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Consumerization and Digitization of Healthcare: Where Marketing Meets Clinical Trials

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EXECUTIVE SUMMARY

BACKGROUND

Consumerization is inexorably taking hold of healthcare, driven by technological advancements and generational expectations, and accelerated by the COVID-19 pandemic. This trend is also transforming the clinical research landscape: novel digital consumer-driven methods for trial recruitment, retention, and interventions are increasingly commonplace. In this workshop, we discussed novel partnerships, opportunities, risks, and barriers to a consumer-oriented, digital transformation of clinical trials.

Key questions for the session included:

- How are novel technologies and digital partnerships (such as social media and wellness companies) currently involved in clinical trials? What could or should be their future role?
- How can a consumer-driven model enhance the flow of information about clinical trials?
- What novel strategies for recruitment and retention should be considered "best practice"?
- What ethical concerns exist regarding identification, enrollment, and retention of trial participants in a consumer-driven, digitized clinical trial? What mitigation strategies exist?
- How can consumerization and digital engagement help overcome access and equity issues and engage hard-to-reach populations in clinical trials?
- What is the role of regulatory bodies and funders in facilitating effective, ethical, and equitable consumer-driven digital trials?

WELCOME AND OVERVIEW

A digital or virtual clinical trial involves using a digital technology to improve components of the trial, such as participant access and engagement, interventions, measurements, and retention. Consumerization of clinical trials means focusing on individualization or greater self-efficacy for participants—reorienting research from being biomedically based to being patient- or population-based. A consumer-oriented strategy fundamentally changes recruitment, retention, and intervention delivery mechanisms, as well as strategies for measurement and

dissemination of outcomes. Consumerization can facilitate digitization of clinical trials and vice versa. Both strategies are common outside the academic research enterprise. Taken together, digitization and consumerization offer great promise for clinical trials. They also present both new and well-known challenges.

SESSION I: RECRUITMENT AND RETENTION

The first session focused on consumerization and digitization of recruitment and retention in clinical trials. Specific topics included making clinical trials more available to diverse participants, how these strategies enable trialists to reach beyond the halls of tertiary and quaternary centers and industry bases, creating partnerships with patients, and applying these new methods to recruitment and retention.

BRICK AND MORTAR STRATEGIES FOR RECRUITMENT AND RETENTION

The first part of the session included academic and industry perspectives on digital and consumer-focused strategies in the context of traditional "brick and mortar" clinical trials, rather than fully virtual trials. Examples include identifying, enrolling, and consenting participants remotely. However, some components of trial enrollment may require in-person interaction, particularly if they involve specimen collection.

Academic Perspective: Examples From Recent Covid-19 Trials

ACTIV-4b

The ACTIV-4b trial studied thrombosis prevention in outpatients with COVID-19. Patients were recruited in emergency and urgent care settings, COVID-19 testing centers, and CVS pharmacies and clinics. Interested patients were presented with e-consent and completed the consent online. Sites followed up with laboratory tests and confirmed patient eligibility and interest. Study drug was shipped directly to participants; participants called to confirm receipt and their medication start date. Participants had weekly follow-up by the coordinating center, 45 days of treatment, and 30 days of safety follow-up.

Recruitment in ACTIV-4b was supported by a central COVID-19 studies website, email or call center for study inquiries, direct-to-participant messaging via the EHR using MyChart, EHR prompts to clinicians, EHR recruitment reports of patients with a positive COVID-19 test result, flyers, and presentations to clinic staff. The coordinating center partnered with clinical research coordinators to handle consent and screening, with the main study team following up. A study flyer was mailed to all age-eligible patients with a positive COVID-19 test shown in the daily EHR recruitment report. Patients received an email link to a video about the trial.

The trial was designed to enroll 7000 patients but was stopped early by the data and safety monitoring board after randomizing 657 patients because of lack of an efficacy signal between the treatment groups. Approximately 85% of patients initiated therapy as randomized; 98% of those who started therapy completed follow-up.

Innovations in the trial including the creation of a research hub by the Duke Clinical Research Institute at a former clinic location which housed all of the coordinating center's COVID-19 trial activities, including study coordination, labs, and visits. The study team added CVS as a recruitment site. For participants who were unwilling to travel with symptomatic COVID-19, the study added a home health group to do lab draws.

ACTIV-6

The ACTIV-6 platform trial is studying whether repurposed medications reduce symptoms, deaths, and hospitalizations in outpatients with mild to moderate COVID-19. The study uses an online system for e-consent and data entry. All follow-up is conducted by phone or REDCap. Participants with a positive COVID-19 test are consented and screened, then randomized; study drug is shipped directly to participants.

There are 97 sites activated, with 92 sites enrolling; 2365 patients have been randomized. More than 9000 patients have expressed interest. Many began the consent process, but only 41% signed the consent. A major reason cited for low consent is that patients thought they would receive active study drug and did not want to be assigned to placebo.

The study is using the same recruitment strategy as ACTIV-4b. In addition, a communications firm has been working to place investigators on local and national television, plus outreach to community clinics and pharmacies near enrollment sites about encouraging their patients to enroll. The Duke Clinical Research Institute developed a social media toolkit with language and images for investigators to use on social media to increase awareness of the study.

One challenge is that there has been no way to conduct weekend enrollment for some sites, which also delays study drug shipment. In addition, coordinator turnover pauses enrollment while new staff is trained, resulting in delays. Having a large number of sites has helped the study team adapt to shifting geographic patterns in COVID-19 spread and with the staff turnover challenge.

Industry Perspective: CVS Health Clinical Trial Services

Most people do not have the opportunity to participate in clinical trials because they are unaware of them, do not know how to participate, or are never asked. However, in surveys, most say they would be willing to participate in trials. Of the relatively small number of people who do participate, the population is disproportionately White. A survey of approximately 2000 CVS Health customers concluded that trial participation was low because of a lack of education about trials. The findings were similar for underrepresented minority groups, though some specific strategies and messages can be helpful in addressing this challenge; for example, African American respondents expressed greater concern about sharing protected health information and about CVS Health using those data to target them. Trusted relationships and direct outreach are key to engaging potential participants. Most people want to hear from a trusted source, such as their physician or pharmacist.

CVS Health is building capability to conduct direct outreach for clinical trials, which can reduce burden on investigators by offering prescreening and other recruitment services. The first step

is identifying the target population. CVS Health has a comprehensive clinical database with 100 million patients, including prescription medication data, medical claims, vaccine and testing records, and demographic information. Engagement strategies include email, phone, direct mail, and in-store engagement. Prescreening services can include e-questionnaires, a call center, onsite screening, or screening at the sponsor's site. Results so far have been positive. The clinical trials center started in 2021, primarily for COVID-19 trials. The center has engaged 7.8 million people, resulting in more than 11,000 enrollments, including 40% non-White participants, substantially higher than the national average in clinical trials.

Future enhancements include developing a community network by continuing to locate CVS MinuteClinics and HealthHUBS in neighborhoods; creating a national prescreening platform to more efficiently determine trial eligibility; creating a patient panel of an online opt-in population of eligible individuals who meet basic criteria and are interested in learning more about clinical trial opportunities; and enhancing predictive modeling to expand and refine data sets, including adding data from insurance lines of business and third-party labs.

So far, there are 2 main differences between people engaged through brick and mortar sites and those engaged through digital strategies. First, there are higher rates of screening failure among patients who are not recruited through their clinician. Second, retention rates from outside populations sometimes exceed those source from investigators, perhaps reflecting self-motivation on the part of people who took the effort to find opportunities to participate.

Discussion

1. There are many ways to reach potential clinical trial participants external to traditional recruitment sites. What is the optimal mix of these various channels?

Digital strategies work best for people who are computer-savvy and have internet access. For example, in the PREVENTABLE trial, there was a clear digital divide between White and Black individuals as reflected in who was opening and responding to the MyChart invitation. Similarly, older populations tend to prefer mailings and phone calls. Racial and ethnic minority populations may prefer in-person approaches. It is difficult to use a single strategy for the entire population. In CVS Health's experience, participation improved with the use of hybrid models of recruitment when the COVID-19 pandemic started. Virtual prescreening opportunities and other digital strategies increased interest in participation, reduced the time burden of learning more about trials before committing to in-person visits, and offered greater flexibility with participants' schedules.

2. What stands in the way of doing better predictive analytics so we can tailor recruitment approaches depending on how a given individual will respond?

One challenge to such a tailored approach is accessing all the connecting data to make predictive analytics possible. Moreover, race/ethnicity and other demographic characteristics are poorly captured in the electronic health record. From some community engagement

experiences, we know that some populations feel comfortable making the decision on their own, and some populations want to hear from a trusted contact such as a physician or pastor.

Even in virtual trials, having a committed study coordinator and a committed physician who can respond to patients' concerns is key to engagement, enrollment, and retention. One strategy is to reach out to local physicians before recruitment begins, so that when patients receive an invitation letter from the study team, the physicians can express awareness of and knowledge about the trial. The patients who are easiest to recruit are those who have heard about the trial from their doctor.

DIGITAL STRATEGIES FOR RECRUITMENT AND RETENTION

The second part of the session addressed optimizing and implementing digital strategies for recruitment and retention.

Academic Perspective: UConn Center for mHealth and Social Media

The Get Social trial compared in-person clinic and remote delivery of a lifestyle intervention for weight loss. Retention was 94% at 1 year. The study demonstrated the power of Facebook groups for recruitment. (Facebooks ads have not been effective for weight loss trials, though other topics have had better success.) The study team approached moderators of Facebook groups for neighborhoods, yard sales, buy/sell groups, and the like to ask about interest in allowing posts about the study. The second most powerful recruitment modality was word of mouth, though the study team did not have good information about what these sources were.

The Mom's Health Chat study tested a Facebook-delivered cancer prevention intervention targeting mothers of teenage daughters. The original recruitment plan was to use school nurses, which was unsuccessful. The study team moved to a Qualtrics survey panel, which led to much faster recruitment in 33 states. Recruitment was totally remote; there was a 72% retention rate at 1 year. One challenge with survey panels is that participants expect surveys rather than trials. Survey panels also tend to produce higher rates of "bogus" participants.

The WW trial tested an online weight loss program. WW was a completely remote, nationwide trial. The sponsor needed study completion within 10 months, including a 6-month intervention. The study team produced a panel in 6 weeks with 92% retention. The NIH ResearchMatch program produced a large portion of the sample. More work is needed to improve the diversity of Facebook samples. ResearchMatch can be helpful in allowing tailored recruitment.

The Fitbit Heart Study tested the ability of a Fitbit device to detect arrhythmias. The study needed a large sample. Fitbit has 31 million active users. Notification-driven recruitment led to recruitment of 500,000 people. Only about 1% of the sample had an arrhythmia. The study then involved 2 telehealth visits to get participants set up on an ECG patch via the app. Of the

participants with an arrhythmia, only 35% completed the first remote visit, and only 19% completed the second remote visit.

One major lesson from these experiences is that there is a tension between recruitment volume and retention in remote trials. Facebook groups produce high yield and can allow for strategies to improve representativeness. The effectiveness of recruitment strategies varies widely by target population and study topic.

The research team has begun using Motivational Interviewing to onboard participants before randomization (Jake-Schoffman DE et al. *Am J Prev Med*. 2021 Oct;61(4):606-617. PMID: 34544560.). The onboarding consists of clinical trial literacy education through a webinar. It sets expectations for participants; explains the scientific principles behind trial methods (such as randomization and how missing data affect study conclusions); explores ambivalence about participating in research; asks participants to make a commitment to themselves and to the trial; and discusses barriers to participation. The purpose of this onboarding is to educate, not to weed people out. For example, in the Get Social trial, the study team lost only 13 people after the webinar. Motivational Interviewing has significantly increased retention rate by reintroducing human, albeit remote, interaction into the recruitment process.

Regulatory Perspective

It is important to be aware that using digital approaches in clinical trial recruitment means mixing medical risk and internet risk, and these risks can be additive. In traditional clinical trials, investigators typically are concerned about accidental loss of confidentiality. However, trials in virtual spaces can expose users to unwanted data sharing and even stealing of personal data. Trialists should recognize and adapt to these risks. People generally are concerned about their privacy, and they do not always know what they give up when they engage digitally. Researchers should understand the features of the software used in their trials and should consider partnering with groups outside of the traditional clinical trials realm to assess and address digital risks.

Industry Perspective: Evidation

Evidation has a community of more than 4 million members who engage in a long-term relationship around permissioned health data sharing. The membership has strong geographic diversity, with 90% of zip codes represented. The community has a user-friendly app interface, and data collection occurs from both consumer- and clinical-grade devices and apps. The core drivers of success are a highly customized, engaging experience; smart rewards and incentives to keep people engaged; and clear consent built on transparency about data use. The team uses strategies that motivate actions with data-driven timing, such as nudges, rewards, benefit loops, and personalization. Digital outreach strategies include push notifications, email, in-app offers, and blog posts.

One example is a large-scale participatory flu monitoring program, the goal of which was to identify Evidation members experiencing early flu symptoms and then activate them toward research. The challenge was catching people at early onset of symptoms. The company used data from wearables to build a machine learning model to predict onset of symptoms. The model has seen over 11,000 people with potential flu-related symptoms referred to the study screener; however, only 2308 completed the screener, and only 9 have been assigned to clinical sites. A major challenge is connecting online behavior to subsequent offline behavior. It will be important to learn more about differences between online and in-person participant populations.

Another example is engagement and retention in the Heartline study, a multiyear, entirely digital program to analyze the impact of a heart health engagement program and irregular heart rhythm notifications on early detection and diagnosis of atrial fibrillation and to improve outcomes including prevention of stroke. Several digital engagement mechanisms have been possible through the digital platform, such as app-based onboarding and screening, building community through sharing research updates, and using points and rewards as compensation. The study app will be deployed in a cohort of 150,000 participants 65 years and older.

Community Perspective: Science37

Decentralized research participation can include a range of digital and in-person components, depending on the study. The Science37 patient path includes an adaptive outreach strategy, prescreening, medical history, e-consent, screening, enrollment, randomization and shipment of study drug, the study period itself. The approach translates into greater enrollment than traditional site-based recruitment.

One example is a recent phase 2 trial of a COVID-19 therapy. Traditional study sites were oversaturated with COVID-19 studies, and patients were hesitant to participate early in the pandemic. The study team set up a fully virtual telemedicine site alongside the 13 brick and mortar sites. The virtual site included direct shipment of study supplies and study drug, direct-from-patient collection of self-administered nasal swabs, and digital outreach and testing/urgent care referrals. Compared with traditional sites, the virtual site had a higher rate of enrollment: 86% percent of the study's patients were enrolled through the virtual site with 97% retention rate. The virtual site was not limited by geography and was able to refine its process along the way as the team figured out the best path to enrollment. Allowing patients to participate from home helped with retention.

In a COVID-19 prevention study using a monoclonal antibody, the virtual site was the top enrolling site, had 13 times faster enrollment, and had 23% participants of color. In a study in a lupus/Sjögren syndrome population using a single virtual site and wearables, along with mobile nurses to collect vitals and blood draws and telemedicine visits for clinical exams, retention was 96%, and more than 50% of the study population was black, Latinx, or Asian.

DISCUSSION

One lesson from the session is that the distinction between traditional "brick and mortar" clinical trials and digital trials is artificial. Traditional and digital strategies are best used in a combination, "click and mortar" strategy. The optimal strategy is trial- and intervention-specific. The session presented several examples of successful approaches and their challenges. Trialists have an opportunity to learn new skills in applying digital approaches while bringing their expertise to test which combinations of approaches work best.

Attendees also discussed the need for trialists to better understand the risks to data privacy and confidentiality in clinical trials conducted in virtual spaces, as well as strategies for protecting data in these trials. Trialists should understand the features of the software used in their studies to ensure the tools can be trusted. Digital trials offer trialists opportunities to build partnerships with groups outside of the traditional clinical trials realm to assess and address digital risks.

Finally, digitization of clinical trials has important implications for equity. The funnel for recruitment is much wider in digital trials. This creates new opportunities for reaching more participants, but it risks missing certain groups during recruitment and may pose challenges for retention of some groups. More research is needed to under and understand differences between participants who are retained in digital trials and those who are lost to follow up.

SESSION II: EQUITY

The second session offered perspectives on equity in digitized and consumer-focused clinical trials.

OPPORTUNITIES AND PITFALLS

Academic Perspective

Community-informed approaches are relevant to digital trials. The All of Us Research Program, the ACTIV studies, and other trials that use digital approaches offer reminders of the importance of diversity in clinical research. Digital approaches are going to leave some people out. We need to make room for these populations to avoid repeating the mistakes of traditional approaches. Not everyone is going to have same capacity or comfort level with digital approaches. It is also important to be aware that it costs more to achieve equity in clinical research. We need to include these populations, even if it costs more and is more difficult.

Industry Perspective: Merck

The COVID-19 pandemic has accelerated the use of digital tools and telehealth. One thing we hear from patients and patient advocate community is that people feel comfortable with

clinicians who come from their own community. Therefore, it is important to diversify the population of physicians who become clinical investigators. It is also important to work closely with patient advisory panels to gain insights into trial design and conduct. Training at investigator meetings should include a focus on health disparities, health literacy and numeracy, and cultural competency. All patient information—whether delivered digitally or on paper—should be understandable and culturally appropriate.

Merck has begun to use dynamic clinical trial enrollment trackers to increase participation by underrepresented groups. For example, in a phase 3 hepatitis C trial, they were able to achieve their enrollment goal of 20% from underrepresented groups.

Patients and patient advocates have significant concerns about digitization. Patients have different preferences regarding how they want to interact. Some want in-person appointments, others are happy with virtual approaches. Data privacy is a priority, and patients from different communities are concerned about how their data are shared and used. Access is another issue. A significant percentage of the US population does not have high-speed internet access and technological literacy. In our zeal to use technology to reach underserved populations, we need to be careful about leaving people behind. Hybrid approaches will continue to be important.

Funder Perspective: PCORI

The mission of PCORI is to support clinical comparative effectiveness research guided by patients, caregivers, and the broader health care community and to reduce disparities in health and health care. The research program has a strong pragmatic focus with trials conducted in real-world populations, settings, and clinical care processes. Broad, representative inclusion is key to understanding subgroup differences. PCORI places an emphasis on patient engagement to identify relevant research questions, support research conduct, and aid in implementing findings. The shift to digital engagement includes consent and enrollment, virtual care delivery and visits, and patient collection/provision of outcome data (such vitals and biospecimens). The approach has been to centralize review of these changes for potential impacts on study rigor and representativeness.

Digitization offers opportunities to facilitate engagement, expand access to clinical trials and specialty care, and ease and enrich data collection. Challenges include barriers to disadvantaged populations (such as broadband access, health literacy and numeracy); security, confidentiality, and privacy of data; data management; and methodologic challenges in data reconciliation and the effects of homogeneity/heterogeneity. Digital tools and their management should themselves be a focus of study to determine their usefulness. Authentic partnerships with patient communities and researchers are needed to overcome these barriers.

DISCUSSION

1. How much of a barrier is access to high-speed internet? What are potential solutions?

In one PCORI trial, a partnership with schools made tablet computers available to participants who would otherwise have been excluded because of lack of access. Community partnerships like this can be key. Financial incentives are also important; people can figure out access on their own if they simply have the financial resources. It is important to budget appropriately to reach populations with access challenges. This can include budgeting for outreach and tools, as well as additional staff time. Funders historically have constrained budgets for these activities, but the restrictions can sometimes be relaxed when there are barriers to enrollment for disadvantaged populations.

2. What are the risks and challenges of digital approaches? What is our role in addressing them?

Setting research priorities in a way that embraces all stakeholders helps avoid problems. Researchers' priorities may not always be consistent with patients' or communities' priorities. The process of setting priorities and defining research questions should represent the variety of perspectives to facilitate the harder task of negotiating a balance among perspectives. One interesting approach is "patient preference trials," which can help prevent losing people who do not want to be assigned to a non-active study arm. Another emerging practice to include a parallel observation group. In seeking to reach underserved and underrepresented populations, it is also critical that recruitment sites have relationships in their communities and that their recruitment reflect the demographic characteristics of their center's catchment area.

SESSION III: ETHICS CONSIDERATIONS AND CONCERNS

Presenters in this session addressed ethical considerations and concerns posted by digital trials.

Industry Perspective

The first presentation raised several key questions for researchers to consider related to ethical concepts and their implications for digital trials. These concepts include trust, which involves privacy and confidentiality; having a truly informed consent process; and representativeness in participation. How do digital and consumer-focused trials relate to these concepts? In a recent decentralized study design for a digital therapeutic for adolescent depression, the trial sought to recruit participants using social media and to use related methods, including remove delivery. The product was designed to be used without visits. Trial exclusion criteria included current or recent suicidality.

This study raised a number of important questions that can be applied to other digitalized trials. For example: When designing such as study, what are the ethical, legal, and regulatory challenges in studying and monitoring a high-risk population remotely? How do you evaluate a product designed to improved accessibility in its intending setting, while still controlling for a range of important design element? How do patients' age and legal status influence the consent process? Does the nature of a smartphone app–based intervention raise questions

about equity and inclusion? How does this format impact remote safety monitoring? Is it better to not assess self-harm if the there is no ability to immediately respond? Finally, what are the obligations of the sponsor, the CRO, and the treating clinician?

Academic Perspective

The next presentation asked, what are the ethical implications of being able to collect all kinds of data that we were not previously able to collect using tools that were not previously available? How do we apply current regulations to this type of research?

ReCODE Health developed a framework and a decision support tool to help researchers and IRBs understand these strategies and their implications, available at recode.health/tools. The framework includes the following components: (1) accessibility and usability, including accessibility to diverse populations; (2) privacy; (3) data management, including appropriate collection and storage protocols, data access permissions, and data security best practices; and (4) risks and benefits. We need to be able to convey this information to people as part of the informed consent process, make the information accessible to people, and build in education as part of the consent dialogue. We also need to make findings accessible to participants after the study is complete.

Our obligation is to make research trustworthy. To make the research enterprise as a whole a trusted enterprise, it is important to consider scientific rigor, including data quality, data authenticity, the data supply chain, and privacy of interactions in telemedicine. It is also important to consider indirect benefits of research. People participate in research for a variety of reasons, including access to technology and services that would not otherwise be available, as well as the social experience of research.

DISCUSSION

It is important to involve patients and communities at the outset in understanding the risk profile of a study. Researchers may not understand patients' privacy preferences without involving patients in the design of the study and its interventions. Different groups have different privacy preferences. For example, there is a digital divide between older and younger patients, and between people with more less savvy with digital tools. Older adults tend to be more protective of data privacy.

Given our unprecedented level of access to data about people, what is the right balance between the societal interest in the answering important health question and individual rights? Is there some magnitude of societal benefit that outweighs individual risk? One of thing we have learned more about during the COVID-19 is how to use standard public health approaches to collect data on individuals for the public good. We have seen similar uses of data in pragmatic trials. However, we justify these uses of data by demonstrating that the study poses minimal risk. The issues are not new, but the digital tools make the opportunities greater.

Individual rights do not always override societal interests; however, individuals can provide vital insight to help ensure the research is trustworthy.

This workshop presented numerous examples of digital approaches to clinical trials. These approaches have raised new opportunities and challenges for recruitment and retention, equitable participation and engagement, and protection of data privacy. Researchers, IRBs, sponsors, and participants need better tools, education, and partnerships to understand these issues and navigate the challenges they pose.