RECRUITMENT FOR RANDOMIZED CONTROLLED TRIALS FOR OLDER ADULTS WITH HYPERTENSION

By
NHAT ANH DUY (RAYDON) TRAN

_____

A Thesis Submitted to The W.A. Franke Honors College

In Partial Fulfillment of the bachelor's degree
With Honors in

Pharmaceutical Sciences

THE UNIVERSITY OF ARIZONA

M A Y 2 0 2 4

Approved by:

Dr. Jeannie Lee
Department of Pharmacy Practice and Science

Abstract

An effective recruitment strategy is vital for the success of randomized controlled trials (RTCs). However, approximately 80% of RCTs did not achieve their initial enrollment target and timeline due to study recruitment being poor-quality and ineffective, or based on RCTs that are rather hypothetical than real-world. Few clinical trials recruit older adults who are 65 years of age or older, resulting in older people being systematically excluded from much clinical research and being underrepresented in RCTs in nearly all areas of medicine. There are many factors contributing to this underrepresentation in research: ageism, benevolent prejudice, and preference for "fit" over "frail" older adults. Different recruitment approaches, namely online, virtual, and in-person, are discussed regarding advantages and disadvantages to observe how these approaches were utilized before and after the occurrence of the COVID-19 pandemic. Hypertension becomes particularly common after the age of 65, affecting more than 60% of people in developed countries. With the increased prevalence rate of hypertension in older adults, the goal of this thesis was to review the literature to assess and identify effective strategies to assist in recruiting older adults with hypertension for the MEDSReM© (Medication Education, Decision Support, Reminding and, Monitoring) system RCT. The MEDSReM RCT is testing technology interventions to improve hypertension medication adherence for older people.

Recruitment for Randomized Controlled Trials for Older Adults with Hypertension

Introduction

Randomized controlled trials (RCTs) are studies prospectively designed to assess the efficacy of a new intervention or treatment and are considered the gold standard in health intervention research [1]. When designing an RCT, recruitment and retaining participants could be one of the most important criteria. In addition to determining outcomes of interest and interventions, researchers must thoughtfully select the desired population to ensure research project success and avoid increasing research waste. To integrate health equity considerations in RCTs and optimize reporting on social determinants of health, the PROGRESS Plus framework (Place of residence, Race/ethnicity/culture/language, Occupation, Gender, Religion, Education, Socio-economic status, Social capital, and "Plus" that embraces other context-specific variables) was developed in 2003 [2]. PROGRESS-Plus is increasingly being used in systematic reviews since it could assist researchers in systematically synthesizing, assessing, and presenting evidence on the intervention efficacy for reducing differential effects of exposures and interventions across social groups [3]. At the same time, recruiting a sufficient number of participants to meet the sample size required could play a vital role in the research finding validity.

Despite the significance of successful recruitment to trial success, there are few published papers on conducting RCT effective recruitment. Approximately 80% of RCTs did not achieve their initial enrollment target and timeline, resulting in drug-developing companies losing revenue of up to $8 million per day [4]. Several large systematic reviews show remarkably few randomized evaluations of recruitment strategies, and many randomized recruitment studies are poor-quality, ineffective, or based on RCTs that are rather hypothetical than real-world [5, 6]. Consequently,

recruitment costs are wasted, and the quality of data could potentially suffer as a result of a reduction in statistical power caused by under-recruitment.

Few clinical trials recruit older adults, generally defined as being 65 years of age or older, resulting in being underrepresented in RCTs in nearly all areas of medicine, although life expectancy in the United States (US) has increased significantly through the past century [7-9]. Many trials do not recruit a sufficient number of participants under medical guidelines also include limited age applicability. Factors such as arbitrary age limits or ethical concerns might also contribute to the underrepresentation of older adults in clinical trials [10-12]. Even studies that do not explicitly exclude subjects based on chronological age fail to recruit adequate older participants. For illustration, a review showed that when comparing the mean age of participants suffering from dementia included in clinical research and the general population, participants with dementia were systematically 8 years younger [13]. Willingness to participate in clinical trials varies with some contradiction across existing literature. Some studies discovered that willingness to participate declined with age, while others indicated older people were more intrigued about research [14, 15]. Increased incidence of comorbidities and age-related health issues, distrust in research, lack of transportation, or impaired comprehension of the consent form may be some obstacles to older adults participating. As a result, different recruitment approaches such as in-person, virtually, or online need to be studied to ameliorate these problems.

Many factors could potentially contribute to the successful RCT recruitment of older participants. Studies show that it is important to prioritize clinically important questions, hire dedicated research staff, and always ensure staff members are adequately trained about trial processes and interventions [16, 17]. Older adults stated that their decision to participate in a study was primarily influenced by their desire to contribute to clinical research and their expectation of personal benefit

[18]. Research has suggested that the information communicated during recruitment appointments could significantly differ in quality and content, resulting in patients frequently reporting an inadequate grasp of RCT concepts and failing to participate [19]. Therefore, I proposed to study how to recruit participants, who are 65 years of age and older, for RCTs effectively online, virtually, and in person. Since I mainly work with older adults with hypertension in Tucson, Arizona, in Medication Education, Decision Support, Reminding and Monitoring System (MEDSReM©) RCT, I focused on studies conducted in this population using pharmaceutical agents. In addition, I studied the adherence rates of older participants to pharmaceutical agents used for hypertension if available in the studies I identified for the recruitment strategies.

RCT Recruitment

1. Importance of recruitment for RCTs enrolling older adults

Researchers must avoid ageism, which could contribute to implicit bias, and acknowledge the need to address older adults' underrepresentation in RCTs. Increased longevity is associated with an increase in the burden of multi-morbidity, frailty, and polypharmacy, resulting in a growing number of medically complex older adults. This population tends to be the subjects experiencing benevolent prejudice, a superficially positive type of prejudice results in a group of members undergoing prejudice in inferior positions in society from positive beliefs and emotional responses. Consequently, a small percentage of older adults believe they are unfit and unworthy to participate in research as researchers have no interest in their issues or activities [20]. Researchers, instead, need to recruit older adults to study more regarding the benefits and drawbacks of RTCs related to geriatric-specific populations and to concurrently help elucidate the safety and efficacy of drugs

and other therapies in this growing population. Moreover, sufficient enrollment of older adults in RCTs is critical for studying safety, dosage, efficacy, and adverse effects. Hence, to avoid ageism and benevolent prejudice, recruiters for RCTs should have prior experience working with older individuals as it could assist them in empathizing with prospective study participants and they could have a better understanding of participants' needs and challenges.

When recruiting older adults for RCTs, physical and medical distinctions between "fit" and "frail" may be taken into consideration. Fit older adults are individuals who, during clinical trials, could meet the standard eligibility criteria and tolerate experimental treatment [21]. Nevertheless, little has been reported about frail older patients, who are less likely to volunteer in research studies. Researchers need to notice that despite having comorbidities, some frail older adults still have an acceptable functional status [22]. As a result, RCTs need to be guaranteed to have sufficient representation of older participants with and without comorbidities to evaluate the efficacy and safety of the treatment thoroughly since failing to recruit adequate older adults for RCTs may place elders at a greater risk for adverse reactions to drugs due to the pharmacodynamic and pharmacokinetic modifications resulting of aging.

In contrast to the aforementioned concerns, many practical advantages can lead to more rigorous and efficient clinical trials when recruiting older adults for RCTs. According to The Belmont Report, a report issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, involving elders complies with the ethical value and principle of justice as the risks and benefits of research are equally shared among all people [21]. The inclusion of higher-risk older adults may enhance study power for many specific clinical events to meet a comparable sample size. Moreover, compared to younger adults, older adults might have fewer constraints on their time and view being involved in clinical studies as leaving

a legacy for future generations, which potentially encourages them to be retained in the trials. Additionally, older adults account for a sizable proportion of end users for cutting-edge treatments; hence, clinical research findings that could apply to them are vital. Inclusion of older adults in RCTs could also reflect wider generalizability and reproducibility in scientific values.

2. Advantages and disadvantages of different recruitment approaches

a. Online

Recruitment for RCTs remains difficult, with patient recruitment being the single most common cause of trial delays. The underrepresentation of older adults in RCTs is due not only to ageism among some researchers, but also to narrow inclusion criteria that eliminate numerous elders with comorbidities and polypharmacy, limited family support, and transportation barriers to and from research sites. Thus, recruiting online using social media advertisements, Google search engine advertisements, or social media platforms such as Facebook® has been brought into practice with the intention to speed up this process and target specific populations, specifically older adults, more efficiently to yield high recruitment rates. There was a study indicating that older adults were more than two-fold active on Facebook® as younger adults [23]. Additionally, another study that was conducted on stroke survivors discovered that online recruitment approaches such as Google AdWords® and Facebook® facilitated them to enroll participants more rapidly, compared to traditional ones such as hanging flyers or calling [24].

Recruiting online for RCTs has several advantages. Employing online recruitment strategies could potentially facilitate researchers to target particular research populations based on location, demographic data, and search terms previously used in user profiles of prospective participants.

Therefore, recruiting online could rapidly attract a large number of subjects at a low cost, foster cross-cultural evaluations, and potentially engage hard-to-reach populations. A Pew survey found that older adults are the most rapidly expanding demographic for smartphone adoption, with 40% reporting using one [25]. Additionally, 67% of older adults use the internet, although they typically fall behind younger adults in their embrace of online technologies [25]. The prospective reach of recruiting via the internet may outweigh that of traditional recruitment approaches; however, there is not much literature that explicitly states that online recruitment strategies outperform traditional offline recruitment strategies.

Online recruitment also has reported challenges. Both time and money must be invested into internet-based recruitment campaigns in order to achieve the best results. The need to make attractive posters or flyers with concise information is indispensable. Additionally, this type of recruitment is expensive to promote studies through advertisements. For optimal recruitment rates, online approaches need not be viewed as a supplement to offline recruitment, but rather as a primary recruitment strategy. Additionally, in the recruitment process, implementing online recruitment methods necessitates quickly communicating with prospective participants and ensuring that participants transferred from the internet-based system are promptly contacted and scheduled for a telephone or in-person screening visit. Otherwise, they might forget or not proactively contact for the call or visit, leading to wasteful time and resources.

b. Virtually

Virtual studies have begun to transform the feasibility of recruiting subjects into RCTs through phone calls and Zoom encounters, especially after the coronavirus disease 2019 (COVID-19)

pandemic. It has been discovered that the best strategy for obtaining a high response following in-person screening is the telephone screening stage [26, 27]. The telephone screening could be used to determine if the participant met the general inclusion criteria and to give an overview of the study. Similar to online recruitment, by shortening recruitment times and eliminating the physical presence of staff at investigation locations, these types of research could lower recruiting expenses. Many prospective participants will have personal and professional obligations that may limit their availability, which is not a concern in virtual recruitment. Many participants request a study interview visit during lunchtime, weekends, or end-of-day interviews. Otherwise, they must take a day off work, which is difficult to schedule on short notice. However, with the virtual recruitment strategy, participants are far more flexible, thereby making it considerably simpler to schedule in a shorter period. Through virtual events, prospective participants might be more interested in being involved in the studies as there is a progressively linked participation to online communities of people with similar health conditions.

On the other hand, recruiting virtually has several drawbacks. Phone calls tend to come in at an inconvenient time when people are not well prepared, leading to potential discomfort and decreased interest. Additionally, an RCT studying the effectiveness of telephone versus the standard face-to-face consultation showed that the combined score of satisfaction and comprehension was lower in the telephone group, mostly due to the satisfaction difference [28]. Recruiting through phone calls might result in a lack of nonverbal communication, specifically body language, which sometimes could provide as much information and build trust among recruiters and participants. In terms of virtual events through Zoom, these events put both recruiters and participants at the mercy of networks and computer software working properly. In addition, connectivity issues and program glitches may uncomfortably disrupt or hinder screenings.

Distractions are one of the most common drawbacks of this recruitment strategy, such as background noise or the temptation to read important emails or handle personal matters in the office during a study recruitment session.

c. In person

In-person recruitment is a traditional method that has been used widely in RCTs. When recruiting in person, both recruiters and participants may notice some body language, and they could also observe nonverbal cues that can be detected through face-to-face interactions, such as positive facial expressions, gestures, and posture. As a result, the relationship may become stronger, and it would be easier to build credibility. Recruiting in person also provides context mainly because they are in the same environment, assisting recruiters to determine the participants' overall interest and enthusiasm for the studies. In addition, in these in-person recruiting events, researchers also have incentives, merchandise, or free giveaways indicating study contact information, to attract prospective participants as well. Not only are incentives helpful in attracting prospective participants but are also helpful in promoting the research. Furthermore, in some RCTs, payments were used as an incentive in RCTs to encourage both participation and retention of prospective participants, or as a reward for behaviors specified, which might become an integral part of the intervention.

Participant recruitment for RCTs is limited to a few physical sites and is based on in-person screening and consent. On-site recruitment takes time to figure out enough eligible participants, in addition to further preparation to consent and enroll participants, incurring higher expenses and delayed responses to pressing research inquiries. Financial issues are one of the biggest

disadvantages of in-person recruitment. To attend physical events, researchers have to pay for tabling, and they sometimes have to pay more if they would like to have a visible table location with high visitor traffic for recruiting. However, estimating how crowded those events would be challenging, leading to a loss of capital due to not being able to recruit sufficient participants as expected. Transportation and merchandise are additional fees that should be taken into account when recruiting in person. A study conducted in 2020 showed that virtually recruited samples surpassed in-person recruited ones concerning the geographical distribution of participants, overall recruitment time, and the average amount of participants recruited per month [29]. Consequently, there are many fees involved in the recruitment process and the success of recruiting is not high, compared to other recruitment approaches.

3. Recruitment strategies pre and post the pandemic

a. Pre-COVID-19 pandemic

Prior to the pandemic, recruitment strategies were quite diverse, including mass marketing, electronic medical record searches, print and electronic posters or brochures, collaboration with patient advocacy groups, word of mouth, or referrals from clinic staff or primary healthcare providers. Mass marketing could work well for common health conditions such as hypertension, yet it may not be effective for uncommon conditions, especially in situations where there are a lot of exclusion criteria. Although numerous participants may be reached through mass marketing, very few are likely to reply, and the cost of enrolling each participant may be high [30]. People with hearing or visual impairments are unlikely to be reached by this approach, and ones with cognitive impairments are unlikely to be recruited by mass marketing either. Similarly, despite being quite simple to produce and distribute, print and electronic posters, brochures, or flyers seem

to have a significantly low recruitment rate [31]. On the other hand, although the number of healthcare professional referrals may be low and cannot be widely disseminated compared to other approaches, the consent rate of referred subjects to participate in studies has been shown to be higher compared with subjects not referred by a healthcare professional [32]. Before COVID-19, elders seemed to prefer in-person interactions to telephone contact, which resulted in higher recruitment rates [33-35]. There are numerous strategies for recruiting possible research participants, and while some pre-pandemic studies attempted to investigate these in various fields, it is still not evident which strategies proved to be most effective [36, 37].

b. Post-COVID-19 pandemic

The usage of technology in all facets of daily life has increased considerably in the last several years. Several studies showed that using technology to enhance aging can help people age well and maintain an active lifestyle [38]. For older adults, numerous technological innovations have been created to promote their independence in carrying out necessary tasks and to maintain relationships with friends and family. Since elders will be expected to utilize interactive technologies in their daily lives whether they are inclined to or not, technological literacy is becoming increasingly vital for the older adult community. After the occurrence of the pandemic, the independence of older people once again needs to be highlighted. There is a growing need for interactive technology to be developed and used to ensure and improve the health of older adults, especially those with comorbidities and polypharmacy.

Similar to the world transition, the COVID-19 pandemic had a significant impact on RCTs, including participant recruitment and screening. A study conducted in post COVID-19 era

indicated that COVID-19 was causing programs to halt or prioritize screening and/or enrollment in specific clinical trials, in addition to discontinuing research-only visits [39]. A screening health assessment of the physical and history is still essential to determine potential risk factors and ensure that participants in physical activity trials are safe. With the development of technology in clinical trials after the pandemic, it could be argued that COVID-19 serendipitously resolved a long-standing problem in the medical field as it has given professionals and researchers the means to provide patients/participants access to so-called "decentralized" clinical trials (DCT). DCTs, clinical trials that are patient-centric and may take place partially or entirely at sites other than the typical trial site, are more accommodating and would enable remote sampling and data collection from the comfort of patients/participants' homes or other community-based clinics or hospitals [40]. RCTs in post COVID-19 era have transitioned to a three-stage screening process, consisting of a telephone screening, an in-person health assessment, and a physical activity assessment, respectively. Early post-pandemic research indicated that clinical efficacy or patient safety outcomes, specifically in cancer care, were not detrimentally impacted by substituting virtual care for in-person assessments [41]. In addition, the majority had a positive perspective when they could provide remote patient care whenever feasible, performed visits remotely, and communicated with sponsors and/or contract research organizations [39].

c. Improvement in recruitment strategies

As aforementioned, this paper focused on how to recruit older adults with hypertension more effectively for the MEDSReM© RCT using an application to promote medication-taking decisions and improve adherence to hypertensive medications. In Tucson's Metropolitan Area, 19.8% of people were 65 years of age or older in 2018, which was in excess of the national rate by almost

four percentage points [42]. Although Tucson might be considered an ideal place to carry out research in aging, having a good strategy would guarantee the success of the clinical trial. In terms of the criteria for recruiting prospective participants, the trial is looking for older adults who are older than 65 years old, self-managing at least one prescribed antihypertensive medication, and using an iPhone. Hence, developing an effective recruitment strategy to attract more prospective participants should adopt a wide variety of recruitment strategies used simultaneously.

Hypertension becomes particularly common after the age of 65, affecting more than 60% of people in developed countries [43]. According to the Centers for Disease Control and Prevention, in the US, the prevalence rate of adults 60 years of age and older with hypertension in 2015–2016 was 63.1% [44]. However, the adherence rate of older adults, who use pharmaceutical agents to control their chronic condition is quite low. Older adults, specifically those who are older than 80 years of age, were traditionally excluded from many studies that aimed to guide the screening and management of hypertension; as a result, the management of high blood pressure in this population has continued to be debatable [45]. Older patients typically have multiple comorbidities that require polypharmacy use and can suffer from cognitive impairments; hence, poor adherence is more prevalent and severe in this population. A study found that less than half (44.1%) of participants fully adhered to prescribed antihypertensive regimens [46]. Moreover, several factors affected the results. For example, the study also indicated that older age, not residing with family, and having a firm belief in the management of hypertension through medical treatment were positively correlated with adherence of older adults to antihypertensive drugs [46] Even though there is a significant number of older people with hypertension in the US overall, recruiting participants for clinical trials is still a challenge.

Several issues should be taken into account before developing a recruitment strategy. Feasibility issues are the first ones that need to be considered. Studies requiring multiple follow-ups and difficult for participants to fully comprehend might have difficulty attracting new participants, especially older adults since they tend to travel more often and suffer more frequently from cognitive decline. In the same way, researchers are reluctant to take part in studies that are excessively complicated or necessitate them to put in a lot of overtime on paperwork. Consequently, considerations for the trial's duration and complexity from the viewpoints of both the patient and the investigator must be made during trial design. To solve the duration issue, researchers should minimize study visits but have still sufficient number of visits to produce reliable outcomes. Regarding complexity issues, researchers should be encouraged to use age-appropriate formats and modify literacy levels for consent forms, promotional materials, and other study forms. This is mainly because according to the National Assessment of Adult Literacy, 71% of adults aged 60 or older reported having trouble using print materials and 80% of them found it difficult to use documents such as forms or charts [47]. A study recommended using large-print reading materials appropriate for third through fifth grade reading levels, accompanying audiovisuals for the visually and hearing impaired, and other culturally and literacy-appropriate clinical teaching aids such as diagrams or charts to improve comprehension in older adults [48]. In addition, to recruit older adults on social media such as Facebook®, the research team could create a more vibrant and easily navigable digital flyer, replacing the original study flyer to promote the study to attract study interest.

It may also be necessary to offer avenues for older adults who have comorbidities or cognitive impairments and are unable to give their full consent to studies to participate in research. In addition to cognitive decline, older adults may also lose their social and financial resources as a

result of retirement, aging, downsizing their living arrangements, and other circumstances [49]. This might be an ethical issue since potential participants may worry that, due to losing these resources, declining to take part in a study could result in the loss of social connections, medical care, retirement benefits, or government-sponsored healthcare or pension benefits [49]. Recognizing these barriers, before requesting consent, trial coordinators must ensure that patients are fully informed about the trial by giving them written information and educating them about it, especially emphasizing that partaking in clinical trials is voluntary and their participation will have minimal to no effects on their social or government benefits. Investigators must take the time to respond to participants' inquiries, especially regarding pharmaceutical agents, in this case, hypertension medications they take during the recruitment process. Since participants can send emails to the research team any time during the day, an official email that every recruiter on the team can access should be created so that they can quickly answer participants' questions. Furthermore, the investigators could ease the participants' worries or burdens by providing relaxing appointment visits, offering to cover parking costs, or applying the DCT concept in some parts of the study such as conducting visits at participants' homes, if applicable.

Survey studies have found that offering monetary incentives as an expression of gratitude, which includes cash or entry into a prize draw, substantially enhances the recruitment of participants, yet employing financial incentives raises several concerns regarding ethics. [50]. Significant financial incentives have been shown to alter participants' decision-making processes by potentially interfering with the informed consent process since they would be more likely to ignore the risks [51]. However, to prevent or lessen early trial withdrawal, if it is determined that offering financial incentives is ethically acceptable, such compensation for their time and participation is essential upon study completion. Hence, it is not encouraged to pay participants in advance of their

involvement since they might leave the study prior to completion; thus, the investigators would want to pay participants after each visit to retain them in the study. In addition, entry into a prize draw such as a self-measured automatic sphygmomanometer could potentially promote participation in RCTs. The availability of funding determines which payment model is most appropriate.

Establishing trust is often emphasized by many researchers in their interactions with potential participants, clinical sites, and community-based personnel [52]. Generally, clinical research tends to be viewed with skepticism and mistrust by nursing home staff, residents, and their families. Since residents of nursing homes are a vulnerable group, caregivers and the relatives of the residents might feel compelled to shield them from "exploitation" or "experimentation" by researchers [53]. In the community settings, to establish trust and provide more detailed information about study participation, recruiters could potentially offer blood pressure screenings and education about blood pressure readings as a service. Researchers have also discussed the benefits of establishing trust with targeted populations that are vulnerable through in-person interactions, frequently referring to this approach as the most efficient means of recruiting older adults for the study. However, the protocol and purpose of the study must be communicated both orally and in writing in a straightforward, approachable, and informal manner that sounds non-threatening to participants' benefits as much as possible. Prospective participants should be encouraged by recruiters to fill out forms, asking for personal contact details and eligibility-related information including age and usage of antihypertensive medications. For prospective participants who recruited through social media, the flyers should include a noticeable link for them to fill out, in addition to an email or phone number on the flyers for them to contact the research team.

Finally, feedback and word of mouth from past participants is important. Informed results of research in which they have participated are greatly appreciated by elders. Giving and asking them for feedback is not only about being polite but also a chance to get participant input on the study's design. Gaining feedback is also an opportunity to set the stage for future study recruitment. Thus, if strong bonds are made, study participants and their relatives, friends, or acquaintances might end up participating in research on a long-term basis. Therefore, for advertisements on social media, the comments section should be turned on for past participants to share their experiences and potential ones to ask questions. However, allowing participants to share is a double-edged sword since good and bad comments could significantly affect the study recruitment. For example, the majority of research has shown that when older individuals are recruited multiple times, the law of diminishing returns is applicable [54, 55]. During the recruitment process, while it is worthwhile to make an effort to contact at least one more time if no response is received, attempting to convince unwilling participants to participate is ineffective and potentially detrimentally affect the research's reliability and reputation if persisting. Consequently, they might report the advertisements, or others would consider the study spam after reading others' comments. Therefore, to reach to more participants while navigating hidden risks, professionalism and cautiousness are important and should be prioritized at every stage.

Conclusion

The growing number of older adults will bear a greater burden of hypertension as the US life expectancy increases. Although adopting healthy practices has been lagging in the US population, modifications to lifestyle have the possibility of helping mitigate this. Additionally, adherence to antihypertensive medications, generally pharmaceutical agents, in older adults is vital for

improving health outcomes and reducing healthcare costs. Older patients constitute the majority of healthcare recipients; hence, their involvement in clinical studies, specifically MEDSReM© RCT, is essential to ensuring that the target patient population can benefit from the findings.

Modifications to study design and programming are necessary to encourage older adults to participate in clinical trials. After the COVID-19 pandemic, DCTs have become more and more popular in the US to attract more participants for the trials owing to their flexibility. Many researchers have started to conduct hybrid decentralized trials, where participants might spend some time on-site for certain study-related tasks, like enrollment, and finish the remaining tasks at home, fostering wider and more generalizable research [56].

Overall, the world has transitioned to working remotely and limiting interaction in person if not necessary. To recruit older adults taking antihypertensive pharmaceutical agents and use an iPhone more effectively, there is a need to use age-appropriate formats when creating both online and physical advertisements and minimize in-person screenings or visits to attract more interest. Since participants can contact the team any time through email published in the advertisements, to ensure that patients are fully informed about the trial and their questions are answered as soon as possible, the study email should be accessed by every recruiter on the team. In addition to offering monetary incentives for study participation, entry into a prize draw like a self-measured automatic sphygmomanometer could promote participation in RCTs and emphasize that MEDSReM© is aiming for the independence of older people. After gaining interest from prospective participants, establishing trust not only from the participants but also from their car partners is vital before participants finalize whether to partake in the study or not. Finally, word of mouth could not be denied as one of the most effective research marketing strategies. Although opening the comments section under advertisement posts on social media is a double-edged sword, reading real

experiences from previous participants could encourage new ones to participate. These suggested strategies for recruitment—while not exhaustive—could potentially offer some direction in creating a well-thought-out strategy to lessen notable health disparities and point out important areas that merit further research in RCT recruitment.

Citations

1. Borawski, K.M., et al., *Levels of evidence in the urological literature.* J Urol, 2007. **178**(4 Pt 1): p. 1429-33.
2. Evans, T. and H. Brown, *Road traffic crashes: operationalizing equity in the context of health sector reform.* Inj Control Saf Promot, 2003. **10**(1-2): p. 11-2.
3. Kunonga, T.P., et al., *A systematic review finds a lack of consensus in methodological approaches in health inequality/inequity focused reviews.* J Clin Epidemiol, 2023. **156**: p. 76-84.
4. Brogger-Mikkelsen, M., et al., *Online Patient Recruitment in Clinical Trials: Systematic Review and Meta-Analysis.* J Med Internet Res, 2020. **22**(11): p. e22179.
5. Caldwell, P.H., et al., *Strategies for increasing recruitment to randomised controlled trials: systematic review.* PLoS Med, 2010. **7**(11): p. e1000368.
6. Treweek, S., et al., *Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis.* BMJ Open, 2013. **3**(2).
7. Banzi, R., et al., *Older patients are still under-represented in clinical trials of Alzheimer's disease.* Alzheimers Res Ther, 2016. **8**: p. 32.
8. Kanapuru, B., et al., *Older adults in hematologic malignancy trials: Representation, barriers to participation and strategies for addressing underrepresentation.* Blood Rev, 2020. **43**: p. 100670.
9. Singh, S. and B. Bajorek, *Defining 'elderly' in clinical practice guidelines for pharmacotherapy.* Pharm Pract (Granada), 2014. **12**(4): p. 489.
10. Carvalho do Nascimento, P.R., et al., *Exclusion of Older Adults from Ongoing Clinical Trials on Low Back Pain: A Review of the WHO Trial Registry Database.* J Am Geriatr Soc, 2019. **67**(3): p. 603-608.
11. Cruz-Jentoft, A.J., et al., *Exclusion of older adults from ongoing clinical trials about type 2 diabetes mellitus.* J Am Geriatr Soc, 2013. **61**(5): p. 734-8.
12. Godlovitch, G., *Age discrimination in trials and treatment: old dogs and new tricks.* Monash Bioeth Rev, 2003. **22**(3): p. 66-77.
13. Schoenmaker, N. and W.A. Van Gool, *The age gap between patients in clinical studies and in the general population: a pitfall for dementia research.* Lancet Neurol, 2004. **3**(10): p. 627-30.
14. Petty, D.R., et al., *"No thank you": why elderly patients declined to participate in a research study.* Pharm World Sci, 2001. **23**(1): p. 22-7.
15. Townsley, C.A., et al., *Understanding the attitudes of the elderly towards enrolment into cancer clinical trials.* BMC Cancer, 2006. **6**: p. 34.
16. Bracken, K., et al., *Recruitment strategies in randomised controlled trials of men aged 50 years and older: a systematic review.* BMJ Open, 2019. **9**(4): p. e025580.
17. Ross, S., et al., *Barriers to participation in randomised controlled trials: a systematic review.* J Clin Epidemiol, 1999. **52**(12): p. 1143-56.
18. Tolmie, E.P., et al., *Understanding why older people participate in clinical trials: the experience of the Scottish PROSPER participants.* Age Ageing, 2004. **33**(4): p. 374-8.
19. Mills, N., et al., *Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study.* Control Clin Trials, 2003. **24**(3): p. 272-82.
20. Crombie, I.K., et al., *Overcoming barriers to recruitment in health research: concerns of potential participants need to be dealt with.* BMJ, 2006. **333**(7564): p. 398.
21. Trimble, E.L., *Concluding remarks: optimal treatment for women with ovarian cancer.* Semin Oncol, 2006. **33**(6 Suppl 12): p. S25-6.
22. Bressler, R. and J.J. Bahl, *Principles of drug therapy for the elderly patient.* Mayo Clin Proc, 2003. **78**(12): p. 1564-77.

23. Cowie, J.M. and M.E. Gurney, *The Use of Facebook Advertising to Recruit Healthy Elderly People for a Clinical Trial: Baseline Metrics.* JMIR Res Protoc, 2018. **7**(1): p. e20.
24. Reuter, K., et al., *General Practice and Digital Methods to Recruit Stroke Survivors to a Clinical Mobility Study: Comparative Analysis.* J Med Internet Res, 2021. **23**(10): p. e28923.
25. *Tech Adoption Climbs Among Older Adults*. 2017: Pew Research Center
26. Gould, J.F., et al., *New Methodologies for Conducting Maternal, Infant, and Child Nutrition Research in the Era of COVID-19.* Nutrients, 2021. **13**(3).
27. Heerman, W.J., et al., *Recruitment methods for survey research: Findings from the Mid-South Clinical Data Research Network.* Contemp Clin Trials, 2017. **62**: p. 50-55.
28. Foss, K.T., et al., *Recruiting to Clinical Trials on the Telephone - a randomized controlled trial.* Trials, 2016. **17**(1): p. 552.
29. Moseson, H., S. Kumar, and J.L. Juusola, *Comparison of study samples recruited with virtual versus traditional recruitment methods.* Contemp Clin Trials Commun, 2020. **19**: p. 100590.
30. Pressel, S., et al., *Participant recruitment in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).* Control Clin Trials, 2001. **22**(6): p. 674-86.
31. Halbert, J.A., et al., *Recruitment of older adults for a randomized, controlled trial of exercise advice in a general practice setting.* J Am Geriatr Soc, 1999. **47**(4): p. 477-81.
32. Baer, A.R., et al., *Engaging referring physicians in the clinical trial process.* J Oncol Pract, 2012. **8**(1): p. e8-e10.
33. Adams, J., et al., *Recruiting older adults for clinical trials.* Control Clin Trials, 1997. **18**(1): p. 14-26.
34. Ford, M.E., S.L. Havstad, and S.D. Davis, *A randomized trial of recruitment methods for older African American men in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.* Clin Trials, 2004. **1**(4): p. 343-51.
35. Zhu, K., et al., *Recruiting elderly African-American women in cancer prevention and control studies: a multifaceted approach and its effectiveness.* J Natl Med Assoc, 2000. **92**(4): p. 169-75.
36. Effoe, V.S., et al., *The use of electronic medical records for recruitment in clinical trials: findings from the Lifestyle Intervention for Treatment of Diabetes trial.* Trials, 2016. **17**(1): p. 496.
37. Johnson, E.J., B.L. Niles, and D.L. Mori, *Targeted recruitment of adults with type 2 diabetes for a physical activity intervention.* Diabetes Spectr, 2015. **28**(2): p. 99-105.
38. Peek, S.T., et al., *Older Adults' Reasons for Using Technology while Aging in Place.* Gerontology, 2016. **62**(2): p. 226-37.
39. Waterhouse, D.M., et al., *Early Impact of COVID-19 on the Conduct of Oncology Clinical Trials and Long-Term Opportunities for Transformation: Findings From an American Society of Clinical Oncology Survey.* JCO Oncol Pract, 2020. **16**(7): p. 417-421.
40. Mahoney, M.E. and S.S. Sridhar, *Clinical trial reform in the post-COVID era.* Ther Adv Med Oncol, 2023. **15**: p. 17588359231183676.
41. Hsiehchen, D., et al., *Clinical Efficiency and Safety Outcomes of Virtual Care for Oncology Patients During the COVID-19 Pandemic.* JCO Oncol Pract, 2021. **17**(9): p. e1327-e1332.
42. Pullen, J., *Tucson's Population Mix Makes it Especially Vulnerable to COVID-19*, in *Making Action Possible for Southern Arizona* 2020.
43. Chow, C.K., et al., *Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries.* JAMA, 2013. **310**(9): p. 959-68.
44. Cheryl D. Fryar, Y.O., Craig M. Hales, Guangyu Zhang, and Deanna Kruszon-Moran., *Hypertension Prevalence and Control Among Adults: United States, 2015–2016.* 2017.
45. Oliveros, E., et al., *Hypertension in older adults: Assessment, management, and challenges.* Clin Cardiol, 2020. **43**(2): p. 99-107.

46. Lo, S.H., et al., *Adherence to Antihypertensive Medication in Older Adults With Hypertension.* J Cardiovasc Nurs, 2016. **31**(4): p. 296-303.
47. Literacy, T.N.A.o.A., *Health Literacy*. 2020.
48. Herrera, A.P., et al., *Disparate inclusion of older adults in clinical trials: priorities and opportunities for policy and practice change.* Am J Public Health, 2010. **100 Suppl 1**(Suppl 1): p. S105-12.
49. Birkland J.L., K.-B.M.L., *What's so special about studying old people? The Ethical, Methodological, and Sampling Issues Surrounding the Study of Older Adults and ICTs.* Proceedings of the Cultural Attitudes Towards Technology and Communication (CATaC) 2010. Vancouver, BC, Canada, 15–18 June 2010., 2010.
50. Martinson, B.C., et al., *Effectiveness of monetary incentives for recruiting adolescents to an intervention trial to reduce smoking.* Prev Med, 2000. **31**(6): p. 706-13.
51. Resnik, D.B., *Increasing the amount of payment to research subjects.* J Med Ethics, 2008. **34**(9): p. e14.
52. Dennis, B.P. and J.B. Neese, *Recruitment and retention of African American elders into community-based research: lessons learned.* Arch Psychiatr Nurs, 2000. **14**(1): p. 3-11.
53. Mody, L., et al., *Recruitment and retention of older adults in aging research.* J Am Geriatr Soc, 2008. **56**(12): p. 2340-8.
54. McHenry, J.C., et al., *Recruitment of Older Adults: Success May Be in the Details.* Gerontologist, 2015. **55**(5): p. 845-53.
55. Ory, M.G., et al., *Recruitment of older participants in frailty/injury prevention studies.* Prev Sci, 2002. **3**(1): p. 1-22.
56. Apostolaros, M., et al., *Legal, Regulatory, and Practical Issues to Consider When Adopting Decentralized Clinical Trials: Recommendations From the Clinical Trials Transformation Initiative.* Ther Innov Regul Sci, 2020. **54**(4): p. 779-787.