

# Ethics of digital therapeutics (DTx)

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**Abstract.** – Digital therapeutics (DTx) are a subset of digital health which are often coupled with artificial intelligence (A.I.) techniques and machine learning systems. DTx differ from common wellness apps or medication reminder tools in that they require “rigorous” clinical evidence. They are emerging as a new treatment option and are being applied in a variety of areas, including type II diabetes, hypertension, chronic respiratory problems, obesity, insomnia, Alzheimer’s disease, various types of dementia or addiction (smoking, alcohol, drugs), anxiety, depression, autism, learning disabilities, and attention deficits. Today, there are roughly 35 to 40 products on the market, 8 of which approved by regulatory agencies. The value of the global DTx market was estimated at USD 1.8 billion in 2018, and it is expected to reach USD 8.9 billion by 2027.

Implementing DTx across healthcare systems raises a number of ethical concerns. The present article aims to provide an overview of the main ethical issues pertaining the assessment, implementation, and use of this emerging technology. The final purpose is to support and facilitate an open and transparent deliberation with regard to DTx.

## Key Words:

Digital therapeutic (DT), Artificial intelligence, Ethics, Deliberation, Decision-making.

## Introduction

Digital therapeutics (DTx) are an innovative type of medical therapy<sup>1</sup>. The term was first used by Sepah et al<sup>2</sup> and it specifically refers to “evidence-based therapeutic interventions driven by high-quality software programs to prevent, manage, or treat a medical disorder or disease”<sup>3</sup>.

Three keywords can be highlighted in this definition: “(1) high-quality software programs, (2) evidence-based, and (3) therapeutic interventions”<sup>4</sup>.

In the first place, DTx are based on software programs, and can be considered a kind of “soft-

ware as a medical device” (SaMD). In addition, they are often coupled with artificial intelligence (A.I.) and machine learning systems<sup>5</sup>.

Secondly, DTx can be considered a subset of digital health, a broad category which includes a wide range of products used across the wellness and healthcare industry<sup>6</sup>. DTx differ from common wellness apps or medication reminder tools in that they require “rigorous” clinical evidence to substantiate intended use and have an impact on the disease status. Furthermore, DTx should not be confused with digital medicine, a category of pharmaceuticals that combine a prescribed medication with an ingestible sensor component<sup>7</sup>.

Lastly, the purpose of DTx is to deliver treatment. DTx products provide therapeutic benefits similar to those of other medical therapies, such as medication or traditional medical devices, even though they “use their own mechanism of action, which differs from those of other types of therapies”<sup>4</sup>.

The application of DTx is becoming increasingly more widespread, including diseases which are related to both behavioral and psychological factors, as well as chronic diseases: type II diabetes, hypertension, chronic respiratory problems, obesity, insomnia, Alzheimer’s disease, various types of dementia or addiction (smoking, alcohol, drugs), anxiety, depression, autism, learning disabilities, and attention deficit disorders.

The world’s first DTx is the mobile application “reSET<sup>®</sup>” produced by Pear Therapeutics in the United States<sup>8</sup>. Approved by the Food and Drug Administration (FDA) in 2017, reSET<sup>®</sup> is an app that applies cognitive behavioral therapy to help patients with drug addiction.

Today, there are roughly 35 to 40 products on the market, 8 of which approved by regulatory agencies<sup>9</sup>. The value of the global DTx market was estimated at USD 1.8 billion in 2018<sup>10</sup>, and it is expected to reach USD 8.9 billion by 2027<sup>11</sup>. With the increased implementation of digital technology brought about by the COVID-19 pandemic, these values could potentially soar even further.

Although DTx are a promising innovation in the field of digital medicine, their use raises a number of ethical concerns. The aim of the present article is to provide an overview of the main ethical issues pertaining to the assessment, implementation, and use of this emerging technology. The final purpose is to support and facilitate an open and transparent decision-making process and deliberation with regard to DTx.

## Materials and Methods

Ethical analyses can be conducted in many ways. We followed the HTA Core Model<sup>®</sup> version 3.0<sup>12</sup>, a comprehensive methodological framework used in the field of Health Technology Assessment (HTA)<sup>13</sup>.

The aim of the tool is to highlight the ethical questions raised by the use of a certain technology in an open and transparent manner, in order to adequately inform decision makers. It includes six different topics, which together cover nineteen issues. These issues stem from “the general values of the population, aims of the healthcare system and values arising from the use of a technology”<sup>13</sup>.

Essentially, the framework serves as a checklist template, and the ethical reflection is elicited by highlighting value issues through a set of questions. In the present work, not all issues of the framework were considered to be relevant. The result of the analysis does not explicitly state the set of issues. Information was gathered through the literature search methodological approach proposed by Droste et al<sup>14</sup>. The answers to the set of questions were summarized and grouped into three paragraphs, which correspond to four fundamental ethical dimensions (beneficence/non-maleficence, autonomy, justice, and explicability). Finally, the analysis was performed by two ethicists whose background is in Medicine (AGS, DS), one ethicist whose background is in Philosophy (PR), and one ethicist whose background is in Biology (CR).

## Results

### **Beneficence/Non-Maleficence**

The decision of implementing new technology requires careful deliberation of the balance between benefits and harms. Positive and negative health effects of DTx have been detected and discussed in literature<sup>1,10,15,16</sup>. Here, a brief summary.

The main benefits about DTx can be summarized as follows:

- **Few side-effects:** DTx have low toxicity and few other associated side-effects when compared to conventional pharmacotherapy. However small, side-effects can be identified. For example, DTx can cause addiction among users<sup>16</sup> to the point that some industries provide addiction-evasion programs to help patients avoid or solve this problem. Therefore, iatrogenic damage should be a point of interest for decision-makers;
- **Continuous monitoring of patients:** DTx are capable of real-time collection and analysis of data, leading to an improvement in the direct and continuous monitoring of patients. This characteristic can have at least two positive consequences: improvement in terms of the degree to which a patient follows medical advice (adherence), and significant increase of interoperable data;
- **Access facilitation:** DTx are generally administered through personal mobile devices, allowing patients to use them with ease in any setting and at any time. One positive effect of this access facilitation can be stigma reduction, as for example in the case of treatment for mental health disorders. DTx can, in fact, facilitate access to therapeutic content within the privacy of a patient’s personal time and environment. Additionally with relevant patient data readily available, physicians can practice more efficiently, cutting down patient waiting list times significantly.
- **Greater personalization:** DTx can improve personalization. As noted by Sverdlov et al<sup>1</sup>, “the digital therapeutic platform can assess an individual’s performance, progress, or proficiency with particular subjects or topics of the therapeutic contained on a much more granular level, allowing for even greater levels of personalization”.

On the other hand, the main potential drawbacks from the use of DTx are:

- **More barriers:** the use of DTx is associated with an increased number of barriers among users: infrastructures, degree of education, presence of professional figures, etc. For example, DTx rely on a stable Internet connection, which may not be accessible to some. To promote the use of DTx, healthcare providers need specific training in order to know how to properly prescribe them to their patients.

Patients also need to be educated on their use and, in some cases, need specific skills in order to comprehend and implement the process in an effective manner. Moreover, DTx require workers with new and specialized skillsets for data collection and analysis as well as for monitoring the proper functioning of devices and applications. Lastly, the employment of “different professional languages” can complicate the coordination and collaboration among the variety of professional figures involved in the implementation of this technology;

- **Compromised privacy and confidentiality:** due to an extensive use of patient data, DTx can increase exposure to health data breaches. With frequent cyber-attacks, there is the growing risk of cybersecurity threats. In addition, other parties may also need access to patient data (such as insurance companies, device manufacturers or cloud storage service programmers and managers). The use of such data can raise complex issues related to confidentiality as well as to the cross-jurisdictional practice of medicine;
- **Greater number of errors:** mistakes made while using DTx can affect a large number of patients at a time if mechanisms for detection and correction are not in place<sup>15</sup>.

### **Autonomy**

The decision of implementing a new technology also requires consideration about patient autonomy. Technologies can indeed alter a person’s self-determination: traditionally, patients can exercise their autonomy by informed consent, the process by which the health care professional discloses appropriate information to competent patients, so that the latter can make a voluntary choice to either accept or refuse the treatment.

Patients are actively involved in DTx. For example, DTx make extensive use of both game and gamification, two strategies that induce active participation and strengthen individual autonomy. However, this poses the question of whether this is in fact in line with the patient interest.

On the other hand, this has the potential, to some extent, to jeopardize a patient’s relationship with the physician. As noted by Mannelli et al<sup>17</sup>, “although the implementation of DTx allows a constant dialogue between clinicians and their patients, there is a risk that excessive reliance on the use of technology may tend to reduce the need for a direct relationship with the physician”.

Beyond these considerations, a list of issues regarding patient self-determination can be identified:

- **Comprehension:** the use of a DTx is generally governed by a user agreement in addition to the traditional informed consent process. As noted by Klugman et al<sup>18</sup>, “when the patient registers his or her digital medicine app or device, he or she will be prompted to indicate agreement. User agreements tend to be long documents [...], written by lawyers, are typically contracts of adhesion and thus not negotiable (i.e., if you do not agree, then you do not get to use the product), can be changed at any time and without notice, and spell out the terms under which the software and hardware can be used: appropriate ways to use the technology, the limits of use, and protections for the company”. User agreement is designed for the benefit of companies, while informed consent is designed for the benefit of patients. Therefore, when patients agree to a DTx user agreement, they may not understand that they are agreeing to the use of their data in research, or for the update of a device;
- **Purposes:** consent to data processing is an important aspect on which the patient should be adequately informed. In cases like DTx, the data identified are transferred electronically. This makes it essential to reassure the patients that information will not be used for unauthorized purposes;
- **Privacy and confidentiality:** one of the key features of DTx is the ability to easily share information with others, such as clinicians, health care providers, insurance companies, programmers, family members, etc. Yet, this can cause particularly complicated issues about how to respect patients’ privacy (right to determine when, how and to what extent the information is shared with others) and confidentiality (obligation to protect the information entrusted);
- **Addiction:** as we noted above, DTx can cause addiction among users, which can interfere with the patient’s self-determination and decision-making ability.

### **Justice**

The use of a certain technology can influence the fairness of the healthcare system or require special considerations in order to ensure that justice is not compromised. For example, some technologies can imply high costs, sometimes

covered with resources from other areas, determining re-allocation of human resources, funding, training, and so on.

Due to access facilitation, DTx can have positive effects on the fairness of the different healthcare systems. An example of this is India, where universal health care is a challenge, and the use of digital tools is helping bridge some gaps<sup>15</sup>.

However, as we noted, the adoption of DTx is associated with an increased number of barriers, such as infrastructures, education, prescription, professional figures, etc. As a consequence, the “digital divide” becomes a sort of new social determinant of health that may end up increasing health inequities rather than reducing them.

Another key question is reimbursement policy, since DTx are currently being reimbursed through a number of different means<sup>17,19</sup>.

### **Explicability**

Explicability is increasingly considered crucial for ethical A.I.<sup>20</sup>. Explainable A.I. is a set of processes and methods that allows human users to comprehend and trust the results and output created by algorithms. Reference is made to the need to obtain “a factual, direct, and clear explanation of the decision-making process”<sup>21</sup>.

A.I. is often characterized by “epistemic opaqueness”, that is to say, the algorithms include elements which a cognitive agent does not or even cannot know. For example, A.I. and machine learning systems can incorporate hundreds of complex personal variables for each patient to provide more customized algorithms and interventions, which may be impossible for a human to evaluate. Training datasets may not always capture social determinants of health or other biases that affect the performance of healthcare algorithms. As a consequence, it could be difficult to evaluate the inner workings of A.I. and machine learning-based DTx, raising the issue of discrimination, even unintentionally.

In turn, this raises the issue of establishing who ultimately will be responsible for patients’ health, with both the artificial intelligence software and the prescribing physician of the digital therapeutic system having a vital role in patient lives.

## **Discussion**

This analysis has identified a range of ethical issues which are related to fundamental ethical principles, such as beneficence, non-maleficence,

autonomy, justice, and explicability. The bioethics community and digital companies should engage in a dialogue over the issues described in the previous section. As noted by Martani et al<sup>22</sup>, “anticipating, planning for, and iteratively addressing the array of ethical issues throughout products’ life cycles will enhance patient, professional, and public trust in these emerging technologies. Importantly, involving not only ethicists but also patient groups, practicing clinicians, and payers in these conversations will also further this goal”.

After having identified and exposed the relevant ethical issues, one should ask for specific recommendations. Should we implement DTx? If so, what type of programs? This review merely provides early input for the decision-making process. It can prepare and facilitate this process; however, the value of DTx is a different and separate matter, and it should still be empirically proven. In other words, even though DTx present both opportunities and potential pitfalls, the decision of implementing them crucially depends on their capacity to be safe, effective, and convenient for patients and society.

How DTx will be evaluated against conventional therapeutics still has to be fully explored, and the clinical testing of DTx poses specific challenges. One challenge is that technical characteristics of the device or software may be upgraded over the course of the trial, and the technology itself may become outdated before the actual end of the trial<sup>1</sup>. Another challenge consists in the fact that blinding may be difficult in a digital intervention trial. Further, the use of a placebo control group may be unethical or not feasible in some cases<sup>7</sup>. Therefore, considering the nature of DTx, one should pose the question: is it possible to make randomizations that are not realistically biased?

Currently, there is no single assessment system or framework of reference, and there is limited information from governing bodies on how to validate digital endpoints. The United Kingdom’s National Health Service (NHS) recently announced new Digital Technology Assessment Criteria (DTAC), which describe the level of evidence needed to demonstrate effectiveness and value for digital technologies that have different functions and risks<sup>23</sup>. The United States introduced the FDA’s digital software pre-certification program<sup>24</sup>. Therefore, a dedicated regulatory framework remains in flux. Moreover, some of these programs have received criticism for lack-

ing clarity of evaluation criteria and providing less stringent standards than the ones used for pharmaceuticals<sup>24</sup>.

In a similar manner, despite some efforts, there is no clear guidance for reimbursement of DTx. The FDA<sup>25</sup> announced that starting in September 2021 DTx will receive a unique device identification number. In Europe, reimbursement pathways for digital health products are developing at different speeds in different countries. Germany, Sweden, and the United Kingdom are relatively established markets in which governments are encouraging the digital health market and have systematized reimbursement pathways. However, there are multiple different reimbursement pathways including universal reimbursement, outpatient care, in-patient care and disease prevention<sup>4</sup>.

Finally, there are uncertainties pertaining to security and data governance. In October 2018, the FDA<sup>26</sup> released a draft guidance regarding cybersecurity in software as a medical device and networked medical devices. The EU is actively responding to the emerging presence of innovative digital health medical devices. For instance, in May 2018 the General Data Protection Regulation (GDPR) was revised and implemented, laying the foundation for data protection and utilization<sup>27</sup>. All this said, this subject is clearly still in its full evolution.

## Conclusions

DTx represent an emerging new treatment option and are being applied in a variety of areas. This paper has identified a range of ethical issues which are related to fundamental ethical principles, namely beneficence, non-maleficence, autonomy, justice, and explicability. DTx present both opportunities and potential pitfalls. Side-effects, monitoring of patients, access, personalization, barriers, privacy, confidentiality, number of errors, comprehension, purposes, addiction, and opaqueness are crucial aspects for a fruitful development of DTx which will have an impact on assessment, decision making, implementation, use, and formation of knowledge and norms. Beyond these considerations, the value of these technologies will crucially depend on their capacity to be safe, effective and convenient for patients and society. Clinical trials to assess DTx pose new logistical, statistical and ethical challenges. In a similar manner, reimbursement

policies as well as security and data governance require clear guidance. Therefore, a stable regulatory approval system that complements the prescription of conventional pharmacotherapy is needed as soon as possible.

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### Conflict of Interest

The Authors declare that they have no conflict of interests.

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### Authors' Contribution

All authors contributed equally to this work. All authors read and approved the final version of the manuscript.

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