Title

Click and mortar opportunities for digitization and consumerism in trials.

Authors

Randell, Rachel
Hornik, Christoph
Curtis, Lesley
et al.

Publication Date

2023-09-01

DOI

10.1016/j.cct.2023.107304

Peer reviewed

HHS Public Access

Author manuscript

Contemp Clin Trials. Author manuscript; available in PMC 2023 September 27.

Published in final edited form as:

Contemp Clin Trials. 2023 September ; 132: 107304. doi:10.1016/j.cct.2023.107304.

"Click and mortar" opportunities for digitization and consumerism in trials

Rachel L. Randell[a,b,*], **Christoph P. Hornik**[a,b], **Lesley Curtis**[a,b], **Adrian F. Hernandez**[a,b], **Tom Denwood**[c], **Camille Nebeker**[d], **Jeremy Sugarman**[e], **Benoit Tyl**[f], **Masahiro Murakami**[g], **Leslie Oley Wilberforce**[h], **Sherry Pagoto**[i], **Ola Vedin**[j], **Tomas Andersson**[k], **Olveen Carrasquillo**[l], **Rowena Dolor**[a,b], **Scott H. Kollins**[a,m], **Jill Pellegrino**[n], **Megan L. Ranney**[o]

[a]Duke University, School of Medicine, Durham, NC, USA

[b]Duke Clinical Research Institute, Duke University, Durham, NC, USA

[c]Population Health Partners LLPShort Hills, NJ, USA

[d]Herbert Wertheim School of Public Health & Human Longevity Science, University of California San Diego, La Jolla, California, USA

[e]Berman Institute of Bioethics and Department of Medicine,Johns Hopkins University, Baltimore, MD, USA

[f]Bayer Healthcare SAS, La Garenne Colombes, France

[g]Eli Lilly & Company, Indianapolis, IN, USA

[h]Evidation, San Mateo, CA, USA

[i]Department of Allied Health Sciences, University of Connecticut, Storrs, CT, USA

[j]Boehringer Ingelheim AB, Sweden

[k]Bio Pharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

[l]Division of General Internal Medicine Co-Director, Miami Clinical & Translational Science Institute (CTSI), University of Miami, Miami, FL, USA

[m]Akili, Inc, Boston, MA, USA

[n]Real World Evidence, CVS Health, Woonsocket, RI, USA

[o]School of Public Health, Yale University, New Haven, CT, USA

Abstract

[*]Corresponding author at: Duke University School of Medicine, DUMC Box 3212, Durham, NC 27710, USA. rachel.randell@duke.edu (R.L. Randell).

Disclaimer

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Background: Digitization (using novel digital tools and strategies) and consumerism (taking a consumer-oriented approach) are increasingly commonplace in clinical trials, but the implications of these changes are not well described.

Methods: We assembled a group of trial experts from academia, industry, non-profit, and government to discuss implications of this changing trial landscape and provide guidance.

Results: Digitization and consumerism can increase the volume and diversity of trial participants and expedite recruitment. However, downstream bottlenecks, challenges with retention, and serious issues with equity, ethics, and security can result. A "click and mortar" approach, combining approaches from novel and traditional trials with the thoughtful use of technology, may optimally balance opportunities and challenges facing many trials.

Conclusion: We offer expert guidance and three "click and mortar" approaches to digital, consumer-oriented trials. More guidance and research are needed to navigate the associated opportunities and challenges.

Keywords

Digital trials; Consumerism; Decentralized trials

1. Background and introduction

Digitization is transforming the landscape of clinical research. In the context of clinical trials, digitization refers to using digital tools and strategies to enhance recruitment, retention, follow-up, data collection, data management, and/or analytics [1]. Terminology varies; herein, we refer to "***digital***" trials that use digital tools and strategies for recruitment, retention, data collection, and analytics [1], "***hybrid***" trials that use some digital tools and strategies but retain in-person, "brick-and-mortar" sites and other elements of traditional trials, and "***virtual***" trials that use digital tools and strategies to conduct all trial activities in a remote format [2]. Digital data collection is increasingly commonplace [3], and at least 15% of trials between 2019 and 2021 used one or more participant-facing digital tool(s) [4]. The United States (US) Congress under the 21st Century Cures Act [5], Food and Drug Administration (FDA), National Institutes of Health (NIH), and National Science Foundation [6] all recognize these changes, which were pre-existing but accelerated by the coronavirus-19 (COVID-19) pandemic [7,8].

Concurrently, trials have been responsive to the wave of consumerism in health care. Consumerism is a paradigm of patients as consumers who proactively seek information and make individualized choices, or "purchases," related to heath [9,10]. Choices can include engaging in trials. Many trials already use consumer-oriented approaches to design and conduct activities, and digital tools give patients unprecedented access to trial information and opportunities.

Although digitization and consumerism are increasingly commonplace in trials, the implications of these changes are not well described. Participants in consumer-oriented trials may differ in expectations and behavior compared to participants in traditional trials. Equipped with powerful technology, researchers, sponsors, and regulatory bodies have an

imperative to explore opportunities to improve longstanding issues with equity, accessibility, and efficiency, but risk worsening the "digital divide"—inequity in access to technology and the Internet.

Digitization and consumerism offer great promise for more equitable, accessible, and efficient trials, but present many challenges. Here, we describe opportunities and challenges for recruitment, retention, equity, and ethics, and offer guidance from experts in the field.

2. Methods

In January 2022, we assembled a group of experts from academia, industry (including pharmaceuticals, healthcare, clinical research, biotechnology, investing), non-profit organizations (including Patient-Centered Outcomes Research Institute [PCORI]), and government (including FDA and Centers for Medicare and Medicaid Services) for a two-day virtual workshop sponsored by the Duke Clinical Research Institute (DCRI). The DCRI Think Tank series has hosted >100 workshops over the past 25 years, in which healthcare and research leaders discuss critical gaps, innovate solutions, and strategize paths forward [11].

Following typical procedures for the DCRI Think Tank series, four academic trial experts (CPH, LC, AFH, MLR) generated the topic, identified and prioritized key content, invited speakers and moderators, and hosted the workshop. The final content areas were Recruitment and Retention, Equity, and Ethics. During the workshop, each content area was reviewed through a series of 3–6 presentations each lasting 5–10-min by speakers from academia, industry, non-profit and/or government, followed by a 30–45-min moderated discussion in which all attendees were invited to share opinions. The workshop was recorded and summarized in notes and workshop proceedings. The manuscript was conceptualized, drafted, and revised by RLR, CPH, MLR, with data organized in the same content areas as the workshop, and drafts were circulated to attendees for ongoing discussion and synthesis of Expert Guidance (Table 1). Additionally, non-systematic literature searches were performed by RLR and MLR as needed for supporting data not specifically reviewed during the workshop.

3. Results and discussion

3.1. Recruitment

Study teams can directly engage and recruit large numbers of participants at high speed and low cost using digital, consumer-facing platforms like social media [12]. The Get Social lifestyle intervention trial (NCT02646618) recruited nearly 30% of >300 participants from Facebook groups, compared to ~1–7% from print and online postings and paid advertisements [13]. Cybervictimization studies report similar successes recruiting through social media [12,14]. Other digital, consumer-facing platforms include volunteer research registries (e.g., the NIH-funded ResearchMatch.org, which has nearly 150,000 volunteers and 1310 studies as of May 2023) and consumer survey platforms (e.g., Qualtrics Market Research). After slower than expected recruitment using traditional approaches, the Mom's Health Chat virtual cancer prevention trial (NCT02835807) shifted to Qualtrics and

subsequently recruited 768 participants across 33 states in 6 weeks [15]. The WW Trial of a 6-month online weight loss intervention (NCT04302389) used both Facebook groups and ResearchMatch.org to identify 152 eligible participants in 6 weeks and complete the trial in 10 months. Additionally, study teams can directly engage the consumer bases of commercial devices. The Fitbit Heart Study leveraged over 31 million active users to recruit nearly 500,000 individuals into an arrhythmia study [16]. Collectively, these platforms connect study teams to an unprecedented number of potential participants.

We identify at least three issues with this recruitment strategy. First, information about potentially eligible participants using social media or a device is often limited upfront. The burden of pre-screening, screening, validating health status, and confirming eligibility then falls to the study team. Though not always problematic, added volume and steps can quickly create bottlenecks in trials needing representative samples or highly specific criteria. Second, participants recruited online may have low participation in subsequent research activities, creating downstream problems with retention (see Section 3.2). Third, the ultimate impact on equity is unclear (see Section 3.3). Overall, a widened funnel of potential participants does not guarantee trial success.

To overcome these issues, digital and consumer-oriented strategies have been developed, including data-driven pre-screening, analytics, and personalized engagement. CVS Health offers a direct-to-patient recruitment platform that uses predictive analytics on demographics and claims data to identify and filter potential participants. Engagement and pre-screening then occurs using a mix of digital and in-person methods [17]. Evidation is a platform of almost 5 million members who share person-generated health data from wearable devices, claims, electronic health records (EHR), and/or biosamples [18]. Members strive to improve individual health through a gamified point system; data are also used to match members with research studies. Evidation's platform enables the Heartline Study evaluating the effects of an iPhone app and Apple Watch on early detection of atrial fibrillation and health outcomes [19]. These data-forward models (Table 2, Row 1) may help narrow the widened funnel of potential participants, though the impact on equity remains unclear.

Digital strategies can also complement traditional "brick and mortar" recruitment. Science 37, an industry leader in virtual trials, used an adaptive outreach approach to recruit and enroll 86% of participants in one virtual arm in parallel to 13 traditional sites in a phase II COVID-19 trial (NCT04504032). Enrollment to the virtual site was 13 times faster than traditional sites. Another approach uses digital strategies to recruit participants who have already passed through "brick and mortar" infrastructure, i.e., "pass-through" model (Table 2, Row 2). The ACTIV-4b trial (NCT04498273) recruited participants who tested positive for the COVID-19 virus in a clinical setting using a mix of print and digital flyers, electronic patient portal messages, phone calls, and mailings. The remainder of enrollment and trial activities were conducted virtually, including mailing study drug directly to participants [20].

Even with "brick and mortar" infrastructure in place, challenges like screen failures persist. The ACTIV-6 trial (NCT04885530) used a mix of clinical sites and community testing centers to recruit participants into a trial of repurposed medications for COVID-19. As of

January 2022, over 9000 expressed interest and 92% began the consent process, but only 41% of those who started provided consent; many who did not complete the consent process reported preference to receive the study drug and not wanting to undergo randomization. Although this completion rate is not atypical for large trials, understanding characteristics of screen failures, and what proportion of failure is attributed to digital aspects of the trial, is increasingly important as digital tools widen the funnel of potential participants. A better understanding of screen failures could allow inclusion through alternative approaches, such as a patient-preference trial design and parallel observational arms.

These challenges demonstrate that trust remains critical to digital trials. While consumer-facing platforms allow highly motivated participants to be recruited and enrolled directly, workshop members shared experiences that screening failure rates are generally higher when participants are not recruited through a health care provider. A CVS Health survey of over 2000 customers found that 50% of respondents would trust their physician and 60% would look to an email from CVS for information about trials [21]. To build trust in digital trials, researchers can contact local health care providers to share information, build awareness, and provide a "warm handoff' to a virtual study team. Science 37 uses a "warm transfer" strategy with a call from a team member, typically within an hour after a potential participant expresses interest online, to conduct pre-screening and provide personalized guidance on the research process prior to connecting to the study team. Researchers funded by the NIH and PCORI also report using warm handoff strategies [22,23].

Though digital and consumer-oriented approaches to trial recruitment can be quite successful, these methods do not overcome all challenges and may, in fact, create more problems. A "click and mortar" approach, combining traditional "brick and mortar" and consumer-oriented, digital methods, may best optimize recruitment in many trial settings.

3.2. Retention

Trial retention can benefit from digital, consumer-oriented methods. Tools used to directly engage participants often have built-in functionality that can also help with retention, like reminders, notifications, and individualized messaging. For example, the IMPACT cyberbullying prevention intervention had nearly 100% retention with an 89% daily response rate, attributed to bi-directional communication within the mobile application (app) [14]. With regulatory approval and participant consent, social media can also be used to locate and communicate with participants. In one study, Facebook was used to locate 19 participants lost to follow up and decreased attrition by 16% [24].

Conversely, trial retention can suffer from consumer-oriented approaches. Workshop members reported that participants who seek out trials as customers may quickly withdraw or drop out with perceived burden (e.g., longer trials, lengthy or complicated data collection) or lack of benefit. Transitioning participants recruited "online" to "offline" activities seems especially difficult. The Fitbit Heart Study recruited nearly 500,000 participants directly through the device's app. Of the 1% in whom arrhythmia was detected, only 1671 (35%) completed the first telehealth study visit and 916 (19%) completed the second telehealth visit [16]. Approaches known to improve retention in traditional trials [25] may not apply to these participants or designs. Studying the behavior of participants recruited digitally is

challenging because upfront information is often limited [26] and behavior of those who do not enroll can be difficult to measure. Trials that rely exclusively on the widened funnel of potential participants from digital engagement may face unique retention challenge

There are digital, consumer-oriented approaches to improve trial retention. One example is active digital onboarding. For three virtual trials of at least 12 months duration, investigators created a webinar to onboard participants; content was developed using motivational interviewing techniques and included setting expectations, explaining scientific principles, exploring ambivalence, making commitments, and discussing barriers. The webinar improved retention to 88–97% in all three trials [27]. Digital tools may also allow participants to actively contribute to the design of the trial and interventions. IMPACT engaged participants in an iterative design process, which may have contributed to its notably high retention [14]. Similarly, the MyCOVIDRisk COVID-19 risk assessment and mitigation app underwent several changes to structure, format, and design based on iterative user feedback, with very high subsequent utilization [28].

Digital trials face tension between recruitment volume and velocity, versus engagement and retention. More work is needed to understand this balance and how to combine tools and methods to fit specific questions and populations.

3.3. Equity

In general, trials under-enroll diverse participants and fail to represent the diversity of both the general population and the population at risk of a disease [29]. Digital recruitment can increase inclusion of groups that are historically under-represented in trials [30]. Science37 conducted a virtual trial of lupus and Sjögren Syndrome in which more than half of the study population identified as Asian, Black, or Latin. Merck developed a dynamic trial enrollment tracker, which helped ensure 20% of participants in a phase III trial of a hepatitis C therapeutic identified as being from under-represented demographic groups [31,32]. Through the use of analytics, predictive modeling, and targeted outreach, 40% of referrals for 15 trials run by CVS Health were non-White. Foundation-funded digital studies have successfully overrecruited youth who identify as Lesbian, Gay, Bisexual, Transgender, Queer/Questioning, and more [14,33].

Not all virtual trials, however, are inclusive or representative. Technology can exacerbate disparities by primarily serving populations who are comfortable with technology and have access to Internet and devices—widening the “digital divide.” Although virtual trials reduce physical barriers of study sites, geographic diversity can actually suffer, as individuals living in rural areas are less likely to have broadband internet and computer access than those in urban areas [34]. Consumer-facing platforms that are not available in multiple languages limit the ability to recruit non-English speakers. Finally, in a hybrid approach that requires a mix, rather than an option, of digital and in-person activities, the digital tools may dissuade participation by some groups.

The ways in which the “digital divide” can exacerbate existing inequities is highlighted by two very large pragmatic trials that used digital and traditional recruitment methods in parallel. The ADAPTABLE trial (NCT02697916) was a pragmatic, decentralized

randomized trial of aspirin doses in over 15,000 adults with cardiovascular disease. A mix of traditional in-person and digital methods were used for recruitment, and an online patient portal in English and Spanish was used for education and electronic informed consent. Individuals who were interested and eligible but did not want to use digital methods could still participate; these participants enrolled during an in-person clinic visit with the help of study personnel using a tablet, i.e., “Parallel” model (Table 2, Row 3). Despite these efforts, about 80% of randomized participants reported White race and 90% Non-Hispanic ethnicity [35]; only 8% of participants who enrolled digitally were Black/African American. The PREVENTABLE trial (NCT04262206) is an ongoing, large, pragmatic trial evaluating the effect of statins on cardiovascular disease in older adults. PREVENTABLE was temporarily halted due to COVID-19 and then shifted to hybrid/virtual methods to recruit and enroll participants. According to investigators from PREVENTABLE, engaging potential participants through patient portal messaging recruited far more White participants than other racial and ethnic groups (email personal communication, August 18, 2022).

These examples demonstrate that digital trials are not a shortcut to equity. As in traditional trials, intentional steps are required to identify, engage, enroll, and retain under-represented populations. Partnering with community representatives and key stakeholders early in trial planning remains critical for needs assessment and planning. Partners can identify digital spaces already used by the community for virtual outreach. For communities with limited access to Internet and devices, non-traditional trial sites, such as schools or mobile vans [36], may be necessary to provide physical infrastructure for research activities. Additional staff time and effort may be needed to onboard and assist participants who are uncomfortable using technology. Creating accurate, culturally appropriate translations of language and imagery in digital outreach and intervention materials also requires time and resources. Budgets and timelines need to be planned accordingly.

The uptake of digital tools in trials, and their impact on diversity, deserves to be studied in its own right. Specific combinations of digital and in-person approaches that are effective in recruiting, enrolling, and retaining diverse and representative populations can inform future trials. One promising development is phased awards through PCORI’s Phased Large Awards for Comparative Effectiveness Research Initiative [37] and the NIH Pragmatic Trials Collaboratory [38]. Initial phases allow for study planning, stakeholder engagement, and pilot testing of recruitment and operations, prior to launching the larger study.

An important consideration for equity is that digital tools may have higher or lower ability to accurately identify and describe populations of interest. Race and ethnicity [39], demographics, and social determinants [40] are poorly captured in EHR and health databases. Workshop members urged for routine use of digital, consumer-facing tools to collect self-reported information. Comparing self-report to other data can help gain insight into representativeness and potential systemic biases that exist in current reporting of populations.

Finally, an opportunity for digital tools to enhance equity in trials is by delivering tailored information. A CVS Health consumer survey concluded that low trial participation was primarily due to lack of knowledge surrounding protection of research participants. Nearly

three-quarters of respondents cited concerns with safety and researcher qualifications, and >80% of respondents who identified as Black or African American also had concerns about protected health information [21]. To address these concerns, information on trial operations, protections, oversight, and privacy/security can be provided in several formats. All patient information, whether digital or paper formats, must be understandable and culturally appropriate. The US Department of Health and Human Services offers videos, printable materials, and infographics in both English and Spanish about human subjects research protections and regulations [41], although comprehensibility and usability across levels of health literacy has not, to our knowledge, been formally evaluated.

Equity in trials will not simply happen because the format changes to digital. Ongoing, active engagement, planning, and trust building with communities remains crucial. Technology should be carefully used and evaluated to ensure it is improving, and not worsening, diversity, inclusion, and representation in trials.

3.4. Ethics and security

Digital and consumer-oriented trials present new ethical, legal, and social implications (ELSIs), including cybersecurity risks. The expertise of many investigators, sponsors, and regulatory bodies is insufficient with respect to rapid adoption of technology, which leaves participants potentially vulnerable to harm. Designing and delivering a digital trial can generate substantial challenges.

Some challenges are familiar to investigators conducting traditional trials, but with a new twist. For example, imagine developing an app to deliver a mental health intervention to adolescents with depression. Potential participants could be identified by screening social media users for communications suggestive of depressed mood. Recruiting, studying, and monitoring would be conducted remotely. Once potential participants express interest, what are “best practices” for obtaining informed consent remotely from a vulnerable population? Should participants with suicidality, and therefore high risk of self-harm during the study, be included? And if so, how can those participants at higher risk be appropriately monitored to ensure safety? How can the privacy and security of highly sensitive, digital health information be guaranteed? How will the remote study team respond to signals of harm [42], and what oversight is required from the research organization and/or sponsor? How can this intervention be delivered equitably? Some trials have addressed these questions, but there is yet to be a body of knowledge supporting consensus around these issues.

Novel cybersecurity risks are also introduced in digital trials. Compared to “brick and mortar” trials, in which flow of information is generally restricted between the investigator site and sponsor database, digital trials typically have information flowing through several channels, increasing risks of data leaks. Potential consequences range from unauthorized disclosure of information to third parties to identity theft. Studies involving commercial devices, like activity trackers and sensors, almost always requires partnerships with third parties, making data ownership, management, and security more complex. The Log4J vulnerability, a security flaw in the code of a widely used, open-source library for logging error messages, underscores the need to understanding software “ingredients” of devices being used to gather data on participants [43]. Cybersecurity risk is additive to other risks in

clinical research and needs to be addressed and mitigated in the trial planning process. Data management structures must be adapted to handle these risks. One risk mitigation suggestion is to include identity theft protection for participants in a trial that requires commercial devices.

Using commercial devices in trials also creates new ELSIs. Not all populations have the same access to devices, but provisioning devices to participants may be considered an undue inducement depending on the perceived value of the device, study population, and duration. Devices using cameras, location services, and other surveillance technology can transmit private data not relevant to the trial from participants and bystanders [44]. Ambient privacy can also be an issue if participants lack a confidential environment to participate in trial activities. Data rigor, accuracy, and quality can also threaten the success of trials using devices. For example, a software update or algorithm change could occur during a trial, without notice or influence by the study team, and compromise data collection and quality. Thus, devices may need additional oversight or certification for use in trials.

Cybersecurity risks and ELSIs raise the importance of a meaningful informed consent process. These issues also increase the complexity of information being conveyed, making the process more challenging. One solution is the “MyTerms” concept, in which potential participants set personalized preferences for receiving information and a machine-learning algorithm presents informed consent information from a specific study in a way that aligns with their preferences [45]. “MyTerms” is an example of harnessing digital tools to improve ethical conduct of trials.

Recognizing the need to increase awareness of ELSIs in digital research, a group of investigators created a decision support tool and framework grounded in ethical principles [46]. Key components are Access & Usability, Privacy, Data Management, and Risks & Benefits, plus a checklist for investigators (https://recode.health/tools). Ongoing guidance and decision support tools are needed for investigators designing digital trials and regulatory bodies charged with protecting research participants. Partnering with potential participants to co-design digital trials may help identify ELSIs and mitigate downstream risks of harm.

Overall, there is a pressing need for more guidance around ELSIs and cybersecurity risks in digital trials. Specific guidance is needed surrounding the selection of appropriate tools and strategies and conveying information to potential participants that results in a meaningful informed consent process. Regulatory bodies and agencies, funders, investigators, and experts share responsibility for learning about these issues. Creating a protected forum for systematic evaluation of mistakes could help inform future studies and reduce the risk of harm.

3.5. Limitations

In this article, we highlight key discussions from our workshop, which is not intended to serve as a comprehensive review on the topic of digitization and consumerism in trials. Important aspects of trials such as assessment were not key workshop content areas. Technology is rapidly changing and new advances and challenges may have emerged since the time of the workshop. An important limitation of both the workshop and the manuscript

are the omission of patient representatives, which was unintentional but resulted from efforts to avoid duplicating content from prior workshops on virtual and hybrid trials and equity. The workshop did feature speakers from PCORI and patient-centered research industry members.

4. Conclusion

In an increasingly digitized and consumer-oriented world, trials have the opportunity to change for the better. New tools create opportunities, but also present challenges. Some challenges are novel and others are pre-existing but exacerbated by the changing landscape. Overall, a “click and mortar” approach can balance opportunities and challenges, but important implications for equity, ethics, and security need to be considered. We provide Expert Guidance (Table 1) and three models (Table 2) for trial partners in academia, industry, non-profit organizations, and government, including regulatory bodies. Several knowledge gaps remain, and additional guidance and research are needed.

Note: At the time this manuscript was revised and resubmitted, CVS had recently announced ending clinical trial services.

Acknowledgements

The authors thank our colleagues from Science 37 for their expertise in decentralized clinical trials that contributed to the workshop and manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Rachel L. Randell is supported by the National Institute of General Medical Sciences and the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Numbers T32GM086330 and T32HD104576. RLR’s spouse has financial relationships with Biogen and Merck & Co, Inc.

Lesley Curtis received contract support from Janssen and Vir Biotechnology and consulting fees from Regeneron.

Adrian F. Hernandez received contract support from Pfizer Inc. and Merck and consulting fees from Merck.

Tom Denwood is employed by Population Health Partners LLP.

Camille Nebeker has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Jeremy Sugarman receives support from NIH grants. He receives consulting fees as part of an Ethics Advisory panel as well as travel reimbursement from Merck KGaA and IQVIA. Dr. Sugarman participates on a Data Safety Monitoring Board for Merck and a Clinical Advisory Panel for Aspen Neurosciences. He also has stock options in Aspen Neurosciences, Inc.

Benoit Tyl is employed by Bayer.

Masahiro Murakami is employed by and owns stock in Eli Lilly & Company.

Leslie Oley Wilberforce is employed by Evidation.

Sherry Pagoto receives research funds from WW International and consulting fees from Fitbit and WW International.

Ola Vedin is employed by Boehringer Ingelheim AB.

Tomas Andersson is employed by and owns stock in AstraZeneca.

Olveen Carrasquillo received support from NIH grants and PCORI. Dr. Carrasquillo received consulting fees from Duke University Medical Center and the University of Florida. Dr. Carrasquillo also participates in the Data Safety Monitoring Board for the NIH COPE Study and is on the Board of Directors for the Health Council of South Florida and Miami-Dade Area Health Education Center.

Scott H. Kollins is employed by Akili, Inc. and owns stock in Akili, Inc.

Jill Pellegrino is employed by CVS Health.

Megan L. Ranney received support from NIH grants and a grant from the University of Wisconsin SMAHRT grant. Dr. Ranney also is a member of the Data Safety Monitoring Board for Project COBALT at the University of Pennsylvania.

Role of funding source

No funding source had any role in the writing of this article or in the decision to submit the article for publication.

Data availability

No data were used for the research described in the article.

Abbreviations:

app	mobile application
COVID-19	Coronavirus-19
DCRI	Duke Clinical Research Institute
EHR	electronic health record
ELSIs	ethical, legal, and social implications
FDA	Food and Drug Administration
NIH	National Institutes of Health
PCORI	Patient-Centered Outcomes Research Institute
US	United States

References

[1]. Inan OT, Tenaerts P, Prindiville SA, Reynolds HR, Dizon DS, Cooper-Arnold K, Turakhia M, Pletcher MJ, Preston KL, Krumholz HM, Marlin BM, Mandl KD, Klasnja P, Spring B, Iturriaga E, Campo R, Desvigne-Nickens P, Rosenberg Y, Steinhubl SR, Califf RM, Digitizing clinical trials, NPJ Digit. Med 3 (2020) 101. [PubMed: 32821856]

[2]. Khozin S, Coravos A, Decentralized trials in the age of real-world evidence and inclusivity in clinical investigations, Clin. Pharmacol. Ther 106 (1) (2019) 25–27. [PubMed: 31013350]

[3]. El Emam K, Jonker E, Sampson M, Krleza-Jeric K, Neisa A, The use of electronic data capture tools in clinical trials: web-survey of 259 Canadian trials, J. Med. Internet Res 11 (1) (2009), e8. [PubMed: 19275984]

[4]. Marra C, Gordon WJ, Stern AD, Stern, Use of connected digital products in clinical research following the COVID-19 pandemic: a comprehensive analysis of clinical trials, BMJ Open 11 (6) (2021), e047341.

[5]. US Food and Drug Administration, Considerations for the use of real-world data and real-world evidence to support regulatory decision-making for drug and biological products, in: 21st Century Cures Act, 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug (accessed 10 November 2022).

[6]. The National Heart Lung and Blood Institute in partnership with the National Science Foundationand the NIH Office of Behavioral and Social Sciences Research, Digital Clinical Trials Workshop: Creating a Vision for the Future, Available from: https://www.nhlbi.nih.gov/events/2019/digital-clinical-trials-workshop-creating-vision-future, 2019.

[7]. Ledford H, The COVID pandemic's lingering impact on clinical trials, Nature. 595 (7867) (2021) 341–342. [PubMed: 34183846]

[8]. Banks MA, Core concept: in the wake of COVID-19, decentralized clinical trials move to center stage, Proc. Natl. Acad. Sci. U. S. A 118 (47) (2021).

[9]. Iliffe S, Manthorpe J, Medical consumerism and the modern patient: successful ageing, self-management and the 'fantastic prosumer', J. R. Soc. Med 113 (9) (2020)339–345. [PubMed: 32910877]

[10]. Sahadevan R, Consumerism in Health Care, Available from:, 2018 10.1056/CAT.18.0281 (accessed 10 November 2022).

[11]. Duke Clinical Research Institute, DCRI Think Tanks Demonstrate What Is Possible, Available from: https://dcri.org/insights/think-tanks/, 2023 (accessed 4 May 2022).

[12]. Kutok ER, Doria N, Dunsiger S, Patena JV, Nugent NR, Riese A, Rosen RK, Ranney ML, Feasibility and cost of using instagram to recruit adolescents to a remote intervention, J. Adolesc. Health 69 (5) (2021) 838–846. [PubMed: 34059428]

[13]. Wang ML, Waring ME, Jake-Schoffman DE, Oleski JL, Michaels Z, Goetz JM, Lemon SC, Ma Y, Pagoto SL, Clinic versus online social network-delivered lifestyle interventions: protocol for the get social noninferiority randomized controlled trial, JMIR Res. Protoc 6 (12) (2017), e243. [PubMed: 29229591]

[14]. Kutok ER, Dunsiger S, Patena JV, Nugent NR, Riese A, Rosen RK, Ranney ML, A cyberbullying media-based prevention intervention for adolescents on instagram: pilot randomized controlled trial, JMIR Ment. Health 8 (9) (2021), e26029. [PubMed: 34524103]

[15]. Buller DB, Pagoto S, Baker K, Walkosz BJ, Hillhouse J, Henry KL, Berteletti J, Bibeau J, Results of a social media campaign to prevent indoor tanning by teens: a randomized controlled trial, Prev. Med. Rep 22 (2021), 101382. [PubMed: 33996394]

[16]. Lubitz SA, Faranesh AZ, Atlas SJ, McManus DD, Singer DE, Pagoto S, Pantelopoulos A, Foulkes AS, Rationale and design of a large population study to validate software for the assessment of atrial fibrillation from data acquired by a consumer tracker or smartwatch: the fitbit heart study, Am. Heart J 238 (2021) 16–26. [PubMed: 33865810]

[17]. C.V.S. Health, CVS Health Clinical Trial Services, Available from: https://www.cvshealth.com/our-services/health-and-wellness-services/clinical-trial-services, 2023.

[18]. Evidation Health Inc, Evidation, Available from: https://evidation.com/partners, 2022 (accessed 22 August 2022).

[19]. Johnson & Johnson, Johnson & Johnson Launches Heartline™, the First-of-its-Kind, Virtual Study Designed to Explore if a New Iphone App and Apple Watch Can Help Reduce the Risk of Stroke, Available from: https://www.jnj.com/johnson-johnson-launches-heartline-the-first-of-its-kind-virtual-study-designed-to-explore-if-a-new-iphone-app-and-apple-watch-can-help-reduce-the-risk-of-stroke, 2022 (accessed 22 August 2022).

[20]. Connors JM, Brooks MM, Sciurba FC, Krishnan JA, Bledsoe JR, Kindzelski A, Baucom AL, Kirwan BA, Eng H, Martin D, Zaharris E, Everett B, Castro L, Shapiro NL, Lin JY, Hou PC, Pepine CJ, Handberg E, Haight DO, Wilson JW, Majercik S, Fu Z, Zhong Y, Venugopal V,

Beach S, Wisniewski S, Ridker PM, A.-B. Investigators, Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4b randomized clinical trial, JAMA. 326 (17) (2021) 1703–1712. [PubMed: 34633405]

[21]. CVS Health Consumer Survey [press release], 2021.

[22]. Betz ME, "Safety in Dementia": An Online Caregiver Intervention, Available from: https://reporter.nih.gov/search/s9noPy4WFk2aH3aA2yHw6A/project-details/10398633, 2021.

[23]. Ranney ML, Increasing Peer Support for Oud Recovery During COVID-19 Through Digital Health: A national Randomized Controlled Trial, Available from: https://reporter.nih.gov/search/D3meB_XBtE2YAYztNVlzmg/project-details/10308885, 2021.

[24]. Mychasiuk R, Benzies K, Facebook: an effective tool for participant retention in longitudinal research, Child Care Health Dev. 38 (5) (2012) 753–756. [PubMed: 21985571]

[25]. Brueton VC, Tierney JF, Stenning S, Meredith S, Harding S, Nazareth I, Rait G, Strategies to improve retention in randomised trials: a cochrane systematic review and meta-analysis, BMJ Open 4 (2) (2014), e003821.

[26]. US Department of Health and Human Services National Institutes of Health, HIPAA privacy rule 45 cfr 164, Available from: https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-C/part-164, 2002 (accessed 10 November 2022).

[27]. Jake-Schoffman DE, Brown SD, Baiocchi M, Bibeau JL, Daubenmier J, Ferrara A, Galarce MN, Hartogensis W, Hecht FM, Hedderson MM, Moran PJ, Pagoto SL, Tsai AL, Waring ME, Kiernan M, Methods-motivational interviewing approach for enhanced retention and attendance, Am. J. Prev. Med 61 (4) (2021) 606–617. [PubMed: 34544560]

[28]. Goldberg EM, Bingaman CS, Perera S, Ranney ML, Mycovidrisk app: development and utilisation of a COVID-19 risk assessment and mitigation application, BMJ Innov. 7 (2) (2021) 363–367.

[29]. Sharma A, Palaniappan L, Improving diversity in medical research, Nat. Rev. Dis. Primers 7 (1) (2021) 74. [PubMed: 34650078]

[30]. Stewart J, Krows ML, Schaafsma TT, Heller KB, Brown ER, Boonyaratanakornkit J, Brown CE, Leingang H, Liou C, Bershteyn A, Schwartz MD, Agrawal V, Friedman-Klabanoff D, Eustace S, Stankiewicz Karita HC, Paasche-Orlow MK, Kissinger P, Hosek SG, Chu HY, Celum C, Baeten JM, Wald A, Johnston C, Barnabas RV, Comparison of racial, ethnic, and geographic location diversity of participants enrolled in clinic-based vs 2 remote COVID-19 clinical trials, JAMA Netw. Open 5 (2) (2022), e2148325. [PubMed: 35157053]

[31]. Furey D, Darasz D, How Merck Improved Clinical Trial Patient Diversity Using a Dynamic Enrollment Tracker, Available from: https://www.drugdev.com/uncategorized/merck-improved-clinical-trial-patient-diversity-using-dynamic-enrollment-tracker/, 2017.

[32]. The MRCT Center of Brigham and Women”s Hospital and Harvard, Case Study: Achieving and Exceeding Clinical Trial Participant Diversity Targets Using Customized Tools, Applications and a Dynamic Enrollment Tracker, Available from: https://mrctcenter.org/diversity-in-clinical-research/wp-content/uploads/sites/11/2021/03/MERCK-Case-Study-full.pdf, 2023. (Accessed 10 November 2022).

[33]. Lunn MR, Lubensky M, Hunt C, Flentje A, Capriotti MR, Sooksaman C, Harnett T, Currie D, Neal C, Obedin-Maliver J, A digital health research platform for community engagement, recruitment, and retention of sexual and gender minority adults in a national longitudinal cohort study-the pride study, J. Am. Med. Inform. Assoc 26 (8–9) (2019) 737–748. [PubMed: 31162545]

[34]. Vogels EA, Some Digital Divides Persist Between Rural, Urban and Suburban America, Available from: https://pewrsr.ch/3k5aU6J, 2021.

[35]. Jones WS, Mulder H, Wruck LM, Pencina MJ, Kripalani S, Munoz D, Crenshaw DL, Efffon MB, Re RN, Gupta K, Anderson RD, Pepine CJ, Handberg EM, Manning BR, Jain SK, Girotra S, Riley D, DeWalt DA, Whittle J, Goldberg YH, Roger VL, Hess R, Benziger CP, Farrehi P, Zhou L, Ford DE, Haynes K, VanWormer JJ, Knowlton KU, Kraschnewski JL, Polonsky TS, Fintel DJ, Ahmad FS, McClay JC, Campbell JR, Bell DS, Fonarow GC, Bradley SM, Paranjape A, Roe MT, Robertson HR, Curtis LH, Shadow AG, Berdan LG, Hammill BG, Harris DF, Qualls LG, Marquis-Gravel G, Modrow MF, Marcus GM, Carton TW, Nauman E, Waitman LR, Kho AN, Shenkman EA, McTigue KM, Kaushal R, Masoudi FA, Antman EM, Davidson DR, Edgley K,

Merritt JG, Brown LS, Zemon DN, McCormick TE 3rd, Alikhaani JD, Gregoire KC, Rothman RL, Harrington RA, Hernandez AF, A. Team, Comparative effectiveness of aspirin dosing in cardiovascular disease, N. Engl. J. Med 384 (21) (2021) 1981–1990. [PubMed: 33999548]

[36]. Manchester University NHS Foundation Trust, Research Van Arrives, Available from: https://mft.nhs.uk/2021/12/15/research-van-arrives/, 2021 (accessed 10 November 2022).

[37]. Trontell A, Parry C, Kennedy J, New Phased Funding Initiative Seeks to Answer Complex Research Questions, Available from: https://www.pcori.org/blog/new-phased-funding-initiative-seeks-answer-complex-research-questions, 2020.

[38]. NIH Pragmatic Trials Collaboratory, Rethinking Clinical Trials: A Living Textbook of Pragmatic Clinical Trials, Available from: https://rethinkingclinicaltrials.org/, 2023 (accessed 24 August 2022).

[39]. Polubriaginof FCG, Ryan P, Salmasian H, Shapiro AW, Perotte A, Safford MM, Hripcsak G, Smith S, Tatonetti NP, Vawdrey DK, Challenges with quality of race and ethnicity data in observational databases, J. Am. Med. Inform. Assoc 26 (8–9) (2019) 730–736. [PubMed: 31365089]

[40]. Cantor MN, Thorpe L, Integrating data on social determinants of health into electronic health records, Health Aff. (Millwood) 37 (4) (2018) 585–590. [PubMed: 29608369]

[41]. Office for Human Research Protections, Available from: https://www.hhs.gov/ohrp/education-and-outreach/about-research-participation/printable-educational-materials/, 2023 (accessed 1 November 2022)..

[42]. Ali J, Morain SR, O'Rourke PP, Wilfond B, O'Brien EC, Zigler CK, Staman KL, Weinfurt KP, Sugarman J, Responding to signals of mental and behavioral health risk in pragmatic clinical trials: ethical obligations in a healthcare ecosystem, Contemp. Clin. Trials 113 (2022), 106651. [PubMed: 34998990]

[43]. USA Department of Health and Human Services, Log4j Vulnerabilities and the Health Sector, Available from: https://www.hhs.gov/sites/default/files/log4j-vulnerabilities-health-sector.pdf, 2022 (accessed).

[44]. Eyal N, Risk to bystanders in clinical trials: a symposium, Clin. Trials 16 (5) (2019) 447–449. [PubMed: 31368795]

[45]. Nebeker C, Leow AD, Moore RC, From return of information to return of value: ethical considerations when sharing individual-level research data, J. Alzheimers Dis 71 (4) (2019) 1081–1088. [PubMed: 31524169]

[46]. Nebeker C, Ellis RB, Torous J, Digital Health Checklist for Researchers (dhc_r), Available from: https://recode.health/tools/, 2019.

Table 1

Expert guidance for digital and consumer-oriented clinical trials.

1	Consider a “click and mortar” approach.	Digital and consumer-oriented approaches can complement traditional “brick and mortar” approaches to recruitment and retention. The specific combination of methods and digital tools employed should be tailored to the research question, intervention, and target population.
2	Use digital tools to enhance engagement and ethics.	Technology offers opportunities to educate potential trial participants on the clinical research process, explain regulatory requirements and oversight, facilitate a truly informed consent process, conduct active on-boarding, increase access to difficult-to-reach populations, and disseminate results.
3	Foster human connections through digital tools.	Trusted health providers and research coordinators remain highly valuable in virtual trials. For example, trusted providers can connect potential trial participants to virtual partners with a “warm handoff.”
4	Dedicate effort and resources to improve equity.	Digital tools have the potential to improve equity but can also worsen existing barriers and create new inequities. The best approach involves selecting appropriate digital tools in close partnership with the community. Funders and regulatory agencies should design budgets and timelines that allow for the extra cost and time required for equitable recruitment, retention, and trial activities. Communities must be involved in all stages of trial planning, conduct, and results dissemination. Investigators need to study how specific communities take-up digital tools in trials so that lessons learned can guide future trials.
5	Be proactive about ethical challenges and potential security weaknesses of digital tools.	Technology is already creating novel ethical and security challenges. Investigators should consult regulatory bodies, agencies, sponsors, and experts in the field to address these concerns, study them, and contribute to the evolution of these new approaches. They need also to ensure that measures are in place to mitigate cybersecurity risks.

Table 2

Three “click and mortar” models for combining digital tools and consumer-oriented approaches with traditional “brick and mortar” clinical trial infrastructure.

Model Description	Strengths	Limitations
Data-forward: *Digital prescreening, followed by human-led enrollment and retention, e.g., CVS Health, Science37.*		
Potential participants are identified digitally, such as through a claims database, EHRs, pharmacy records, and/or social media (in accordance with privacy regulations). Analytics, online surveys, or filters help narrow potential participants based on specific eligibility criteria and/or measurable health behaviors that increase likelihood of participation. The potential participant is contacted directly, such as through a personalized e-mail, through a trusted health care provider, or via a phone call. Individuals are directed to an in-person or remote clinical or research site in which they interact with a real human to enroll in the trial. Subsequent trial activities take place in-person or virtually, perhaps augmented with digital reminders and activities, such as email reminders and surveys completed at home after a study visit.	• May be able to access large numbers of potential participants. • May increase participant diversity. • May be helpful for rare disease populations.	• Success of prescreening depends on the quality and quantity of data on potential participants. • Requires analytics expertise. • May be limited by trust and data security concerns among potential participants, and data privacy regulations. • May be difficult to translate “online” to “offline” behavior. • Limited capacity of in-person research sites may create bottlenecks.
Pass-through: *In-person engagement, followed by digital enrollment and retention, e.g., ACTIV-4b* [20].		
Potential trial participants are identified when passing through the doorway of “brick and mortar” infrastructure, such as a clinical care site or pharmacy. In-person engagement can include printed materials and flyers and discussion with trial staff and/or care providers. Once the individual expresses interest, they are directed to an online portal for enrollment and active on-boarding. The remainder of trial activities are primarily virtual, but may have in-person components, such as for blood draws. Frequent engagement through digital tools may enhance retention, especially in longer trials	• In-person prescreening may reduce screen failures. • Can help with trials that require biospecimens to determine eligibility or are time-sensitive. • May increase trust	• Fewer potential participants than “Dataforward” approach. • Operational challenges with “brick and mortar” infrastructure can create bottlenecks and slow the enrollment process
Parallel: *Simultaneous use of digital and in-person methods, where methods can be tailored to the individual or groups of individuals, e.g., ADAPTABLE* [35].		
Prescreening, recruitment, enrollment, trial activities, and retention occur digitally and in-person simultaneously. Potential participants decide which method they would like to use. For example, a potentially interested participant could sign up for a virtual or in-person information session to learn more about a trial. If the trial is targeting a specific population known to prefer digital approaches (e.g., young, tech-savvy volunteers), engagement and retention can be tailored to that group. Conversely, efforts to engage and retain groups of individuals that may be less likely to uptake digital resources (e.g., older patients, specific racial/ethnic groups), focus primarily on in-person methods.	• Provides flexibility for diverse populations. • Can adapt to participants for which the trial uptake behavior is not well known. • Helpful in large, multicenter studies where uptake may vary across sites. • Knowledge gained from trial uptake can inform future trials.	• High cost, high complexity. • May require longer time to conduct trial activities. • Could create subpopulations requiring separate analyses. • Sponsors may not want to fund all methods.

EHR = Electronic Health Record.