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Digital Therapeutics as a New Therapeutic Modality: A Review from the Perspective of Clinical Pharmacology

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The promise of transforming digital technologies into treatments is what drives the development of digital therapeutics (DTx), generally known as software applications embedded within accessible technologies—such as smartphones—to treat, manage, or prevent a pathological condition. Whereas DTx solutions that successfully demonstrate effectiveness and safety could drastically improve the life of patients in multiple therapeutic areas, there is a general consensus that generating therapeutic evidence for DTx presents challenges and open questions. We believe there are three main areas where the application of clinical pharmacology principles from the drug development field could benefit DTx development: the characterization of the mechanism of action, the optimization of the intervention, and, finally, its dosing. We reviewed DTx studies to explore how the field is approaching these topics and to better characterize the challenges associated with them. This leads us to emphasize the role that the application of clinical pharmacology principles could play in the development of DTx and to advocate for a development approach that merges such principles from development of traditional therapeutics with important considerations from the highly attractive and fast-paced world of digital solutions.

The origin of digital therapeutics (DTx)—or using a software to treat—comes historically from the idea to digitalize certain forms of non-pharmacological interventions, such as cognitive behavioral therapies (CBTs). Today, DTx have proven to be effective in many areas where non-pharmacological interventions are known to play a critical role, such as for a variety of indications commonly gathered under the umbrella term of "mental health."[1] In this area, DTx are considered to be optimally positioned to increase access to care by reducing the need for face-to-face appointments and the fear of being stigmatized, by removing the monetary barrier and hurdles related to transports, or by compensating the shortage of healthcare providers.

From the initial idea of digitalizing CBT, DTx have evolved and continue to expand the range of embedded digital interventions and targeted areas. In **Table 1** we compiled a nonexhaustive list of references across a variety of indications where DTx are currently developed, used or foreseen to play a key role for patients.[2–41] This illustrates why their development is associated with significant promise, in particular for tackling the continuously growing burden of chronic diseases.[42]

Together with this fast evolution and despite the fact that several DTx are currently on the market with various medical claims associated with them, there is a consensus that a clear definition of DTx is still needed, as well as finding the most appropriate evaluation and regulatory framework for their development.

Regarding the definition, there exists no formal definition to date but the Digital Therapeutic Alliance (a global consortium aimed at promoting DTx development) has proposed a definition according to which DTx are evidence-based therapeutic interventions driven by high-quality software programs to prevent, manage, or treat a medical disorder or disease.[43] In this review, we rely on this definition as our focus is on digital solutions as a therapeutic modality and in consequence, digital solutions that make a general lifestyle claim, such as wellness, are out of scope of this review.

In the United States—where the development experiences are the most numerous—most DTx are classified as medical devices by regulatory authorities due to claims falling under the medical device jurisdiction[44] and approval/clearance for commercialization is obtained through the 510(k) or De novo pathways.[45] In addition, in the European Union, there is a general understanding that DTx solutions should be classified as medical devices. In addition, the few national reimbursement frameworks that address software suggest the need for DTx to be CE marked in order to get reimbursed (example with the DiGA reimbursement pathway in Germany[46]).

For digital solutions claiming a therapeutic benefit, there is a need for high-quality evidence of safety and efficacy based on clinical trials as a basis for their approval.[47] Increasing the amount of evidence of safety and effectiveness is acknowledged as a significant need among the challenges associated with the development of DTx[48] and requires specific guidelines about aspects of their effectiveness evaluation as well as for their clinical development, for example, to conduct blinding and assign comparators.[49,50]

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Table 1 Nonexhaustive list of references compiled for an overview of DTx application across a variety of therapeutic conditions

Category	Target	References	Comment	Type	Publication year
Behaviors and mental disorders	Anxiety and/or depression	https://pubmed.ncbi.nlm.nih.gov/25786025/	Internet and computer-based CBT	Meta-analysis	2015
		https://pubmed.ncbi.nlm.nih.gov/31250242/	Computer-based CBT and mobile apps	Review	2019
		https://pubmed.ncbi.nlm.nih.gov/28456072/	Smartphone applications	Review	2017
		https://pubmed.ncbi.nlm.nih.gov/28241179/	Internet-based CBT	Meta-analysis	2017
		https://pubmed.ncbi.nlm.nih.gov/29068266/	Internet-based CBT	Randomized clinical trial	2018
		https://pubmed.ncbi.nlm.nih.gov/25645168/	Internet-based CBT	Randomized clinical trial	2015
		https://pubmed.ncbi.nlm.nih.gov/32624013/	Smartphone applications	Randomized clinical trial	2022
	Eating disorders	https://pubmed.ncbi.nlm.nih.gov/33761233/		Review	2021
	Psychiatric and somatic disorders	https://pubmed.ncbi.nlm.nih.gov/25273302/	Cover few studies across several indications	Review	2014
	Schizophrenia	https://pubmed.ncbi.nlm.nih.gov/26546039/	Smartphone apps	Review	2015
	ADHD	https://pubmed.ncbi.nlm.nih.gov/33515870/	Smartphone apps and wearable technologies	Review	2021
		https://pubmed.ncbi.nlm.nih.gov/33334505/		Randomized clinical trial	2020
	Bipolar disorder	https://pubmed.ncbi.nlm.nih.gov/28594196/	Online and mobile technologies	Review	2017
Substance related disorders	Drug usage	https://pubmed.ncbi.nlm.nih.gov/36339845/	Cannabis use	Review	2022
		https://pubmed.ncbi.nlm.nih.gov/36055736/		Review	2022
		https://pubmed.ncbi.nlm.nih.gov/24700332/		Randomized clinical trial	2014
		https://pubmed.ncbi.nlm.nih.gov/28295758/	Illicit substance use	Meta-analysis	2017
		https://pubmed.ncbi.nlm.nih.gov/33140981/	Real world observational evaluation | opioid use	Randomized clinical trial	2021
	Alcohol misuse	https://pubmed.ncbi.nlm.nih.gov/24937483/		Meta-analysis	2014
Neurological and development disorder	Autism	https://pubmed.ncbi.nlm.nih.gov/33736943/	DTx as one of the two areas cover in the review	Review	2021

(Continued)

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Table 1 (Continued)

Category	Target	References	Comment	Type	Publication year
Symptoms	Phobia (of heights)	https://pubmed.ncbi.nlm.nih.gov/30007519/	VR	Randomized clinical trial	2018
	Insomnia	https://pubmed.ncbi.nlm.nih.gov/33226269/	Prescription DTx | overview of safety and efficacy	Review	2020
		https://pubmed.ncbi.nlm.nih.gov/26615572/	Internet-based CBT	Review	2016
		https://pubmed.ncbi.nlm.nih.gov/35162009/	External auditory stimulation	Review	2022
		https://pubmed.ncbi.nlm.nih.gov/36400549/	CBT	Review	2023
	Pain	https://pubmed.ncbi.nlm.nih.gov/34807837/	Low back pain	Review	2021
		https://pubmed.ncbi.nlm.nih.gov/35770137/	Opioid-based pain | VR and mobile apps	Review	2022
		https://pubmed.ncbi.nlm.nih.gov/35599969/	VR | adults and pediatric	Review	2022
Nervous system diseases	Migraine	https://pubmed.ncbi.nlm.nih.gov/36660558/		Review	2023
	Neurological dysfunction	https://pubmed.ncbi.nlm.nih.gov/34018047/		Review	2022
	Stroke rehabilitation	https://pubmed.ncbi.nlm.nih.gov/31587534/		Review	2019
	Parkinson's disease	https://pubmed.ncbi.nlm.nih.gov/33646177/		Review	2021
Digestive systems disease	Gastrointestinal indications	https://pubmed.ncbi.nlm.nih.gov/36375993/		Review	2022
		https://pubmed.ncbi.nlm.nih.gov/32510249/	Irritable bowel syndrome|CBT	Review	2020
		https://pubmed.ncbi.nlm.nih.gov/36847206/	Irritable bowel syndrome|brain-gut behavioral therapy	Review	2023
Nutritional and metabolic diseases	Diabetes	https://pubmed.ncbi.nlm.nih.gov/32325045/	Focus on AI but include section on DTx	Review	2022
Heart diseases	Hypertension	https://pubmed.ncbi.nlm.nih.gov/35726619/		Review	2022
		https://pubmed.ncbi.nlm.nih.gov/33340672/		Review	2021
	Cardiac rehabilitation after heart failure	https://pubmed.ncbi.nlm.nih.gov/36085358/		Review	2022
Oncology	Supportive care	https://pubmed.ncbi.nlm.nih.gov/32533435/		Review	2020

ADHD, attention-deficit/hyperactivity disorder; AI, artificial intelligence; CBT, cognitive behavioral therapy; DTx, digital therapeutics; VR, virtual reality.

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Whereas being fundamentally different from conventional pharmaceutical products, DTx must include—by definition—a (digital) active ingredient, driving the therapeutic effect.

This statement is what led us to present this review from the perspective of clinical pharmacology: we asked ourselves how the tools and methods of clinical pharmacology—aimed at characterizing response variability by focusing on the study of this active ingredient and its interaction with the targeted pathological processes—could positively contribute to the development of DTx.

The active ingredient for a DTx is the software, including the algorithms, and because the active ingredient is not in the systemic circulation, traditional clinical pharmacology principles do not translate exactly. However, they can be adapted to the particularities of DTx.[51]

As a new and rapidly evolving field, there are many aspects of traditional pharmacological drug development that have not yet been considered in the context of DTx. We have performed a review of DTx clinical studies to get a better sense of the current development landscape and to identify gaps in areas for which we think that the principles of pharmacology could benefit DTx development.

REVIEW OF RANDOMIZED CONTROLLED TRIALS OF DIGITAL THERAPEUTICS

Clinicaltrials.gov was used as the search engine for clinical trials of digital therapeutics. The search was performed using the keywords "digital therapeutic" or "digital therapeutics" in the "title/acronym" search bar of the advanced search page. The search was performed on March 15, 2023. The start date (estimated date on which the clinical study opens for recruitment) range was December 2015 to September 2023 with median in May 2021. The completion date (estimated date the final participant was examined or received an intervention) range was July 2016 to October 2028 with median in November 2022.

The search generated 270 studies. Studies with "withdrawn" status or indicating "no longer available" as status ($n = 5$ in total) were removed from this list.

Among the 265 remaining studies, 51 (~20%) were removed because they were considered out of scope. This happened most of the time when the word "digital" generated a search hit but was used in reference to the word "finger" (e.g., digital ulcer) or in reference to imaging techniques (e.g., digital subtraction angiography) or in reference to a "digital workflow" of conventional treatment.

We additionally excluded 50 other studies from our main analysis which, while referring to potential digital therapeutic solutions, presented elements which we evaluated not compatible with our working definition. We later comment on the reasons that these studies were not included in the primary analysis.

The remaining 164 studies represent clear illustrations of digital therapeutics as a therapeutic modality and we report below the main learnings from an exploratory analysis of these selected studies as an overview of the DTx development landscape today.

Based on the status data element on the database, the majority of the studies were either recruiting ($n = 55$, 34%) or completed ($n = 53$, 32%). Although the majority of the studies are or were located in the United States ($n = 93$; 57%), Sweden was the second country in terms of number of studies ($n = 8$). China, the United Kingdom, and South Korea share the third position in terms of number of studies per country with seven studies. It is worth noting that the studies' location data element involved 24 countries worldwide and with that, covered the 5 continents with 100 studies in the Americas (representing 61% of all studies), 39 in Europe (24%), 22 in Asia (13%), 2 in Oceania (Australia), and 1 in Africa (Kenya).

We show in **Figure 1** maps of the world, Europe, and Asia summarizing study location and the repartition of the number of studies in all 5 continents.

DTx clinical trials are typically small studies. By analyzing the enrollment data element—defined as the estimated target or actual number of subjects enrolled—we found that the median was 100 human subjects (57 at the first quartile and 254 at the third quartile). Less than 10% of the studies involved more than 500 patients ($n = 14$) and less than 3% more than 1,000 patients ($n = 6$).

Almost all studies were interventional studies (96%, $n = 158$). The majority of studies were randomized ($n = 127$, 77%) and indicated "treatment" as the primary purpose ($n = 120$, 73%). Other purposes include supportive care ($n = 16$, 10%) and prevention ($n = 10$, 6%). A single study indicated "basic science" in its primary purpose.

For a majority of the studies, the phase was not informed (value "not applicable" in the phases data element for 95%, $n = 156$) potentially indicating a difficulty or inadequacy for using the traditional drug development phases framework for such studies.

For the few studies where the phases were indicated, there was not a single early phase study (i.e., phase I, proof-of-concept, feasibility, or first-in-human).

Finally, universities and academic centers were dominant as sponsors. Large pharmaceutical companies sponsored only 6 studies (<4%) and their sample size was not different from the median size of 100 subjects, as reported above.

Figure 2 shows the histogram of enrollment data as well as repartition of studies with respect to their design and phases.

The majority of the trials were studying conditions falling in the conditions topic "behaviors and mental disorders" ($n = 55$, 34%) or "symptoms and general pathology" ($n = 32$, 20%). In the first category, depression, anxiety, and attention-deficit/hyperactivity disorder (ADHD) represented 65% of all studies (36 studies among which 21 studies were for depression).

For the second category, sleep disorders and pain represented up to 84% of the all studies (27 studies).

From the age data element (presence of the word "child" in that element), we found that a significant proportion of the studies involved or involved the pediatric population (14%, $n = 23$).

Figure 3 shows the conditions studied with a focus on the 2 main categories as well as the repartition of studies with respect to the pediatric population.

Summary of trial characteristics

Clinical testing of DTx happens worldwide with the United States, China, South-Korea, and some European countries being the leading world regions. The studies are relatively small (~ 100 participants), interventional, and very often randomized. The

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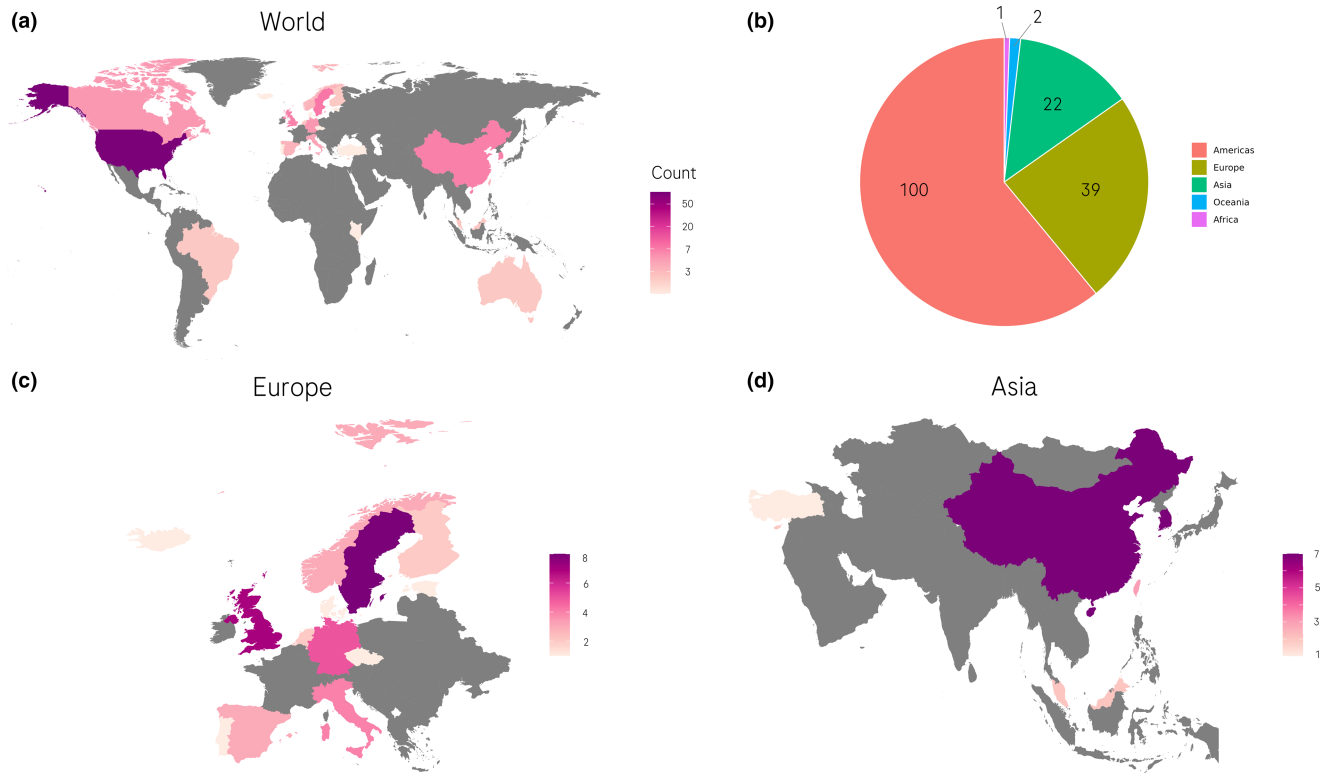

Figure 1 Number of studies per country. World view (**a**), Europe (**c**; Russia is not represented for visual considerations, no study was reported in Russia), Asia (**d**), and repartition of number of studies per continents (**b**).

main conditions studied are depression and anxiety, ADHD, pain, and sleep disorders, and for some of these indications, they often involve the pediatric population. The majority of these studies aimed at showing treatment benefit thus comparable to late phases even if the phase of the study is almost never informed and that the typical sample size better corresponds to pilot (early-stage) studies. However, we found that this is not representative of the case of studies that were used to support regulatory clearance. In fact, we have retrieved sample size information from 6 studies related to 4 US Food and Drug Administration (FDA) *de novo* cleared products[45] to find that the mean sample size was much larger with 230 subjects.

ANALOGIES WITH NOTIONS FROM TRADITIONAL DRUG DEVELOPMENT

Although being fundamentally different from conventional therapies, we found elements of the studies of digital interventions for which it is interesting to draw analogies with more traditional pharmacological interventions clinical development. These include the notion of "active ingredient" and of "formats" of the (digital) therapeutic as well as the notions of "precision dosing," "optimal combinations," and "post-marketing" studies.

Active ingredient

Although being fundamentally different from conventional drugs, DTx must include an active ingredient driving the therapeutic effect. Originally, the DTx active ingredient was often digital CBT, but the expansion of the range of products and applications leads to a large variety of active ingredients being studied, beyond the original CBT. Delineating the active ingredient of an intervention is fundamental for building an understanding of the mechanism of action of an intervention; and this understanding is a key step for intervention optimization.

Located in Brazil, the study NCT05375851 is a 12-week randomized trial aimed at evaluating the efficiency of a digital intervention composed by psychoeducational videos and the administration of digital symptom rating scales in 60 adults with generalized anxiety disorder. In the experimental arm, the treatment is composed of the digital intervention and the treatment is usually mainly composed of biweekly online consultations. The comparator arm is only composed of online consultations. This example is interesting because there is a clear therapeutic intervention even if different from the usual digital CBT. Indeed, the combination of dedicated educational video accessed by the patients in between the consultations—and whose content is discussed between the patient and the clinician during the consultations—with the administration of digital symptom rating scales are considered as active ingredients of the intervention. In addition to that, there is a clear intention to treat and evidence generation, as the primary end point, is the clinical change as measured by the Generalized Anxiety Disorder-7 (GAD-7) scale score, used as an end point for pharmacological interventions.

Formats

Another element that emerged from our analysis, that raises interesting parallels with traditional pharmaceutical clinical

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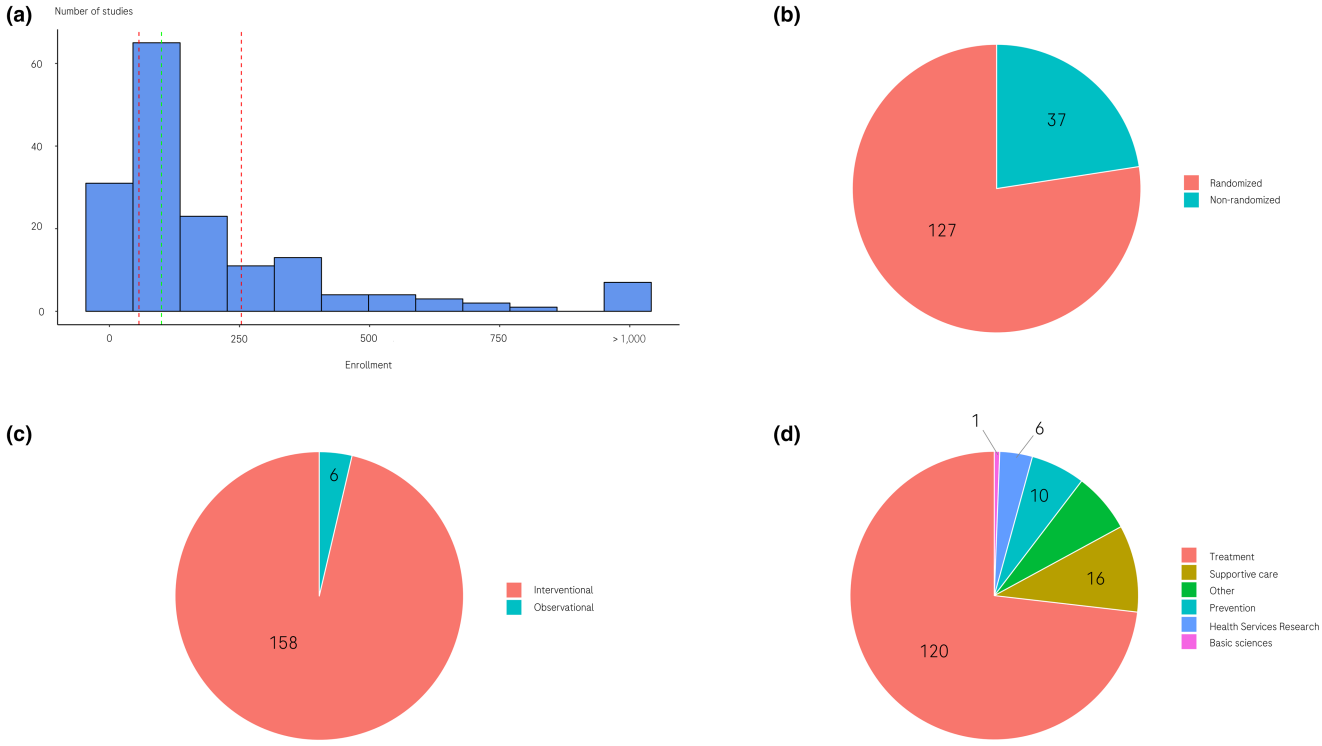

Figure 2 Enrollment per study with vertical lines representing median (green), first and third quartiles (red;**a**), distribution of randomized vs. nonrandomized studies (**b**), interventional vs. observational (**c**), and main purpose (**d**).

development, is the concept of different formats. For example, the purpose of the study NCT05710965 is to evaluate 3 different investigational wearable digital interventions for children with ADHD. In this randomized interventional study, 150 participants are divided within 3 groups, each of these using a different format of a wearable device intervention. The differences among the groups concerns how therapeutic vibrations and/or assistive messaging should be best provided to the subject by the wearable device. Here, again, there is a clear digital intervention (therapeutic vibration and messaging), a clear intention to treat with generation of evidence (the primary end point is the ADHD rating scale), and, in addition to that, the study tests scenarios which could be considered similar to the testing of different formats of the same modality.

Precision dosing and optimal combination

We further highlight two studies focusing on questions for which clinical pharmacology and pharmacometrics play an essential role when these are investigated from the perspective of pharmacological modalities.

The study NCT05473013 is an interventional randomized factorial design study in 264 subjects in the United States and aims to identify the effects of self-monitoring approaches and 2 types of micro-interventions when combined with standard CBT for bulimia nervosa and binge eating disorder.

Self-monitoring approaches refer either to the self-monitoring protocol as part of the traditional behavioral treatment or an enhanced skill monitoring via a smartphone application. The two micro-interventions take the form of reminder messages sent to the subject as push notifications either at random times or following a just-in-time adaptive intervention (JITAI) "dosing" approach.

The objectives of the study are multiple. They include the evaluation of the optimal complexity of both self-monitoring and micro-interventions on eating behaviors.

They also include exploration of target engagement in the sense of the right level of complexity for each component, and, finally, they include the quantification of the interaction effects between the self-monitoring and the micro-interventions approaches.

Beyond the clarity of the digital intervention, the intention to treat, and the evidence generation, this study is also a clear example of important research and development activities to support the development of successful digital therapeutics with topics such as deciphering the mechanism of action, better understanding target engagement, testing precision dosing, and testing potential synergies between several digital interventions. Although the development phase of the study is not indicated, this could be a good illustration of an early clinical development study (a proof-of-concept or feasibility study, comparable to a phase I) where the most promising levels of complexity identified could become essential core elements of a further developed product.

The study NCT05456607 is also a very good example of a clinical study potentially matching an early phase in traditional pharmacological clinical development because the main question is around the optimal scheduling (sequencing) of 2 digital interventions, one targeting insomnia and the other one targeting depression, to assess

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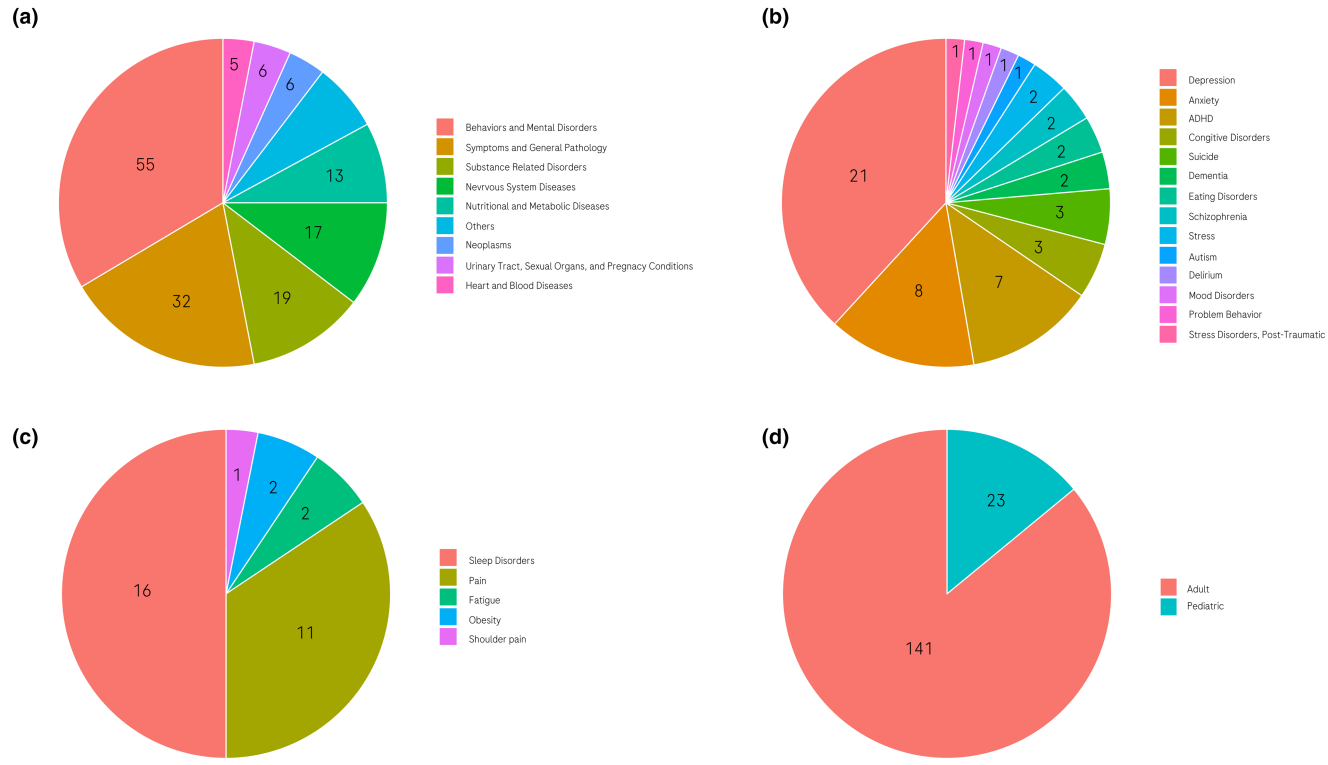

Figure 3 Conditions category of the selected studies (**a**) focus on "Behaviors and Mental Disorders" (**b**) and "Symptoms and General Pathology" (**c**). Distribution of studies with respect to the population (pediatric or adult;**d**). ADHD, attention-deficit/hyperactivity disorder.

highest response rate in 1,500 adults suffering from both depression and insomnia.

Postmarketing studies

The integration of DTx within the healthcare system is an active field of research, which is not in the focus of the present review. Still, we highlight this study as an example of a "postmarketing" (comparable to a phase IV) study showing on-going efforts to research the optimal way to integrate digital interventions in primary care. Positioned as health service research (see **Figure 2**), the DIGITS trial (NCT05160233) researches the conditions for optimal impact of digital treatment use on health services. It is a large recruiting interventional study located in the United States aiming to optimize the implementation of digital treatments for opioids and other substance use disorders in primary care. The study, with a target enrollment number of 13,000 human subjects, will test the benefit of health coaching and/or practice facilitation with the use of the FDA authorized prescription digital therapeutics.

ADDITIONAL OPPORTUNITIES OF DTX

Beyond the parallelism with traditional drug development highlighted in the previous section, our analysis revealed at least two characteristics or applications of digital interventions that are worth presenting, to highlight the potential benefit of this new therapeutic modality. In the following sections, we highlight a few studies illustrating the application of DTx in preventive medicine and the diversity of modalities and areas of impact of DTx, demonstrating how such digital solutions can be complementary to conventional treatments to increase positive impact to health care and society globally.

Prevention

The two following studies illustrate the potential of DTx as an interventional modality which could play an important role for prevention.

The DigitalStart trial (NCT02921841) is an interventional, randomized study that aims to develop a digital HIV prevention intervention tailored to adolescents in mental health treatment including—as core elements—affect regulation and cognitive monitoring in sexual situations.

The study, involving 125 subjects, compared this digital intervention with digital general health promotion information on nutrition, sleep, smoking, and exercising but without the core elements of the experimental arm. We consider this an interesting example because there is a clear intention to prevent associated with the generation of evidence (e.g., on knowledge on HIV) and a clear therapeutic intervention with the distinction between an intervention with an active ingredient (affect regulation and cognitive monitoring) and without.

The study NCT01754090 is another example of DTx development for prevention.

The interventional study, randomized, involving 244 at-risk drinkers in Norway aims to test if an online multisession alcohol intervention following a screening session improves treatment effect compared with the situation where subjects are given

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access to an online booklet about the effects of alcohol following the screening session. The access to the online booklet is here considered as a nonintervention. On the contrary, the intervention (online multisession follow-up program) is based on supporting the patient with continued self-regulation throughout the behavior change process through key aspects, such as goal setting, tracking of consumption, personalized content delivery to prevent relapse, emotion regulation, and access to educational material.

Intervention diversity

Another interesting observation generated by our analysis concerns the wide range of intervention modalities and therapeutic areas or conditions for which DTx are currently being investigated.

The study NCT02431390, for example, is a randomized 2-arm study involving 80 participants and aims to evaluate a digital system composed of a robotic (digital) glove to improve upper extremity function of patients with stroke. A robotic glove is a physical glove equipped with sensors used for rehabilitation. In the experimental group, the robotic glove is the digital intervention delivering 20 training sessions where the subjects play games or puzzles for rehabilitation of upper limbs. The system provides biofeedback to users. The active comparator group is composed of conventional occupational therapy. In this example, whereas different from other types of digital intervention reviewed so far, there is a clear intervention (a glove providing biofeedback), a clear intention to treat and evidence generation as the primary end point is the change in upper extremity function.

The study NCT04011540 is another example illustrating the diversity of possible digital interventions digital therapeutics can be made of. The study—which aims to better understand how patient electronic communication can be used in psychiatric treatment—evaluates the efficiency of receiving digital data through a personalized dashboard prior to a scheduled mental health session. Health-related quality of life and depressive symptoms questionnaires are part of the outcomes. In this case, the intervention is the personalized data dashboard.

EXCLUDED STUDIES

As mentioned before, we excluded 50 studies from our exploratory analysis. We have summarized the reasons for this choice in the following.

Reason 1: It is not clear whether there is an intervention

We found studies for which it was difficult to identify the "intervention" delivered to the patient. In such cases, it was also difficult to identify what the active ingredient of the DTx would be and, thus, trying to explore the potential added value of clinical pharmacology became obsolete.

Examples included studies involving digital sensors and passive monitoring of vital signs or symptoms. A DTx can of course incorporate sensors with the objective to support or tailor the therapeutic (digital) intervention delivered but per se, sensors and passive monitoring are digital solutions which may not represent a therapeutic intervention. Sensors and passive monitoring could be considered as interventions in cases similar to the study above on a data dashboard for mental health therapy. In that case, it is the data collected by the sensors and presented to the patient in a particular format which are assumed to trigger a mechanism that could have an impact on the disease.

It is worth noting that unclarity and "gray areas" will always remain with respect to this, as illustrated by the on-going research activities about the difficult topic of appropriate controls for DTx. Indeed, for solutions delivering psycho-social, cognitive, or behavioral content, just providing structure and creating positive engaging experiences and rewards may improve symptoms in addition to the specific therapeutic content.[52] Overall, this supports the idea that the evaluation of whether there is intervention or not should not be taken as a black and white process or viewed as an exclusion criteria but it confirms this topic as an important one because actually, a digital solution without a clear therapeutic intervention may not be truly inert and have some therapeutic efficacy.

Reason 2: The "active ingredient" of the intervention is not digital

To increase access to care, digital tools can be used as a vector of conventional non-digital treatment. When the tool is considered as a vector only, then it may be deprived of any active ingredient per se. One clear example is a telehealth service. Whereas the presence of the digital component cannot be argued (the patient is connected to a health provider via a digital device), the active ingredient of the intervention is not related to the digital device, but is administered by the physician in the form of therapy. For such types of digital solutions to be considered as potential therapeutic modalities under our definition detailed earlier, there must be an identifiable digital active ingredient within the solution itself.

Other studies we excluded for a similar reason were studies of digital dosing systems, such as digital inhaler for the treatment of asthma or software for precision dosing. A dosing algorithm is not considered as a therapeutic modality but as a clinical decision support tool. The active ingredients of these interventions are not digital but are within the pharmacological compound. The digital solution is used to optimize its effect but the active ingredient remains in the conventional therapeutic modality.

Reason 3: There is no hypothetical mechanism of action

Similar to the presence of a digital active ingredient, the development of DTx as a therapeutic modality requires a hypothesis on a potential mechanism of action (i.e., a therapeutic model), linking the construct to its targeted effect. For modalities such as small or large molecules, these models will include biodistribution, target engagement, modulation, or effects on biomarkers, for example.

Although it is probably not possible to translate these model components to the breadth and variety of potential digital therapeutic interventions, still, potential mechanisms of action should be hypothesized and explored. For example, for digital intervention targeting behaviors and mental disorders, such therapeutic models will involve cognitive processes. The development of a therapeutic modality as a therapeutic innovation is known to be extremely difficult. The absence of a hypothesis on the drivers and core elements explaining the response and desired effect lower the chances for successful development.

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For example, studies involving devices offering access to educational material without this being formatted in the context of a clear intervention, or studies not specifying the type of content, how it is delivered, whether it is supposed to synergize with other interventions, are studies we excluded because the presence of a hypothetical mechanism of action was unclear.

Further examples are studies where the digital intervention is delivered to another person than the subject with the condition with the idea that inducing a change in that person, because of their role and relationship with the subject, will support the subject to reach a therapeutic objective; for example, training parents to be able to adopt the right strategy for children with conditions such as ADHD. Another example of this indirect effect model are studies we reviewed on digital therapeutic interventions for the training of clinicians and practitioners with evidence generation on the subject with the conditions.

All these examples could be highly relevant and potentially transformative in ultimately addressing the patient needs, but they also incorporate additional layers of complexity because the therapeutic model should integrate processes happening outside (in the environment) of the subject with the conditions which could be extremely complex and raise a large number of critical questions among which: which data should be collected to better understand these underlying processes?

Reason 4: There is generation of evidence, but not on the intended therapeutic benefit

The generation of evidence is within our working definition of DTx but it is worth specifying that such evidence needs to be about the therapeutic intent directly.

Several studies of DTx have as primary objective to increase adherence to a conventional pharmacological "companion" intervention. Although it could be argued that more adherence would translate into more benefits, such studies are aimed at optimizing an existing (non-digital) intervention and thus the corresponding device might not be considered as a therapeutic modality per se, similarly as electronic pill dispensers are not considered a therapeutic modality.

Another situation we have encountered is where the evidence is centered around the adherence to the digital solutions itself. If the digital solution is already approved as a therapeutic intervention, then it is the same situation as described in the previous paragraph. But if the digital solution is to yet to be approved, then such studies may not be considered as qualifying for supporting the approval for a DTx as a therapeutic modality. Developing DTx as therapeutic modality may need to involve early-stage studies focusing on the adherence as a necessary, but not sufficient condition. The ultimate objective is evaluation of effect on validated clinical end points.

OPPORTUNITIES AND RECOMMENDATIONS

We propose a list of recommendations discussing DTx benefits and challenges from the point of view of clinical pharmacology.

Increase the understanding of mechanism of action through modeling

There are fundamental differences between DTx and pharmacological treatments, yet, the fact that it is about digital interventions should not prevent developers from prioritizing research to understand mechanism of action and underlying pathophysiological processes of response; this understanding being recognized as a core element of successful drug development.[53,54]

For DTx targeting behaviors and mental health, models of mechanism of actions, such as quantitative data-driven disease and therapeutic models, could be quite different from pharmacometric and disease models applied for conventional therapy. In particular, they may be less focusing on biological processes and more on behavioral processes, including cognition, emotion, and affect regulation. They may mimic the approach consisting of focusing on upstream causes rather than downstream consequences of disordered behavioral states to lead to innovation and discovery.[55] Research has made progress in understanding the theoretical mechanisms behind indications such as anxiety and depression and this resulted in some testable hypothesis regarding treatment optimization[56] including for digital interventions.[57]

The development and use of DTx comes together with a significant paradigm shift when it comes to the data collected and the opportunity to leverage them for further optimizing development and usage. For traditional pharmacological compounds, data used to analyze the compound's pharmacological properties are usually collected through invasive methods for patients (e.g., blood sampling and tissue biopsies) and cannot be taken too frequently.

Generally, the generation of data through the use of DTx should be much less constrained and could support digital phenotyping[58]—given the identification of reliable and meaningful biomarkers—contributing to the further development of quantitative psychiatry considered to be key for conditions known to be highly heterogeneous.[59] Such high dimensional longitudinal data can also drive real-time optimization of the digital interventions via modeling and artificial intelligence techniques.[60]

DTx seems particularly well-suited for model-based (drug) development and precision dosing because it offers the possibility for real time, remote, and automated collection of high volumes of patient-level data on therapy administration and impact on end points. It is foreseen that combined with sensors, real-time patient state could be inferred and prompts the administration of the optimal dosing regimen for each patient in order to achieve an outcome.

Research needed beyond the topics of engagement and adherence

Intense research activities in the field of DTx focus on the question of increasing and keeping high engagement. This is a clear necessary condition for the successful development of DTx.

Within this research theme lies the topic of creation and maintenance of the therapeutic alliance (i.e., the working alliance between clinician and patient), which is a central consideration in traditional face-to-face therapies. Such objectives could be reached with human support[61] or without (i.e., being fully automated),[62] which in the case of specific conditions, such as mental illness, is associated to high complexity[63] because the way each individual engages with the technology also depends on behavioral and cognitive aspects.

In fact, how to efficiently integrate coaching and messaging support to keep users engaged is an intense field of research.[64,65] We, as users of mobile technologies, get annoyed with frequent messages

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and suggestions from our smartphone. For this reason, the topic of "receptivity" or how to understand when is the right time to send a notification to have full attention from the user is key to the success of DTx, and most of the current efforts in this area are concentrated around optimizing the features of the interventions to increase its chance to be "receptioned."

The latest technological and algorithmic development—such as just in time adaptive interventions or JITAI[66] to optimize such supports are very interesting. Such approaches, in fact, come as an inspiration for the field of pharmacometrics as they could also be applied to the topic of pharmacological intervention dose optimization and be particularly relevant for inclusion of multidimensional drivers (biomarkers in addition to pharmacokinetics, for example) through approaches such as reinforcement learning.[67]

Beyond engagement, many studies testing JITAI focus on the problem of reaching an intermediate end point potentially related to a long-term desired clinical outcome. For instance, reaching an objective in terms of a daily physical activity (proxy) to reduce the risk of coronary disease (desired clinical outcome).

But whereas it is a necessary condition to have DTx with high levels of engagement and optimized for users to reach a proxy, it is not a sufficient condition for developing DTx as therapeutic modalities. It is important to extend these efforts and position the optimization of DTx in a holistic fashion, integrating together with the topic of engagement, the relationship between the proxy to be achieved and the long-term clinical outcome. Then, DTx optimization is similar to the "precision dosing" problem for pharmacological interventions and corresponds to optimizing the intervention to reach a long-term objective, requiring good models for target engagement, and optimal dosing for safety and efficacy taking into account special populations.

In our opinion, this represents a significant opportunity for the field of clinical pharmacology and modeling to get closer to the field of DTx development.

We propose an illustration of such a concept in **Figure 4**. Whereas step 1 (engagement) is mostly covered in DTx literature, we will discuss in the following more around the elements of steps 2 (proxy/biomarker) and 3 (long-term clinical outcome).

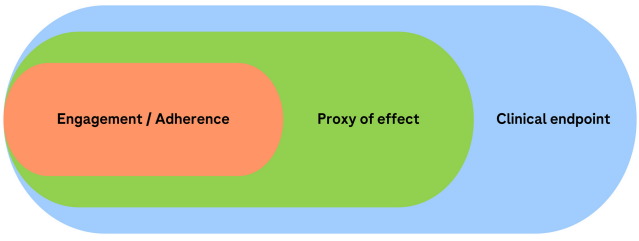

Figure 4 Most R&D activities dedicated to DTx optimization currently focus on the topic of engagement/adherence (orange) and to the reach of proxy of effect (green). To optimize DTx as therapeutic modalities, it is critical to integrate, within this optimization problem, the effect on validated clinical end points. As for the precision dosing of pharmacological compounds, this will require the development and use of disease/therapeutic models integrating the concepts of target engagement, mechanism of action, long-term efficacy, and safety, as well as the population for which dosing should be different. DTx, digital therapeutics; R&D, research and development.

Right dose and right patients

Some efforts have been undertaken to discuss important concepts and challenges in studying dose–response relationships in digital health interventions.[68] In our review, only a minority of studies have integrated the concept of optimal dosing and population of DTx or even only have highlighted the importance of better understanding drug response variability and the relationship among the dose, the target population, and the effect of DTx. However, for DTx to be effective, they should be studied with the aim of understanding this relationship and thus experimentally identifying the optimal dosing given the target population and the expected therapeutics action. Optimal dosing strategies for DTx, generally, seems to be viewed as the higher the better. A clear example is with gamified DTx which, whereas primarily aimed at increasing engagement, are implicitly based on a concept of the more exposure the better. However, as for conventional drugs, it should not be assumed for DTx that more exposure is always better. For drugs, for pharmacological interventions, it is recognized currently by both developers and regulators that a monotonic relationship between dose/exposure and effect should be treated as a hypothesis, given the complexity of underlying biological processes involved potentially leading to the emergence of nonlinear and non-monotonic relationships between dose and effect. In absence of any robust evidence, DTx developers should assume that optimal dosing is a topic of research and study it, both at the level of populations and individuals in early clinical settings.

For example, for a mobile application, investigating this topic could lead to the study whether it is better to take the digital intervention 30 minutes every 3 days or 10 minutes every day, similarly to testing different "release formulations" for conventional drugs.

The topic of adapting the dosing regimen to special populations should also be carefully considered. The study of how doses should be adapted to special populations is a key deliverable of clinical pharmacology studies. In the absence of any theoretical argument supporting the absence of response variability in DTx, developers should look carefully early if some individuals respond differently and try to disentangle why (see ref. 69 for a review dedicated to DTx for hypertension highlighting this need). This could be done by early clinical studies to look for particular responders and dissecting with data-driven analysis the reasons for such variability in responses. This appears particularly important knowing the significant proportion of DTx studies involving a pediatric population.

Finally, similar to clinical trials to support drug development, diversity in the clinical trials for digital therapeutics is also critical. Including a population that correctly represents the diverse range of the intended users population is not only a regulatory requirement, but also an opportunity for DTx to support one of the big promises of digital health: democratization of health care; first, because a large proportion of today's developed solutions are for behavioral and mental disorders, conditions for which minorities are particularly exposed (see the education material from the American Psychiatric Association[70]); and second, because DTx should contribute in removing barriers related to access to effective treatment even if digital accessibility remains an area where improvements are still needed to reduce inequalities.[71] The potential synergies between the characteristics of DTx (remote data

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collection and at-home therapy administration) and innovation in delocalization of clinical trials can facilitate the involvement in studies of patients from minorities, underserved populations, and low-income areas.

Adverse effects and combinations

For digital interventions, the absence of adverse effects should not be assumed by default, as all individuals will not have the same response. On the contrary the default should be the expectation of variability in response and potential intervention-related side effects. Experimental studies should be designed to address such questions together with meta-analysis following existing efforts, such as in ref. 72 investigating deterioration and its moderators within randomized trials on internet-based guided self-help for adult depression.

Another area where clinical pharmacology is known to deliver substantial added value to the development of medicine is the investigation and prediction of the consequences of different interventions interacting together. The same problem would be relevant also for DTx and we have highlighted earlier a clinical study focusing on this question.

LIMITATIONS AND OTHER IMPORTANT UNCOVERED AREAS

This review is of course not exhaustive and there are important themes inherent to the successful development of DTx, which we have not discussed. One of them is quality and data privacy for which we can refer the readers to the following review focusing on mobile applications for bipolar disorder discussing the topic.[73] DTx, as many other digital health solutions, have the potential to generate, collect and store Personal Health Information of the users. This characteristic, whereas opening potential opportunities to increase the clinical utility of the tools by facilitating information sharing across the care team, also presents challenges to the DTx development and validation processes. Although a detailed discussion on these challenges is beyond the scope of this review, it is worth mentioning two critical examples: ensuring digital data security (or cybersecurity) and setting up a correct Data Governance. Cybersecurity is a well-recognized challenge to the implementation of digital and connected technologies in health care, and a risk to the patients' safety.[74–76] Data security is already the scope and focus of several regulatory efforts by different authorities For example, the FDA released several guidances for pre- and postmarketing assessment and monitoring of cybersecurity.[77] With the increasing adoption of DTx solutions, and the appearance and development of new use cases for the collection and sharing of digital health data, fit-for-purpose standards and principles for the governance of these data will be necessary[78,79] to solve significant ethical considerations.[80]

Another important topic not covered here includes revenue streams for DTx, for example, reimbursement, for which readers can refer to ref. 48 where the authors comment that, as DTx offer the possibility for collecting real-time patient-reported outcomes, they could be well-suited for value-based reimbursement. We believe that the application of clinical pharmacology principles and its benefit in better anticipating response variability will further support the idea of value-based reimbursement strategies. In addition, the review[81] explores how national reimbursement agencies across Canada, the United States, the United Kingdom, Germany, France, and Australia handle DTx submissions. Health technology assessment frameworks include the establishment of the cost-effectiveness profile, the therapeutic value as well as the impact on a patient's health and budget. Future perspectives of reimbursement in other countries, such as South Korea, have also been published.[82]

We also chose to not discuss in detail the topic of engagement as it is recognized as a major barrier for the field. As said, this topic is currently the focus of significant research activities. We can refer the reader to the book from Jacobson, Kowatsch, and Marsch[71] which discuss research on the concept of receptivity to mobile health interventions. In particular, they report a conceptual framework around the study of receptivity structured by three key processes: "receiving, processing, and using support" meaning that the target person is able to receive the foreseen support that it has enough cognitive capacity to process it and able to take action and implement. As mentioned, sophisticated data-driven techniques are being developed to optimize this process and in particular to have JITAI in order to optimize engagement.

CONCLUSIONS

Today's development of DTx seems to be characterized by a will to generate evidence as quickly as possible for the device to be qualified by health authorities and susceptible to be later reimbursed according to local jurisdictions. Not surprisingly, when reviewing the clinical studies of DTx, we found a multitude of small studies sharing similar design elements: randomized but with a relatively small number of patients. This finding is not new and has already been highlighted in the literature.[83]

The desire to generate data quickly to support approval of a DTx is understandable and should be supported as much as possible. However, it is necessary to balance speed with generating the right evidence to ensure the DTx is studied and used in the most appropriate way for patients to maximize the chances of success for establishing efficacy, safety, and health authority approval and to ensure appropriate clinical uptake of the DTx.

We have highlighted several areas for which the application of clinical pharmacology principles could help contribute to a firm foundation for successful transformation of digital technology into medicines. These areas are the development of models on the mechanism of action of the digital active ingredient on the targeted pathological processes, understanding the impact of the DTx on the underlying mechanisms, and how this produces efficacy, ensuring the right dose of the DTx is used and how that might vary between different patients and situations to deliver maximum benefit for as many patients as possible. This moves beyond today's DTx focus on engagement and adherence, although that still remains important. The techniques and expertise of clinical pharmacology will be very useful, especially the application of modeling methods similar to those used today in quantitative systems pharmacology and pharmacometrics and that will be informed by the high-density longitudinal data that DTx captures.

For the success of the development of DTx as a therapeutic modality, the collaboration of those who understand diseases

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and patients, those who have experience of developing other treatment modalities, and those who know about digital solutions is critical.

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