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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

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, biomarkers, and therapeutics.

Given the diversity of digital product types 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 internationally recognized guidance, users are often unable to differentiate between DHTs based on products' intended use.

Digital therapeutics (DTx) as defined in this document represent a decade-old category of medicine that can be used as standalone therapies or integrate into clinical care pathways alongside pharmaceuticals, clinician-delivered therapies, and other medical devices.

Standards exist for various non-DTx DHT product categories and varying DTx product definitions and best practices are emerging at the industry level (see Annex A), yet no DTx-specific publication exist. This document centres on DTx's use of software 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 provides medical interventions that are based on clinical evidence 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 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 for human use and that are used in the context of a disease, disorder, condition, or injury. It does not address products that are intended for veterinary uses 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 and 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
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]

3.3
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".]

3.4
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: DTx software can integrate with ancillary components to form a DTx system by:

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

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

— integrating with tandem medical interventions (i.e. clinician-delivered therapies, pharmaceuticals, SiMD, other DHT components).

Note 2 to entry: DTx can function independently or in addition to other interventions.

Note 3 to entry: Includes secondary prevention and tertiary prevention.

Note 4 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.

3.5
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 of 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]

3.6
medical intervention
activity intended to maintain or to 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, or to assist an individual with activities of daily living, or to support physical and mental well-being

3.7
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.]

3.8
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]

3.9
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[6], modified — 'may' changed to 'can'.]

3.10
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

3.11
health
state of complete physical, mental and social well-being and not merely the absence of disease or infirmity

[SOURCE: WHO 1948[7]]

3.12
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]

3.13
cybersecurity
state where information and systems are protected from unauthorized activities, such as access, use, disclosure, disruption, modification, or destruction to a degree that the risks related to violation of confidentiality, integrity, and availability are maintained at an acceptable level throughout the life cycle

[SOURCE: ISO 81001-1:2021, 3.2.13]

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
digital therapeutic software
DTx software
software intended to be used specifically for treating or alleviating a disease, disorder, condition, or injury of individual persons

3.17
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[9], modified — Note 1 deleted.]

3.18
digital therapeutic system
digital therapeutic (DTx) software plus general purpose computer platform and any inputs or outputs necessary for DTx functioning

3.19
tandem medical intervention
two or more medical interventions, each capable of producing a positive therapeutic benefit, when implemented together are expected to produce a higher level of benefit than either one alone

3.20
secondary prevention
includes procedures that detect and treat preclinical pathological changes and thereby control disease progression

[SOURCE: PANDVE 2014[10]]

3.21
tertiary prevention
impact caused by the disease on the patient's function, longevity, and quality-of-life once the disease has developed and has been treated in its acute clinical phase

[SOURCE: PANDVE 2014[10]]

3.22
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, 3.3.4, modified — Note 1 to entry replaced with new note 1 to entry.]

3.23
safety
freedom from unacceptable risk

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

3.24
effectiveness
ability to produce the intended result

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

3.25
primary prevention
prevent the onset of specific diseases via risk reduction by altering behaviours or exposures that can lead to disease or by enhancing resistance to the effects of exposure to a disease agent

[SOURCE: PANDVE 2014[10]]

3.26
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.]

3.27
combination medical intervention
two or more medical interventions that are necessary, which, in combination are sufficient to produce a positive therapeutic benefit

3.28
artificial intelligence as a medical device
AIaMD
subset of software as a medical device that incorporates artificial intelligence or machine learning

[SOURCE: MHRA 2022[16]]

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, others use software to deliver a medical intervention that directly impacts a disease, disorder, condition, or injury. Without a common internationally recognizable definition of a DTx, healthcare decision makers are not able to appropriately identify DTx products and distinguish them from other DHTs to determine which products will best meet patients' needs and expectations.

National regulatory and reimbursement frameworks for DHT and DTx are increasingly emerging. While most national frameworks reference some version of a DHT framework, under which various subsets of DTx products can fall, one country (the Republic of Korea) has developed a DTx-specific framework:

— In South Korea, the Ministry of Food and Drug Safety established a regulatory framework for DTx as a subcategory of SaMD,[17] largely based on the International Medical Device Regulators Forum's (IMDRF) SaMD definition[6].

— The National Institute for Health and Care Excellence (NICE) Evidence for Effectiveness functional classification of DHTs includes three tiers of DHTs based on potential risk to users. The top tier includes the categories of inform clinical management, drive clinicial management, treat a specific condition, and diagnose a specific condition. DTx products are not specifically categorized[18].

— In Germany's Fast-Track Process for Digital Health Applications [digitale Gesundheitsanwendungen (DiGA)],[19] DTx products that are classified under the European Union's Medical Device Regulation (MDR) Class I and Class IIa can qualify as a subset of DiGA, but Class IIa and Class III DTx products do not currently qualify under this framework.

Without a consistent, internationally recognized definition of a DTx and eventual corresponding quality standards, it is difficult for policymakers and other healthcare decision makers to develop appropriate frameworks that properly distinguish DTx from other software categories and establish harmonized expectations related to DTx function, reliability, and real-world impact.

5 Considerations

5.1 DTx Attributes

5.1.1 Impact on patient care

Digital therapeutic software (DTx software) is responsible for the directly attributable impact on patient health, similarly to pharmaceuticals and clinician-delivered therapies are responsible for their own clinical impact.

DTx products include indications for secondary prevention and tertiary prevention. Primary prevention does not qualify based on a disease, disorder, condition, or injury not being present.

DTx products are generally able to operate with little or no clinician control or intervention. While DTx therapies can be supplemented with clinician-delivered interventions, DTx software is classified differently from clinical decision support (CDS) tools and is therefore not intended to solely augment a human decision.

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 do have intelligence.

5.1.2 Relationship to SiMD

DTx software typically forms a subset of Software as a Medical Device (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 DTx software is hosted on general purpose hardware