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Digital Interventions and Their Unexpected Outcomes - Time for Digitalovigilance?

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Abstract. The application of digital interventions in healthcare beyond research has been translated in the development of software as a medical device. Along with corresponding regulations for medical devices, there is a need for assessing adverse events to conduct post-market surveillance and to appropriately label digital health interventions to ensure proper use and patient safety. To date unexpected consequences of digital health interventions are neglected or ignored, or at least remain undescribed in literature. This paper is intended to raise awareness across the research community about these upcoming challenges. We recommend that - together with developing a new research field of digitalovigilance - a systematic assessment and monitoring of adverse events and unexpected interactions be included in clinical trials, along with the reporting of such events and the conduct of meta-analyses on critical aspects.

Keywords. Digital health intervention, mHealth, adverse events, medical device, digital technology, internet-based interventions

1. Introduction

In recent years, under the umbrella of the advancements in digital health, a vast corpus of medical informatics research has been built up using methodologies and approaches involving social media, serious games, and digital interventions. Furthermore, the application of these tools beyond research has been translated in the development of

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software as a medical device (SaMD) [1,2], defined by the International Medical Device Regulators Forum as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device", and their implementation as digital therapeutics. A key element of the regulation of SaMDs is the need to include medical evidence supporting the use of the software and the need to provide adequate labeling and instructions to ensure its proper use. In addition, a post-market surveillance system should be implemented to follow up potential adverse events, including side effects derived from use of the SaMD, harms, problems or other incidents.

2. Methods

The question arises as to how research related to digital health interventions addresses the above mentioned regulations and requirements, and what are the related challenges. In this paper, we consider a few examples to start raising awareness on this topic. We identified related challenges from the use of different technologies applied in the research of digital interventions.

3. Results

In Germany, digital health interventions, so-called DiGA, already undergo a certification process and, as a result, some DiGA can already be prescribed. These include apps for the detection, monitoring, treatment, or alleviation of medical conditions. To be recognised as DiGA, apps must conform to data protection legislation and information security, and must be interoperable and provide preliminary data on the benefits they provide [3]. They also need to be CE-certified as medical products in the EU's lowest-risk classes. In this way, the DiGA assessment "appraises an app with regards to its safety, performance, data protection, information security, medical effectiveness, interoperability, its ability to bring positive health effects and advance the healthcare system." [4]. To qualify as DiGA, a comparative study must prove a positive care effect, either as a medical benefit or a patient-determined improvement of structures and processes. The regulations, however, do not explicitly require assessment of apps' adverse events. One might wonder how patient safety - because it is supposed to be appraised through the assessment - is ensured when those aspects are not assessed.

A similar observation can be made when looking at publications on clinical trials studying digital health interventions, using digital biomarkers or digital endpoints, or utilizing digital technologies to measure biological changes. Publications on clinical trials with drugs follow the CONSORT guidelines to ensure that all relevant information about the trial is reported for transparency. An adapted version of the CONSORT guidelines, the CONSORT-EHEALTH [5], recommends describing an eHealth intervention with all its facets: use parameters, access, publication of source code, description of the development process, and quality assurance methods. By the end of October 2022, Google Scholar identified 1,395 papers referring to these guidelines since their publication in 2011, demonstrating that the guidelines still remain unconsidered by most researchers when having in mind the number of publications on digital health interventions. When the CONSORT-EHEALTH guidelines were published, describing harms and unintended effects such as privacy breaches or observations on unexpected

effects or uses, was not 1 of the 17 essential items that a digital health intervention should report, but instead was listed as a highly recommended item to report.

However, when looking at publications on clinical trials using digital technologies, such aspects are considered only rarely, if at all. We searched for harms reported in systematic reviews on clinical trials related to virtual reality, chatbots and serious games indexed in PubMed. Specifically, when searching for systematic reviews on "virtual reality and clinical trials" we retrieved 111 publications. Of those, 18 unique papers (16%) contain the keyword "adverse" and only 10 (9%) report on evidence related to adverse events; 3.6% of the systematic reviews considered adverse events, but did not find sufficient data to make an assessment. For chatbots applied in healthcare we found no review describing adverse events, though this might be due to the fact that this technology was little studied the last few years and few clinical trials are available.

A similar search for serious games resulted in 15 systematic reviews of which 2 (13%) reported on adverse events, but only 1 paper reported evidence [6]. As exemplified, for serious games that are applied in a population with substance use problems, we would intuitively assume that effects related to addictions to gaming are studied. However, we could not find a study assessing potential negative side effects that could be due to the game playing as part of a digital health intervention. One reason for this finding could be conflicting perspectives on the same event related to a technology use: Serious games are intended to increase engagement and adherence to the intervention. On the other hand, substance use results in frequent use, even overuse - but how to distinguish the one from the other? Studies on this question are still missing or maturing.

These examples raise questions: Why do we find such limited evidence on adverse events related to digital exposure? Are funding industry or other conflicts of interest influencing the underreporting of adverse events? Might it be that researchers are not yet aware of possible adverse events of technology or that they ignore them?

Sometimes the negative aspects of technology use are studied independently from clinical trials that study the outcome of a technology use. As exemplified, social media are used to support communication with peers during an intervention [7] to educate, receive and provide social support, to support sharing of tracking activities, for infoveillance [8] and for gamification [7]. Using social media as a health intervention or to distribute health interventions comes with multiple risks for adverse events. Becoming a victim of cyberbullying [9,10] or misinformation [11] could be some possible adverse events - but only a few studies report on them. On the other hand, studies on cyberbullying in social media are available [12] and misinformation also has been assessed by researchers.

So far, scientific literature has focused on the evaluation of individual digital interventions and tools in controlled research environments, such as randomized clinical trials for SaMD approval. However, with an increasing use of portable technologies, mobile apps, and other technologies to deliver health interventions – for example the M-Health Index & Navigation Database (https://mindapps.org/), which contains more than 600 apps and reviews [13,14] – we can imagine that interactions between the technologies do occur, e.g., "app-app-interactions." Furthermore, it is important to recognize the vast and largely unregulated digital environment [15] where exposure to different internet and digital media can lead to unintended interactions. These sorts of interactions are the equivalent to food-drug interactions in drug research, and an example of these interactions are the use of apps for smoke quitting and the exposure to online tobacco advertising or misinformation. However, a consideration and critical review of those interactions when studying digital health interventions is missing.

4. Discussion

The aforementioned examples demonstrate that there is a need to conduct research on unexpected consequences related to digital health interventions similarly to pharmacovigilance, which comprises activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem in the context of pharmaceutical drugs (Figure 1). We strongly recommend researchers and developers of digital health interventions consider aspects described during design, development and critical assessment of digital health interventions.

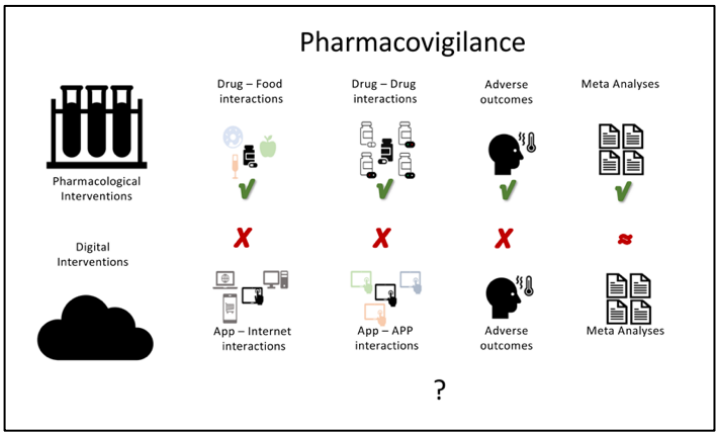

Figure 1. Similarities between pharmacological interventions and digital interventions. Areas where digital interventions are lacking research are highlighted in comparison with pharmacological interventions.

First, adverse events and unexpected interactions should be systematically assessed and monitored. One of the parameters to be considered is the system environment, which should include other apps or related tools used or installed when the adverse event happened. This aspect relates to the investigation of "App-App" interactions and also involves explicitly conducting studies about adverse events of digital health interventions. Given that individuals may use more than one technology or app, it is necessary to acknowledge potential "App-App" interactions and therefore develop novel methodologies and solutions to investigate the effects of the simultaneous use of different digital health interventions as these effects might be positive or negative depending on whether they potentiate or weaken their health outcomes. It is therefore essential to also identify the causes of an effect that results from applying a digital health intervention.

Second, adverse effects that occurred in a study applying a digital health intervention should be reported carefully. A systematic reporting of side effects related to the digital exposure to specific technologies might help to identify common effects on specific individuals, which might help to prevent these adverse effects in future users. More than 10 years have passed since the CONSORT-EHEALTH guidelines were published [5]. Those reporting guidelines still have to be updated to include the reporting of adverse events in studies related to the digital exposome according to new challenges linked to rapidly evolving digital technologies.

Third, meta-analyses that assess critical aspects in studies should be conducted. Only an aggregation of results on adverse effects of digital health interventions will allow us to judge –and address– the actual risk of unexpected patient harm.

5. Conclusions

In the light of these recommendations and challenges, we envision the establishment of a new research area that specifically focuses on investigating and standardizing assessment and reporting methods of unexpected consequences related to digital exposure as part of health interventions. Similar to pharmacovigilance (monitoring of drug safety) and algorithmovigilance (monitoring of artificial intelligence) [16] "digitalovigilance" – a research field for collecting, detecting, assessing, monitoring, and preventing adverse effects caused by digital health interventions – could be established.

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