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Health informatics — Personalized digital health — Digital therapeutics health software systems

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Foreword

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This document was prepared by Technical Committee ISO/TC 215, *Health informatics*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

As the healthcare sector evolves, there is an increasing demand for the production and appropriate use of digital health technologies (DHTs) across patient care settings. DHTs represent a broad spectrum of products ranging from clinician-facing electronic prescribing systems, telemedicine platforms, and decision support systems, to patient-facing wellness apps, diagnostic tools, monitoring products, digital biomarkers, and therapeutics.

Given the diversity of digital products available, it is important for patients, clinicians, and healthcare decision makers to have the ability to clearly distinguish between the numerous types of DHTs on the market. Without harmonized international guidance, healthcare decision makers and users are often unable to differentiate between, assess, and optimize the appropriate use of DHTs in practice based on the intended use of each product.

Digital therapeutics (DTx), as defined in this document, represent a type of medical product that can be used as standalone therapy, incorporated into a multi-functional DHT, or integrate into clinical care pathways alongside clinician-delivered therapies, pharmaceuticals, medical devices, or other DHTs.

Standards exist for various non-DTx DHT product categories and varying DTx product definitions, best practices, and country-level standards exist at the industry level (see Annex A), yet no DTx-specific international standards exist. This document centres on the ability of DTx to generate and deliver validated and measurable medical interventions directly to patients. It is relevant to patients, clinicians, healthcare decision makers, and product manufacturers.

Health informatics — Personalized digital health — Digital therapeutics health software systems

1 Scope

This document lists characteristics of a category of health software: digital therapeutics (DTx). DTx products generate and deliver medical interventions that are based on clinical evidence, have demonstrable positive therapeutic impacts on patient health, and produce real-world outcomes. Product use cases (see Annex B) demonstrate the variety of products represented in this quickly growing industry.

This document provides an overview of how DTx relates to other ecosystem constructs, including medical devices, software as a medical device (SaMD), software in a medical device (SiMD), and other digital health technologies (DHT). It also addresses relevant health and medical device software standards that have various degrees of applicability to DTx.

The focus of this document is on therapeutic products that are used in the context of a disease, disorder, condition, or injury for human use. It does not address products that are intended for veterinary use or for general wellbeing. Additional exclusions of this document include DTx market access pathways (i.e. prescription, non-prescription pathways), medical device requirements, product risk assessment, clinical evidence requirements, data security, patient privacy considerations, and product authorization pathways.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
digital health technology
DHT
system that uses computing platforms, connectivity, software, and sensors for healthcare and related uses

Note 1 to entry: These technologies span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a medical product, in a medical product, or as an adjunct to other medical products (devices, drugs, and biologics). They can also be used to develop or study medical products.

[SOURCE: BEST Resource[1]]

3.2
system
combination of interacting elements organized to achieve one or more stated purposes

[SOURCE: ISO/IEC/IEEE 15288: 2015, 4.1.46, modified — Notes to entry deleted.]

3.3
user
person using the system for a health-related purpose

Note 1 to entry: The user can be the subject of care directly, or an individual assisting (as proxy for) the subject of care.

[SOURCE: ISO 81001-1:2021, 3.1.14]

3.4
intended use
intended purpose
use for which a product, process or service is intended according to the specifications, instructions and information provided by the manufacturer

Note 1 to entry: The intended medical indication, patient population, part of the body or type of tissue interacted with, user profile, use environment, and operating principle are typical elements of the intended use.

[SOURCE: ISO/IEC Guide 63:2019, 3.4, modified — Added admitted term "intended purpose".]

3.5
digital therapeutic
DTx
health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has a demonstrable positive therapeutic impact on a patient's health

Note 1 to entry: Many jurisdictions consider DTx a medical device.

Note 2 to entry: DTx can integrate with ancillary components to form a DTx system by:

— using general purpose hardware or platforms (i.e. smartphone, tablet, computer, watch, headset), input or output components (i.e. wearables, sensors), pharmaceuticals, or patient or clinician support components necessary for DTx functioning;

— using patient- and context-specific data to generate a medical intervention.

Note 3 to entry: DTx can function independently or in addition to other interventions, such as integrating with:

— other DHT components (i.e. monitoring, diagnostic, clinical decision support) as part of a multi-functional DHT product;

— tandem medical interventions (i.e. clinician-delivered therapies, pharmaceuticals, medical devices, DHTs).

Note 4 to entry: DTx includes secondary prevention and tertiary prevention.

Note 5 to entry: DTx is produced in compliance with good product life cycle (PLC) management practices, through use of a quality management system which encompasses demonstrated safety and effectiveness, and post-market surveillance.

3.6
medical device
instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of

— diagnosis, prevention, monitoring, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury,

— investigation, replacement, modification, or support of the anatomy or of a physiological process,

— supporting or sustaining life,

— control of conception,

— disinfection of medical devices,

— providing information by means of in vitro examination of specimens derived from the human body,

and which does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which can be assisted in its intended function by such means

Note 1 to entry: Products which can be considered to be medical devices in some jurisdictions but not in others include:

— disinfection substances,

— aids for persons with disabilities,

— devices incorporating animal and human tissues,

— devices for in-vitro fertilization or assisted reproductive technologies.

[SOURCE: ISO/IEC Guide 63:2019, 3.7]

3.7
medical intervention
activity intended to maintain or improve an individual's health or functioning, or to alter the course of a disease, disorder, or condition for the better, or to restore function lost through disease or injury

3.8
health software
software intended to be used specifically for managing, maintaining or improving health of individual persons, or the delivery of care

Note 1 to entry: Health software fully includes what is considered software as a medical device.

[SOURCE: IEC 82304-1:2016, 3.6, modified — Note 2 to entry deleted.]

3.9
evidence
directly measurable characteristics of a process or product that represent objective, demonstrable proof that a specific activity satisfied a specified requirement

[SOURCE: ISO/IEC 21827:2008, 3.19]

3.10
software as a medical device
SaMD
software intended to be used for one or more medical purposes that performs these purposes without being part of a hardware medical device

Note 1 to entry: SaMD is a medical device and includes in-vitro diagnostic (IVD) medical device.

Note 2 to entry: SaMD is capable of running on general purpose (non-medical purpose) computing platforms.

Note 3 to entry: "without being part of" means software not necessary for a hardware medical device to achieve its intended medical purpose.

Note 4 to entry: Software does not meet the definition of SaMD if its intended purpose is to drive a hardware medical device.

Note 5 to entry: SaMD can be used in combination (e.g. as a module) with other products including medical devices.

Note 6 to entry: SaMD can be interfaced with other medical devices, including hardware medical devices and other SaMD software, as well as general purpose software.

Note 7 to entry: Mobile apps that meet the definition above are considered SaMD.

[SOURCE: IMDRF 2013,[7] modified — 'may' changed to 'can'.]

3.11
software in a medical device
SiMD
software that is used as an integral part of a specified hardware medical device or is intended to drive a hardware medical device

3.12
health
state of complete physical, mental and social well-being and not merely the absence of disease or infirmity

[SOURCE: WHO 1948[8]]

3.13
risk
combination of the probability of occurrence of harm and the severity of that harm

Note 1 to entry: The probability of occurrence includes the exposure to a hazardous situation and the possibility to avoid or limit the harm.

[SOURCE: ISO/IEC Guide 63:2019, 3.10]

3.14
privacy
freedom from intrusion into the private life or affairs of an individual when that intrusion results from undue or illegal gathering and use of data about that individual

[SOURCE: ISO/TS 27790:2009, 3.56]

3.15
positive therapeutic impact
favourable or useful response to, effect resulting from, or outcome of a medical intervention

3.16
component
collection of system resources that a) forms a physical or logical part of the system, b) has specified functions and interfaces, and c) is treated (e.g. by policies or specifications) as existing independently of other parts of the system

[SOURCE: IETF RFC 4949,[10] modified — Note 1 deleted.]

3.17
tandem medical intervention
two or more medical interventions, each capable of producing a positive therapeutic benefit, when implemented together, which are expected to produce a higher level of benefit than either one alone

3.18
secondary prevention
intervention for individuals or groups that demonstrate early psychological or physical symptoms, difficulties, or conditions (i.e. subclinical problems), which is intended to prevent the development of more serious dysfunction or illness

[SOURCE: APA [11]]

3.19
tertiary prevention
intervention for individuals or groups with already established psychological or physical conditions, disorders, or diseases

Note 1 to entry: Tertiary interventions include attempts to minimize negative effects, prevent further disease or disorder related to complications, prevent relapse, and restore the highest physical or psychological functioning possible

[SOURCE: APA [11]]

3.20
quality management system
part of a management system with regard to quality

Note 1 to entry: Requirements for a quality management system are given in ISO 9001.

[SOURCE: ISO 9000:2015, 3.5.4, modified — Note 1 to entry replaced with new note 1 to entry.]

3.21
safety
freedom from unacceptable risk

[SOURCE: ISO/IEC Guide 63:2019, 3.16]

3.22
effectiveness
ability to produce the intended result

[SOURCE: ISO 81001-1:2021, 3.2.5]

4 Context

The digital health landscape encompasses a broad range of technologies, with each serving a specific purpose. While some DHTs are used for wellness, medication adherence, monitoring, or patient diagnosis, DTx products use software to generate and deliver a medical intervention that directly impacts a disease, disorder, condition, or injury. Without a common international DTx definition, healthcare decision makers are not able to consistently identify DTx products and distinguish them from other DHTs and medical devices to determine which products best meet patient and population needs and expectations.

National regulatory, assessment, and reimbursement frameworks are increasingly emerging to better enable DHT market and patient access:

— In 2010, the U.S. Food and Drug Administration (FDA) granted its first Class II 510(k) medical device clearance to a DTx product,[15] and in 2017, its first de novo product clearance[16].

— In 2013, the International Medical Device Regulators Forum (IMDRF) published 'Software as a Medical Device (SaMD): Key Definitions' to establish a common framework for regulators to incorporate converged controls into their regulatory approaches for SaMD[7].

— In 2018, the Belgian Federal Government launched the mHealthBelgium platform for mobile apps that are CE-marked as a medical device[17].

— In 2019, England's National Institute for Health and Care Excellence (NICE) released the Evidence for Effectiveness functional classification of DHTs that categorizes three tiers of DHTs based on potential risk to users. The framework was updated in 2022[18].

— In 2020, Germany launched a Fast-Track Process for Digital Health Applications [digitale Gesundheitsanwendungen (DiGA)],[19] with Class I or Class IIa medical devices under the European Union's Medical Device Regulation (MDR) qualifying for DiGA recognition.

— In 2020, the South Korea Ministry of Food and Drug Safety (MFDS) established a DTx-specific regulatory framework, recognizing DTx as a subcategory of SaMD[20].

— In 2022, the European Taskforce for Harmonized Evaluation of Digital Medical Devices (DMDs) launched to provide a blueprint for appropriate assessment procedures and methodologies in Europe, with the overall goal of enabling a harmonized approach for European assessment, national appraisal, and reimbursement by statutory health insurance organisations for distinct subclasses of DMDs[21].

— In 2023, France is launching a fast-track DMD reimbursement pathway for therapeutic and remote monitoring products. The Prise En Charge Anticipee (PECA) decree will allow a temporary one-year reimbursement of DMD products until they provide further robust clinical evidence[22].

While momentum in developing and implementing national DHT, DMD, or mHealth frameworks continues to build, there are inconsistencies in how DTx products are named and classified, in addition to what qualification requirements these products are expected to meet (aside from the Republic of Korea, which has developed a DTx-specific national framework).

Developing a consistent, internationally recognized definition of a DTx and eventual corresponding quality standards will enable policymakers and other healthcare decision makers to develop appropriate regulatory, assessment, reimbursement, or patient access frameworks that properly distinguish DTx from other product types and establish harmonized expectations related to DTx function, reliability, and real-world impact.

5 Considerations

5.1 DTx Attributes

According to the Digital Therapeutics Alliance (DTA), DTx products require certain fit-for-purpose standards due to their agile development processes, mechanisms of action, ability to generate real-time outcomes, ongoing iterative nature, lower potential risk profiles, and place in clinical therapy. Although DTx-specific standards incorporate aspects of existing pharmaceutical and medical device frameworks, they should include any necessary tailor-made components that enable appropriate and efficient DTx product design, capability, and performance assessments[23].

5.2 Impact on patient care

DTx has direct impact on patient health, similar to how pharmaceuticals and clinician-delivered therapies have direct impact on patient health.

DTx products can be used by patients independently (i.e. without professional guidance). Many products, however, offer the possibility of professional guidance, referred to as guided self-management interventions, or can be supplemented with clinician-delivered interventions, called a blended intervention or combined treatment[24].

DTx are not intended to solely augment a human decision and are therefore classified differently from clinical decision support (CDS) tools.

DTx products are autonomous and differ from Medical Device Data Systems (MDDS), a class of systems that has no intelligence and serves as an accessory to other regulated technology that does have intelligence.

5.3 Relationship to SiMD

DTx typically forms a subset of SaMD. Software whose sole intent is to operate a medical purpose device (SiMD), regardless of whether the software is embedded or remote, does not qualify as a DTx. However, if the DTx is hosted on general purpose hardware (i.e. VR headset), even if the hardware is customized,

branded, or locked for a specific function, the product qualifies as a DTx since the headset is general purpose and not a medical purpose device.

For example, if a virtual reality (VR) headset is branded and used exclusively with DTx, the headset is still considered to be general purpose hardware, as opposed to a medical purpose hardware. In this case, VR software is loaded on the headset, but this software is not "embedded" in the hardware to control a medical purpose device, as defined for SiMD devices. Further discussion is warranted related to the relationship between VR, SaMD, and SiMD since in this example, the VR software controls the headset hardware only to the extent needed for visual display. Yet, since the VR software needs to be paired with a headset to function and will not be effective if displayed on another platform such as a smartphone, it cannot be strictly classified as SaMD.

5.4 DTx in context of a DTx System

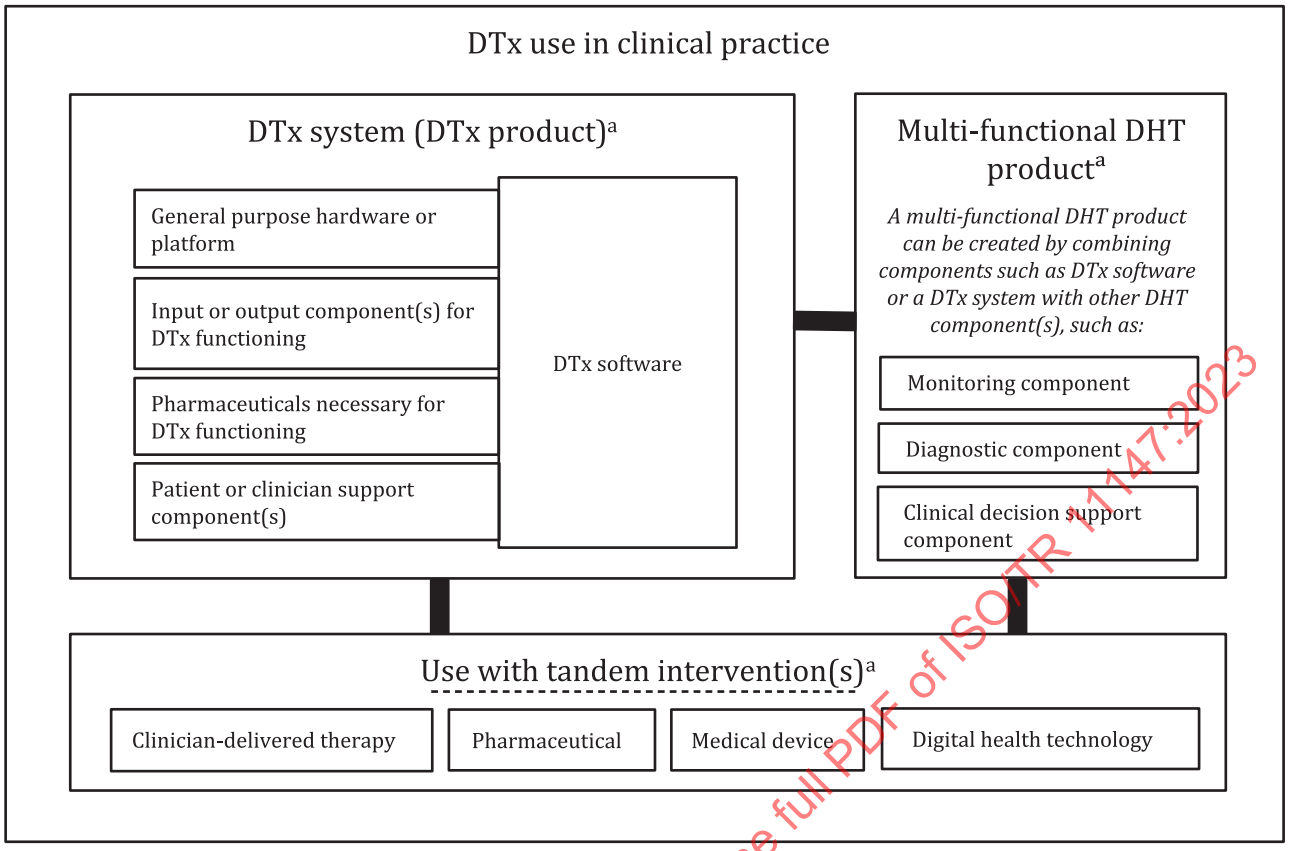
While this document focuses on software, there are other components (i.e. general purpose hardware, input and output components, pharmaceuticals) that can be incorporated into or work alongside a DTx system or software.

First, as shown in Figure 1, a DTx system (also commonly referred to as a DTx product) includes DTx software and any structural elements necessary to facilitate and enable the DTx to generate and deliver its medical intervention. Components necessary for the software to function can include hardware (i.e. smartphone, tablet, computer, watch, headset, sensors), input or output components (i.e. wearables, sensors, software, operating system), pharmaceuticals, or patient or clinician support components (i.e. coaching, real-world outcomes dashboard). A DTx system can also include other required components, such as a quality management system. While hardware components are typically general purpose in nature, as discussed above, it is still possible for the hardware to be customized, branded, or locked for a specific function.

Second, similar to how a pharmaceutical product can incorporate multiple active components in a single product, a multi-functional DHT product can combine a DTx system or software with other DHT component(s) (i.e. monitoring, diagnostic, clinical decision support features). In this case, it is important for clinicians, patients, and other users to understand the intended use and functionality of each individual component. Additionally, it is important for authorities with jurisdiction and policymakers to understand the intent, performance, and outcomes associated with each component. This allows product evaluators to assess the respective safety, efficacy, and impact of each system component based on its intended use (i.e. therapeutic, monitoring, diagnostic, wellness, decision support), in addition to each component's direct impact on the safety, efficacy, and impact of the multi-functional DHT product.

Third, DTx products can work alongside other tandem medical interventions to deliver a cohesive therapy. Components that can form this level of a DTx system include other therapeutic categories (i.e. clinician-delivered therapies, pharmaceuticals, medical devices, DHTs).

Whether a patient uses a multi-functional DHT product, or a combination of a DTx or multi-functional DHT product with a tandem medical intervention, they should have a clear understanding of what components are part of the system.



a Examples provided are representative of potential components. Inclusion in the diagram does not imply necessity for clinical practice.

Figure 1 — Use of DTx system in clinical practice

6 DTx in relation to ecosystem constructs

6.1 Existing ecosystem constructs

Existing ecosystem constructs, as shown in Figure 2, including medical devices, SaMD, SiMD, and DHT, directly relate to DTx, but individually, do not sufficiently define DTx products. However, when viewed in relation to each other, they provide more context on the DTx industry's positioning. Boxes representing each industry do not correlate to the size of the industry they represent.

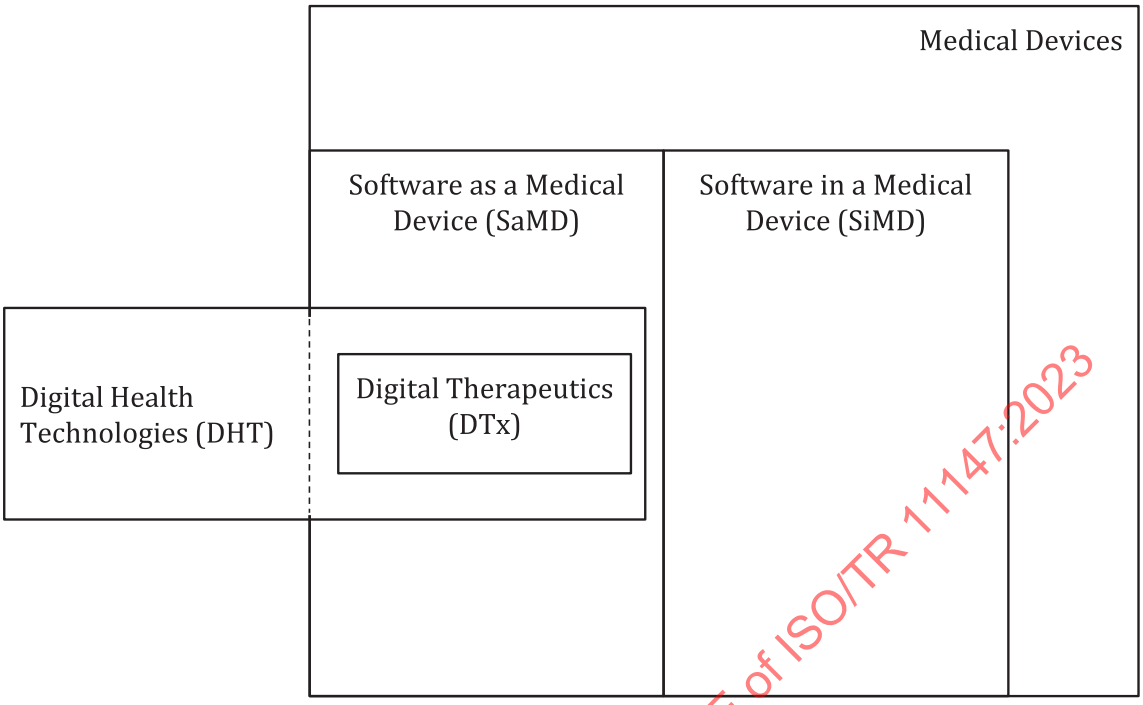


Figure 2 — Relationship of DTx, medical devices, and DHTs

6.2 Medical device

While digital therapeutics typically qualify as a medical device, there can be situations in certain regulatory jurisdictions where DTx products cannot be regulated as a medical device or the jurisdiction does not yet have regulations in place that pertain to digital therapeutics.

6.3 Software as a Medical Device (SaMD)

In many national regulatory frameworks, DTx products are associated with the International Medical Device Regulators Forum's (IMDRF) definition of SaMD. While DTx products typically qualify as SaMD, IMDRF's SaMD framework is non-specific to digital therapeutics and includes numerous non-DTx products.

The IMDRF SaMD framework categorizes product intended use by two major factors: the significance of the information provided by the SaMD to the healthcare decision, and the state of the healthcare situation or condition.

In assessing the significance of the information provided by the SaMD to the healthcare decision, the following three categories are considered[25]:

— To treat or to diagnose: Infers that the information provided by the SaMD will be used to take an immediate or near term action:

  — To treat/prevent or mitigate by connecting to other medical devices, medicinal products, general purpose actuators or other means of providing therapy to a human body.

  - To diagnose/screen/detect a disease or condition (i.e. using sensors, data, or other information from other hardware or software devices, pertaining to a disease or condition).

- To drive clinical management: Infers that the information provided by the SaMD will be used to aid in treatment, aid in diagnoses, to triage or identify early signs of a disease or condition will be used to guide next diagnostics or next treatment interventions:
  - To aid in treatment by providing enhanced support to safe and effective use of medicinal products or a medical device.
  - To aid in diagnosis by analysing relevant information to help predict risk of a disease or condition or as an aid to making a definitive diagnosis.
  - To triage or identify early signs of a disease or conditions.
- To inform clinical management: Infers that the information provided by the SaMD will not trigger an immediate or near-term action:
  - To inform of options for treating, diagnosing, preventing, or mitigating a disease or condition.
  - To provide clinical information by aggregating relevant information (e.g. disease, condition, drugs, medical devices, population, etc.).

6.4 Software in a Medical Device (SiMD)

While DTx products do not typically qualify as SiMD, they are able to directly interface with medical devices containing SiMD as part of the broader DTx system.

DTx excludes software that is running on hardware that is declared by a manufacturer to be a regulated medical device, such as the SiMD product examples of closed loop physiologic control systems, implantables, ventilators, etc.

However, if the DTx is hosted on general purpose hardware (i.e. VR headset), even if the hardware is customized, branded, or locked for a specific function, the product still qualifies as a DTx since the headset is general purpose and not a medical purpose device.

6.5 Digital Health Technology (DHT) Frameworks

6.5.1 DHT Overview

The digital health landscape encompasses a broad range of technologies, with each serving a specific purpose. There are numerous examples of DHT frameworks, three of which are provided below - one from an industry perspective, one from a national perspective, and one from a regional perspective. At this point, there is no international harmonization of DHT frameworks.

6.5.2 Digital Therapeutics Alliance (DTA)

The DTA DHT landscape includes the following categories[26]:

- enterprise systems and support products;
- clinician services and support tools;
- patient-facing wellness and support products;
- patient-facing diagnostic and monitoring tools;
- patient-facing therapeutic intervention products.

DTx products are included as a subcategory under patient-facing therapeutic interventions.

6.5.3 National Institute for Health and Care Excellence (NICE)

NICE's functional classification of the DHT ecosystem is intended to be a pragmatic approach to differentiating the main functions of the types of DHTs that are expected to be most widely developed and used in the UK health and social care system.

Prior to August 2022, this DHT framework included three tiers of product types[27]:

- Tier C: Interventions:
  - Preventative behaviour change;
  - Self-manage;
  - Treat;
  - Active monitoring;
  - Calculate;
  - Diagnose.
- Tier B: Understanding and communicating:
  - Inform;
  - Health diaries;
  - Communicate.
- Tier A: System impact:
  - System services.

Following August 2022, the three-tier framework was updated to recognize[18]:

- Tier C: DHTs for treating and diagnosing medical conditions, or guiding care choices:
  - Inform clinical management;
  - Drive clinical management;
  - Treat a specific condition;
  - Diagnose a specific condition.
- Tier B: DHTs for helping citizens and patients to manage their own health and wellness:
  - Communicating about health and care;
  - Health and care diaries;
  - Promoting good health.
- Tier A: DHTs intended to save costs of release staff time, no direct patient, health or care outcomes:
  - System services.

According to NICE, software that is embedded in a physical medical device is excluded from this group of DHTs.

6.5.4 European Commission DG communications networks, content, and technology

In 2020, a final report prepared for the European Commission DG Communications Networks, Content and Technology, included a segment on the impact of various DHTs can have on patient care in France and Germany. DHTs included in the report[28]:

- Online interaction:
  - Teleconsultation;
  - Remote monitoring of chronic disease patients;
  - e-Triage;
  - e-Booking.
- Paperless data:
  - Unified electronic health record/exchange;
  - e-Prescribing;
  - Clinician's virtual assistants (AI);
  - Intra-hospital staff communications.
- Workflow/automation:
  - Nurse mobile connectivity;
  - RFID-tracking;
  - Barcoding medication administration;
  - Process/logistics automation through robotics;
  - Vital parameter tracking (eICU);
  - e-Referrals.
- Outcomes transparency:
  - Performance dashboards;
  - Patient flow management;
  - Clinical decision support;
  - Advanced payor analytics;
  - Genetic testing.
- Patient self-care:
  - Chronic disease management tools;
  - Medical chatbots;
  - Disease prevention tools;
  - Patient support networks;
  - Digital diagnostic tools;
  - Virtual reality for pain treatment.

Similar to the NICE framework, this list of DHTs does not specifically acknowledge DTx products, and further illustrates the many ways that technologies within the DHT category are categorized in national and regional policies.

7 Medical device software standards

There are currently no International Standards that directly address DTx product definitions, standards, and expectations. Various International Standards set the stage for DTx-specific standards, but do not reflect DTx specifically. Therefore, this document presents initial concepts that can be used to develop DTx-specific standards.

The following standards can be used during the development of medical software, health software, including DTx products:

— IEC 82304-1[5] applies to the safety and security of health software products designed to operate on general computing platforms and intended to be placed on the market without dedicated hardware, and its primary focus is on the requirements for manufacturers. It covers the entire lifecycle including design, development, validation, installation, maintenance, and disposal of health software products.

— ISO/TS 82304-2[29] provides quality requirements for health apps and defines a health app quality label in order to visualize the quality and reliability of health apps. Intended for use by app manufacturers as well as app assessment organizations in order to communicate the quality and reliability of a health app. Public can use the health app quality label and report when recommending or selecting a health app for use, or for adoption in care guidelines, care pathways and care contracts.

— IEC 62304[30] defines the life cycle requirements for medical device software. The set of processes, activities, and tasks described in IEC 62304 establishes a common framework for medical device software life cycle processes.

— ISO 13485[31] specifies requirements for a quality management system where an organization needs to demonstrate its ability to provide medical devices and related services that consistently meet customer and applicable regulatory requirements.

— ISO 23903[32] enables the advancement of interoperability from the data/information exchange paradigm to knowledge sharing at decreasing level of abstraction, starting at IT concept level (semantic coordination) through business domain concept level (agreed service function level cooperation), domain level (cross-domain cooperation) up to individual context (skills-based end-user collaboration).

— ISO 81001-1[3] provides the principles, concepts, terms and definitions for health software and health IT systems, key properties of safety, effectiveness and security, across the full life cycle, from concept to decommissioning. It also identifies the transition points in the life cycle where transfers of responsibility occur, and the types of multilateral communication that are necessary at these transition points. ISO 81001-1 also establishes coherent concepts and terminology for other standards that address specific aspects of the safety, effectiveness, and security (including privacy) of health software and health IT systems.

— IEC 80001-1[33] specifies general requirements for organizations in the application of risk management before, during and after the connection of a health IT system within a health IT infrastructure, by addressing the key properties of safety, effectiveness and security whilst engaging appropriate stakeholders.

— ISO 13131[34] provides processes that can be used to analyze the risks to the quality and safety of healthcare and continuity of care when telehealth services are used to support healthcare activities. Using risk management processes, quality objectives and procedures are derived which provide guidelines for the operations of telehealth services.

— HL7's Unique Mobile Health Application Identifier (UMHAI) Project[35] provides a unique identifier that uniquely identifies mobile health application instances as installed on a mobile device.

Annex A
(informative)

Landscape analysis

A.1 Digital therapeutic best practices

In 2018, DTA published core principles applicable to all DTx products[36]:

In 2019, DTA published criteria and standards that reflect methods DTx products can use to demonstrate alignment with core principles[37].

A.2 Digital therapeutic standards

A.2.1 National Council for Prescription Drug Programs (NCPDP)

The United States-based National Council for Prescription Drug Programs (NCPDP) published in August 2021, "Background and Guidance for Using the NCPDP Standards for Digital Therapeutics"[38]. It covers multiple standards that relate to DTx product use in the context of the U.S. prescribing system, such as:

— Billing units for digital therapeutic products;

— DTx product identifiers;

— Communication of formulary and benefit information to prescribers;

— Real-time prescription benefit information;

— Standard transactions that facilitate the transfer of prescription data;

— Prior Authorization (PA) transactions exchanged in a real-time request and response mode;

— New prescription orders from the prescriber to a pharmacy so that it can be dispensed to a patient.

A.2.2 Consumer Technology Association (CTA)

The Consumer Technology Association (CTA) is in the process of developing DTx-related standards. Their first standard is "Definitions and Characteristics of Digital Therapeutics (ANSI/CTA-2098)"[12].

Annex B
(informative)

DTx use cases

B.1 General

The following de-identified use cases provide examples of DTx products and a context for their use in real-world settings. These products have been chosen based on their alignment with the definition of a DTx.

B.2 Use case: Software hosted on a general purpose device for diabetes management

Product intended use: Supports multiple cardiometabolic conditions and comorbidities across type 1 and type 2 diabetes, hypertension, heart failure, and prediabetes, while providing behavioural health insights.

Product components: It includes software intended for use on mobile phones or personal computers in the home or in professional healthcare settings. The mobile version works on or offline.

Directions for use: This DTx is intended to provide secure capture, storage, and transmission of glucose data, as well as information to aid in diabetes self-management. It analyses and reports glucose test results and supports medication adherence. AI systems leverage individual's data to provide unique, personalized, real-time clinical guideline-based coaching messages (motivational, behavioural, and educational) based on patient glucose values and trends. The software also allows for entry of other diabetes-related healthcare information and provides educational information.

The following product insulin management features are for prescription use only:

— For bolus insulin users with type 1 or type 2 diabetes, this product includes an insulin dose calculator to allow patients to use their prescribed regimen to calculate a dose of bolus insulin for a given amount of carbohydrates and glucose value.

— For basal insulin users with type 2 diabetes, this product includes an Insulin Adjustment Program (IAP) which calculates appropriate long-acting basal insulin doses for titrating insulin levels based on configuration by a healthcare provider. The healthcare provider must activate the IAP and configure it with patient-specific parameters.

— For bolus insulin users with type 2 diabetes, the product IAP calculates appropriate dose adjustments of bolus insulin based on configuration of a healthcare provider. Qualified type 2 diabetes patients are those who are not achieving glycaemic targets despite optimization of their basal insulin dose or their current bolus insulin regimen.

— For premixed insulin users with type 2 diabetes, the product IAP calculates appropriate dose adjustments of premixed insulin based on the configuration of a healthcare provider. Qualified type 2 diabetes patients are those who are not achieving glycaemic targets and who do not take other types of insulin.

Place in therapy: This product is complementary to current therapies, including pharmacologic-related, diet-related, exercise-related, or knowledge-related therapy pathways. It is not intended to replace the care provided by a licensed healthcare professional.

B.3 Use case: Software paired with sensors and headphones for post-stroke rehabilitation

Product intended use: Improve walking impairments, mobility, and related functional outcomes caused by neurologic diseases and injuries (i.e. chronic stroke) through Rhythmic Auditory Stimulation (RAS).

Product components: Platform combines sensors, software, general purpose hardware (i.e. smartphone, tablet), headphones, and music with advanced neuroscience to target neural circuitry.

Directions for use: To use this product, the patient clips sensors onto his or her shoes, puts on a pair of headphones, and starts a session. As the patient begins walking, the sensors collect baseline gait data. Software algorithms continuously receive real-time gait data from sensors to curate, augment, and individualize personalized rhythmic stimulus delivered as music clinical interventions for each patient in real-time based on that user's data. The patient will continue to listen to the music and walk to the beat. DTx algorithms constantly assess the user's entrainment ability and quality of walking, and provide auditory stimuli to progress them toward an objective clinical goal.

Place in therapy: This product is complementary to current therapies. It is not intended to replace the care provided by a licensed healthcare professional.

B.4 Use case: Software hosted on a general purpose device for substance use disorder management

Product intended use: It is intended to increase abstinence from a patient's substance of abuse during treatment and increase retention in the outpatient treatment program.

Product components: Software is hosted on a general purpose device (i.e. smartphone, tablet).

Directions for use: This DTx provides cognitive behavioural therapy (CBT), as an adjunct to a contingency management system, for patients age 18 and older who are currently enrolled in outpatient treatment under the supervision of a clinician. It is indicated as a 12-week prescription-only treatment for patients with Substance Use Disorder (SUD), who are not currently on opioid replacement therapy, who do not abuse alcohol solely, or who do not abuse opioids as their primary substance of abuse.

It is comprised of 62 interactive modules: 32 core modules and 30 supplemental modules. Core modules focus on key community reinforcement approach (CRA) concepts, an intensive form of validated neurobehavioral therapy for SUD, building skills to support behaviour change and prevent relapse.

An associated dashboard for clinicians and other health care providers can be used as part of treatment. The dashboard displays information about patients' use of the product, including lessons completed, patient-reported substance use, patient-reported cravings and triggers, compliance rewards, and in-clinic data inputs such as urine drug screen results.

Place in therapy: This product cannot be used by individuals outside active enrolment in a SUD treatment program. It can only be used as an adjunct to face-to-face counselling and contingency management. Patients will continue to take their medications as directed by their healthcare provider.

B.5 Use case: Software used with a Virtual Reality (VR) headset for chronic lower back pain

Product intended use: Prescription-use immersive virtual reality system intended to provide adjunctive treatment based on CBT skills and other evidence-based behavioural methods for patients (age 18 and older) with a diagnosis of chronic lower back-pain (defined as moderate to severe pain lasting longer than three months). The device is intended for in-home use for the reduction of pain and pain interference associated with chronic lower back pain.

Product components: Product utilizes software on an immersive virtual reality system.