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Are the changes resulted from the COVID-19 pandemic on digital health technologies going to stay?

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It is unequivocal that the COVID-19 pandemic upended all the aspects of our current lives. Clinical research was evidently not immune to that. Research laboratories were closed for months at the beginning of the pandemic and then re-opened with general restrictions (van Dorn, 2020). The closure of research laboratories in the US and other countries led scientists and regulators to propose distance-learning solutions to continue being conducted rapidly. One important aspect here is that both stakeholders were involved in the solution (the scientists designing the trial and the regulators approving the trials). This undoubtedly created a fertile condition to nurture the use of digital health technologies in clinical research.

The first important question was whether the clinical trial needed to occur in-house (in the laboratory). Here three factors need to be analyzed: (1) the consent process, (2) the assessments, and (3) the intervention. One interesting aspect is that for most clinical trials, there have already been technologies that can prevent bringing the subject to the laboratory.

The consent process is a good example. There are some important issues with the consent form process that needed to be considered. The first one is to ensure that there will be a private and confidential connection with a potential research subject if the consent process is to be done virtually. There have been many improvements in tools that can ensure a private and safe connection between the investigator and the research subject. For instance, professional accounts in Zoom and Teams platforms ensure encrypted communication (audio and video calls) between the two parties. Another critical component in the consent process is the informed consent document. A good option is the e-Consent via REDCap. This encrypted system provides standardized tools (e.g., online questionnaires and digital signature tools) to obtain consent and store consent documentation. It has been shown that REDCap e-consent framework adheres to federal guidelines for research consent (Chen et al., 2019). Given the technical requirements and the current need for virtual consenting, Institutional Review Boards (IRBs) have been more open to accepting virtual or electronic consent using these new tools.

The other important aspect to consider is the assessment. There has also been a significant improvement in instruments to collect distant information, including new portable in-home devices to collect health data such as vital functions (e.g., heart rate, respiration, temperature, and blood pressure) and physical activity. A good example are the several wearables and smartwatches that are showing good detection accuracy compared with gold standard techniques (Fuller et al., 2020). Also, the familiarity of video calls with several platforms such as skype, and zoom has provided a real possibility of video call

assessments, especially for questionnaires assessed by the investigator. One example is the Hamilton Depression Rating Scale. A recent systematic review showed that measuring psychiatric symptoms remotely by mobile apps or under videocall supervision is feasible and acceptable in clinical and research environments (Goldberg, Buck, Raphaely, & Fortney, 2018).

A final challenge to consider is the intervention and whether it is possible to administer the intervention remotely. Of course, this is not an issue for drug trials as drugs are designed to be self-administered, sending them to subjects is also not a challenging situation. However, for trials involving behavioral interventions, such as physical therapy or psychotherapy, and trials involving medical devices such as noninvasive brain stimulation, some challenging aspects must be considered. There have been many trials looking at home-based psychotherapy either administered via a web-platform or by a psychotherapist connected via a video call. For instance, a recent meta-analysis of computer-assisted cognitive-behavioral therapy (CCBT) for depression has found favorable results, and studies comparing CCBT with face-to-face treatment have reported no differences in outcome (Wright et al., 2019). Similarly, the field of medical devices has also seen an advance in home-based techniques. The technique of brain stimulation with transcranial direct current stimulation (tDCS) is an example. This technique was developed to be applied in treatment centers by a trained professional. However, our research group and others have developed home-based methods of this technique. In a recent trial in fibromyalgia patients, we showed that a self-administered home-based anodal-tDCS (over the left dorsolateral prefrontal cortex ((DLPFC)) reduced 62% the pain scores after treatment with no dropouts during the trial (Brietzke et al., 2020). These results underscore the great potential of home-based interventions in brain stimulation research.

Given all these improvements, there has been a clearer regulatory pathway for fully remote or online clinical trials looking for regulatory approval. In the US, for instance, the Health and Human Services Office has extended approval for many new telehealth platforms and allowed license flexibility for physicians attending people from different states, which could help with medical monitoring during remote clinical trials (Moore & Munroe, 2020). An interesting question would be for international trials as regulations are different. By way of example, the Brazilian National Health Agency (Anvisa) issued a flexibilization of operational requirements concerning clinical trials taking place in Brazil, providing the option of virtual inspections for compliance assessment of good clinical practices (Anvisa, 2020). In view of the social distancing, isolation, and quarantine measures implemented during the Covid-19 pandemic, these fueled the longstanding efforts for the legalization of telemedicine (Telemedicine Act, 2020), including its use in clinical trials. Until April 2020, remote interactions between medical doctors and patients were prohibited by the Brazilian Federal Council of Medicine, except in urgent or emergency cases. To sustain the momentum, the Brazilian Ministry of Health (Brazilian Ministry of Health, 2020) recently issued an action plan for healthcare digitalization that includes telemedicine as one of its cornerstones. For an in-depth discussion on the challenges and opportunities of remote clinical trials, please refer to Shore C. et al. (Shore, Khandekar, & Alper, 2019).

It is clear that COVID-19 catalyzed the development of novel technologies of digital health and the regulatory acceptance of clinical trials using these technologies, facilitating the implementation of inexpensive well-powered transcontinental multicenter clinical trials, and improving the studies' external validity by including participants who are geographically distant or who have difficulties in reaching research sites (usually underrepresented in clinical trials). In a simple search in Clinicaltrials.gov we found 21 clinical trials using the search words "remote clinical trial" OR "online clinical trial" OR "virtual clinical trial", although the number is small yet, most of them were registered during 2020; thus, we could expect an increase of this methodology during the coming years. It is logical that although some researchers may prefer the traditional trials for scientific reasons, the expertise and experience with remote clinical trials will help to change the landscape of clinical research in the next 5 years. It is possible that we will also learn some issues and a few steps back will be necessary. However, the move to fully remote clinical trials will not be stopped and several advantages may be seen soon with this new science.

Conflict of Interest

Dr. Fregni is the editor-in-chief of the Principles and Practice of Clinical Research journal. Therefore, he excused himself from the peer-review process and

followed the journal guidelines for peer-reviewing when an editor co-authors a manuscript. He did not influence the editorial process and final publication decision. KP is a member of the editorial team, therefore he excused himself from the editorial process.

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