Chiara Mannelli[1], Elio Borgonovi[2,3], Italia Agresta[4], Paolo Barbanti[5]
Enrico Caiani[6], Oriana Ciani[3], Lucio Da Ros[2], Antonio Ferrari[7]
Sabrina Grigolo[8], Gualberto Gussoni[9], Alberto Malva[2,10]
Francesco Perrone[11], Alice Ravizza[12], Giuseppe Recchia[2,13]
Eugenio Santoro[14], Silvia Stefanelli[15], Andrea Tomasini[4], Carlo Petrini[16]

Digital therapeutics: ethical aspects

Introduction

Digital technology applied to healthcare offers remarkable opportunities to improve sustainable access to health and deliver better quality of care. This has led to a proliferation of smartphone- and web-based health applications that are changing the ways patients manage their health and interact with physicians. Digital tools to manage health - of which health-re-

[1]*Candiolo Cancer Institute, FPO-IRCCS, Candiolo (TO)*
[2]*Smith Kline Foundation, Verona*
[3]*CERGAS, SDA Bocconi School of Management, Milano*
[4]*Italian national Association of People with Rheumatological and Rare Diseases (Associazione Nazionale Persone con Malattie Reumatologiche e Rare - APMARR)*
[5]*Pharma & Biotech Advisors srl, Milano*
[6]*Politecnico of Milano, Electronics, Information and Biomedical Engineering Department*
[7]*IQVIA Ltd, Durham, NC, United States*
[8]*European Patients' Academy / EUPATI Non-Profit Organization*
[9]*Department for Clinical Research - "Centro Studi" FADOI (Italian Scientific Society of Internal Medicine), Milan*
[10]*Italian Society of General Medicine and Primary Care (Società Italiana di Medicina Generale e delle Cure Primarie - SIMG)*
[11]*Clinical Trials Unit, IRCCS National Cancer Institute, "Fondazione Pascale", Napoli*
[12]*Use-Me-D, Torino*
[13]*daVinci Digital Therapeutics, Milano*
[14]*Laboratory of Medical Informatics, Mario Negri Institute for Pharmacological Research, Milano*
[15]*Stefanelli & Stefanelli Legal Chambers, Bologna-Milano*
[16]*Bioethics Unit and Ethics Committee, Italian National Institute of Health (Istituto Superiore di Sanità), Roma*

lated apps are a subset - can be situated across a broad spectrum: from non-interventional apps like those designed for fitness, to non-regulated direct-to-consumer apps, to prescription-only tools[1]. This heterogeneous array of continuously emerging technologies, collecting and processing sensitive health-related data, raises a number of specific concerns associated with safety, efficacy, privacy, and accountability. The overarching issue in this regard is that most digital technologies in healthcare do not follow a regulatory pathway; and, in some cases, there may even be a degree of ambiguity in the manufacturer's description of their intended use.

In this chapter we will analyse the ethical concerns relevant to the application and implementation of digital therapeutics (DTx), as a subset of the broader field of "digital health". As stated elsewhere in this book, DTx are medical devices delivering therapeutic interventions, in which a high-quality software application or algorithm constitutes the "active principle". DTx need to be clinically validated through rigorous evidence-based clinical studies (both pilot and pivotal), approved by regulatory authorities, and preferably prescribed by physicians. These characteristics differentiate DTx from most of the other health products that fall under the more general heading of digital health (e.g., wellness apps that can be downloaded from online stores, or others that are available on a smartphone and measure heart rhythm). The implementation of DTx is aimed at: i) making available devices of proven efficacy and safety, to integrate or replace traditional treatments or provide a therapeutic option for a wide range of chronic diseases and clinical conditions; ii) fostering equitable healthcare provision by improving access to effective therapeutic solutions; and iii) empowering patients and caregivers, through their direct engagement in their own care management. However, these undoubtedly promising statements of intent should be adequately nuanced, and their implementation requires thorough ethical evaluation. Indeed, the collection and processing of sensitive health data have reshaped the concepts of privacy and confidentiality, raising the need to address relevant ethical issues that are far broader in scope than the obvious data protection concerns.

Without claiming to be exhaustive, this chapter focuses on ethical issues raised by the implementation of DTx. The aim is to provide a basis for engagement with potential stakeholders, about a critical area of concern within the thorough and wide-ranging evaluation to which this emerging healthcare trend must be subject.

1. Digital therapeutics: a universal and equitable approach

In the challenge of achieving universal health coverage, one of the World Health Organization's greatest commitments, it has become increasingly clear that e-health can potentially play a crucial role. In this respect, implementation of DTx represents an important step towards equitable health service provision, grounded in the fundamental principles of universality, fairness and equity, and in adequate safeguards for the sustainability of national health systems - particularly those characterized by universal access. To be successful, the implementation of DTx in healthcare should take these fundamental principles into account, in both the development and post-marketing phases.

Development phase

The principles of universality, fairness and equity should play a key role in the development process of DTx. Selection bias, with cultural, educational, gender or geographical components, has been reported in the literature on clinical development of drugs and other health technologies[2]. The concerns thus raised also apply to DTx development, and must be addressed in order to ensure that controlled experimental settings are as consistent as possible with real-world conditions. In addition, ensuring fairness in the development phase means that DTx and the underpinning algorithms cannot be allowed to replicate - or, even worse, exacerbate - health inequities. Examples of development phase bias feeding into such inequities are melanoma detection applications trained only on white skin, or algorithms that delay lung cancer diagnosis or underestimate need for extra care in patients of low socio-economic status[3].

DTx should be the output of a co-design process that involves software developers, clinical experts and patients' representatives as partners, while other stakeholders may also be included in specific cases - e.g., representatives of the caregivers or providers who would be in charge of the digital solution's deployment or post-marketing assessment.

Before approval, DTx are subject to strict verification and validation activities, as specified in local regulatory requirements, in order to demonstrate their safety, impact on quality of life, technical and clinical performance, and - last but not least - their clinical benefit. During the post-marketing phase, the DTx owner is subject to procedures that ensure quality control over the software's entire life-cycle.

Greater engagement of patients and/or caregivers in the development phase (optimization of usability, definition of study endpoints, proposal of methods for enhancing adherence to therapy, etc.) is of paramount importance, and potentially of great benefit. The experiential knowledge of patients with respect to their disease can offer a telling contribution to the therapeutic value of DTx (e.g., by making it more user-friendly): this is particularly significant, considering that the therapeutic success of DTx is largely linked to patient empowerment and engagement.

Post-marketing phase

During the post-marketing phase, generation of real-world data is all-important. The implementation of DTx can offer a unique opportunity to promote equitable provision of healthcare, but there are several major factors related to their use that may hinder this positive aspiration. Usability of DTx depends on users (both patients and healthcare professionals) fulfilling a number of specific requirements or preconditions, in terms of infrastructure, tools, financial resources and skills. In order to interact with DTx, the patient needs both a device (not necessarily latest-generation, but certainly not too old) and a stable connection. While in some circumstances the fulfilment of these two requirements may seem a given, in others - especially for those people who would benefit most from the implementation of digital health coverage - this is not the case. These basic needs should therefore be factored into DTx development, dissemination and adoption strategies. The CoViD-19 pandemic, which in many countries has forced the closure of schools and the implementation of distance learning activities, has highlighted how many families still struggle to cope with the digital divide. In the health sector, the need to ensure adequate and widespread remote monitoring for patients with chronic diseases (e.g., diabetes) has in some cases prompted policymakers to make the necessary IT platforms available to patients free of charge. The fulfilment of these requirements depends on financial considerations - both devices and connections come at a price - but also on geographical factors, as there are areas in which a stable connection does not depend on the prospective user's ability to pay. As regards skills, it should be highlighted that the chance to interact with DTx requires a certain level of digital proficiency. Elderly people with reduced mobility are an example of a group that would greatly benefit from the implementation of DTx for better care or improved access to it, but unfortunately they may be short on digital literacy and thus unable to rely on such

support. In this context, the presence of relatives and caregivers may prove fundamental with a view to bridging the digital literacy gap.

Adequate prior assessment of the patient's/caregiver's preparedness and digital proficiency plays a key role - a consideration that should be kept in mind by physicians when deciding whether to prescribe DTx.

Against this backdrop, inclusivity must be prioritized so that otherwise vulnerable user categories are not denied access to DTx. To this end, the DTx functions and interface should be made as intuitive as possible even for inexperienced users. In addition, physicians prescribing the therapy should dedicate time to prospective users and their caregivers (when available), in order to familiarize them with the process. Potential language barriers also require attention: DTx should be made available in a wide range of languages, in order to facilitate user interaction. As a general concept, the language should adapt to the user, and not vice versa. An obvious problem in this regard is that the groups most in need of improved access to care may be illiterate, or speak only minority languages not supported by the system. Finally, there can be barriers related to the availability of devices - and therefore, ultimately, to equity of access: here, the financial burden associated with the use of DTx could be mitigated by making the required equipment available free of charge, or providing reimbursements.

These considerations should play a key role in ensuring that DTx mitigate concerns regarding equity of healthcare provision, rather than exacerbate the digital divide[4].

A critical point is access to these therapies. In theory, DTx - as is the case with drugs - could be used in different ways, from self-prescription to direct payment by the patient, to reimbursement by the national/public health system for DTx prescribed by the physician. Reimbursement policy, obviously applicable only in some health systems, should clearly identify those products that the health authorities have considered to have an adequate - and, if possible, also innovative - therapeutic value. A proper basis can thus be provided for guaranteeing equity and universality of access to this type of therapy.

Finally, we should not forget that, albeit probably to a lesser extent than drugs, DTx are not free from the risk of undesirable effects. As in the case of traditional therapies, careful evaluation of the safety profile associated with DTx is possible thanks to pre-authorization pivotal studies, as well as post-marketing surveillance: the latter makes it possible to obtain information on broader, heterogenous populations, and on long-term safety too. An equally interesting topic is the problem of dropout during clinical studies, or actual

use, of DTx. Close attention to DTx design and user feedback, greater involvement of patients in the development phase and greater user engagement (by such means as emails, texted reminders, etc.) are points that could help reduce dropout rates and therefore optimize the therapeutic value of DTx.

2. Digital therapeutics and patients

The digitalization of health holds intrinsic promise of greater patient education and empowerment, promoting adherence to therapy and active engagement in the healthcare implementation decision-making process. In this perspective, the chance to manage one's own health data with no direct intervention by a healthcare professional is believed to strengthen individual autonomy and enhance the patient's responsibility. However, this begs the question of whether we are sure that this is what patients want. In addition, the promise of empowerment as a result of digitalization has been challenged from different viewpoints that deserve adequate ethical appraisal, with DTx as a case in pojnt. The arguments raised against the promise of empowerment can be broadly divided into two categories:

a. those that recognize empowerment from the implementation of digital health, but highlight possible side effects; and

b. those that challenge the nature of patient empowerment associated with digital health.

According to the first line of argument, while patient empowerment is frequently associated with positive implications, there is a flip side. Patient empowerment has, to some extent, the potential to jeopardize the relationship with the physician. 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. In this respect, while the implementation of DTx might play a significant role in the sustainability of the healthcare system, and while the resulting (and admittedly unquantifiable) empowerment of patients has positive implications for their engagement and their care management, both these aspects imply a reframing of the patient-physician relationship. Within this reframing of roles, patients' involvement in management of their own health and in the related decision-making must not come at the expense of dialogue and direct interaction with the treating physician - whose role will, indeed, prove possibly

even more crucial when considered within the overall dynamics and potential of DTx. The role of the physician remains central with a view to ensuring correct evaluation and clinical management of the therapy, albeit with a greater degree of patient independence. Finally, there is the further risk that patients might feel abandoned by their physicians if their reliance on DTx becomes excessive. While a connection between the physician and the patient is still required in the case of DTx, fragile and vulnerable patients might feel that they are missing the benefit of direct, face-to-face interaction with a caring human being.

According to the second line of argument challenging the role of digital health as a source of patient empowerment, the applications concerned - rather than enhancing autonomy - induce patients to comply with a medical regimen by disciplining them and influencing their behaviour. In other words, the reasoning is that individuals using health-monitoring devices are subject to so-called "chilling effects", making them behave in a certain way[5]. According to this viewpoint, the rationale for a certain behaviour is not grounded - as the empowerment-based perspective holds - in the individual motivation to act in a certain way, but in the awareness of being constantly monitored. This prompts the argument that digital health promotes adherence to a certain discipline, rather than encouraging the strengthening of self-determined values[6,7]. An additional critique is that such an approach, rather than strengthening patients' autonomy, assigns them practical tasks (like monitoring symptoms and providing updates) that are generally carried out by physicians and that may entail some stress.

Regardless of the nature and degree of the autonomy promoted by digital tools, the patient's self-management and independence from the physician certainly appear to be greater. Care should therefore be taken to ensure that, rather than slacken interaction with the physician, this patient empowerment associated with DTx becomes an opportunity to strengthen a relationship based on cooperation, with sharing of responsibility and decision-making, so as to achieve better healthcare outcomes. Such an approach makes patients and their caregivers feel that, from the development to the implementation of DTx, their point of view is relevant and their needs are being factored in. Above all, patients' participation provides vital insights into the user's viewpoint. In the long run, this participation and empowerment could positively impact health outcomes, as a sense of engagement should motivate patients to contribute proactively

while also reinforcing their adherence to protocols and therapies. According to this view, empowered patients and their caregivers feel included in the healthcare process. Fostering such a conception of empowerment could provide a basis for a greater sense of the patient's responsibilities, whereby compliance with a medical regimen does not depend merely on their awareness of being monitored by a device.

It will therefore be the task of the prescriber to educate the patient to use these therapies correctly, avoiding self-diagnosis, do-it-yourself treatments and emotional overload for more fragile patients.

A relationship with a software package

Though the essential relationship between patients and physicians must not be relegated to history by the advent of DTx, there is no denying that a major shift in approach is under way. When relying on DTx, the patient interacts mainly with the software. This raises some concerns in terms of professional ethics, since having the therapy managed by an algorithm can potentially disrupt the healthcare provider-patient relationship with the clearly defined obligations that provide a common ground of trust, transparency, and safety between the two[8]. This is particularly true in the context of mental health, where fully autonomous, artificial intelligence-based treatment paradigms are not limited to provision of low-level support (e.g., comfort, social interaction): they also have the potential to carry out high-level therapeutic interventions that are traditionally the exclusive preserve of highly qualified health professionals such as psychoterapists[9,10].

These new approaches potentially contribute to progressive disintermediation[11] between the patient and the physician, increasing the risk of shifting medicine from the "art of curing" to a "science of measurement", where the inner life and feelings of the patient would be forgotten, and interpersonal communication would be secondary to the healthcare provider's informational function[12].

This new scenario requires close observation and study of the implications that transfer of tasks and responsibilities to a software could have, in terms of two important considerations: the perceived role of the doctor, and the feeling of trust that the patient could develop towards the software. In experiencing a sense of independence and self-judgement, the patient could possibly develop a confrontational attitude towards his/her healthcare professional, which would raise the need to rethink medical training or to redirect patient expectations[7].

3. Digital therapeutics: privacy, confidentiality, cybersecurity

DTx, which consist of clinically validated software performing therapeutic functions, are expected to provide a clinical benefit by processing incoming data in order to generate outputs that are able to influence the patient's behaviour. Indeed, the value of DTx is based precisely on the data collected, processed and evaluated (and also possibly used to update/optimize the technology): this applies not only to the pre-authorization phase of evidence-based clinical validation, but - above all - to that of real-world data generation. Hence the need to find a balance between this dynamic and the protection of confidentiality. One variable influencing this balance is the way these therapies are managed - particularly with regard to the doctor's/healthcare professional's role as a guarantor (though the US model is the prime example of a more marked disintermediation in the doctor-patient relationship, with a preference for direct involvement of the technology's manufacturer/developer).

According to the European legal framework, the data managed by DTx are among the so-called special categories of personal data, whose processing is regulated by specific conditions in order to safeguard privacy. Considering the sensitivity of such data, the European General Data Protection Regulation (GDPR) establishes that special categories of personal data shall be processed according to principles of "lawfulness, fairness and transparency"; shall be "collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes"; shall be "limited to what is necessary in relation to the purposes for which they are processed"; shall be accurate; shall be kept in a "form which permits identification of data subjects for no longer than is necessary for the purposes for which data are processed"; and shall be processed in a "manner that ensures appropriate security of personal data".

Against this backdrop, the focus should be narrowed to the ethical significance and implications of the term "fairness". It is crucial to point out that Article 5 of the GDPR, relating to the general legal principles that have to be respected in data processing, refers in letter a) to the "principle of fairness": by its very nature, this legal principle covers all ethical concerns related to the data processing entailed in DTx.

A relevant source in this regard is the EDPB (European Data Protection Board) document, Guidelines 4/2019 on Article 25 Data Protection by Design and by Default (final draft 20 October 2020). These Guidelines

state that "fairness is an overarching principle which requires that personal data should not be processed in a way that is unjustifiably detrimental, unlawfully discriminatory, unexpected or misleading to the data subject."

Further discussion of the legal framework associated with the processing of special categories of personal data goes beyond the scope of this chapter, but can be found elsewhere in this volume (see Casalicchio E. *et al.*, "Data protection and cybersecurity in digital therapeutics"). What is important from our viewpoint is that the outlined framework serves as a basis for discussing a number of ethical considerations regarding privacy, confidentiality and cybersecurity, in relation to DTx and data processing.

The increasing pace of technological progress, of which DTx provide an excellent example in the healthcare field, has outstripped the traditional conception of privacy. As a simple illustration of this, before the advent of technology as we know it today, any of us could theoretically have felt free to disappear without trace. Nowadays, this would be much more complicated. We are constantly localized and monitored by portable devices[13] that we interact with all day long, providing a ready supply of information related to ourselves. Digital tools know our likes and dislikes on nearly every subject, from political orientation to brands of clothing: they know our habits, our lifestyle choices, and many other traits of our behavior. This raises obvious concerns about the need to ensure that such an abundant source of individual data is used with due care and attention. This is why the implementation of DTx involves a shift in the concepts of privacy and confidentiality. Physicians are no longer the immediate collectors of medical information from patients: devices are. Within this framework, health data collected by DTx constitute sensitive information whose privacy, integrity, and confidentiality require appropriate standards of cybersecurity. The aim is for these data to be protected from unauthorized access or criminal use, phenomena whose incidence is increasing rapidly in the digital world. Once data are collected and processed, they might be stolen, reproduced, and subject to unlimited use. They might also be sold to third parties, for marketing and research. In addition, health records might be used to profile users for advertising purposes[14], or made available on an unauthorized basis to insurance companies as a basis for calculating premiums in relation to health status. Insofar as DTx users have limited awareness and perception of such issues, and of the possible fallout from data breach or piracy, adequate cybersecurity measures should be implemented.

Against this backdrop, the informed consent process associated with

the use of DTx plays a central role in order for prospective users to acquire knowledge regarding the nature and amount of data collected, their possible further use, and the measures put in place to safeguard privacy and confidentiality. Patients relying on DTx need to be properly informed in relation to these points, and should be allowed adequate time to ponder their consent or refusal. Despite the all-important role of informed consent, however, the continuing progress of big data analytics means that establishing clear boundaries is far from straightforward in practice [15]. As Lucivero and Jongsma point out, relying on informed consent is troublesome in a "consumer-focused domain where the mediation of healthcare professionals and researchers is shrinking" [7]. Confidentiality related to health data and records is jeopardized where there is no clear demarcation line between the commercial and medical domains, meaning that online purchases indicative of lifestyle choices can be matched with medical data [7]. Where such a distinction is blurred, there is the need to focus on which data should remain protected, and how.

From this perspective, in order to foster the implementation of DTx, additional efforts should be made to ensure a comprehensive view of the intended and actual use of collected and processed data [7]. Only in this way can preventive measures be set up to safeguard privacy and confidentiality, allowing patients to receive adequate information so that they can make an informed choice regarding the collection and processing of personal data.

4. Digital therapeutics: a reliable pathway

DTx can be seen as exemplary of a reliable and approved pathway by which to realize the benefits of health-related digital technology. Amidst the proliferation of digital tools, the implementation of DTx ideally offers an important, qualified component with a view to delivering sustainable care and improving healthcare access for those in need. The spread of DTx, and their practical relevance to care and assistance, are closely related both to the related clinical benefits and to the regulatory framework.

In order for digital tools to be seen as reliable and widely adopted, users, caregivers and clinicians must be confident of their safety and efficacy, while the tools themselves must obviously earn this trust. Given their therapeutic role, DTx should be developed through appropriate clinical trials that support manufacturers' claims in relation to efficacy, safety and in-

tended use; consistent with this, they must then be subject to a regulatory authorization process for specific therapeutic indications. The prevailing trait of DTx should be the clear and continuous link between the user and the prescribing physician, who is in charge of constantly monitoring the treatment's effects on the user. The certified pathway providing the basis for authorization of DTx is synonymous with accountability for all data collected, while also ensuring the safety and efficacy of delivered care. Certification of this kind is the only way to foster the sustainability of the healthcare system and, at the same time, to effectively deliver better care and improved access to it without exploiting patients' vulnerabilities.

In terms of European Regulations, the key concepts of safety, efficacy, privacy and accountability are described in the two applicable core regulations: the GDPR and the Medical Device Regulation (MDR).

Common to both sets of regulations is a safe-by-design (privacy-by-design) life-cycle approach, in relation to specific international standards (particularly IEC 62304 and the ISO 27000 family). Additionally, the GDPR and MDR have the same approach to accountability, with both stating that the medical device manufacturer is required to appoint a data protection officer and a person responsible for regulatory compliance. The MDR, moreover, requires an evidence-based medicine approach to the efficacy evaluation, specifying that this must be interpreted as clear application of state-of-the-art methods to clinical validation by means of clinical trials.

Overall, the contents covered above highlight how the implementation of DTx requires careful ethical evaluation and adequate education and awareness for clinicians, patients and society at large. Clinicians, who are responsible for prescribing DTx and monitoring their effects, should be formally required to receive adequate digital health training as part of their ongoing professional education: this will enable them to handle related clinical and ethical issues. Patients too stand to benefit greatly from education and awareness. As the spread of direct-to-consumer and unregulated apps becomes increasingly rapid, patients should be properly instructed in regard to the value of their health data, and possible consequences deriving from unintended or unauthorized uses of sensitive items. To this end, patients should be made aware of the differences among digital health tools available on the market - ranging from products of certified providers to unregulated direct-to-consumer apps. This will enable them to make an informed decision in relation to processing of their data. One proposed solution involves the development of labels[16] - like those already used for

foods - to guide users in their choice. Such a system, currently under discussion at regulatory level, would provide an immediate and accessible way to understand the main features of the various digital tools, with a view to comparing them and choosing accordingly.

What is known

- The rapidly emerging use of DTx in healthcare is reshaping the ways of delivering and receiving appropriate therapeutic support. However, these undoubtedly promising trends should be adequately nuanced, and their implementation must be subject to a thorough ethical evaluation.

What is uncertain

- Despite the considerable promise of DTx, the consequences of their clinical implementation are uncertain and deserve appropriate ethical assessment. Relevant concerns in this respect are reliability, safety, privacy, confidentiality, and the physician-patient relationship.

What we recommend

- We recommend active promotion of detailed ethical discussion, starting from the early development stages of DTx. This would provide a sound ethical basis for development of DTx, with timely learning of lessons related to identification of inaccuracies, negative implications, and gaps between intended and actual use.

Bibliography

1. Gordon WJ, Landman A, Zhang H, Bates DW. Beyond validation: getting health apps into clinical practice. *npj Digital Medicine* 2020; 3: 14.

2. Glickman SW, McHutchison JG, Peterson ED, et al. Ethical and scientific implications of the globalization of clinical research. *N Engl J Med* 2009; 360: 816-23.

3. Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. *Science* 2019; 366: 447-53.

4. Moghaddasi H, Amanzadeh M, Rahimi F, Hamedan M. eHealth equity: current perspectives. *J Int Soc Telemed eHealth* 2017; 5: e9.

5. Penney JW. Chilling effects: online surveillance and wikipedia use. *Berkeley Tech LJ* 2016; 31: 117.

6. Sharon T, Zandbergen D. From data fetishism to quantifying selves: self-tracking practices and the other values of data. *New Media Soc* 2017; 19: 1695-1709.

7. Lucivero F, Jongsma KR. A mobile revolution for healthcare? Setting the agenda for bioethics. *J Med Ethics* 2018; 44: 685-9.

8. Martinez-Martin N, Kreitmair K. Ethical issues for direct-to-consumer digital psychotherapy apps: addressing accountability, data protection, and consent. *JMIR Ment Health* 2018; 5: e32.

9. Inkster B, Sarda S, Subramanian V. An empathy-driven, conversational artificial intelligence agent (Wysa) for digital mental well-being: real-world data evaluation mixed-methods study. *JMIR Mhealth Uhealth* 2018; 6: e12106.

10. Fiske A, Henningsen P, Buyx A. Your robot therapist will see you now: ethical implications of embodied Artificial Intelligence in Psychiatry, Psychology, and Psychotherapy. *J Med Internet Res* 2019; 21: e13216.

11. Eysenbach G. Medicine 2.0: social networking, collaboration, participation, apomediation, and openness. *J Med Internet Res* 2008; 10: e22.

12. Kleinpeter E. Four ethical issues of "E-Health". *IRBM* 2017; 38: 245-9.

13. Tangari G, Ikram M, Ijaz K, et al. Mobile health and privacy: cross sectional study *BMJ* 2021; 373: n1248.

14. Ebeling MFe. Healthcare and big data. Digital specters and phantom objects. US: Palgrave Macmillan, 2016.

15. Doerr M, Maguire Truong A, Bot BM, et al. Formative evaluation of participant experience with mobile eConsent in the App-mediated Parkinson mPower study: a mixed methods study. *JMIR Mhealth Uhealth* 2017; 5: e14.

16. Bates DW, Landman A, Levine DM. Health apps and health policy: what is needed? *JAMA* 2018; 320: 1975-6.