How Can Clinical Trial Recruitment Be Optimized and What Role Can Technology Play?
Executive Summary

While it is widely acknowledged that the outcomes of clinical trial recruitment strategies need to be improved, there remains a large gap between the hoped for outcomes and available solutions. This gap is important from an equity perspective - under-resourced, hard-to-reach, marginalized and minority communities tend to have poor access to new treatments. This limits the generalizability of clinical research to such groups, and their access to treatments that could be life-saving.

In this report, we explore the current state of knowledge on clinical trial recruitment, with specific regard to best practices and challenges in recruitment, and whether digital tools could support this process. We identified several factors that can influence the decision to participate in clinical trials. They include the prospect of health benefits to the patient or their community, the stigma associated with certain health conditions, the design and accessibility of the study, financial considerations, the adequacy or lack thereof of information, and psychological factors on the part of the patient, community and care team. The majority of the studies which examined digital strategies for improving recruitment found them feasible and cost-effective. Additionally, digital strategies were often helpful as a complement to traditional recruitment strategies and in reaching hard-to-reach populations.

Recruitment strategies, whether digital or traditional, could be optimized by adopting some identified best practices. These include: using a multi-modal approach for recruitment, optimizing communication and trust with stakeholders, developing clinical capacity for studies, using appropriate incentives, and continually paying attention to study strengths and challenges in order to adjust the study design accordingly.

We also present the results of a pilot recruitment drive for Radiant Clinical Research. Users of the Sickweather application who were in the specified market region, and/or who reported common cold symptoms within that region were invited to participate in research on an investigational cold remedy spray. The use of a digital tool provided the unique advantage of participant tracking, which can inform the improvement of clinical trial recruitment processes.

Additionally, given the time bound nature of the recruitment process, the use of the Sickweather application made it possible to advertise the opportunity to a wide range of prospective, symptomatic, participants within a short time frame.

This pilot suggests that clinical trial recruitment, like certain behavioral health initiatives, may need to be stage-appropriate in order to ensure optimal recruitment. Therefore, the appropriateness of the transtheoretical model of change to clinical trial recruitment will need to be further explored in future studies. Subsequent studies will integrate the best practices identified from the literature, while comparatively assessing recruitment using Sickweather and more familiar tools in traditional advertising, paying attention to factors such as cost-effectiveness, stage appropriateness, participant flow through the process, and the potential role of incentives.
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Introduction

Clinical trials give patients the opportunity to choose new treatments as soon as they are available (Unger et al., 2016). Additionally, when patients are enrolled into trials faster, treatment advances can happen faster thus improving health outcomes (Unger et al, 2016). However, recruitment remains a significant and common challenge in clinical trial design and administration (Harman et al., 2015; Butler et al., 2015; Bower et al., 2014; Oviedo-Joekes et al., 2015; Courcoulas et al., 2014; Lebensburger et al., 2013).

This is particularly important from the perspective of health equity and parity of access to treatment: recruitment tends to be most difficult for sub-populations that need treatment the most — people with chronic, rare and/or often stigmatized conditions, rural populations, high risk subgroups, low income populations, older populations, ethnic minorities, amongst others (Lebensburger et al., 2013; Shah et al., 2014, Colon-Lopez, 2016). Clinical trial participation could potentially reduce rural-urban health disparities (Bergeron et al, 2013) and yet clinical trial participation is low among rural and African American communities (Tanner et al, 2015).

While the majority of rural citizens tend to have the insurance coverage necessary for clinical trial participation, other barriers like poor knowledge, poor literacy levels and poor accessibility tend to limit their participation in clinical trials (Bergeron et al., 2013). Lower income patients who are potentially more sensitive to the financial burdens associated with trial participation are less likely to take part in trials, thus excluding them from access to the newest treatments (Unger et al, 2013). Langford et al. (2014) also found that while being above sixty-five (65) was associated with lower clinical trial recruitment, being male or having a higher grade level score for consent form readability was associated with lower clinical trial refusal rates. This difficulty in recruiting certain subsets of the population could also compromise the representativeness of clinical trials and hence the generalizability of their outcomes.

According to Chen et al. (2014), less than 2% of the trials of the National Cancer Institute focus primarily on ethnic minorities, again reinforcing the prerogative from a health equity standpoint, of improving such populations’ participation in clinical trials. Older patients, who have the majority of cancer diagnoses are underrepresented in clinical trials (Hurria et al., 2014). Among this demographic, challenges such as high exclusion and refusal rates and the presence of cognitive impairments limit their participation. This leads to poorly powered trials and poor generalizability of such trial findings, which then makes it difficult to adopt new and potentially life-saving interventions (Clegg et al., 2015).

Improving clinical trial recruitment can therefore help improve the awareness and treatment of health conditions in underrepresented communities and sub-populations, and potentially help reduce health disparities. This study had the following aims: 1) to explore the feasibility of using digital means for clinical trial recruitment, as well as the literature on challenges and best practices for improving clinical trial participation with a particular emphasis on digital tools as a facilitator and 2) to pilot the use of a Sickweather, a crowdsourced surveillance platform for clinical trial recruitment and compare the success on this platform against traditional platforms.
Phase 1: Assessing the feasibility of Sickweather for recruiting clinical trial participants

Radiant Clinical Research employed the Sickweather app to drive symptomatic participants in their market regions of interest to a new nasal spray cold remedy. The trial was time sensitive, demanding that the participants be symptomatic within 48 hours of the trial. In April 2017, Sickweather sent push notifications to app users in twenty regions, corresponding to the twenty markets for the Radiant Clinical Research clinic trial. The markets spanned the following states: Minnesota, Arizona, Iowa, Nebraska, California, Ohio, Alabama, South Carolina, Florida, Illinois, Texas, Utah, Colorado and Missouri.

Prospective participants in the market regions of interest to the study were recruited through three main ways. The first was an in-app ‘Map Marker’ assigned to the nearby spatial location of a clinical trial on the map on the Sickweather application. The second was an in-app ‘Illness Notification’ that was sent to Sickweather users who reported symptoms of the common cold on the Sickweather application and who were within a 25 mile radius of the clinical trial location at the time of reporting their symptoms. The third was through a ‘Push Notification’ sent to the devices of the users of the app in the market regions of interest. The push notification message sent to the Sickweather users was as follows:

“Have a cold? Help local researchers evaluate an investigational nasal spray! Swipe to learn more”

Sickweather users could express a positive interest in the study by either swiping the push notification for more information, tapping the map marker and the sign up button, or by responding “yes” to an illness notification. On either occasion, such users were put into Radiant’s onboarding flow in another browser.
FIGURE 1

Figure 1 above shows the flow of clients through the recruitment process. The use of the Sickweather application made it feasible to track clients’ flow through each stage from advertising to either engagement or a positive or negative response. This creates an opportunity to better understand prospective participant involvement, non-involvement or attrition and the reasons behind each of these outcomes. This is a unique advantage that using a digital tool provides.

The data show that the reach of the three different methods was markedly different. Push notifications had the widest reach, whereas illness notifications given their higher specificity, had the lowest reach. However, despite their low reach, outreach using illness notifications had the highest rate of response, with 81.67% of the users contacted providing a yes or no response. This is in comparison to 2.89% of the users who clicked through on the push notification, and the 13.75% who clicked on the map marker. By comparison, several advertising measurement organizations that track trends in click through rates of display advertising have benchmarked average click through rate performance of mobile display advertising between 0.05% - 0.1% which is significantly lower than all three of the targeting methods used in this case.

This suggests that studies may need to tailor recruitment to the participant condition, making sure to recruit participants at a stage appropriate point in time. If this is the case, this would align with the transtheoretical model of behaviour change (Prochaska et al., 1997). This model of behaviour change posits that individuals progress through change in six stages namely precontemplation, contemplation, preparation, action, maintenance, and termination. Health promotion programs aimed at eliciting behavior change are more successful when using interventions that are matched to the stage of the prospective participant (Prochaska et al., 1997). This may also be applicable to recruitment to clinical trials and will need to be explored in a study with a larger sample size.
PHASE 2: Appraising the literature on challenges, opportunities and best practices for clinical trial recruitment

We also conducted a review to assess the current state of knowledge on using digital tools for clinical trial recruitment.

Figure 2: Literature review flowchart

Figure 2 shows the procedure for conducting this review. First of all, we consulted Google Scholar and the Cochrane Review to identify studies on clinical trial recruitment. We used Google Scholar because of its comprehensiveness as a database of peer-reviewed studies. Given the need to identify evidence-based studies, we also included the Cochrane Review in this search.
We used the following keywords in the search: clinical trial recruitment, best practices in clinical trial recruitment, challenges in clinical trial recruitment, digital tools for clinical trial recruitment, innovation in clinical trial recruitment, clinical trial recruitment using social media, clinical trial recruitment barriers, optimizing clinical trial recruitment.

Studies that specifically concerned challenges and solutions to clinical trial recruitment were included in the search. For contemporary relevance, we limited this search to articles published after 2013. The search originally yielded one hundred and thirty-three (133) articles, fifty-two (52) from Cochrane Review and eighty-one (81) from Google Scholar. Upon a deeper reading of the articles, thirty-two (32) studies were excluded from the review due to a lack of relevance to the topic. These articles covered clinical trials but rather than focusing on the process of recruitment, focused on the clinical trial outcomes. Five (5) studies were excluded because they were published before 2013. Thirteen (13) repetitions of articles were removed. Finally, three (3) articles were removed because their full versions were unavailable and therefore could not be analysed. We eventually arrived at a shortlist of eighty-one (81) articles.

Each of these articles was critically read to 1) understand the prevalent methods of clinical trial recruitment 2) understand the challenges faced in the recruitment of clinical trial participants 3) understand the best practices and limiting factors for clinical trial recruitment, especially with regard to using digital tools as a potential solution to recruitment challenges.
Findings

Figure 3: Bar chart categorizing the reviewed papers by health topic of interest

Figure 2 above categorizes the reviewed papers by the health condition they were primarily concerned with, where applicable. As seen above, many of the papers focused on chronic conditions, improving recruitment of hard to reach populations such as ethnic minorities, LGBT populations, rural communities, African American communities, and the elderly; stigmatized conditions such as mental health issues and HIV/AIDS. This further ingrains equity as a key value and driver behind efforts to improve clinical trial recruitment methods. Often the communities who need more health investments remain the ones most difficult to reach in order to conduct research on improving their health conditions.

Upon review, factors that either facilitated or militated against clinical trial recruitment were grouped into the categories below:

1) **Anticipated health benefits:** Study participants sometimes choose to participate in studies because of anticipated benefits to themselves or to others. A study by Colon-Lopez (2016) found that 98% of the participants in an anal cancer clinical trial among people living with HIV/AIDS thought that their participation would potentially improve their health. Altruism also influences the decision to participate and people may be motivated to participate because they think that the study will help people with similar conditions or that the study is aligned with the priorities of their community (Aventin et al., 2016; Jenkins et al., 2013; George et al., 2014).
2) **Stigma:** Another barrier to recruitment is stigma. Some chronic conditions, for example, vulvodynia which involves pain during sexual intercourse are difficult to recruit for simply because people are reluctant to talk about them (Bachour et al, 2017).

3) **Accessibility:** Accessibility influences the recruitment and long-term retention of research participants (Gandhi et al., 2015; Smith et al., 2016). Accessibility challenges range from difficulty in accessing study sites, to inability to meet up with the frequency of treatment visits (Gandhi et al., 2015). Some areas do not have the facilities to conduct clinical trials or may be rural and hard to gain access to for recruitment purposes (Smith et al., 2015; Tanner et al., 2015).

4) **Finances:** Socioeconomic variables can also play a role in which participants are recruited (Bachour et al, 2017). These include factors like race, level of education, household income, employment status, amongst others (Bachour et al, 2017). Not only are lower income patients less likely to take part in clinical trials, they are also more sensitive to potential expenditures that patients incur such as copayments, coinsurance, or other costs of participation (Unger et al., 2013). Other financial costs to consider include time off from work, the cost of purchasing child care, the cost of transportation, among others (Unger et al., 2013).

5) **Information:** Information is often a barrier to clinical trial recruitment. This takes two forms - inadequate communication of trials and the rationale behind them (Tanner et al., 2015; Colon-Lopez, 2016; Lebensburger et al., 2013) as well as information that is considered excessive or too complex by potential participants (Kaur et al., 2013; Clegg et al., 2015).

6) **Study design:** Other challenges concern the nature of the clinical trial including factors such as the type of treatment, the treatment duration, the variations in treatment required for trial evaluation as well as the time and severity of the condition (Clegg et al., 2015; Jenkins et al., 2013; Geed et al., 2017). For example, patients may refuse to participate if they are not assigned to the trial arm that they prefer, or if they do not want to be randomized (Kaur et al., 2013; Lebensburger et al, 2013).

7) **Psychological barriers from patient and care team:** Patient decision is often behind the decision not to enrol in clinical trials (Rodriguez-Acevedo et al., 2016). Patients’ and gatekeepers’ attitudes to trials involvement more generally as well as their judgment of potential risks and rewards of specifically clinical trials play a role in their eventual decision to participate or not participate in clinical trials Hughes Morley et al.,2015; Kaur et al., 2016; Tanner et al., 2015; Stamford et al., 2015; Lebensburger et al., 2013; Colon-Lopez, 2016).

This includes subjective assessments of potential benefits of the study, credibility of the study team, and assessments of the alignment of interventions with stakeholders’ ethos (Aventin et al., 2016). There is often a historically based mistrust of participation in trials that needs to be overcome, especially among ethnic minorities such as African-Americans who have a historical basis for this skepticism (Durant et al., 2014; George et al., 2014).

Some of these psychological factors not only concern the patient but also concern the doctor-patient relationship. For example, doctors and nurses may not be comfortable approaching potential trial participants (Donovan et al., 2014). There might also be issues around establishing the effectiveness of the potential intervention and with aspects of patient eligibility (Donovan et al., 2014). This can make recruitment difficult. Patients’ perceptions of whether or not their doctors want them to participate in the study could also be related to their participation in the study (Jenkins et al., 2013).
Given the above-mentioned factors, we can hypothesize that digital tools may address some of the identified barriers to trial recruitment such as the need for more information, stigma, access and the financial costs of study participation. We therefore reviewed these papers to identify cases where digital methods were used to improve recruitment. We identified twenty three of such cases. Of these twenty three, we explored whether digital approaches such as the use of social networking sites, free and paid advertisements, amongst others were feasible and/or cost effective relative to the study aims. This means that digital strategies were either successful in achieving the outreach or recruitment goals of the researchers, were more successful than comparators and/or were less expensive for about the same output.

Figure 3 below shows the results.

![Chart showing the results of digital tools in improving recruitment to clinical trials.](image)

**Figure 4: Were digital tools useful in improving recruitment to clinical trials?**

The majority of the studies reported digital tools as either objectively useful as measured through success in recruitment, or qualitatively useful based on general consensus among the researchers or community of practice for recruiting, especially among hard to reach and minority groups (Pyatak et al., 2017; Storrar et al., 2015; LeBlanc et al., 2013; Gorman et al., 2014). Such communities ranged from minority youth (Bull et al., 2013) to youth with symptoms of depression (Rice et al., 2014), to young smokers (Frandsen et al., 2013; Ramo et al., 2014; Gioia et al., 2016) to LGBT populations (Raviotta et al., 2016; Martinez et al., 2014), HIV positive individuals (Yuan et al., 2014), amongst others. Digital tools could therefore help to increase the representation of diverse communities, people with chronic conditions, substance users, and underserved populations in clinical trials (Ryan et al., 2013; Park et al., 2013; Batterham et al., 2014, Gupta et al., 2015; Bull et al., 2013; Rait et al, 2015).
Another potential advantage of digital tools lies not only in recruitment but in providing social support for trial participants. This includes peer support through social networks (Ryan et al., 2013, Zhang et al., 2015) as well as being information repositories that can be used to educate physicians and potential trial participants (Thompson et al., 2014, Goldberg et al., 2015).

Finally, we explored the factors that boosted recruitment into clinical trials, including digitally driven recruitment. We detail them below:

1) **Using a multi-modal approach:** Based on the studies reviewed, multi-modal strategies which incorporate multiple digital strategies such as websites and traditional outreach methods such as the network of primary care staff, family and friends, could be a way to recruit participants and keep trial participants engaged while still maintaining cost-effectiveness (Cobb et al., 2014; Khatri et al., 2015; Shere et al., 2014; Greco et al., 2016, Ramsey et al., 2016). According to Ryan et al. (2013), multi-modal strategies incorporating both social networking avenues and traditional methods of recruitment tend to be the most effective. This could also improve the enrollment of underrepresented populations in trials (Heller et al., 2014; Bachour et al., 2017).

2) **Communication:** Communication was vital to participant recruitment and engagement (Bower et al., 2014) regardless of the method of recruitment used. Rather than simply accepting patients’ preferences, the training of recruiters to explore and discuss patients’ preferences and potentially helping them to open their mind to prospective treatments, could help patients reconsider their views and possibly overcome their hindrances to participating (Paramasivan et al., 2014; Mills et al., 2014).

Part of this process of monitoring could include: sending reminders to prospective participants (Treweek et al., 2013), frequent contact with participants using means such as text messaging, social networking sites and face-to-face contact (Stratton et al., 2015), the use of informative recruitment aids (Lewis et al., 2016), optimizing incentives (Bower et al., 2014), as well as tailoring messaging to various platforms in use (Martinez et al., 2014). Treweek et al. (2013), and Syngna et al. (2015) found that the use of opt-out strategies was more effective than using opt-in procedures in contacting potential study participants.

Another aspect of improved communication is ensuring the engagement of multiple stakeholders in the study, and tailoring messaging to the multiple digital platforms being used (Frew et al., 2013; Martinez et al., 2014; Pike et al., 2013). Given the difficulty in recruiting ethnic minorities, it is also important to understand historical and cultural reservations around trial participation and address these challenges in order to improve trust (Ford et al., 2013).
3) **Improving clinical capacity:** It is important to build study infrastructure in order to improve trial retention. This includes the development of adequate systems and monitoring, proper training of site staff and support; improving the recruitment process, increasing recruitment centres as needed; staff engagement; development of good communication strategies between all stakeholders namely participants, collaborators and core study team; and optimized leadership (Bower et al., 2014; Dickson et al., 2013; Strong et al., 2016; Levett et al., 2016).

4) **Continual monitoring and iteration of the study:** This is necessary to troubleshoot potential study challenges and to optimize study strengths. Pike et al. (2013) found that identifying and sharing best practices with other recruitment sites could increase recruitment of populations for which recruitment has previously been difficult. Continual monitoring, potentially through quality improvement methods such as run charts and intervention cycles which have worked in achieving and sustaining high rates of recruitment (Sauers-Ford et al., 2017), will also alert the study team to the need for a potential change of strategy. This could include the use of re-randomization to improve recruitment (Kahan, 2016), the need to extend the time of the study, the need to expand the geographical focus of recruitment, or to motivate health professionals to invite their patients to the study (Jorgenson et al, 2014).

**Limitations and Future Research**

This study has provided useful information for optimizing future recruitment processes including those that are facilitated by digital tools. Notwithstanding, there are certain limitations worth mentioning. Firstly, the number of studies which made use of digital tools was quite low. Secondly, some of the studies reviewed made use of self-reported data and did not use a representative sample of the population due to the challenges of meeting sample size requirements in recruitment.

Future research comparatively assessing the effectiveness of digital recruitment strategies, especially in comparison to other strategies, will improve knowledge and practice. Such research should include not only information on outreach but on maintaining engagement and reducing drop-out (Anguera et al., 2016). Another important issue is privacy. Research into best practices around data management to ensure privacy of data gotten and/or used in digital recruitment, will support this growing body of work (Rosa et al., 2015).

This report also demonstrates a unique advantage of the use of digital tools for recruitment, which is that they allow for tracking participants’ progress through the clinical trial. Technology-enabled tracking of participants’ flow through each recruitment stage allows for a much more detailed analysis of participants’ involvement, lack of involvement, and progress or attrition through clinical trial recruitment. This provides an opportunity for a data driven approach to quality improvement in clinical trial recruitment processes.

We hope to build on this study by integrating the best practices from the literature while also comparatively assessing recruitment with Sickweather to traditional means such as television, direct mail and radio. We also hope to assess the cost-effectiveness of digital clinical trial recruitment in a subsequent study. Furthermore, we will assess the use of incentives and their impact on participation in clinical trials. This will contribute to the growing and much needed discourse around innovation in clinical trial recruitment, specifically through the use of digital tools like the Sickweather application.
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