Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.52.008289

Can Digital Technology Change the Face of Clinical Trials? A Narrative Review

Jaquellyne Gurgel Penaforte-Saboia[1]*, Vanessa Lauanna Lima Silva[2], Daniel Autran Cavalcante Araujo[3], Alexandre Saboia Leitão Junior[4], Natasha Vasconcelos Albuquerque[1,6], Carlos Eduardo Barra Couri[7] and Renan Magalhães Montenegro Junior[1,5]

[1]*Clinical Research Unit, Walter Cantidio University Hospital, Federal University of Ceará, Brazil*

[2]*Department of Neurosciences and Behavioral Sciences, Ribeirão Preto School of Medicine, University of São Paulo, Brazil*

[3]*Department of Internal Medicine, Sinai-Grace Hospital/Detroit Medical Center, Wayne State University School of Medicine, USA*

[4]*Department of Surgery, Federal University of Ceará, Brazil*

[5]*Department of Clinical Medicine, Federal University of Ceará, Brazil*

[6]*Department of Community Health, Federal University of Ceará, Fortaleza, Brazil*

[7]*Center for Cell-based Therapy, Ribeirão Preto Medical School, University of São Paulo, Brazil*

***Corresponding author:** Jaquellyne Gurgel Penaforte-Saboia, Clinical Research Unit, Walter Cantidio University Hospital, Federal University of Ceará, Fortaleza, Brazil

ARTICLE INFO

Received: August 25, 2023

Published: September 05, 2023

Citation: Jaquellyne GurgelPenaforte-Saboia, Vanessa Lauanna Lima Silva, Daniel Autran Cavalcante Araujo, Alexandre Saboia Leitão Junior, Natasha asconcelos Albuquerque, Carlos Eduardo Barra Couri and Renan Magalhães Montenegro Junior. Can Digital Technology Change the Face of Clinical Trials? A Narrative Review. Biomed J Sci & Tech Res 52(4)-2023. BJSTR. MS.ID.008289.

ABSTRACT

Randomized clinical trials (RCTs) are the gold-standard method for clinical research. However, major intrinsic challenges to their conduct exist, such as elevated costs, long duration, and difficulty in recruiting. Digital Technology (DT) can provide innovative solutions to overcome these challenges. The aim of this review is to critically evaluate its use in clinical research.

Keywords: Digital Clinical Trials; Digital Technology; Randomized Clinical Trials

Abbreviations: RCTs: Randomized Clinical Trials; DT: Digital Technology; CT: Clinical Trials; DCT: Digital Clinical Trials; FDA: Food and Drug Administration

Introduction

In times of evidence-based medicine, randomized clinical trials (RCTs) represent one of the highest degrees of scientific evidence, being regarded as the gold standard method of clinical research [1]. The publication of well-designed clinical trials (CT) is capable of rapidly changing current medical practices, contributing greatly to advances in patient care [1,2]. Nevertheless, an important gap in RCT production has been identified. A systematic review of publications between 1995 and 2016 identified only 24 RCTs for Clinical Decision Support for clinical oncology practice [3]. Intrinsic challenges of RCTs that hinder their implementation have been widely noted, including difficulty with adequate patient enrollment, high dropout rates, high costs, and

long duration [4]. Researchers have been looking for ways to overcome these challenges, for instance by using methods such as Adaptive Trial Design, Large Simple Trials, and Digital Clinical Trials (DCT) [5,6]. Guo et al argue that traditional CT methods should be reviewed in search of more innovative and agile approaches [7]. The Clinical Trials Transformation Initiative, a public-private partnership with the US Food and Drug Administration (FDA) and more than 60 other organizations, recognizes Digital Technology (DT) as a way to improve the quality and efficiency of CT [8]. Advances in the field of DT have revolutionized the way RCTs are conducted [9]. In the past few years, there has been an exponential growth in the number of CTs published on ClinicalTrials.gov that use the term mHealth, defined as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices" [10,11]. Recent data from North America, Europe, and Asia revealed that over 35% of pharmaceutical industries were implementing DT in their CT, while 94% planned to increase its use soon [12].

This review will explore the role of DTs as a means of mitigating some of the difficulties in conducting RCT, focusing on four principal areas:

(i) Enrollment and dropout

(ii) Data collection

(iii) Costs

(iv) Duration

Discussion

Trial Enrollment and Dropout

Data analysis from the ClinicalTrials.gov registry showed that over 90% of interventional trials enrolled fewer than 100 participants, while only 3–4% enrolled more than 5000 participants [13]. One-third of the trials did not reach the desired sample size [14]. In a review, eighty-one out of 395 RCTs listed on ClinicalTrials.gov were discontinued early, mainly due to problems with recruitment [15]. Researchers have been increasingly evaluating the potential usefulness of complementing recruitment strategies, for example, with DT, in order to include the greatest possible diversity of participants in RCTs [16,17]. There is evidence that social media can be an excellent recruitment method for hard-to-reach populations [18]. Many of the traditional RCTs undesirably restrict the study population to those living in geographic proximity to the study site [19,20]. Only a small percentage of the potential pool of eligible individuals gets invited to participate in clinical trials, limiting not only the number of participants but also the diversity of the sample, which can lead to biased results from an artificially homogeneous population [21-23]. Performing DCTs may allow remote patient participation, enabling the recruitment of otherwise unreachable individuals [24]. In 2016, one of the first applications (APP) developed to conduct a DCT was published. The trial aimed to assess the effects of nutrition labels on food purchases. In approximately 1 year, it was possible to randomize more than 2,000 patients. That showed promise for improving recruitment, delivery of the intervention, and data collection [25]. As an example, Anguera et al. managed to recruit a large number of participants in a short time and with minimal costs in a study of patients with depression that was carried out through mobile devices [26].

While the recruitment of participants can be leveraged in DCTs, participant retention could be a challenge [27]. In 2019, the average patient dropout rate in clinical trials was around 19% [28]. Some older studies have shown that DCTs had a higher dropout rate. This was in part due to less interaction between participants and researchers [29-33]. On the other hand, more recent data showed that modern DCTs may be able to increase participant engagement through more active and secure two-way communication, as well increase patients' trust in investigators. They can improve patients' experience and, ultimately, reduce dropout rates [9,24,27,33]. Another typical barrier to the recruitment and permanence of patients in clinical trials is the Hassle Factor of the study. Many studies are investigator-centric, requiring participants to physically attend the clinical site for sample and data collection [9,24,34]. DCTs facilitate decentralization, often allowing the participation of patients without having to leave their location or even their homes, substantially reducing potential inconveniences. Furthermore, DCTs can help mitigate a historical problem associated with randomization in RCTs that can occur when investigators are able to predict who will be randomized to each strategy (e.g., randomization by odd/even dates of birth). Automated randomization processes generated by DT are virtually impossible to be corrupted [2,35]. Accordingly, whether by expanding participation, reducing the hassle factor, or enhancing engagement, DCTs can offer unique features to increase patient recruitment and diminish dropout rates.

Data Collection

In RCTs, data security is extremely relevant, especially regarding the reliability and integrity of the information. DT has allowed a meaningful change in the way data is collected, without interfering with the fundamental principle of ensuring its authenticity, confidentiality, and integrity [6]. While computerized data collection reduces the chances of human error in recording responses [36,37], DT enables computationally intensive encryption for the privacy of participants [27]. DT allows data collection in settings outside a health facility and in real-life conditions, enabling access to new endpoints that have been otherwise impossible to collect in the past [8,24]. Nevertheless, as these technologies enable the continuous collection of new and diverse data, they can bring novel computational and statistical challenges. In addition to prioritizing the collection of critical data for the central scientific questions of CTs, the use of artificial intelligence combined with traditional biostatistical methods can be useful to address the issues associated with interpreting the vast amount of data capable of collection through DT [17,38].

Another major advantage of DTs is the ability to capture data without the presence of a member of the study team, as well as the possibility to monitor adverse events in real time through linked electronic health records [24,27]. On the other hand, when participants themselves enter information into online platforms, there is an increased risk of obtaining inaccurate (such as confusing descriptions of adverse events) or even fictitious data [35,38]. Choosing study protocols that promote the involvement of participants in decisions about data inclusion, as well as the use of digital tools capable of grouping information and analyzing trends to facilitate the identification of fictitious data, are valid strategies to minimize this obstacle [39]. Aside from that, investigators should know how to assess the accuracy and consistency of the DT chosen for data capture. This is essential for ensuring reliable capturing, processing, storage, and transfer of information, providing objective data that accurately represents the outcome [39].

Costs

Healthcare costs have been progressively increasing, leading to a significant economic impact in a world with finite resources [40]. The costs associated with CT are also progressively escalating and are often the greatest barrier to their implementation [41,42]. Data collected over the 2010–2015 period from seven major pharmaceutical companies showed that the median cost for a pharmaceutical industry phase 3 trial was US$21.4 million [43]. Another study reported that these amounts reached up to US$52.9 million [44]. Still, a growing body of evidence has demonstrated the economic benefit of mHealth interventions. A recent systematic review of thirty-nine studies that aimed to evaluate the economic impact of using mHealth tools, showed they were cost-effective and economically beneficial [40]. A study commissioned by the US Department of Health and Human Services showed that the wider use of mobile technologies is one of the most effective means of reducing clinical trial costs for drug development [44]. The US Institute of Medicine has recommended creating digital data collection systems to reduce healthcare costs. This recommendation, along with the Health Information Technology for Economic and Clinical Health (HITECH) Act, increased the adoption of electronic health record systems in the United States from 20.8% in 2004 to 85.9% in 2017 [45,46]. The slow enrollment is a major contributor to increased costs [41,46]. We have already discussed extensively how the use of DT can be useful to improve recruitment strategies. Eliminating ethnic health disparities is one way to significantly reduce overall medical costs [47]. However, in traditional RCTs, minority representation remains inadequate [22,48-50]. Lack of information and understanding about research, and limited access to specialized care centers that serve as referral sources for clinical trials make it difficult to recruit minority populations [51,52]. Jerome et al. by evaluating the use of DT as a strategy to increase patient access to ongoing RCTs, showed that digital media is a cost-effective vehicle to promote awareness of CT [16]. Classically, RCTs tend to have an investigator-centric approach. Study participants often need to travel to academic facilities where investigators and diagnostic technologies are concentrated [27]. Costs with administrative staff (11–29% of the total) and site monitoring (9–14% of the total) were key drivers of direct costs [44,53]. In DCTs, it is possible to capture data and monitor participants remotely, eliminating most patient travel requirements and allowing for the downsizing of research staff [17,28,54].

Duration

More than 70% of the total time required in the development of a new drug (6 to 10 years) is spent in clinical trials [55,56]. Moreover, a low enrollment rate can increase the planned RCT time by almost two times [46]. In contrast, it is known that the development of mHealth tools for clinical trials can be able to accelerate recruitment [57]. Espie et al. used DT in several studies and managed to quickly recruit a large number of participants. Notably, one trial recruited 3755 participants within 24 hours [58]. In addition, several ways in which DT can optimize the recruitment rate have been described above. The need for protocol review also increases CT duration [59]. Data from Tufts CSDD's 2016 Cost Study reported that CTs with one or more global changes lasted about 18% longer than those without adjustments [60]. Most substantive amendments are implemented while the clinical trial is ongoing, and the delay in implementing these changes is directly associated with increasing the duration of CT with amendments [61,62]. On the other hand, the continuous learning and near-real-time adaptability of DCTs can significantly reduce this interval of amendment implementation, ultimately reducing the duration of RCTs [17].

Conclusion

A growing body of data has demonstrated that digital technology can be an effective way of conducting the RCTs promoting more effective randomization, reducing the time and costs associated with the study, and improving data quality and security. However, the use of DT in RCTs is still in the early stages of implementation and, as with any new approach, some considerations must be mentioned. For instance, the frequent requirement for complex statistical methods; the possibility of some adjustment in the design and outcomes of the traditional RCT to better adaptation to the DCT; the need for a digital research infrastructure that, in addition to the elevated level of data security, guarantees the validation and usability of the chosen DCT; and the need to implement the interchangeability of several electronic sources to allow portability of DCT data.

Acknowledgment

Not applicable.

Funding

This work was supported by Universidade Federal do Ceará, FUNCAP and CNPq.

Conflict of Interest

The authors have no conflicts of interest to declare.

References

1. Li W, He SJ, Wang Y, Cheng XR, Jia X (2007) Adaptive designs for clinical trial. Chinese Journal of Epidemiology 28(6): 605-607.
2. Naylor AR (2016) Randomized controlled trials: still the backbone of vascular surgery? Gefasschirurgie 21(1): 25-30.
3. Pawloski PA, Brooks GA, Nielsen ME, Olson-Bullis BA (2019) A systematic review of clinical decision support systems for clinical oncology practice. Journal of the National Comprehensive Cancer Network 17(4): 331-338.
4. Fuster V, Bhatt DL, Califf RM, Michelson AD, Sabatine MS, et al. (2012) Guided antithrombotic therapy: current status and future research direction: report on a National Heart, Lung and Blood Institute working group. Circulation 126(13): 1645-1662.
5. Bauer P, Bretz F, Dragalin V, König F, Wassmer G (2016) Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls. Statistics in Medicine 35(3): 325-347.
6. Califf RM (2014) Large simple trials: really, it can't be that simple!. European heart journal 35(9): 549-551.
7. Guo C, Ashrafian H, Ghafur S, Fontana G, Gardner C et al. (2020) Challenges for the evaluation of digital health solutions—A call for innovative evidence generation approaches. NPJ digital medicine 3(1): 110.
8. Clinical Trials Transformation Initiative (n.d.).
9. Dockendorf MF, Hansen BJ, Bateman KP, Moyer M, Shah JK, et al. (2021) Digitally enabled, patient-centric clinical trials: shifting the drug development paradigm. Clinical and Translational Science 14(2): 445-459.
10. Kay M, Santos J, Takane M (2011) mHealth: New horizons for health through mobile technologies. World Health Organization 64(7): 66-71.
11. Kakkar AK, Sarma P, Medhi B (2018) mHealth technologies in clinical trials: Opportunities and challenges. Indian journal of pharmacology 50(3): 105-107.
12. Burrows A (2017) mHealth and the Adoption of Mobile Technologies in Clinical Trials. Informa Connect.
13. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, et al. (2012) Characteristics of clinical trials registered in ClinicalTrials. gov, 2007-2010. JAMA 307(17): 1838-1847.
14. Campbell MK, Snowdon C, Francis D, Elbourne DR, McDonald AM, et al. (2007) Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study 11(48): 3,5-105
15. Chapman SJ, Shelton B, Mahmood H, Fitzgerald JE, Harrison EM, et al. (2014) Discontinuation and non-publication of surgical randomised controlled trials: observational study. BMJ, pp. 349.
16. Jerome RN, Dunkel L, Kennedy N, Olson EJ, Pulley JM, et al. (2019) To end disease tomorrow, begin with trials today: digital strategies for increased awareness of a clinical trials finder. Journal of Clinical and Translational Science 3(4): 190-198.
17. Steinhubl SR, Wolff-Hughes DL, Nilsen W, Iturriaga E, Califf RM (2019) Digital clinical trials: creating a vision for the future. NPJ digital medicine 2(1): 126.
18. Topolovec-Vranic J, Natarajan K (2016) The use of social media in recruitment for medical research studies: a scoping review. Journal of medical Internet research 18(11): e286.
19. Brundisini F, Giacomini M, DeJean D, Vanstone M, Winsor S, et al. (2013) Chronic disease patients' experiences with accessing health care in rural and remote areas: a systematic review and qualitative meta-synthesis. Ontario health technology assessment series, 13(15): 1-33.
20. Clark LT, Watkins L, Piña IL, Elmer M, Akinboboye O, et al. (2019) Increasing diversity in clinical trials: overcoming critical barriers. Current problems in cardiology 44(5): 148-172.
21. Anderson A, Borfitz D, Getz K (2018) Global public attitudes about clinical research and patient experiences with clinical trials. JAMA Network Open 1(6): e182969-e182969.
22. Murthy VH, Krumholz HM, Gross CP (2004) Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA 291(22): 2720-2726.
23. Oh SS, Galanter J, Thakur N, Pino-Yanes M, Barcelo NE, et al. (2015) Diversity in clinical and biomedical research: a promise yet to be fulfilled. PLoS medicine 12(12): e1001918.
24. Kothare PA, Jadhav PR, Gupta P, Harrelson JC, Dickmann L (2018) Harnessing the potential of emerging digital health and biological sampling technologies for clinical drug development: promise to reality. Clinical Pharmacology & Therapeutics 104(6): 1125-1135.
25. Volkova E, Li N, Dunford E, Eyles H, Crino M, et al. (2016) Smart RCTs: development of a smartphone app for fully automated nutrition-labeling intervention trials. JMIR mHealth and uHealth 4(1): e5219.
26. Anguera JA, Jordan JT, Castaneda D, Gazzaley A, Areán PA (2016) Conducting a fully mobile and randomised clinical trial for depression: access, engagement and expense. BMJ innovations 2(1): 14-21.
27. Brouwer WD, Patel CJ, Manrai AK, Rodriguez-Chavez IR, Shah NR (2021) Empowering clinical research in a decentralized world. NPJ Digital Medicine 4(1): 102.
28. Coulter B (2023) Optimizing the cost of clinical trials.
29. Glasgow R, Nelson C, Kearney K, Reid R, Ritzwoller D, et al. (2007) Reach, engagement, and retention in an Internet-based weight loss program in a multi-site randomized controlled trial. Journal of medical Internet research 9(2): e11.
30. Verheijden MW, Jans MP, Hildebrandt VH, Hopman-Rock M (2007) Rates and determinants of repeated participation in a web-based behavior change program for healthy body weight and healthy lifestyle. Journal of medical Internet research 9(1): e1.
31. Couper M, Peytchev A, Strecher V, Rothert K, Anderson J (2007) Following up nonrespondents to an online weight management intervention: randomized trial comparing mail versus telephone. Journal of Medical Internet Research 9(2): e16.
32. Bull SS, Vallejos D, Levine D, Ortiz C (2008) Improving recruitment and retention for an online randomized controlled trial: experience from the Youthnet study. AIDS care 20(8): 887-893.
33. Oliveira RMD, Duarte AF, Alves D, Furegato ARF (2016) Development of the TabacoQuest app for computerization of data collection on smoking in psychiatric nursing. Revista latino-americana de enfermagem 24: e2726.
34. Sibai T, Carlisle H, Tornetta III P (2012) The darker side of randomized trials: recruitment challenges. JBJS 94(Supplement_1): 49-55.
35. Murray E, Khadjesari Z, White IR, Kalaitzaki E, Godfrey C, et al. (2009) Methodological challenges in online trials. Journal of Medical Internet Research 11(2): e9.
36. Fanning J, McAuley E (2014) A comparison of tablet computer and paper-based questionnaires in healthy aging research. JMIR research protocols 3(3): e38.

37. Giduthuri JG, Maire N, Joseph S, Kudale A, Schaetti C, et al. (2014) Developing and validating a tablet version of an illness explanatory model interview for a public health survey in Pune, India. PLoS One 9(9): e107374.

38. Fernandez ID, Groth SW, Reschke JE, Graham ML, Strawderman M, et al. (2015) eMoms: Electronically-mediated weight interventions for pregnant and postpartum women. Study design and baseline characteristics. Contemporary Clinical Trials 43: 63-74.

39. (2022) Clinical Trials Transformation Initiative. Considerations for Advancing the Use of Digital Technologies for Data Capture & Improved Clinical Trials.

40. Iribarren SJ, Cato K, Falzon L, Stone PW (2017) What is the economic evidence for mHealth? A systematic review of economic evaluations of mHealth solutions. PloS one 12(2): e0170581.

41. Moore TJ, Zhang H, Anderson G, Alexander GC (2018). Estimated costs of pivotal trials for novel therapeutic agents approved by the US Food and Drug Administration, 2015-2016. JAMA internal medicine 178(11): 1451-1457.

42. Eisenstein EL, Lemons II PW, Tardiff BE, Schulman KA, Jolly MK, et al. (2005) Reducing the costs of phase III cardiovascular clinical trials. American heart journal 149(3): 482-488.

43. Martin L, Hutchens M, Hawkins C, Radnov A (2017) How much do clinical trials cost. Nat Rev Drug Discov 16(6): 381-382.

44. Wong HH, Jessup A, Sertkaya A, Birkenbach A, Berlind A et al. (2014) Examination of clinical trial costs and barriers for drug development final. Office of the Assistant Secretary for Planning and Evaluation, US Department of Health & Human Services P. 1-92.

45. Office of the National Coordinator for Health Information Technology (n.d.) Office-based Physician Electronic Health Record Adoption, Health IT Quick-Stat #50.

46. Getz K (2015) The Cost of Clinical Trial Delays.

47. LaVeist TA, Gaskin D, Richard P (2011) Estimating the economic burden of racial health inequalities in the United States. International Journal of Health Services 41(2): 231-238.

48. Burchard EG, Oh SS, Foreman MG, Celedón JC (2015) Moving toward true inclusion of racial/ethnic minorities in federally funded studies. A key step for achieving respiratory health equality in the United States. American journal of respiratory and critical care medicine 191(5): 514-521.

49. Chow EA, Foster H, Gonzalez V, McIver L (2012) The disparate impact of diabetes on racial/ethnic minority populations. Clinical Diabetes 30(3): 130-133.

50. Sardar MR, Badri M, Prince CT, Seltzer J, Kowey PR (2014) Underrepresentation of women, elderly patients, and racial minorities in the randomized trials used for cardiovascular guidelines. JAMA internal medicine 174(11): 1868-1870.

51. George S, Duran N, Norris K (2014) A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders. American journal of public health 104(2): e16-e31.

52. Durant RW, Wenzel JA, Scarinci IC, Paterniti DA, Fouad MN, et al. (2014) Perspectives on barriers and facilitators to minority recruitment for clinical trials among cancer center leaders, investigators, research staff, and referring clinicians: enhancing minority participation in clinical trials (EMPaCT). Cancer 120: 1097-1105.

53. Sertkaya A, Wong HH, Jessup A, Beleche T (2016) Key cost drivers of pharmaceutical clinical trials in the United States. Clinical Trials 13(2): 117-126.

54. Hall H, Perelman D, Breschi A, Limcaoco P, Kellogg R, et al. (2018) Glucotypes reveal new patterns of glucose dysregulation. PLoS biology 16(7): e2005143.

55. Kaitin KI, DiMasi JA (2011) Pharmaceutical innovation in the 21st century: new drug approvals in the first decade, 2000–2009. Clinical pharmacology & therapeutics 89(2): 183-188.

56. Shah N (2004) Pharmaceutical supply chains: key issues and strategies for optimisation. Computers & chemical engineering 28(6-7): 929-941.

57. Cleary M (2018) How mHealth technology is revolutionizing clinical research. Value & Outcomes Spotlight 4(5): 20-23.

58. Espie CA, Carl JR, Stott R, Henry AL, Miller CB (2018) Digital medicine needs to work. The Lancet 392(10165): 2694.

59. Getz KA, Zuckerman R, Cropp AB, Hindle AL, Krauss R, et al. (2011) Measuring the incidence, causes, and repercussions of protocol amendments. Drug information journal: DIJ/Drug Information Association 45: 265-275.

60. DiMasi JA, Grabowski HG, Hansen RW (2016) Innovation in the pharmaceutical industry: new estimates of R&D costs. Journal of health economics 47: 20-33.

61. Getz KA, Stergiopoulos S, Short M, Surgeon L, Krauss R, et al. (2016) The impact of protocol amendments on clinical trial performance and cost. Therapeutic innovation & regulatory science 50(4): 436-441.

62. McGinnis J M, Stuckhardt L, Saunders R, Smith M (2013) Best care at lower cost: the path to continuously learning healthcare in America.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.52.008289

Jaquellyne Gurgel Penaforte-Saboia. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php