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Clinical Trial Data Management and Electronic Recruitment Solutions: Impactful Ways to Promote Successful Clinical Trials Using EDC, Mobile Applications and Social Media

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Abstract

Clinical trials continue to grow in complexity and, in turn, the cost of running a clinical trial is ever-increasing. Improving the Probability of Success (POS) for a clinical trial should be at the forefront of every trial manager's focus. Delays, whether in terms of missed recruitment targets or data collection inefficiencies, must be proactively addressed in order for trial funds to be budgeted in the most effective manner. Data solutions such as electronic Case Report Forms (eCRFs) or social media subject recruitment tools oftentimes carry high upfront or fixed costs but can lead to faster trials with fewer errors that are more likely to reach recruitment and other milestones.

Keywords: Trials • Clinical • Research • Success • Execution • Recruitment • EDC • Technology

Abbreviations

POS: Probability of Success; ECRF: Electronic Case Report Form; FDA: Food and Drug; CRF: Case Report Form; RCT: Randomized Controlled Trial; AUD: Australian Dollar; EDC: Electronic Data Capture; IITs: Investigator Initiated Studies.

Introduction

The process of planning and conducting a clinical trial is complicated and it is associated with various risks and issues. Clinical trials require significant investments of human, financial, time and other resources. Poor study planning and management are often contributing factors to the failure of clinical trials, which are very common occurrences. It is estimated that about 34.6% of all clinical trials fail during Phase 1, while 51.7% and 51% fail during the Phase 2 and Phase 3 respectively [1]. It is possible to increase Probability of Success (POS) rates of clinical trials by implementing effective technological solutions in order to more appropriately utilize limited research funds.

Clinical trials are on track to become a nearly $70 billion dollar per year industry by 2027 [2]. Implementation of effective clinical trial technologies has the potential to move funds spent on avoidable expenditures back into the research and development pipeline with a focus on new therapeutic discoveries. As new technologies permeate clinical trials, regulatory agencies will need to adopt a more flexible approach that ensures data integrity while not creating an unwarranted burden for the researchers and sponsor organizations. Some progress has been made in this regard including a 2017 draft industry guideline which provides FDA commentary on the use of wearable technologies in clinical trials [3].

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Literature Review

Use of technological solutions in clinical trial conduct

The appropriate use of available technology is one of the most important factors influencing the POS of a clinical trial. In clinical research, evidence must show that the technology improves the design of clinical trial [4] or contributes to a more robust study. There are many ways that technologies, including e-technologies, can be used throughout the different stages of a clinical trial, including recruitment of the participants, engagement and retention of the participants, data collection, data management, data analysis and even delivery of the intervention. The primary benefit is that the use of new technologies can shorten the time required for various trial-related activities; e.g. social media advertisements can shorten the recruitment timeline, e-informed consent can expedite the pre-screening process and the use of automated text messaging can reduce the time study nurses spend on contacting participants to remind them of upcoming visits. Further, technologies can improve communication between study staff and participants, improve engagement of participants, and reduce time needed for data collection. This holds particularly true for trials that are dealing with a large number of participants or extensive data sets, as the initial investment will quickly pay off in terms of a shorter overall study duration [4]. Also found that the use of advanced technological solutions can shorten the time that site staff spend on delivering the study intervention(s) and collecting the source data from those interventions, and that "challenges of using e-technologies can be overcome with careful planning, useful partnerships, and forethought."

From a data management standpoint, the use of technologies such as e-CRFs, pre-programmed data checks, wearable sensors and statistical controls implemented in systems such as SAS ® greatly reduce the risk of human error and support the delivery of both qualitative and quantitative study analyses in a timely manner. Further, as both researchers and participants across all age levels continue to become more comfortable with technologies in general, it is reasonable to assume that they will also become more inclined to using electronic solutions in clinical trials too. A survey of 2,000 patients in 2015 showed that more than 25% of participants approved of sharing their health data with pharmaceutical companies and 72% confirmed that they would agree to sharing their health data with doctors other than their own [5].

Fleischmann [6] explored whether electronic Case Report Forms (eCRFs) were more time-saving than paper Case Report Forms (CRFs). The authors conducted this research as part of an ongoing weight-loss clinical trial. The authors noted that previous studies had found significant advantages of e-CRFs over paper CRFs, specifically, that e-CRFs improved the quality of data obtained and were more convenient both for participants and personnel. Building upon this knowledge, the authors explored the effectiveness of e-CRF

solutions in terms of time savings. The study used quantitative methodology and quantitative data analysis to identify differences in relation to time savings. The sample used in this study consisted of 27 participants and two study coordinators/research nurses. Desktop computers were used for e-CRF data entry purposes. The authors found that, when entering data from source records such as medical charts or clinical notes, the completion of e-CRFs was a faster practice compared to transcribing source records onto paper CRFs. The difference was 8.29 ± 5.15 min on average, for electronic data entry, compared to 10.54 ± 6.98 minutes on average for paper CRF entry. In this small sample, no errors associated with e-CRFs were found, while three errors were recorded on the paper CRFs. As further confirmed by Fleischmann [6].We know that the use of e-CRFs is both a convenient and effective tool for data collection. This is arguably most noticeable in the query resolution process as an electronic query can be placed remotely by the study monitor and resolved remotely by the study coordinator/research nurse. For obvious reasons, this is a far more efficient process than relying on physical visits to the site for all query resolutions or back-and-forth communication *via* facsimile. The authors concluded that the use of e-CRFs led to a 23% reduction in overall time associated with patient-reported measures and a 16% reduction in time for nurse-reported measures, thus confirming that e-CRFs are both less time-consuming and result in higher quality of data.

Technological solutions and clinical trial participant recruitment

As noted above, technological solutions can also be used to recruit research subjects. The process of participant recruitment is complicated, and it is often difficult to find a sufficient number of participants willing to participate in clinical trials, even for common illnesses. Similarly, for relatively rare diseases and injuries, it can be difficult to find the required number of participants with the underlying disease or injury. Research shows that only 35% of studies in the UK meet enrollment goals [7]. This results in an extended recruitment phase which is time-consuming and inflates the trial budget.

Participant recruitment costs can carry an enormous financial burden for the study sponsor. A study [8] reported that the price for one enrollee ranged from $156 obtained from direct marketing to $5,040 per enrollee obtained *via* gas-pump advertising. Further, we know that the use of new technologies and innovative marketing strategies can reduce the costs associated with recruitment. Walters state that the most commonly reported problem with clinical trials is the process of recruitment. It is often slower than initially expected by the researchers, and it often results in an incomplete sample being recruited.

Traditionally, recruitment of participants was conducted with the help of print, radio, and TV advertisements [9]. Unfortunately, about 90% of potential participants recruited *via* traditional marketing strategies are not eligible to participate in a clinical trial. This is because traditional marketing strategies target a wide audience of people, which decreases the likelihood of targeting patients who meet the study-specific inclusion criteria. Costs associated with traditional marketing strategies are high compared to more modern and targeted solutions. For example, in the United States, the setup costs for a television commercial range between $63,000 and $8,000,000. This is in addition to the ongoing costs of airing the commercial [10]. For most clinical trials, these are unmanageable costs. Radio advertisements may cost up to $20,000 per week [9] which is still a very high price for most sponsors, especially when considering that the radio and TV audiences are both declining [11,12]. Both radio and TV require professional call centers to manage potential participant inquiries. Due to the decreasing audience and high costs, even sponsors who can afford traditional recruitment campaigns should very carefully consider whether they are the most effective methods of identifying trial participants. E-marketing and internet technologies can significantly reduce costs because of the shorter marketing journey associated with the recruitment of the participants, and contribute to the success of a clinical trial.

E-recruitment helps to significantly reduce recruitment costs because it requires fewer total financial resources and it is more effective for reaching the target audience. The main advantage of e-advertising is that it is possible to use segmentation and targeting strategies. It reduces cost per participant and increases the chances that potential participants will meet the requirements of inclusion criteria. For instance, people suffering from the particular ailment may do online searches for information relevant to their condition. The search results pages can be set up so that the patient is shown advertisements on current clinical trials related to their disease this is so-called contextual advertising. E-advertising can reduce recruitment cost to $35 per one participant, and occasionally even less [9].

A quantitative study conducted [13] examined the effectiveness of various recruitment strategies. In total, 289 participants were recruited in a large, single-center Randomized Controlled Trial (RCT). The study researched the impact of the patient-doctor relationship and acupuncture as a treatment for irritable bowel syndrome patients [13]. Among the recruitment strategies used were paid advertisements in newspapers, flyers, and brochures, advertising in public mass-transit, the internet and referrals. The effectiveness was measured by using the following parameters: enrollment rate, fractional cost, fractional enrollment, fractional enrollment-cost ratio and efficacy index. The findings of this study (Figure 1) suggest that the internet is the least expensive and the most effective way to recruit participants, followed by multi-sources, which is closely followed by referrals. In total, the company spent $75,056 for recruitment of 289 participants, of which the vast majority was spent on traditional recruitment strategies, which in turn were found to be significantly less effective than the e-recruitment efforts. Recruiting *via* the internet was found to result in the highest enrollment rates, compared to other recruitment strategies. This supports claims made by Smith and Manna [9] that the use of the internet provides better targeting, and delivers direct advertising to the most relevant people, i.e. potential participants. As for cost per call and enrollment, the internet was the second most cost-effective recruitment method as shown in Figure 1. Cost per call for each potential participant recruited *via* the internet was $24, while cost per enrolled subject was $92. A/V media had the highest cost per call and cost per enrollment, $79 and $584 respectively. As previously noted, the authors spent $75,056 total in recruiting 289 participants. If the authors had used the internet only, they would have spent approximately $26,588 to recruit the same number of 289 participants. Hence, e-recruitment can save upto 60%-70% of recruitment costs compared to more traditional outreach methods. That being said, each trial is unique and there are many factors influencing the cost per participant. It is possible that, in some cases, traditional media can be more effective. However, in the vast majority of cases, internet advertising should be considered as the main recruitment strategy, especially if limited resources are available (Figure 1).

Akers and Gordon [14] conducted a similar study on the effectiveness of e-recruitment with a particular focus on recruitment *via* Facebook. As described by the authors, the benefit of social media recruitment versus general e-recruitment is that the message can be targeted to a much narrower (and presumably more appropriate) audience of potential study subjects. Facebook clinical trial advertisements work by showing Facebook users advertisements developed by the researchers and giving them an opportunity to learn more about the trial or contact the researchers if they are interested in participating. As with all other social media advertisements, there are complex algorithms in place which target the most relevant users based on the input of the advertisement purchaser. A clear advantage to this approach is that it does not require special skills beyond computer proficiency that any social media user already has, and it does not require a great level of knowledge related to e-marketing, as the social media algorithms will automatically target the relevant audience if given the correct inputs. In their study, [14] did not use the services of marketing professionals and created a Facebook advertisement campaign without external help. According to the results of the study, their Facebook advertisement campaign for an RCT to teach support skills to female partners of male smokeless tobacco users, reached 6.6 million women; 5.63% of those female partners visited the study home page. The advertising campaign resulted in a cost of $112.48 per randomized participant thus proving that e-recruitment *via* social media can be effective and often requires far fewer resources than traditional recruitment strategies. That being said, there are also clear disadvantages to using social media e-recruitment. For example, Hope [15] showed that the user demographic may be skewed toward younger people rather than the elderly because younger people tend to be more likely to use such technologies. Therefore, clinical trials researching

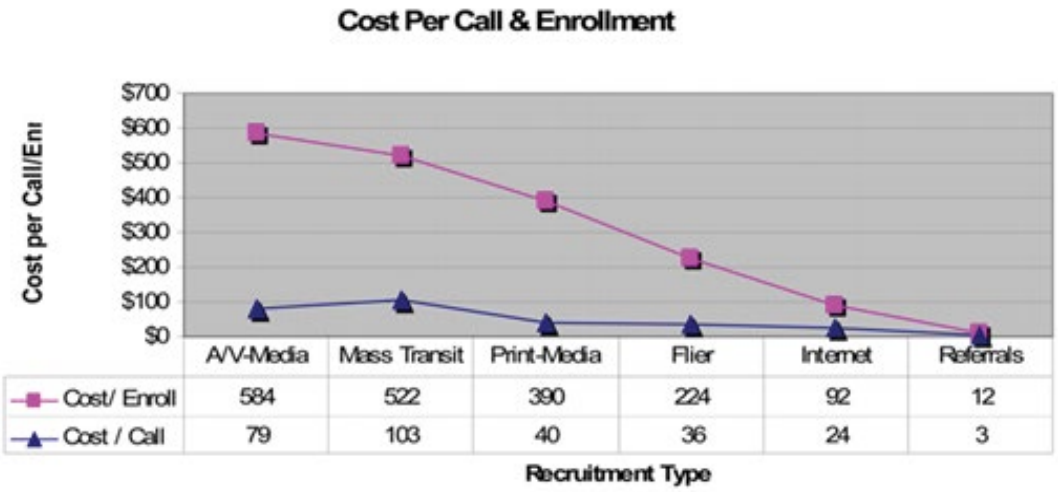

Figure 1. Cost per call and enrollment. (Ferman et al., 2008, p. 12.).

conditions which require older study participants should likely not rely solely on social media recruitment.

A study by Pedersen [16] focused on recruiting young adult veterans *via* Facebook. Though not a "vulnerable population" as defined by GCP or the Belmont Report, this population is at higher risks of developing various mental and psychological disorders because of direct involvement in military conflicts. Further, as noted by the authors, it is known that only half of eligible veterans seek care through the U.S. Veterans' Health Care System meaning that studies conducted at these centers are at a significant disadvantage in terms of the potential patient population that could present for their clinical trials. In their study, the researchers recruited 1,000 participants *via* a Facebook advertising strategy similar to the one described above. Their campaign targeted a young population aged 18-34 who had served in the U.S. military. This results in a potential audience of 4.6 million people. Three major advertising strategies were used, including promotions of Facebook posts made on the study's official page, direct promotions of the survey website, and an invitation to 'like' the study's Facebook page. Advertisements related to the direct survey website promotion contained brief information regarding the purpose of the study. Other advertisements were shown in the Facebook news feed and encouraged participants to interact with the researchers' Facebook page. Further, potential participants would have also seen whether their Facebook connections 'liked' their advertisements. Some, but not all, of the advertisements mentioned a $20 incentive. The results of the recruitment drive can be seen in Figure 2.

The advertisements were actively shown for only seven days, yet they were seen by 1.58 million Facebook users. The researchers spent $7,209 on this Facebook advertising effort and were able to recruit 1023 veteran participants, resulting in a very reasonable cost of $7.05 per participant. The results of this study are promising and indicate that Facebook recruitment can be quite effective for reaching highly targeted populations that are difficult to reach with other methods. Similar engagement from a traditional recruitment platform (e.g., newspaper or radio) would have resulted in exponentially higher costs (Figure 2).

A quantitative study on smoking habits [17] also proved that social networking websites should be considered as the primary recruitment method, because of their effectiveness, availability, and low cost per participant. They compared traditional recruitment strategies, including flyers, radio, newspaper advertisements, word-of-mouth and e-recruitment *via* Facebook ads [17]. Frandsen created several advertisements on Facebook and set their daily budget at Australian Dollar (AUD) 30.00. Using this method, the authors found 414 potential participants, 228 of whom were found by using Facebook, while 148 came *via* other social media. The total budget of the Facebook advertising campaign was AUD 5184.14. As for traditional media, the authors spent AUD 4344.10. The authors found that Facebook was more cost-effective than traditional media for recruiting respondents. However, they also found that it was less cost-effective in relation to completed participants. This can potentially be explained by age differences between the two groups. Participants recruited *via* Facebook were significantly younger compared to participants recruited *via* traditional media and less confident in their attempts to quit smoking. It is possible that the authors did not do effective segmentation and did not identify the target audience properly, which resulted in a higher cost per completed participant. Nevertheless, the study shows that Facebook can be used to recruit large samples of participants within relatively short time periods and at a lower cost, if it is used properly.

A study by Cowie and Gurney [18] recruited healthy volunteers aged 60 years or older, for a clinical trial. These authors also used Facebook advertising campaigns to recruit their participants. In addition, the authors used traditional recruitment strategies including personal referrals, newspaper advertisements, billboards, direct mailing, and outreach events, all managed by the study CRO. On Facebook, the researchers targeted their audience by their recorded interests, including medical research, Alzheimer's disease research, and the Alzheimer's Association. In the eight weeks that the social media recruitment campaign was active, the researchers enrolled more participants than in the 11 weeks prior, showing that Facebook, in combination with traditional recruitment strategies, is more effective than traditional recruitment strategies alone. It was also a more cost-effective solution per enrolled subject. Cowie and Gurney concluded that researchers should consider Facebook as a viable recruitment tool. The authors found that Facebook advertising can be a cost-effective method to recruit people aged 60 years and older into Phase 1 clinical trials. Further, they also concluded that men were more likely to click on the Facebook advertisement as they showed higher engagement rates than women users.

Another study conducted by Burrell [19] shows how cell phone applications (apps) can be used to recruit participants. The authors of this study needed to recruit participants for a rectal microbicide product research trial. The target population chosen for this study is at-risk men who have sexual activity with men (MSM). Using traditional methods of recruitment for such targeted populations is presumed not to be a cost-effective approach. The authors used GRINDR, which is an app used by MSM. As with many similar apps, it relies on GPS technology to locate and connect users. The authors note that at the time of their research, there were about 46,400 GRINDR users in Los Angeles, of whom 70% were daily users of the app. About 32,480 GRINDR users received the recruitment material created by the researchers and 137 users were contacted through phone calls and email. In total, 24 participants were recruited by using GRINDR. The authors note that advertising through this social media was more effective than traditional advertising. In fact, participants who were recruited through GRINDR had a higher rate of successful screening visits and

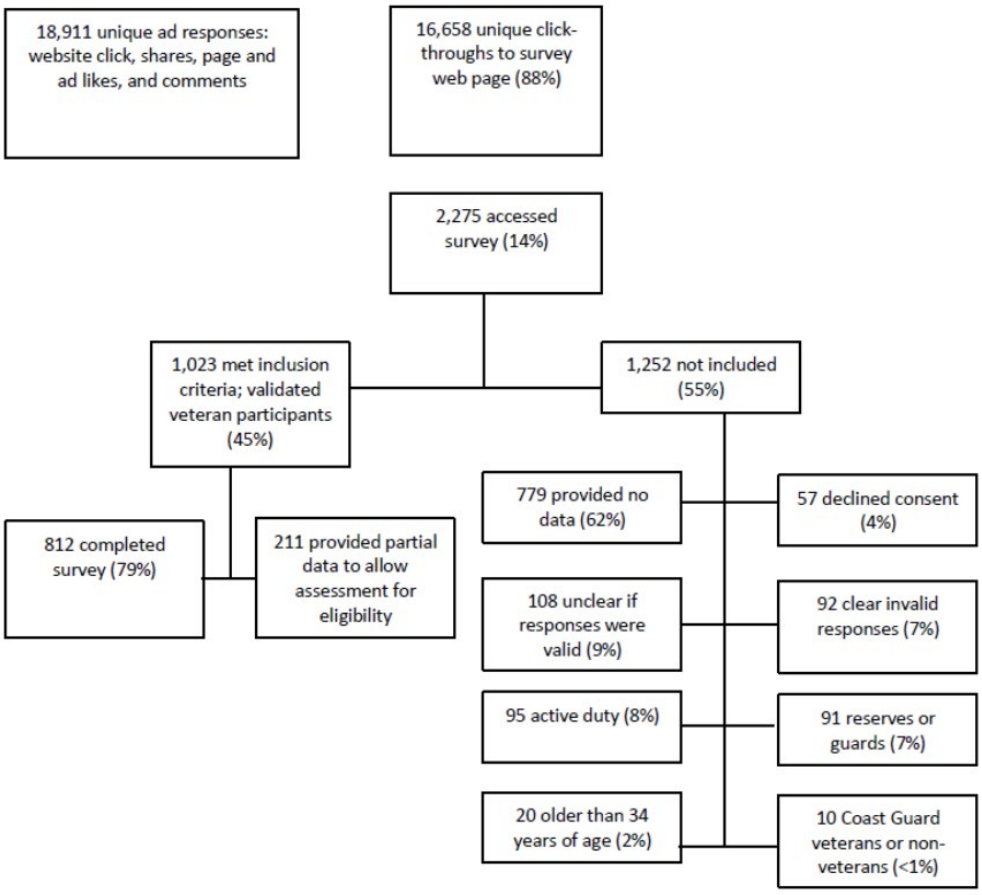

Figure 2. Flow diagram of sample participants. (Pedersen et al., 2015, p.5).

a higher enrolment rate. Furthermore, the authors noted that these participants were more reliable and had higher retention rates [19,20]. state that launching advertising in GRINDR did not require specific technical skills and knowledge.

Discussion and Conclusion

The studies comparing the effectiveness of electronic data-collection methods all provide similar results and prove that electronic Case Report Forms (eCRFs) collected *via* Electronic Data Capture (EDC) systems are cost and time effective. Many major industry sponsors, including GlaxoSmithKline, Merck and Novartis, have recognized this and made a commitment to 100% EDC (Applied Clinical Trials Editors, 2010). That being said, the research is limited to large, and in many cases, sponsored trials. It is still reasonable to assume that a very small study (e.g., a pilot or feasibility trial conducting in an academic environment) involving only a few participants and a short follow-up timeframe without an investigational product – can still be conducted effectively in a traditional (non-technology heavy) setting. This is due to the high costs of obtaining a database platform license, programming, hardware/servers, user training and ongoing clinical data management services throughout the course of the trial. Further, researchers should carefully weigh the scope of their trial versus the capabilities of the electronic data-collection systems. For less complicated studies, such as Investigator Initiated Studies (IITs), open-source platforms such as Open Clinica remain viable solutions when five or six-figure EDC budgets are not viable. These systems are available to all academic researchers and although they require technical know-how, they may be still less time-consuming than paper CRFs.

In general, the vast majority of studies comparing various recruitment strategies state that e-recruitment strategies, and particularly recruitment *via* Facebook, is more effective than traditional media. Still, the research shows that traditional clinical trial advertising is very common. Further, there is a lack of studies comparing the effectiveness of various e-recruitment strategies, such as contextual targeting in Google, recruitment *via* Facebook, advertising on YouTube, and other strategies. There is a need to fill this gap in the scientific literature and conduct more studies on this topic. However, it is evident that for the vast majority of clinical trials, recruitment *via* the internet, mobile applications and social media networks is more cost-effective than recruitment *via* traditional methods.

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