD in clinical practice
- ☐ Undertake a contractual requirements analysis (i.e., outcomes or value-based contracting)
- ☐ Other:

When may it not be necessary to conduct an RWE study?

- ☐ RCT and other studies have already demonstrated sufficient safety, efficacy, effectiveness, and economic outcomes for formulary placement and coverage decisions
- ☐ DTx-generated RWD data and analysis provide sufficient outcomes and metrics for clinicians and HCDMs
- ☐ System data analyses provide sufficient insights for clinical and economic assessments
- ☐ Other:

Benefit of RWE Studies

Which target groups are most likely to benefit from an RWE study for this product?

- ☐ Regulatory (i.e., post-market surveillance, product claims expansion)
- ☐ Clinicians (i.e., point-of-care decisions, determining how DTx use impacts other therapies and clinical outcomes, assessing short- and long-term health impacts)
- ☐ Patients (i.e., decisions related to healthcare options)
- ☐ HCDMs and payors (i.e., economic reviews, formulary review assessment, product use case evaluations, general research, risk reduction dashboards, quality improvement projects, population impact evaluations, background for future contractual considerations)
- ☐ Clinical guideline developers (i.e., clinical practice guideline decisions)

- Policy makers (i.e., product impact on populations, disease state improvements)
- Industry stakeholders (i.e., life sciences organizations)
- Other:

Evaluating an RWE Study (First RWE Study)

If the DTx manufacturer submits an RWE study as part of this Guide, the following criteria may be used to assess the trial.

Study name:

Study citation:

Who was responsible for conducting this RWE study?

- DTx manufacturer
- Health system or clinical team
- Employer
- Payor
- Academic institution
- Third-party entity
- Other:

What inputs were included in this RWE study?

- DTx-generated RWD outcomes
- Outputs from other devices, sensors, wearables, and plug-ins
- Health system sources (i.e., data from claims databases, EHRs, disease state registries)
- Other:

What considerations were incorporated in the RWE study design?

- Demonstrates that it is fit-for-purpose and of appropriate rigor
- Involves key stakeholders in designing and/or informing RWE studies
- Has pre-specified objectives, including specific hypotheses and target populations
- Ensures that data are collected and analyzed per pre-established protocols

- Provides opportunities to replicate study and outcomes
- Represents the real-world patient population
- Evaluates statistical significance and clinical meaningfulness in a representative sample of patients with the condition being treated
- Other:

RWE study outcomes are:

- Meaningful, providing relevant and context-informed evidence sufficient for interpretation, drawing conclusions, and making decisions
- Valid, meeting scientific and technical quality standards to allow causal interpretations
- Expedited, with incremental evidence synchronized with the decision making process
- Transparent, auditable, and reproducible
- Impactful, providing outcomes related to disease-specific healthcare resource utilization, evaluation of total healthcare resource utilization, etc.
- Other:

Where is/will the RWE study results be published?

- Publicly, in a peer-reviewed publication
- Publicly, available in a white paper
- Internal analysis (i.e., informal report, formal report)
- Other:

Who has/will have access to RWE study results?

- HCDM and/or payor
- HTA or formulary review committee
- Point-of-care clinician
- Patient and/or caregiver
- Publicly available
- Other:

Evaluating an RWE Study (Second RWE Study)

If the DTx manufacturer submits an RWE study as part of this Guide, the following criteria may be used to assess the trial.

Study name:

Study citation:

Who was responsible for conducting this RWE study?

- ☐ DTx manufacturer
- ☐ Health system or clinical team
- ☐ Employer
- ☐ Payor
- ☐ Academic institution
- ☐ Third-party entity
- ☐ Other:

What inputs were included in this RWE study?

- ☐ DTx-generated RWD outcomes
- ☐ Outputs from other devices, sensors, wearables, and plug-ins
- ☐ Health system sources (i.e., data from claims databases, EHRs, disease state registries)
- ☐ Other:

What considerations were incorporated in the RWE study design?

- ☐ Demonstrates that it is fit-for-purpose and of appropriate rigor
- ☐ Involves key stakeholders in designing and/or informing RWE studies
- ☐ Has pre-specified objectives, including specific hypotheses and target populations
- ☐ Ensures that data are collected and analyzed per pre-established protocols
- ☐ Provides opportunities to replicate study and outcomes
- ☐ Represents the real-world patient population
- ☐ Evaluates statistical significance and clinical meaningfulness in a representative sample of patients with the condition being treated
- ☐ Other:

RWE study outcomes are:

- ☐ Meaningful, providing relevant and context-informed evidence sufficient for interpretation, drawing conclusions, and making decisions
- ☐ Valid, meeting scientific and technical quality standards to allow causal interpretations
- ☐ Expedited, with incremental evidence synchronized with the decision making process
- ☐ Transparent, auditable, and reproducible
- ☐ Impactful, providing outcomes related to disease-specific healthcare resource utilization, evaluation of total healthcare resource utilization, etc.
- ☐ Other:

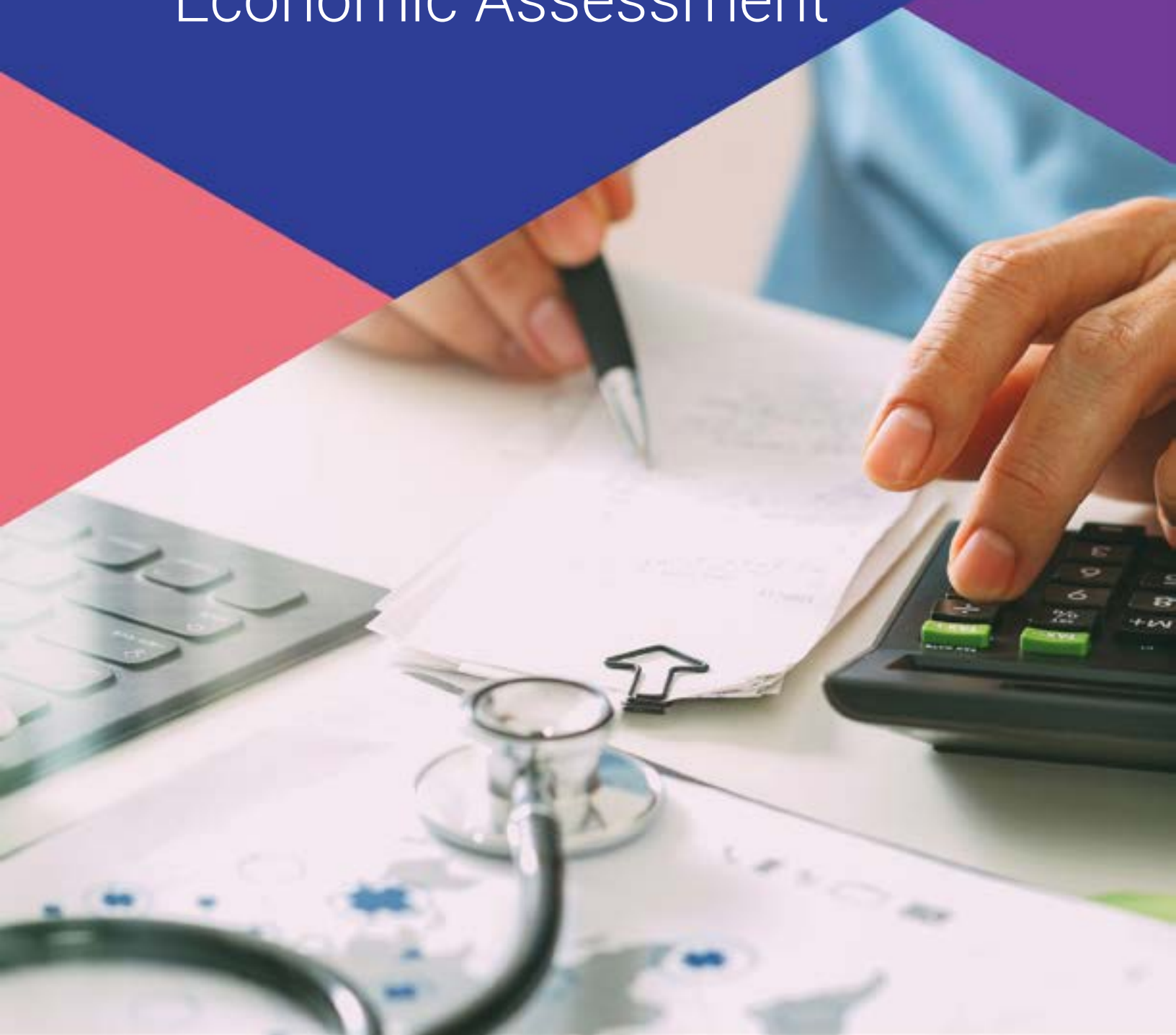
Where is/will the RWE study results be published?

- ☐ Publicly, in a peer-reviewed publication
- ☐ Publicly, available in a white paper
- ☐ Internal analysis (i.e., informal report, formal report)
- ☐ Other:

Who has/will have access to RWE study results?

- ☐ HCDM and/or payor
- ☐ HTA or formulary review committee
- ☐ Point-of-care clinician
- ☐ Patient and/or caregiver
- ☐ Publicly available
- ☐ Other:

DTx Product Evaluation: Economic Assessment



Step 19: Preparing for a DTx Economic Analysis

It is important for HCDMs to develop consistent expectations for the types of economic data that DTx manufacturers are required to develop and submit for formal review. Compared to non-digital therapies, DTx products enable HCDMs to conduct cost analyses with data that are generated in real-time by the product and provide specific insights at the individual and patient population levels.

Check all that apply.

Economic analysis is intended to be applicable for the following setting(s):

- ☐ Regional (i.e., European Union):
- ☐ National (i.e., country-level):
- ☐ Sub-national (i.e., provincial, state, local decision-making bodies):
- ☐ Organizational (i.e., payor, employer):
- ☐ Other:

What is the purpose of conducting a product-specific economic evaluation analysis for this product?

- ☐ Assess DTx therapy impact on costs, revenue, and other economic implications
- ☐ Compare therapy to existing alternatives and standard of care
- ☐ Enable contracting processes (i.e., outcomes, value-based arrangements)
- ☐ Gather information about healthcare system implementation costs and considerations
- ☐ Assess current gaps in care, barriers to treatment, inequalities, and resulting economic inefficiencies
- ☐ Inform decision making to enable an equitable, efficient, and high-quality health system
- ☐ Understand place of the DTx product in varied patient use settings and its impact on healthcare costs for patients, clinicians, and payors
- ☐ Other:

What steps should be completed in advance of this economic analysis?

- ☐ Competitive analysis to assess similar or alternative therapies/technologies available, the current standard of care, and associated costs of various treatment paradigms
- ☐ Third-party evaluations to demonstrate evidence of economic benefit and/or return on investment (ROI)
- ☐ Identifying partner organizations who share common goals and could provide additional resources to complete a study
- ☐ Other:

What are possible sources of economic data that should be included in DTx economic evaluations for this product?

- ☐ Product cost and how it relates to utilization (i.e., direct and indirect costs and requirements)
- ☐ Clinical trial outcomes (i.e., RCTs, observational studies)
- ☐ DTx-generated RWD (i.e., patient utilization and engagement metrics, clinical measurements and outcomes, PROs, dissemination speed and DTx product reach, usability)
- ☐ RWE studies (i.e., population-level impacts, clinical setting-specific outcomes, product utilization, outcomes, healthcare costs, impact of costs through use of RWD)
- ☐ Retrospective analyses (i.e., data from chart reviews, medical and pharmacy claims, electronic medical records, or other novel sources of data)
- ☐ Demonstrated/measured financial impact (i.e., system costs and savings, impact on underserved or undertreated populations, economic modeling, incremental cost-effectiveness ratio results, resource utilization, cost offsets)
- ☐ Other:

Cost analysis types HCDMs may use to evaluate DTx product economic impact include:

- ☐ Budget impact model (local or regionalized data)
- ☐ Cost-utility analysis
- ☐ Cost-consequence analysis
- ☐ RWE
- ☐ Cost-effectiveness analysis
- ☐ Cost-benefit analysis
- ☐ Cost-minimization analysis
- ☐ Other:

Potential economic evaluation models HCDMs may consider using for this therapy include:

- Unit price-based pricing, based on the cost of the product and volume of use
- Outcomes-based contracting, where the overall price is based on product outcomes/savings
- Risk-bearing contracts, where employers/health plans bear some risk for providing high-quality care at low costs
- Average cost per member, including per member per month (PMPM)
- Subscription model, with product access for a specified number of patients
- Case rate model, including payments made per number of patients treated
- General contracting processes, where manufacturers and payors agree on mutually beneficial terms
- Patient-funded, with no third-party reimbursement
- Other:

Step 20: Undertaking a Formal Economic Analysis

Initial economic analysis inputs may be provided by a DTx manufacturer and include clinical trial results, RWD outcomes, RWE studies, and health economic outcomes research (HEOR). Additionally, health systems may provide setting-specific inputs to improve economic modeling, including payor-generated outcomes related to system costs and payor-generated claims data to demonstrate local product impact. Ongoing DTx-generated individual and population-level RWD are beneficial to include for long-term analyses.

Check all that apply.

Who is responsible for completing product-specific economic analyses:

For initial analyses?

- ☐ DTx manufacturer
- ☐ HCDM/payor
- ☐ Other:

For ongoing analyses?

- ☐ DTx manufacturer
- ☐ HCDM/payor
- ☐ Other:

Who is responsible for generating data for analyses:

For initial analyses?

- ☐ DTx manufacturer
- ☐ HCDM/payor
- ☐ Other:

For ongoing analyses?

- ☐ DTx manufacturer
- ☐ HCDM/payor
- ☐ Other:

What is the ideal focus of a product-specific economic analysis?

- ☐ Setting-specific
- ☐ Multi-setting
- ☐ Other:

What components should be included in a product-specific economic analysis?

- ☐ Structured summary of objectives
- ☐ Economic analysis background
- ☐ Therapy setting of use
- ☐ Population(s) included in analysis
- ☐ Claims data
- ☐ Analysis methods (study design, inputs)
- ☐ Analysis results (plus uncertainty analyses)
- ☐ Conclusions
- ☐ Other:

Are results of this type of economic analysis published in peer-reviewed literature?

- ☐ Yes
- ☐ No
- ☐ Other:

What point(s) in the product life cycle is most appropriate for conducting this economic analysis?

- ☐ Pre-market phase
- ☐ Market approval phase
- ☐ Post-market phase
- ☐ Other:

Suggested cadence of economic analysis reviews:

- ☐ This product does not require subsequent cost analyses following the initial evaluation
- ☐ This product should undergo periodic cost analysis updates (i.e., ongoing product iterations, product optimization)
- ☐ This product requires an annualized (or similar) cost savings assessment to understand patient utilization of services (requires use of data from the HCDM)
- ☐ Other:

If additional evidence for future economic analyses needs to be developed later:

Expected timelines include:

Anticipated costs typically include:

Entities generally responsible for covering new expenses:

Other:

Step 21: Key Considerations for a DTx Economic Impact Evaluation

Through their ability to generate real-world outcomes, DTx products provide accurate patient and population-level insights for economic assessments, HEOR, and long-term forecasts. The following high-level framework provides the types of direct and indirect costs that HCDMs may use to evaluate the economic impact of DTx products.

Data for the initial phases of assessing direct and indirect economic impact are typically provided by the DTx product manufacturer. Although HCDMs are encouraged to provide setting or patient-specific insights for the initial evaluation processes, these data play a key role in ongoing direct and indirect economic impact analyses.

Assessing Direct DTx Product Economic Impact

What is the cost of the DTx course of therapy vs. a traditional or comparator therapy (i.e., replacement, new costs)?

What costs may be avoided by using the DTx product vs., or in addition to, a traditional or comparator therapy (i.e., costs related to in-person/virtual or pharmaceutical therapy, medication processing, administration, monitoring, storage)?

What durability of effect is the therapy expected to provide (i.e., short-term impact, long-term impact)?

What cost savings are generated by the DTx therapy (i.e., positive overall impact on patient health condition, long-term cost avoidance, faster therapy dissemination, measurement-based care)?

What follow-on costs may be generated by the DTx therapy (i.e., booster therapies)?

What costs are incurred or covered by the payor or other entities (i.e., employer, health system, clinician, patient)?

What is the overall cost effectiveness of the DTx therapy vs. a traditional or comparator therapy?

Assessing Indirect Economic Impact

What clinical or economic benefits are derived from data generated by the DTx product (i.e., impact of DTx-generated insights on overall care, therapy optimization, patient and population-level decisions, remote data analysis by qualified non-clinician teams)?

What health system savings are generated by the DTx therapy (i.e., clinician productivity, end user work presenteeism and productivity, implementation economies of scale when multiple DTx products are integrated into a system)?

What is the impact on clinician productivity, patient reach, and workflows?

What impact will this therapy have on the patient journey and experience (i.e., available personalized care options, increased convenience, on-demand care, patient preference)?

What societal value is created (i.e., prevent productivity loss, reduce caregiver burden, improve population health, increase access to and speed of therapy dissemination)?

Step 22: Factors That Affect DTx Therapy Economic Impact

In addition to standard cost analysis inputs, HCDMs take into account the following considerations that may directly and indirectly impact economic value.

Check all that apply.

Patient and Caregiver Clinical Outcome Considerations

DTx therapy economic evaluation should take into account:

- ☐ Clinical, behavioral, and health impact of the therapy for the targeted disease
- ☐ Cost savings related to product impact on other health conditions
- ☐ Cost savings related to product impact on or avoidance of adverse events, side effects, or comorbidities
- ☐ Patient and caregiver improved quality of life, satisfaction, and fulfilled expectations
- ☐ Convenience of and remote access to the active interventions provided by the DTx product, including:
  - Increased number of settings for care delivery (i.e., home, school, work, clinical environment)
  - Increased frequency of active care delivery (i.e., nights, weekends, between traditional care visits)
  - Societal impact and improved access to underserved populations (i.e., rural, urban, undertreated)
- ☐ Other:

Clinician and Health System Administrative Considerations

DTx therapy economic evaluation should take into account:

- ☐ Resources necessary to educate and enable clinicians to authorize and use DTx products in practice
- ☐ Short- and long-term impact on clinician workflow efficiencies and productivity
- ☐ Economies of scale achieved through the implementation of multiple DTx or digital health products into a single health system or platform
- ☐ Financial and administrative resources that may be freed up to create further capacity in the system
- ☐ Alignment with long-term digitization trends in the health ecosystem (i.e., compatibility with telehealth, virtual care)
- ☐ Product impact on national or local health system performance and quality ratings
- ☐ Clinical and financial value of applying insights generated by product back into patient-care settings
- ☐ Overall economic impact on the clinical practice or health system (positive, neutral, or negative budget impact)
- ☐ Other:

Payor Considerations

DTx therapy economic evaluation should take into account:

- ☐ Potential impact of DTx product on disease incidence, prevalence, target population, and current cost of care (i.e., increased therapy opportunities, forecasted rate of disease state improvement, estimated magnitude of disease state resolution)
- ☐ Measures that may be derived from DTx products (i.e., therapy utilization, magnitude of outcomes)

- Review of results from other types of studies such as pharmacoeconomic modeling, healthcare utilization, comparative effectiveness, and productivity studies
- Savings related to the deployment of value and outcomes-based payment models
- Billing codes and processes that apply to the use and delivery of the DTx product
- Other:

Employer Considerations

DTx therapy economic evaluation should take into account:

- Employee retention and satisfaction
- Employee presenteeism/absenteeism and productivity at work
- Ability to address disparities and critical social determinants of health
- Therapy impact on costs and outcomes vs. current standard of care
- Expanded benefits and non-traditional therapy options for mental, behavioral health, and chronic conditions
- Market differentiation and recognition
- Other:

Step 23: Health Technology Assessment (HTA) Considerations

Existing HTA frameworks[2] in Europe related to DTx already share a certain set of requirements (i.e., CE marking as a medical device), but requirements still vary related to interoperability and evidence.

HTA frameworks for evaluating DTx products are increasingly being established across Asia, Australia, and Europe. Current HTA examples include the mHealth Belgium Validation Pyramid Framework, the German DiGA Fast Track framework, and the UK NICE Evidence Standards Framework for Digital Health Technologies and Digital Technology Assessment Criteria (DTAC) frameworks. Many countries are now embarking on their own efforts to develop DTx and digital health frameworks, so it is important for them to have access to best practices established at the country and industry level.

The following HTA evaluations have already been conducted for this product:

The following HTA evaluations are underway for this product:

Check all that apply.

Forthcoming and renewed HTA evaluations for this product should include the following costs and economic evaluation considerations:

Resource Utilization

- ☐ Types of resources used when delivering the assessed technology (vs. comparators, if applicable):
- ☐ Amounts of resources used when delivering the assessed technology (vs. comparators, if applicable):
- ☐ Measured and/or estimated costs of the assessed technology (vs. comparators, if applicable):
- ☐ How the technology modifies the need for other technologies and use of resources (vs. comparators, if applicable):

[2] HTA Core Model source: https://eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf (page 205)

- [ ] Likely budget impacts of implementing the technologies (vs. comparators, if applicable):

- [ ] Other:

Measurement and Estimation of Outcomes

- [ ] Primary measured and/or estimated health-related outcome(s) of the assessed technology (outcome identification, measurement, and valuation):

- [ ] Other:

Examination of Costs and Outcomes

- [ ] Estimated differences in costs and outcomes between the technology and its comparator(s):

- [ ] Other:

Characterizing Uncertainty

- [ ] Possible uncertainties surrounding the costs and economic evaluation(s) of the technology:

- [ ] Other:

Characterizing Heterogeneity

- Extent that differences in costs, outcomes, or cost-effectiveness can be explained by variations between subgroups using the technology:
- Other:

Validity of the Model(s)

- Methodological assumptions that can be made in relation to the technology:
- Extent that estimates of costs, outcomes, or economic evaluation(s) should be considered as providing valid descriptions of the technology:
- Other:

Implementing Digital Therapeutics in Practice

Enabling DTx implementation and patient access to this category of medicine

Step 24: DTx Product Implementation and Engagement

This framework provides HCDMs with an industry-level guide to measuring the effectiveness of practices used to implement DTx products in clinical settings. DTA does not provide advice on optimal business models or strategies for specific DTx products.

Payors are encouraged to use this framework for all DTx product types, with the recognition that each product has specific considerations to enable end user success.

Check all that apply.

DTx "Engagement Chain"[3]

The DTx Engagement Chain comprises five steps for HCDMs and DTx manufacturers to consider in relation to targeting, outreaching to, activating, engaging with, and supporting individual patients.

A. Target

Patient targeting process for this product may include:

- ☐ Determine which patient population is most suited for the use of the DTx therapy (Note: this is more selective than simply identifying all patients with a particular condition)
- ☐ Analyze patient data to determine greatest product impact and ROI
- ☐ Identify and target patients by disease (i.e., disease severity, urgency of medical need)
- ☐ Prioritize individuals who will be most successful with treatment

Options to target appropriate patients may include:

- ☐ Patient geography
- ☐ Disease state and/or comorbidity
- ☐ Acuity or severity of disease state
- ☐ Demographic parameters
- ☐ Social determinants
- ☐ Target clinical measures
- ☐ Other:

Metric: Measured as "n"

Responsible entities: DTx manufacturer may provide initial parameters. HCDM is responsible for population data analysis, patient identification, and prioritization.

[3] The "DTx Engagement Chain" is a registered trademark of Welldoc, Inc. It has been adapted with Welldoc's permission for use by DTA.

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B. Outreach

Patient outreach process for this product may include:

- ☐ Determine the outreach modalities to make the target patient population aware of the DTx product
- ☐ Undertake targeted education efforts
- ☐ Engage patients, and caregivers as appropriate, through marketing activities

Options for patient outreach may include:

- ☐ Advertising (i.e., general, social media)
- ☐ Enterprise-level awareness campaign (i.e., employer, payor, health system, hospital, clinic)
- ☐ Education via a clinician (i.e., in-person or virtual clinical team engagement)
- ☐ Targeted direct patient outreach (i.e., phone, email, mail)
- ☐ Other:

Metric: Measure the "Outreach to Target" ratio, where 100% is perfect outreach

Responsible entities: DTx manufacturer may assist HCDM in conducting awareness campaigns for patients, caregivers, and clinicians.

C. Activate

Patient activation process for this product may include:

- ☐ Validate patients who meet criteria for the treatment
- ☐ Authorize or prescribe DTx therapy for the patient
- ☐ Convert the patient from product authorization
- ☐ Deliver product access code and necessary product components to patient
- ☐ Ensure DTx product is installed and activated

Degree of direct clinician engagement in this phase may include:

- ☐ Clinician needs to be involved in this phase
- ☐ Clinician could be involved in this phase
- ☐ Clinician does not need to be involved in this phase

Options for patient activation may include:

- Referral or authorization from a clinician, employer, or payor (i.e., non-prescription DTx product)
- Patient self-activation process (i.e., non-prescription DTx product)
- Prescription from a qualified clinician (i.e., prescription DTx product)
- Activation and setup by a clinician, clinical team, or health coach (i.e., non-prescription or prescription DTx product)
- Other:

Metric: Measure "Activation to Outreach" ratio, where 100% is perfect activation

Responsible entities: DTx manufacturer is primarily responsible for product activation and enrollment post-product authorization or prescription.

D. Engage

Patient engagement process for this product may include:

- Implement strategy to optimize patient engagement and ongoing utilization with DTx product
- Coordinate shipping date, logistics, and care management
- Identify a care coach for the patient throughout the protocol
- Assess ongoing impact of therapy and patient-specific treatment outcomes

Options for patient engagement may include:

- Ad hoc engagement (i.e., in-product features)
- Programmatic engagement (i.e., enterprise incentives)
- Clinician-guided (i.e., clinical team engagement)
- Other:

Metric: Measure "Engagement to Activation" ratio, where 100% is perfect engagement

Responsible entities: DTx products are able to generate patient-specific insights for patients, clinicians, payors, and DTx manufacturers in alignment with privacy and security requirements to assess ongoing engagement and product performance.

E. Support

Patient support process for this product may include:

- ☐ Support patient use of DTx product
- ☐ Conduct patient follow up inquiries
- ☐ Track long-term data accumulation, trends, and impact

Options for patient support may include:

- ☐ In-product support
- ☐ Remote customer care services
- ☐ Clinical team support
- ☐ HCDM follow up
- ☐ Other:

Metrics: Measure traditional metrics, such as call center performance (i.e., inbound calls, issue resolution) and patient satisfaction

Responsible entities: Depending on the specific product and settings of use, DTx manufacturer and HCDMs share responsibility for ongoing patient support and data outcomes tracking.

Step 25: Determining Full-Scale Launch vs. an Implementation Pilot Study

An implementation pilot study is a limited-scale test of processes and procedures particularly focused on the feasibility and acceptability of an approach to be used in practice. Implementation studies do not answer the question, "Does this intervention work?," nor do they always reflect the exact impact the intervention is going to have with wider adoption of the tested protocol. Phased or full-scale integration may be preferable to conducting a post-market implementation study.

Check all that apply.

When is it appropriate to conduct an implementation study for this product?

Potential questions to answer through a post-market implementation study may include:

- ☐ What method will optimize adoption and access to the DTx product for a specific population?
- ☐ In a specific setting, what is the best way to identify, engage with, and maintain patient adherence to therapy?
- ☐ How does this product impact a specific aspect of the patient journey?
- ☐ What additional factors may assist end users in following therapy requirements?
- ☐ Which product utilization and target population adoption success measures should be tied to contractual agreements?
- ☐ What is the acceptability and feasibility of this product in specific real-world settings?
- ☐ Other:

Setting-specific questions for a post-market implementation study may include:

- ☐ *Health plans:* How does the product impact clinicians' workflow and ability to care for patients?
- ☐ *Employers:* What impacts does the product have on subsets of employee presenteeism, absenteeism, retention, and performance?
- ☐ *HTA evaluators:* What country-specific tactics may be required to scale the product across target populations?
- ☐ Other:

When is it NOT appropriate to do an implementation study for this product?

The most common misuses of post-market implementation studies include:

- ☐ Attempting to assess baseline safety and efficacy of the DTx therapy.
- ☐ Undertaking a pilot when a phased or full implementation is an appropriate next step.
- ☐ Assuming that limited-scale results may be substituted for collecting and analyzing RWD outcomes in a full-scale on-the-market environment.
- ☐ Evaluating a product that is still in its initial development phase.
- ☐ Other:

Commentary: HCDMs face a difficult decision when determining whether to undertake a pilot study or implement a product at full-scale.

» As a first step, HCDMs should identify DTx product(s) that demonstrate strong clinical impact via high-quality studies (i.e., RCT).

» Implementation studies should be focused and are most appropriate to assess how to integrate a product within a specific environment.

» Not all product launches in a new healthcare setting require an implementation pilot to ensure a successful rollout.

Step 26: Clinical Team Engagement

Digital therapeutics provide clinicians with multiple benefits, including expanded therapeutic options for patient care and access to actionable data insights. DTx products are able to integrate into existing workflows, expand clinicians' ability to actively treat patients, and optimize information available for making clinical decisions.

DTx-generated insights may be leveraged by clinicians to:

- ☐ Assess impact of therapy toward patient goals
- ☐ Apply actionable insights to optimize, adjust, recommend, escalate, or de-escalate therapy
- ☐ Use targeted data sets to help with challenging patient cases
- ☐ Detect adverse events and/or non-optimal outcomes
- ☐ Develop a better understanding of medication usage
- ☐ Provide ongoing monitoring and/or measurement
- ☐ Other:

Degree of clinician involvement in the use of the DTx product (in-person or virtual):

- ☐ Independent product use by patient, without clinician involvement
- ☐ Independent product use by patient, following a clinician's recommendation, authorization, or prescription
- ☐ Intermittent clinician assessment and therapy adjustment
- ☐ Recommended clinician engagement, monitoring, and therapy adjustment
- ☐ Required ongoing clinician engagement, monitoring, and therapy adjustment
- ☐ Other:

The following clinicians, (i.e., diabetes educator, dietitian, dentist, nurse, nurse practitioner, occupational therapist, pharmacist, physical therapist, physician, physician's assistant, psychiatrist, psychologist, speech and language pathologist):

- ☐ Engage with the DTx therapy in some capacity:
- ☐ Are able to authorize use of the DTx therapy:

Following initial DTx product authorization, subsequent clinician requirements may include:

- ☐ Periodic review of patient-specific outcomes during therapy
- ☐ Review of final patient-specific therapy outcomes at the conclusion of therapy
- ☐ No follow-up steps are necessary for this product once the therapy is initiated
- ☐ Other:

Clinical support services provided by the DTx manufacturer, if applicable, include:

- ☐ One-time engagement with a clinician who may authorize qualifying patients' use of the product
- ☐ Health coaching services (ad hoc services)
- ☐ Health coaching services (built-in component of therapy)
- ☐ Other:

Entities potentially involved in the various phases of DTx-related care include *(check all boxes that may apply)*:

	Advisory Team	Product Evaluation Team	Payor Entity	Compliance Team	Product Access Team	Authorizing Clinician	Clinical Support Team	Other
Initial assessment of the product's intended use, safety, and efficacy	☐	☐	☐	☐	☐	☐	☐	☐
Product authorization for patient access (i.e., prescription, non-prescription DTx)	☐	☐	☐	☐	☐	☐	☐	☐
Dispensing or distributing DTx product (i.e., access code, affiliated components)	☐	☐	☐	☐	☐	☐	☐	☐
Patient education related to product purpose and anticipated outcomes	☐	☐	☐	☐	☐	☐	☐	☐
Product integration with IT and other technology systems	☐	☐	☐	☐	☐	☐	☐	☐
Product onboarding (i.e., logistical product use considerations)	☐	☐	☐	☐	☐	☐	☐	☐
Review and assessment of patient-specific data and outcomes	☐	☐	☐	☐	☐	☐	☐	☐
Therapy optimization following an evaluation of clinical outcomes	☐	☐	☐	☐	☐	☐	☐	☐
Product maintenance or support	☐	☐	☐	☐	☐	☐	☐	☐
Other:	☐	☐	☐	☐	☐	☐	☐	☐

	Advisory Team	Product Evaluation Team	Payor Entity	Compliance Team	Product Access Team	Authorizing Clinician	Clinical Support Team	Other
Other:								
Other:								

» Advisory team (i.e., patient advisory board, caregivers, practicing care team members)
» Product evaluation team (i.e., HTA body, P&T committee, formulary developers, innovation divisions)
» Payor entity (i.e., payor, employer, health plan strategy and budgetary approval teams)
» Compliance team (i.e., legal, regulatory, privacy, security teams)
» Product access team (i.e., technical infrastructure, implementation, support teams)
» Authorizing clinician (i.e., clinician qualified to authorize patient use of the product)
» Clinical support team (i.e., administrative representatives, clinical practice implementation teams)

Step 27: Payment Codes

Depending on which country or region a DTx product will be used within, HCDMs have access to multiple coding options that enable them to quantify and be reimbursed for use of the product, affiliated services, and/or clinician engagement.

The following codes may apply to this particular DTx product:

Therapy Indication:

Target Disease State/Indication	**Code Set** (i.e., ICD, SNOMED)	**Specific Code(s)**

DTx Product Codes:

	Relevant Code Set (i.e., Unique Device Identifier, HCPCS, Durable Medical Equipment)	**Specific Code(s)**
DTx product:		
Affiliated DTx product components:		
Services provided by the DTx product:		
Other:		
Other:		

Clinician-Specific Codes:

Clinician	Relevant Code Set (i.e., CPT Codes)	Specific Code(s)
Assessment of the product		
Authorization of the product		
Time spent with patient related to the product		
Services provided related to the product		
Resources utilized related to the product		
Other:		

Step 28: Ensuring Quality Data Sets

Digital therapeutics produce a variety of data sets. Various subsets of this data are processed via clinically validated algorithms and subject to ongoing data accuracy and reproducibility validation processes.

DTx manufacturers use numerous mechanisms to prevent patients and clinicians from receiving incomplete, inaccurate, or biased results. As such, data generated by DTx products that meet industry core principles and standards should be reliable, accurate, and integrable with complimentary systems.

When DTx-generated data are multi-directional, data from this DTx product may:

- ☐ Be incorporated into existing healthcare systems and interfaces (i.e., EHRs, order entry systems, clinical decision support systems)
- ☐ Receive data inputs from external devices and systems (i.e., sensors, EHRs)
- ☐ Other:

To ensure data integrity and consistency at the system level when integrating DTx data sets into existing systems, the following considerations should be taken into account:

- ☐ Matching the appropriate patient identifiers between the DTx product and IT system
- ☐ Tracing data provenance during product use, including key inputs, sources, entities, systems, and processes that influence data set of interest
- ☐ Ongoing evaluation processes to ensure integrity and accuracy of any newly combined data sets
- ☐ Identification of data limitations or potential holes in combined data sets
- ☐ Specifying the timing of when data points were generated within separate sets and determining potential implications on clinical assessment decisions
- ☐ Cleaning combined data sets prior to patient, clinician, or payor display
- ☐ Other:

Preventionary measures to ensure data integrity may be necessary if:

- ☐ Unstructured data from other systems mixes with DTx-generated data
- ☐ Data sources via unapproved sensors or inputs are introduced into DTx systems and factored into outcomes generation
- ☐ Other:

Commentary: DTx products may be used in alignment with pre-established protocols for other software-based medical devices. With the proper protocols and processes, data integrity can be fully preserved throughout the product use and life cycle.

Step 29: Access to DTx Product Outcomes

Clinical data generated by digital therapeutics are processed by clinically validated algorithms and are therefore clinically actionable and able to be used in direct care delivery and optimization. Data generated by DTx products are subject to interoperability standards and are governed by national and regional privacy standards and regulations (i.e., privacy notices, access to personal data, right to erasure, restriction of use, and consent).

How Is Data Access Enabled?

DTx product uses the following interoperability standards and processes:

- ☐ Fast Healthcare Interoperability Resources (FHIR): An HL7 standard for exchanging healthcare information electronically
- ☐ Standardized Application Programming Interfaces (APIs)
- ☐ International standards (i.e., ISO/IEEE 11073) to ensure the product is interoperable with all applicable hardware, software, service, and/or drug components
- ☐ Health information exchange(s) (HIE) to exchange health-related information among entities according to nationally recognized standards
- ☐ Other:

How Is Data Protected?

Data may be:

- ☐ De-identified
- ☐ Encrypted
- ☐ Provided to HCDMs in aggregate form at the population level
- ☐ Subject to “appropriate permissions”
- ☐ Stored in secure servers
- ☐ Other:

Given the appropriate authorization, data sharing is possible with:

- ☐ Primary or authorizing clinician
- ☐ Additional healthcare team members
- ☐ Patient
- ☐ Caregiver
- ☐ Employer, payor, or other authorizing entity
- ☐ Other:

Where may end users, clinicians, and payors access relevant data?

- ☐ In-product interface (i.e., via patient device)
- ☐ Standalone portal and/or dashboard
- ☐ EHR portal
- ☐ Embedded in clinical decision support pathways
- ☐ Delivered via fax, email, or PDF
- ☐ Other:

Where may caregivers access data outcomes?

- ☐ In-product interface (i.e., via patient/caregiver device)
- ☐ Standalone portal and/or dashboard
- ☐ EHR portal
- ☐ Delivered via fax, email, or PDF
- ☐ Other:

What forms of rights do end users have?

- ☐ Privacy notice (i.e., covering data processing, use, and disclosure of personal details)
- ☐ Access to personal data (i.e., correcting, removing, or limiting data, and portability)
- ☐ Right to erasure (i.e., forgotten, deleted, or anonymized)
- ☐ Restriction of use (i.e., data for archives only)
- ☐ Consent (i.e., offering degrees of control to the individual)
- ☐ Other:

Step 30: Product Integration

When digital therapeutics are integrated into health systems, products are granted access to clinical information from sources within and outside of the system and use that information to provide direct clinical care. Product integration and interoperability requirements differ based on the intended practice setting of use (i.e., inpatient health system, outpatient clinic, patient home environment).

Integration considerations for this product include:

	Product Offerings to Enable Integration (including DTx manufacturer and third-party offerings)	**Requirements for the Health System**	**Additional Considerations**	**Not Applicable**
Include DTx product in electronic formulary and/or prescribing systems				☐
Connect DTx product to EHR				☐
Incorporate product into the prescription dispensing system				☐
Send data from the DTx product to the health system (i.e., EHR, dashboards)				☐
Write data from the health system into the DTx product				☐

	Product Offerings to Enable Integration (including DTx manufacturer and third-party offerings)	**Requirements for the Health System**	**Additional Considerations**	**Not Applicable**
Connect product to relevant third-party vendors				☐
Port relevant data from DTx product into payor systems				☐
Connect DTx product with payor billing modules				☐
Deliver product access to the patient				☐
Send data to patient portal				☐
Other:				☐

Supplemental Materials

Supplemental Materials

The attached documents further support the information provided in this Guide:

Document Title	Description	Step of the Guide This Document Supports	Additional Notes

Document Title	Description	Step of the Guide This Document Supports	Additional Notes

Setting-Specific Considerations

Horizon Scanning

Concluding Insights

Appendix

Glossary of Terms

Digital Health Technology (DHT): Apps, programs, and software used in the health and social care system. They may be standalone or combined with other products such as medical devices or diagnostic tests.[4]

Digital Therapeutic (DTx): Digital therapeutics deliver to patients evidence-based therapeutic interventions that are driven by high-quality software programs to treat, manage, and prevent a disease or disorder. They are used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes.[5]

Health Technology Assessment (HTA): The systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational, and ethical issues of a health intervention or health technology. The main purpose of conducting an assessment is to inform policy decision making.[6]

Intended Use: The term "intended use / intended purpose" is the objective intent of the manufacturer regarding the use of a product, process, or service as reflected in the specifications, instructions, and information provided by the manufacturer.[7]

Pharmacy & Therapeutics (P&T) Committee: An advisory committee that is responsible for developing, managing, updating, and administering the drug formulary system.[8]

Real-World Data (RWD): Real-world data are the data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources.[9]

Real-World Evidence (RWE): Real-world evidence is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWE can be generated by different study designs or analyses, including but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective).[10]

[4] https://www.nice.org.uk/corporate/ecd7/chapter/glossary#digital-health-technologies-dhts

[5] https://dtxalliance.org/wp-content/uploads/2021/01/DTA_DTx-Definition-and-Core-Principles.pdf

[6] https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/assessment

[7] https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf

[8] https://www.ashp.org/-/media/assets/policy-guidelines/docs/endorsed-documents/endorsed-documents-principles-sound-drug-formulary-system.ashx

[9] https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

[10] https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Digital Therapeutics Alliance

Founded in 2017, the Digital Therapeutics Alliance (DTA) is a non-profit trade association of industry leaders and stakeholders engaged in the evidence-driven advancement of digital therapeutics. As the leading international organization on digital therapeutic thought leadership and education, DTA provides patients, clinicians, payors, and policy makers with the necessary tools to evaluate and utilize DTx products.

DTA's members—including organizations dedicated to manufacturing, evaluating, supporting, and utilizing DTx products—work to transform global healthcare by advancing high-quality, clinically validated digital therapeutics to improve clinical and health economic outcomes.