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.

Contents

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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 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	CLINICIANS	DTx MANUFACTURERS
▪ 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	▪ 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	▪ A rubric to pre-populate and distribute to appropriate entities (in particular, the DTx Manufacturer version of this Guide, which is 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 is 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	CLINICIANS 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?	- 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?

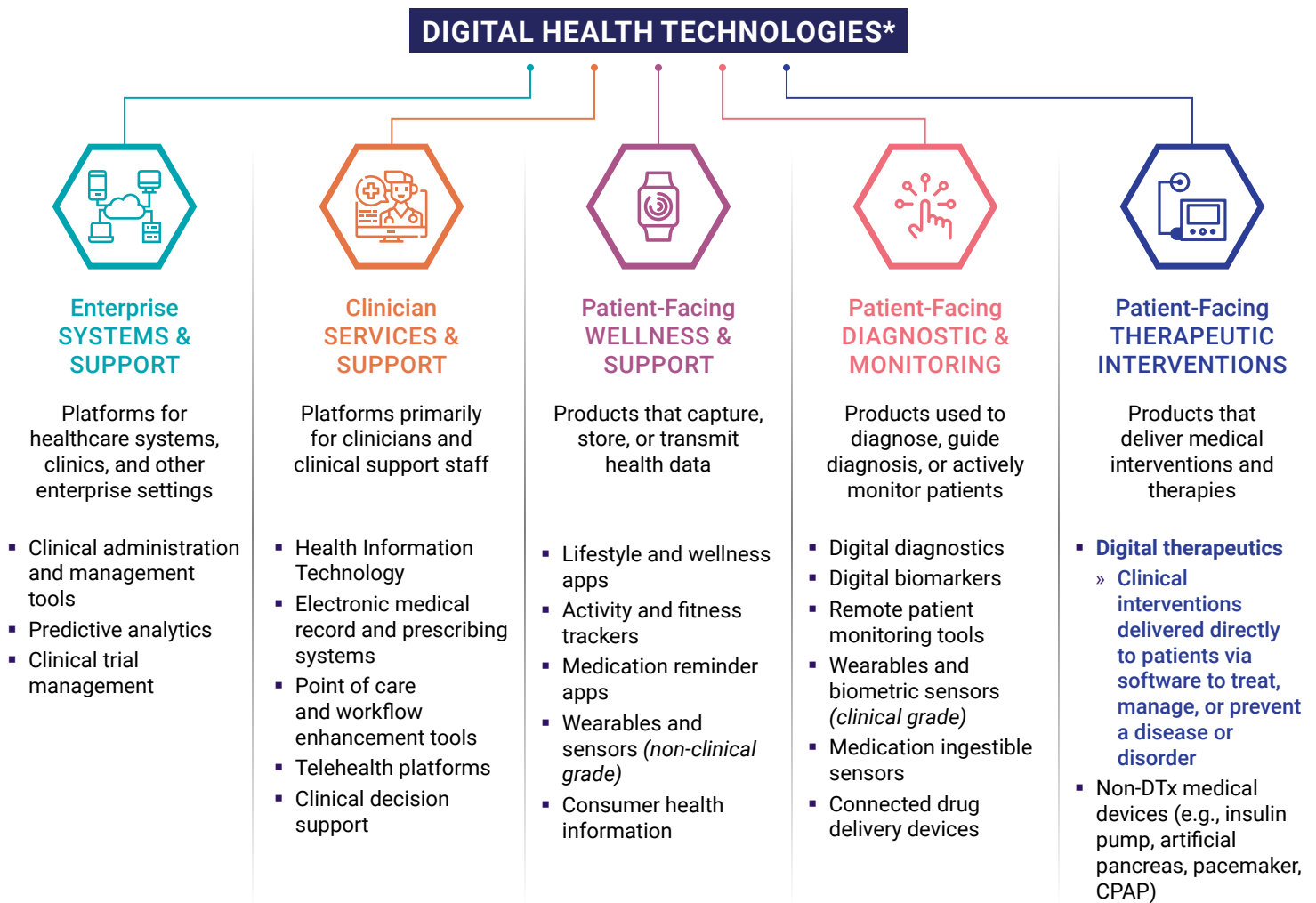| HEALTHCARE PAYORS NEED TO KNOW	POLICY MAKERS NEED TO KNOW
- What type of product are we covering? - How will it benefit patients at the individual and population levels? - What types of clinical and economic outcomes should we expect?	- What level of risk does each product pose to patients? - What 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.

DIGITAL HEALTH TECHNOLOGIES*

Enterprise SYSTEMS & SUPPORT

Platforms for healthcare systems, clinics, and other enterprise settings

- Clinical administration and management tools
- Predictive analytics
- Clinical trial management

Clinician SERVICES & SUPPORT

Platforms primarily for clinicians and clinical support staff

- Health Information Technology
- Electronic medical record and prescribing systems
- Point of care and workflow enhancement tools
- Telehealth platforms
- Clinical decision support

Patient-Facing WELLNESS & SUPPORT

Products that capture, store, or transmit health data

- Lifestyle and wellness apps
- Activity and fitness trackers
- Medication reminder apps
- Wearables and sensors *(non-clinical grade)*
- Consumer health information

Patient-Facing DIAGNOSTIC & MONITORING

Products used to diagnose, guide diagnosis, or actively monitor patients

- Digital diagnostics
- Digital biomarkers
- Remote patient monitoring tools
- Wearables and biometric sensors *(clinical grade)*
- Medication ingestible sensors
- Connected drug delivery devices

Patient-Facing THERAPEUTIC INTERVENTIONS

Products that deliver medical interventions and therapies

- **Digital therapeutics**
  - » **Clinical interventions delivered directly to patients via software to treat, manage, or prevent a disease or disorder**
- Non-DTx medical devices (e.g., insulin pump, artificial pancreas, pacemaker, CPAP)

*Categorizations of the digital health technology ecosystem will continue to evolve. This is a select representation of a broad, diverse ecosystem.
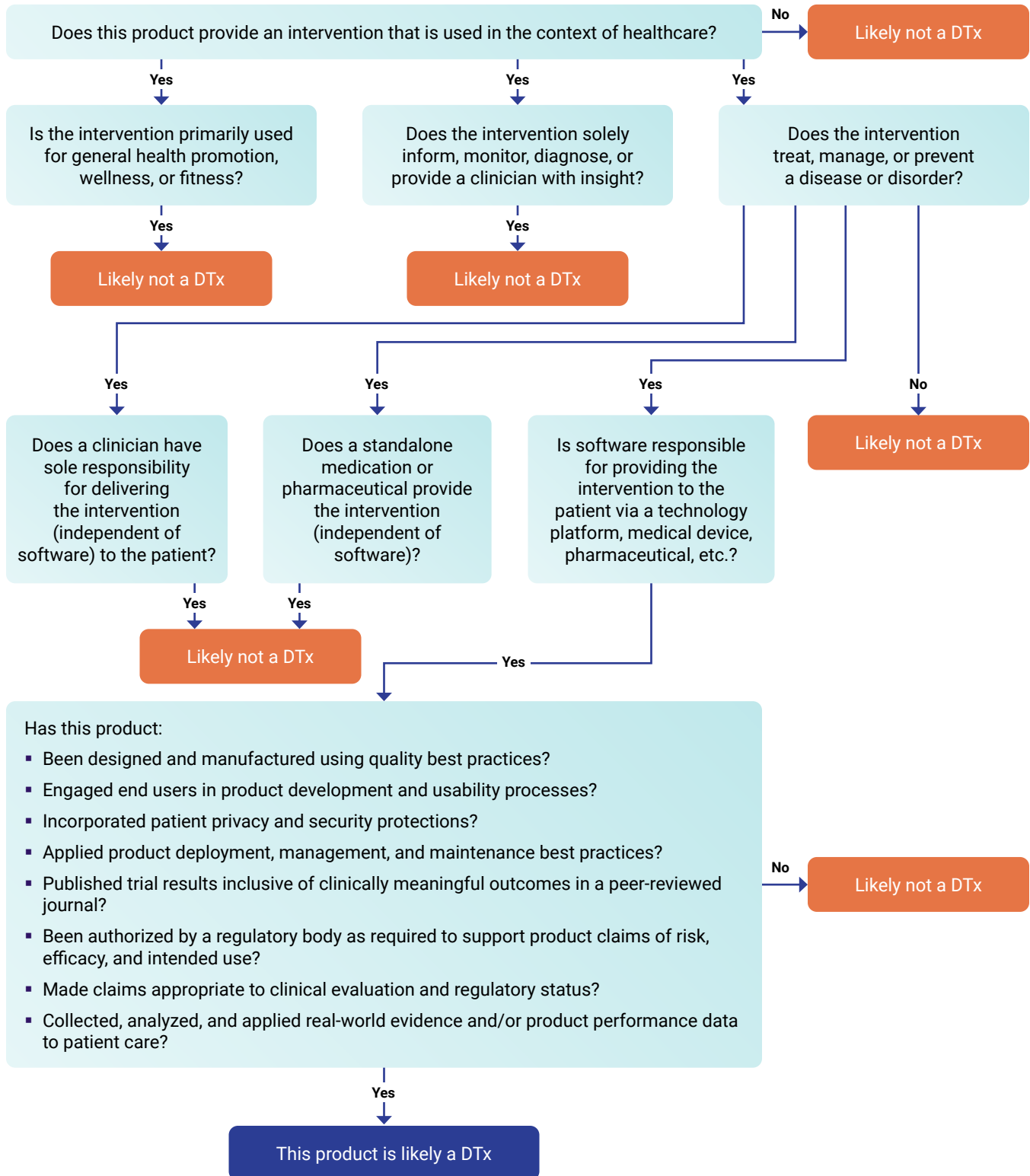
Even though this Guide focuses on digital therapeutics—products that deliver clinical interventions directly to patients via software to treat, manage, or prevent a disease or disorder—DTx products may also integrate a variety of other digital capabilities into their product offerings, such as wearables 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.

Does this product provide an intervention that is used in the context of healthcare? — **No** → Likely not a DTx

Yes ↓ | **Yes** ↓ | **Yes** ↓

Is the intervention primarily used for general health promotion, wellness, or fitness?

Does the intervention solely inform, monitor, diagnose, or provide a clinician with insight?

Does the intervention treat, manage, or prevent a disease or disorder?

Yes ↓ Likely not a DTx

Yes ↓ Likely not a DTx

No → Likely not a DTx

Yes | **Yes** | **Yes**

Does a clinician have sole responsibility for delivering the intervention (independent of software) to the patient?

Does a standalone medication or pharmaceutical provide the intervention (independent of software)?

Is software responsible for providing the intervention to the patient via a technology platform, medical device, pharmaceutical, etc.?

Yes | **Yes** → Likely not a DTx

Yes ↓

Has this product:

- Been designed and manufactured using quality best practices?
- Engaged end users in product development and usability processes?
- Incorporated patient privacy and security protections?
- Applied product deployment, management, and maintenance best practices?
- Published trial results inclusive of clinically meaningful outcomes in a peer-reviewed journal?
- Been authorized by a regulatory body as required to support product claims of risk, efficacy, and intended use?
- Made claims appropriate to clinical evaluation and regulatory status?
- Collected, analyzed, and applied real-world evidence and/or product performance data to patient care?

No → Likely not a DTx

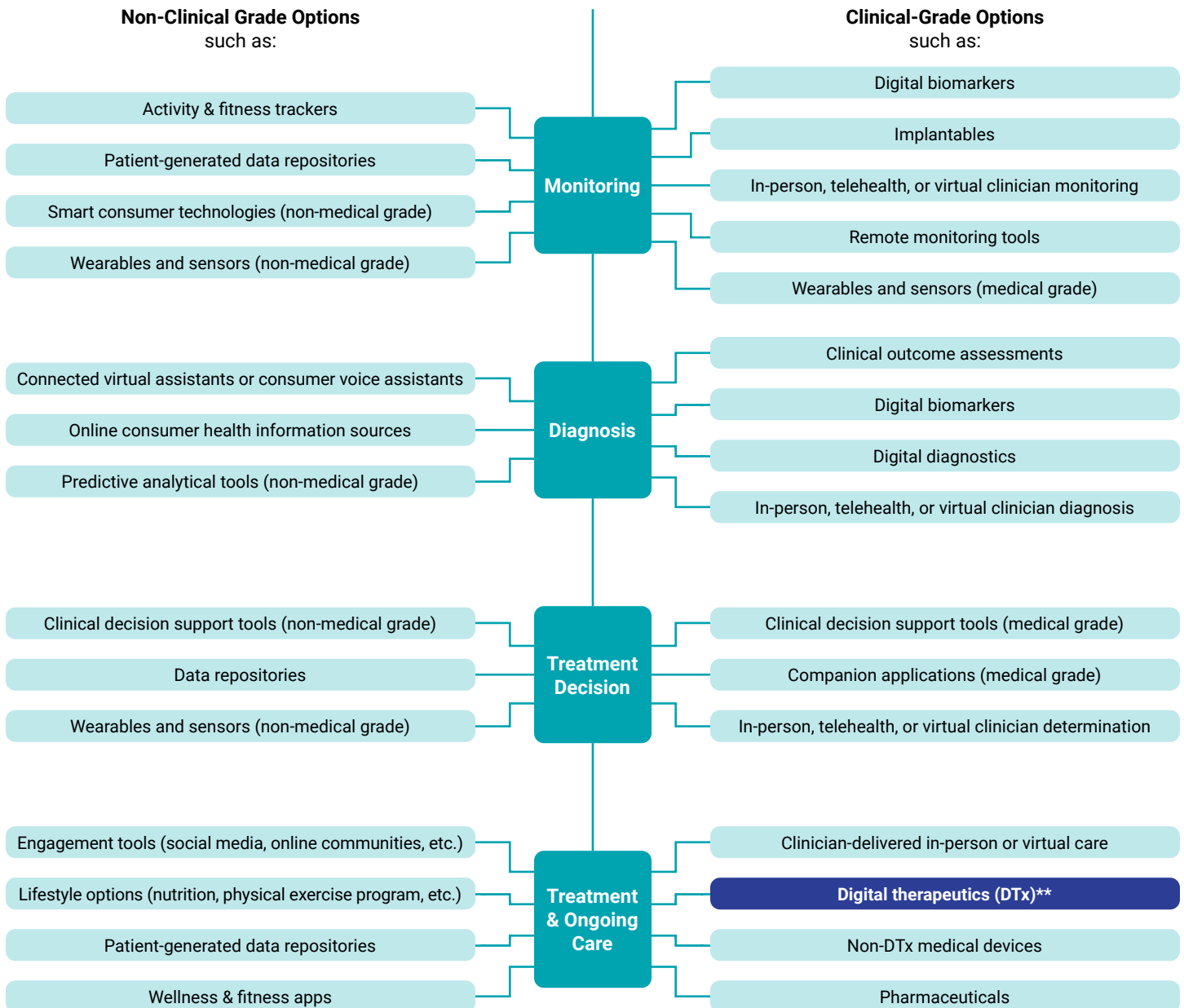**Yes** ↓

This product is likely a DTx

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:*

Non-Clinical Grade Options
such as:

Clinical-Grade Options
such as:

Monitoring

Non-Clinical Grade Options:
- Activity & fitness trackers
- Patient-generated data repositories
- Smart consumer technologies (non-medical grade)
- Wearables and sensors (non-medical grade)

Clinical-Grade Options:
- Digital biomarkers
- Implantables
- In-person, telehealth, or virtual clinician monitoring
- Remote monitoring tools
- Wearables and sensors (medical grade)

Diagnosis

Non-Clinical Grade Options:
- Connected virtual assistants or consumer voice assistants
- Online consumer health information sources
- Predictive analytical tools (non-medical grade)

Clinical-Grade Options:
- Clinical outcome assessments
- Digital biomarkers
- Digital diagnostics
- In-person, telehealth, or virtual clinician diagnosis

Treatment Decision

Non-Clinical Grade Options:
- Clinical decision support tools (non-medical grade)
- Data repositories
- Wearables and sensors (non-medical grade)

Clinical-Grade Options:
- Clinical decision support tools (medical grade)
- Companion applications (medical grade)
- In-person, telehealth, or virtual clinician determination

Treatment & Ongoing Care

Non-Clinical Grade Options:
- Engagement tools (social media, online communities, etc.)
- Lifestyle options (nutrition, physical exercise program, etc.)
- Patient-generated data repositories
- Wellness & fitness apps

Clinical-Grade Options:
- Clinician-delivered in-person or virtual care
- **Digital therapeutics (DTx)****
- Non-DTx medical devices
- Pharmaceuticals

*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 Product Evaluation Considerations

> Based on the Industry Core Principle that all DTx products should:
> ✅ **Treat, manage, or prevent a disease or disorder.**

DTx Product Basics

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

Potential evaluation considerations include:

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
» Approved indication(s)
» Directions for use
» Duration of therapy
» Dosing regimen
» Potential adverse events
» Risks or warnings
» Drug interaction(s)
» Device interaction(s)

Intended environment of therapy delivery, such as:
» Patient setting (i.e., home, work, school)
» Healthcare setting (i.e., clinic, hospital)
» Aged or disability residential care (i.e., nursing home, rehabilitation center)

Intended environment of ongoing therapy use, such as:
» Patient setting (i.e., home, work, school)
» Healthcare setting (i.e., clinic, hospital)
» Aged or disability residential care (i.e., nursing home, rehabilitation center)

Stage of development the product is currently in, such as:

» 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

Most recently released version of the DTx product

In addition to the DTx product delivering a therapeutic intervention directly to a patient via software, whether 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

Product's current stage of commercialization in the target jurisdiction of use, such as:

» 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

Product's stage of reimbursement in the target or other jurisdictions, such as:

» 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

Based on the Industry Core Principle that all DTx products should:
✅ **Produce a medical intervention that is driven by software**

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 been the only therapeutic option available to patients. However, with the introduction of digital therapeutics, patients may now have the opportunity to benefit from software-based therapies to achieve their therapeutic goals.

Potential evaluation considerations include:

The product's ability to directly impact patient needs and clinical outcomes, such as:

» 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, such as:

» 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

Whether the DTx has a comparator therapy

How the DTx therapy relates to the current standard of care, such as:

» 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

How the intervention aligns with evidence-based clinical guidelines, such as:

» 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

Data sets that may be used to determine patient progress in therapy, such as:

» 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)

> Based on the Industry Core Principle that all DTx products should:
> ✓ **Incorporate design, manufacturing, and quality best practices**

DTx Product Technical Considerations

Digital therapeutics are typically 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.

Potential evaluation considerations include:

Technical Considerations

DTx product's ability to function:

» As a standalone product

» With built-in capacity to integrate data streams and outputs with other products

» As part of a multi-product platform

Product's use of the following to generate therapeutic interventions through:

» Static algorithms

» Artificial Intelligence (AI) functionalities

» Machine Learning (ML) functionalities

DTx manufacturer process to prevent biases in therapeutic algorithms

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

» Software malfunction

» Hardware malfunction

» Integration malfunction

» Affiliated product malfunction

Data Infrastructure and Storage

Identifying entities typically responsible for:

» Data storage/hosting

» Data access

» Data ownership

» Data upkeep/deletion

Typical frequency of:

» Software patches

» Operating system updates

» Cybersecurity improvements

Measures tracked for DTx product uptime availability

Measures tracked for DTx product reliability

Data storage that may be hosted on a:

»   Private cloud

»   Public cloud

»   Hybrid cloud

»   Multicloud

Based on the Industry Core Principle that all DTx products should:

✅ **Engage end users in product development and usability processes**

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.

Potential evaluation considerations include:

Components required for the software to deliver its therapeutic value, such as:

» 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)

DTx product use on the following host technology(ies), such as:

» Smartphone

» Tablet

» Laptop or desktop computer

» Headset

» Wearable

» Medical device

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

» Hardware or affiliated medical device

» Wearable or sensor

Hardware components that may be:

» Patient-owned

» Provided to the patient

Level of network connection required for product use, such as:

» Does not require a sustained network connection (offline-capable)

» Requires ongoing basic network connection

» Requires ongoing broadband or high data connection

Product software compatibility with:

» iOS

» Android

» Web

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

» 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

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.

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.

Potential evaluation considerations include:

DTx product ability to account 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

Product Usability

» 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

Patient Protection

» Product provides necessary device and information security

» Patient data is protected

End User Support

» 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

Product Design Process

» Human factors testing, physiological tracking methods

» Qualitative research (i.e., focus groups, observational sessions, user interviews)

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 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.

Potential evaluation considerations include:

To use the product appropriately, individual patients may:

» 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

Patient financial considerations for the product may include:

» 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

Typical patient costs for the product

Clinical benefits the product provides patients with, such as:

» 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

Environmental and social benefits the product provides patients with, such as:

» 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)

Additional consumer friction points the product may address

Based on the Industry Core Principle that all DTx products should:
✅ **Incorporate patient privacy and security protections**

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.

Potential evaluation considerations include:

Manufacturer information security risk management and governance frameworks to account for information security controls, risk management, etc.

Cybersecurity certifications and/or accreditations the manufacturer and/or product maintains, such as:
» ISO/IEC 27001
» HITRUST
» SOC 2

Product cybersecurity credentials that are:
» Self-attested
» Externally certified
» Neither

Whether the scope of the certified company and/or product components are appropriate to their purpose

How the DTx product verifies:
» 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)

Protocols in place to address a data breach or other privacy/data security crisis

Manufacturer engagement in vulnerability testing

Other measures the manufacturer uses 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.

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.

Potential evaluation considerations include:

DTx product provides end user with a privacy notice that may describe:
- » 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

Patient may be able to consent and authorize how personal digital health data are:
- » Stored
- » Shared
- » Saved
- » Incorporated in digital health records

Types of personally identifiable and sensitive data the product gathers

Types of internal company policies and procedures to determine how information is collected, protected, and used

Data storage on a:
- » Public cloud
- » Private cloud
- » Dedicated server

Data storage in various geographic location(s)

Product insurance liability coverage

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

Policies that govern third-party access and utilization of data

Types of data that may be shared from the DTx product with third-parties

DTx manufacturer procedures in case of a potential data privacy breach

DTx Product Evaluation Considerations

Based on the Industry Core Principle that all DTx products should:

✓ **Apply product deployment, management, and maintenance best practices**

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.

Potential evaluation considerations include:

Product Authorization

Patient access to the product that 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 me

» "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

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

Product Distribution

Patient receipt of a product access code, if necessary, 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

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

DTx hardware product components (i.e., sensors, wearables) that are:

» Retained by the patient following product use

» Returned to the DTx manufacturer following product use

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.

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 often 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

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

» 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

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

» Engage with the DTx therapy in some capacity

» 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

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)

DTx Product Evaluation Considerations

Clinician engagement in DTx-related care may include:

» 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

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.

Potential implementation considerations include:

DTx "Engagement Chain"[1]

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 | B. Outreach | C. Activate | D. Engage | E. Support |

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

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[1] 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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Metric: Measured as "n"

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

| A. Target | B. Outreach | C. Activate | D. Engage | E. Support |

### 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)

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.

| A. Target | B. Outreach | C. Activate | D. Engage | E. Support |
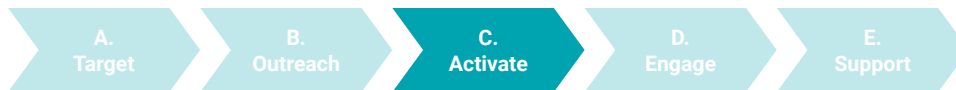
C. Activate

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)

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.

| A. Target | B. Outreach | C. Activate | D. Engage | E. Support |

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)

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.

| A. Target | B. Outreach | C. Activate | D. Engage | E. Support |

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

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.

Based on the Industry Core Principle that all DTx products should:

✅ **Publish trial results inclusive of clinically meaningful outcomes in peer-reviewed journals**

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.

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

Potential study designs include:

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

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.

Real-World Outcomes

RWD generation:

» Product performance and technical outputs

» End user and clinician engagement and satisfaction measures

RWE generation:

» Pragmatic clinical trial using an RCT-type design, with real-world elements

» RWE as a retrospective or prospective observational study

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

Economic Evaluation
» Budget impact analysis
» Cost-benefit analysis
» Cost-effectiveness analysis
» Cost-utility analysis
» Cost-minimization analysis

Systematic Review
» Meta analysis

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.

Potential evaluation considerations include:

Study Basics

Study name

Publication name and citation

Trial registry number

Whether the study protocol was modified after registering in clinicaltrials.gov or a similar registry

Study status:
» Currently underway
» Completed, but not published
» Completed and published
» Study partners (i.e., university, CRO)
» Sponsor or funding source(s)
» Study peer-review status

Study Design
Clinical study design used, such as:
» RCT
» Non-randomized controlled trial
» Prospective, single arm trial
» Cohort study
» Case-control study
» Case study
» Pragmatic clinical trial
» RWE

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 that may be representative of:
» General population
» Target population

Dataset balance across:
» Gender
» Ethnicity
» Age

Clinical Outcomes

Key findings of the study

Primary endpoint

Secondary endpoints

Comparator used

Treatment and intervention used, dosing regimen

Concomitant therapies, washout period

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.

The following criteria are based upon the tenets of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework.[2]

Potential evaluation considerations include:

Study accounts for the following considerations:

Risk of Bias
- » Potential limitations in the design or conduct of the study are identified
- » Conflicts of interest among study contributors are identified

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

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

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

Publication Bias
- » Potential holes in evidence are accounted for
- » Outcomes are generated from experimental/interventional data
- » Published studies underwent a peer-review process

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

Based on the Industry Core Principles that all DTx products should:

✅ **Be reviewed and cleared or certified by regulatory bodies as required to support product claims of risk, efficacy, and intended use**

✅ **Make claims appropriate to clinical evaluation and regulatory status**

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.

Potential evaluation considerations include:

Jurisdictions the product has completed regulatory reviews and/or received market authorization in, including:

» Jurisdiction (country or region)

» Regulatory or notified body

» Clearance, certification, or approval date

» Regulatory class (product classification)

» Product indication

» Other regulatory designations

Jurisdictions the product is undergoing regulatory and/or market authorization review

Jurisdictions the product does not require regulatory review and is marketed

Based on the Industry Core Principle that all DTx products should:

✔ **Collect, analyze, and apply real-world evidence and/or product performance data**

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.

Potential evaluation considerations include:

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 a DTx 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)

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)

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)

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.

Potential evaluation considerations include:

How DTx-generated RWD outcomes may be used in practice, such as:

» 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

Additional data sources that may be merged with DTx-generated RWD, such as:

» 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

Who is responsible for analyzing and delivering RWD outcomes, such as:

» DTx manufacturer

» Health system

» Clinician

» HCDM/payor

Level of the DTx-generated data source chain reviewers and clinicians may see, such as:

» Raw data

» Processed data

» Data trends

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.

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.

Potential evaluation considerations include:

Conducting an RWE Study

Situations most appropriate to develop RWE for a DTx product, such as:

» 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)

When it may not be necessary to conduct an RWE study, such as:

» 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

Benefit of RWE Studies

Target groups most likely to benefit from an RWE study for this product, such as:

» 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)

Evaluating an RWE Study

Who conducted the RWE study, such as:

» DTx manufacturer

» Health system or clinical team

» Employer

» Payor

» Academic institution

» Third-party entity

Inputs included in the RWE study, such as:

» 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)

Considerations incorporated into the RWE study design, such as:

» 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

Verification that 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.

Where the RWE study results are published, such as:

» Publicly, in a peer-reviewed publication

» Publicly, available in a white paper

» Internal analysis (i.e., informal report, formal report)

Who has access to RWE study results, such as:

» HCDM and/or payor

» HTA or formulary review committee

» Point-of-care clinician

» Patient and/or caregiver

» Publicly available

DTx Product Evaluation:
Economic Assessment
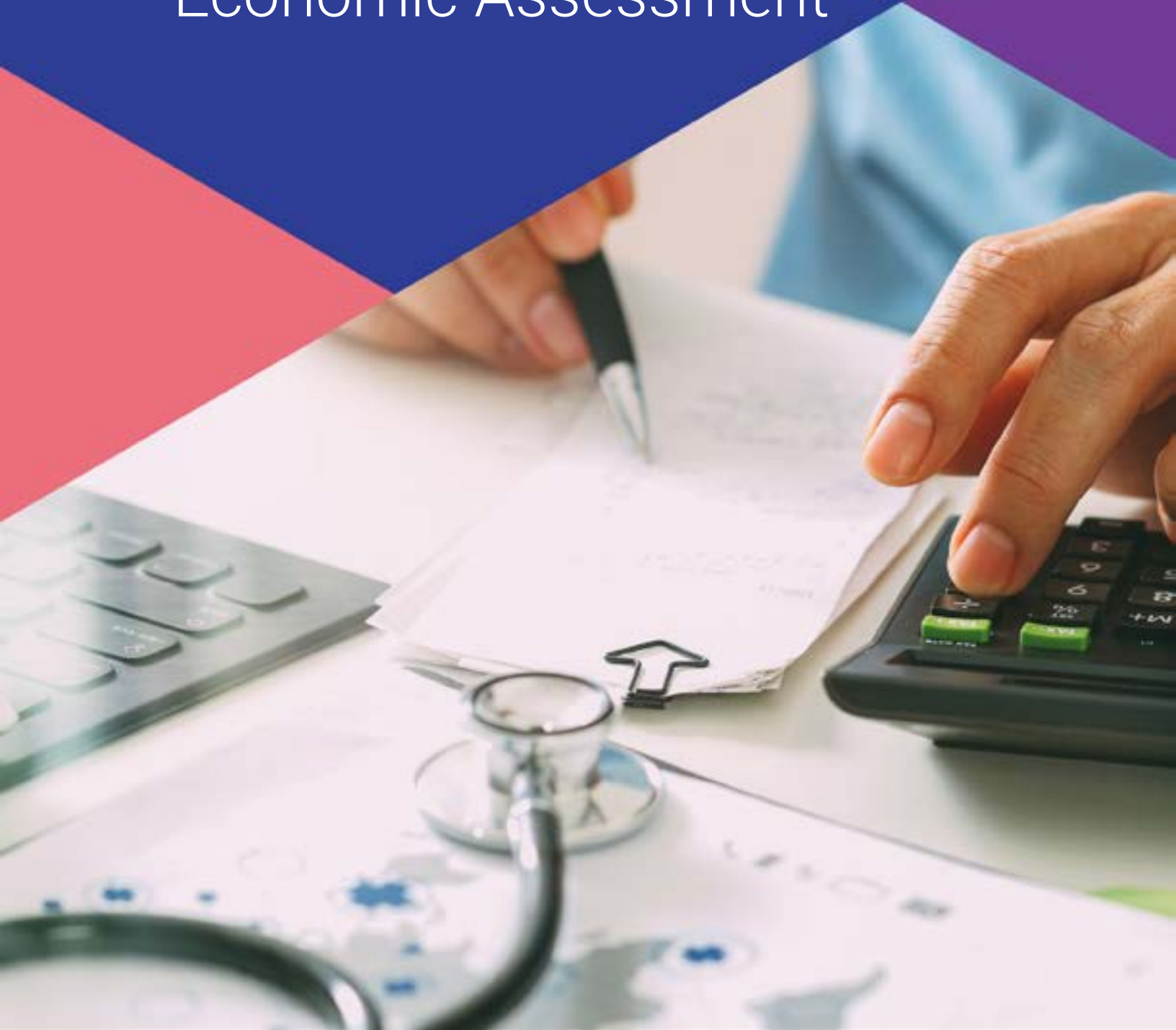
Preparing for a DTx Economic Analysis

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.

Potential considerations include:

Purpose of conducting a product-specific economic evaluation analysis for a DTx product, such as:

» 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

Steps to be completed in advance of this economic analysis, such as:

» 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

Possible sources of economic data to be included in DTx economic evaluations for the product, such as:

» 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)

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

Potential economic evaluation models HCDMs may consider using for the therapy:

» 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

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.

Potential considerations include:

Entity responsible for completing product-specific economic analyses

Entity responsible for generating data for analyses

Components that could 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

Whether results of this type of economic analysis are published in peer-reviewed literature

Point(s) in the product life cycle most appropriate for conducting this economic analysis:

» Pre-market phase

» Market approval phase

» Post-market phase

Suggested cadence of economic analysis reviews, such as:

» Product does not require subsequent cost analyses following the initial evaluation

» Product should undergo periodic cost analysis updates (i.e., ongoing product iterations, product optimization)

» Product requires an annualized (or similar) cost savings assessment to understand patient utilization of services (requires use of data from the HCDM)

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

» Expected timelines

» Anticipated costs

» Entities generally responsible for covering new expenses

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 Economic Impact

» Cost of the DTx course of therapy vs. a traditional or comparator therapy (i.e., replacement, new costs)

» Costs that 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)

» Durability of effect the therapy is expected to provide (i.e., short-term impact, long-term impact)

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

» Follow-on costs generated by the DTx therapy (i.e., booster therapies)

» Costs incurred or covered by the payor or other entities (i.e., employer, health system, clinician, patient)

» Overall cost effectiveness of the DTx therapy vs. a traditional or comparator therapy

Assessing Indirect Economic Impact

» Clinical or economic benefits 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)

» Health system savings 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)

» Impact on clinician productivity, patient reach, and workflows

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

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

Factors That Affect DTx Therapy Economic Impact

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

Potential considerations include:

Patient and Caregiver Clinical Outcome Considerations

DTx therapy economic evaluation could 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)

Clinician and Health System Administrative Considerations

DTx therapy economic evaluation could 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)

Payor Considerations

DTx therapy economic evaluation could 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

Employer Considerations

DTx therapy economic evaluation could 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

Health Technology Assessment (HTA) Considerations

Existing HTA frameworks[3] 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 these HCDMs to be involved in the development of best practices established at the country and industry level.

HTA evaluations for a DTx product could 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)

» Likely budget impacts of implementing the technologies (vs. comparators, if applicable)

Measurement and Estimation of Outcomes

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

Examination of Costs and Outcomes

» Estimated differences in costs and outcomes between the technology and its comparator(s)

Characterizing Uncertainty

» Possible uncertainties surrounding the costs and economic evaluation(s) of the technology

Characterizing Heterogeneity

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

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

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

Appendices

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

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

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

2. **What level of evidence has the product generated?**
   » 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)

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

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

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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

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

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)

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

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

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

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]

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[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

DTx Product Examples[11]

This list provides examples of DTx products that are manufactured by DTA member companies, in addition to select references of clinical study outcomes. Each product attests to aligning with DTA's Core Principles. DTA does not certify or accredit DTx products. The below information is provided for educational purposes and does not constitute official claims or product endorsements. This is not a comprehensive list of DTx products available to patients.

DTx Product Name	Manufacturer	Disease or Disorder	Sample Clinical Outcomes
BlueStar® and BlueStar Rx®	Welldoc	Diabetes, types 1 & 2	Patients using BlueStar typically achieve a 1.7 to 2 points average decrease in HbA1c in the first 3 to 6 months of usage.
d-Nav®	Hygieia	Diabetes, type 2	Results of clinical studies, published in peer-reviewed articles, evaluating the d-Nav Program showed that patients had significantly improved their A1C with a lower frequency of both mild and severe hypoglycemia.
Dario Blood Glucose Management System®	Dario Health	Diabetes, types 1 & 2	People with high-risk type 2 diabetes improved their A1C by 1.4% over 12 months.
Daylight®	Big Health	Generalized anxiety disorder (GAD)	Daylight helped 71% of patients achieve clinical improvement in anxiety.
deprexis®	Orexo	Depression	deprexis® demonstrated a statistically significant improvement of depression symptoms when used as adjunctive therapy.
EndeavorRx®	Akili Interactive	Attention-deficit/ hyperactivity disorder (ADHD)	EndeavorRx demonstrated improvements in ADHD impairment with responder rates ranging 40–55% after 1-month treatment and 68% following a second month of treatment.
Freespira®	Freespira, Inc	Panic disorder, panic attack, and post-traumatic stress disorder (PTSD)	*Panic disorder and panic attack:* 86% panic attack free immediately post-treatment and 73% panic attack free at 12 months post-treatment. *PTSD:* At 6-months post-treatment, 89% reported significant decrease in symptom based on CAPS-5 Score (validated PTSD assessment) and 50% were in remission.

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[11] Specific references to sample clinical outcomes are found in the individual product profiles on DTA's Product Library.

DTx Product Name	Manufacturer	Disease or Disorder	Sample Clinical Outcomes
HelloBetter Diabetes & Depression	HelloBetter	Depressive symptoms in diabetes, type 1 or 2	RCT demonstrated that 64% of patients experienced a substantial reduction of symptoms and 45% of patients had no clinical symptoms after 6 months.
leva	Renovia	Urinary incontinence	In an adequately-powered RCT, participants using leva report statistically and clinically significant symptom improvement as early as 4-weeks and continued improvement through the 8-week study period, as measured by validated outcome measures and compared to an active control.
Insulia®	Voluntis	Diabetes, type 2	Insulia is an aid in the management of type 2 diabetes.
Kaia Health®	Kaia Health	Musculoskeletal pain	Kaia Health, when compared with standard of care, resulted in a 136% reduction in pain.
Kaiku Health®	Kaiku Health	Cancer care	Kaiku Health improved overall survival, improved health-related quality of life, earlier detection of symptoms and/or relapse.
Nerivio®	Theranica	Migraine	Seven out of ten migraine patients using Nerivio see significant pain relief; four out of ten experience pain freedom.
Propeller®	Propeller Health	Asthma and chronic obstructive pulmonary disease (COPD)	Propeller has demonstrated a 58% increase in asthma medication adherence, a 78% reduction in rescue inhaler use, and a 63% increase in asthma control.
reSET®	Pear Therapeutics	Substance use disorder (SUD)	Among patients whose primary addiction was not opioids, adding reSET® to outpatient therapy more than doubled abstinence rates (40% vs. 18%). Among all patients, adding reSET® to outpatient therapy improved rates of retention (76% vs. 63%).
reSET-O®	Pear Therapeutics	Opioid use disorder (OUD)	Adding reSET-O® to outpatient treatment using buprenorphine increased retention of patients with OUD by almost 15%.

DTx Product Name	Manufacturer	Disease or Disorder	Sample Clinical Outcomes
Sleepio®	Big Health	Sleep disorders	Sleepio helped 76% of patients achieve clinical improvement in insomnia.
SparkRx	Limbix	Symptoms of depression in adolescents	Research demonstrated that SparkRx resulted in a clinically meaningful reduction in depression symptoms. 24% of participants showed a treatment response and 17% were in remission by the end of the intervention.
Somryst®	Pear Therapeutics	Insomnia	Somryst patients experienced: » 45% in the amount of time it took to fall asleep » 52% reduction in the amount of time spent awake at night » 45% reduction in the severity of insomnia symptoms.
TALi®	TALi Digital	Attention impairments	Neurodiverse children exhibit not only significant gains in attention after completing the 5-week training program, but are sustained 3 months later with additional numeracy improvements also observed.
Vorvida	Orexo	Alcohol use	Vorvida® demonstrated a statistically significant reduction in average daily alcohol consumption at 3 and 6 months when compared to care-as-usual.

Note: Please visit the DTA Product Library for specific references to each of the data points included above.

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.