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Recruitment and Retention Strategies for Clinical Trials in Alzheimer's Disease

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Abstract

Recruitment for clinical trials is challenging for any disease but is particularly so for Alzheimer's disease (AD). In the past three years, our site has recruited almost 600 subjects into our AD primary prevention and treatment trials, and diagnostic studies. In this article, we describe which strategies have had the best yield and which have had a modest or low yield.

High yield is loosely defined as any recruitment activity that yields a high number of interested or eligible participants per the expense or time/staff invested in the recruitment effort. For example, a high-yield recruitment strategy is direct mailings for primary prevention trials. Low yield is defined as any recruitment activity that yields a low number of interested or eligible participants per the expense or time/staff invested in the recruitment effort. For example, direct mailing to physicians generally does not yield many subjects. Recruitment for primary prevention trials and treatment trials differ in approach.

Recruitment of subjects is much more expensive than previously reported in the literature. It is important to build this expense into budgets. Subjects that do not qualify for their desired study may be candidates for other studies. Minority recruitment presents unique challenges above and beyond the overall challenges of successful recruitment in to AD clinical trials.

Increased attention is being focused on Alzheimer's disease (AD) clinical research as a direct result of the rising number of people with AD. This is accompanied by challenges of recruitment of subjects into clinical trials. These challenges include increasing awareness of clinical research programs, overcoming physical obstacles to participation (e.g. transportation) and recouping fixed costs (i.e. staff salaries and facility charges) that are incurred in clinical recruitment. Challenges can be further accentuated by research design and restrictions of entry criteria.[1] Nonpharmacological intervention trials generally fare better than medication trials in terms of patient recruitment.[2]

Well-designed studies for the treatment and prevention of AD are in development or underway. To bolster enrollment, it is critical that researchers move towards a corporate mentality for recruitment. Subjects do not automatically sign up simply because there are worthwhile scientific developments underway in the community. Subjects' fears, desires, and sense of reward need to be addressed.

In this article, we review strategies for recruitment and retention that seem to work and those that do not. We describe real costs associated with recruitment in order to realistically portray what is involved in patient recruitment and the associated costs. We categorize strategies into high yield, medium yield, and low yield with yield defined as the number of patients enrolled per unit of time or money spent. This definition is intentionally imprecise as to allow the reader to determine what would be best for his/her site.

1. Importance of the Infrastructure

Clinical trials are not conducted in a vacuum and a variety of key factors, as discussed in this section, may influence recruitment.

1.1 The Reputation of the Local Institution

The reputation of the local institution, university, or healthcare system can enhance or diminish the image of the center and the investigators. If a local healthcare system is well regarded, it enhances the credibility of the clinical trials. Conversely, when investigators are investigated for malfeasance, clinical trials at the named medical center suffer across the board.

1.2 Using Volunteers as Ambassadors

Many hospitals and healthcare systems have legions of volunteers, usually retirees. These volunteers have a natural allegiance to their institutions and thus may serve as ambassadors to their respective communities. They can be used to distribute posters and brochures and spread information by 'word of mouth'.

1.3 Media Relations Department

An effective media relations department which has contacts with local media outlets and that is motivated to work with the investigator enhances the investigator's ability to reach a wider audience. This is especially important in facilitating the reporting of new trials or research related to current trials in local news outlets.

1.4 Decentralizing 'Detail Pieces'

People need to associate the study with the local site. It is important to ensure that the local site label is on all brochures. For example, in several of our studies, we created fact sheets (total cost of $US0.60/sheet) and 'doc cards' (3 × 5 inch cards with study descriptions and inclusion/exclusion criteria on them for local physicians to keep in their pockets; total cost of $US1.00/card) specific to our site. If the study is multicenter, and the subject receives mailings, it may not be understood that the study is being conducted locally.

1.5 Patient Confusion About Studies

All clinical research staff should be knowledgeable about all ongoing studies within the division. This will enable them to clarify which study may be appropriate and potentially suitable for prospective subjects.

1.6 Providing Tours of the Research Facility

Tours potentiate enrollment into studies by exposing people to the science and environment involved. It enhances familiarity with the site.

Table I. Strategies for recruitment depend on the study type

Prevention studies	Treatment studies	Diagnostic/nonpharmacologic intervention studies
CMS/direct mailing	Study completers/nonqualifiers from other studies	Brain donation programs/Alzheimer's disease centers
News articles	Brain donation programs/Alzheimer's disease centers	News articles
'Research day' (promotional 'kick-off' event)	News articles	Study completers/nonqualifiers from other studies
Paid advertisements	Physician referrals	
	Paid advertisements	

CMS = Centers for Medicare and Medicaid Services.

1.7 Using Brain Donation Programs/Alzheimer's Disease Centers/Memory Disorders Clinics

It is important to ensure that consent forms have a clause 'permission to contact for other studies' that allows subjects to indicate their choice and that a system is in place to contact them (e.g. a database).

1.8 Physical Environment and Location

For seniors, seemingly minor obstacles including parking, ease of access to the facility (i.e. how far they have to walk), having clear directions to the facility, and distance from their home can affect recruitment and retention.

2. High-Yield Strategies for Prevention and Treatment Trials

Primary prevention trials are expensive and can require the involvement of thousands of subjects to meet statistical endpoints.[3] A lot of expense is incurred in the recruitment of subjects. The strategy of recruitment for primary prevention trials differs from that for treatment trials; for prevention trials, recruitment occurs directly with potential participants whereas recruitment for treatment trials often enlists a third party (e.g. a physician) to engage in the recruitment. Thus, the strategies used for recruitment in prevention and treatment trials differ (table I). Table II describes some of the real expenses in recruitment and highlights strategies that have relatively good yield per expense involved.

2.1 'Research Day'

A promotional 'kick-off' event for large studies without an entrance fee yields a significant amount of publicity and can increase interest in participation. At the launch of the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), 1100 people attended the Sun Health Research Institute's SHRI's 'Research Day' including celebrities, newspaper reporters, and television and radio reporters. Invitees included members of the press, executives, and senior administrative staff from the hospital, financial donors, volunteers, and participants in our studies and programs. There were celebrity signings and endorsements, refreshments, and opportunities for the faculty to meet with members of the community. The 'Research Day' event netted 200 inquiries and resulted in 42 subjects who were ultimately enrolled in ADAPT i.e. a 4% yield. The cost of the event was $US11 000, which means that $US262 was spent per subject enrolled.

2.2 Brain Donation Programs/Alzheimer's Disease Centers/Memory Disorders Clinics

Every participant in longitudinal cognitive assessment programs should be screened as potential subjects for clinical trials during annual and other scheduled assessments. These programs provide a sustained source of subjects for prevention and treatment trials. Generally, these participants are favorably inclined to participate in studies. Currently, brain donors, i.e. those with consent

Table II. Recruitment strategy and cost per enrolled subject

Recruitment strategy	Cost per enrolled subject ($US)
'Research day' (promotional 'kick-off' events)	$262
Brain donation program/Alzheimer's disease centers/memory disorders clinics[a]	≤$10
News articles	$0
CMS/direct mailings	$350–1500 (average $1000)
Call centers	$3000
Paid advertisements	Variable
Enlisting physician referrals	Variable
Local community presentation	Variable

a 'In-house' programs that can recruit patients directly.

CMS = Centers for Medicare and Medicaid Services.

for post-mortem brain donation, comprise 10% of all clinical trial participants at SHRI.

2.3 Local and National News Articles for Prevention and Treatment Trials

AD is very newsworthy locally and nationally, and media opportunities should be capitalized. Media outlets often are looking for breaking stories related to AD research. One strategy is to tie national release of new research findings to local clinical studies related to that topic through media contacts. For example, the local major market paper wrote a story about one of our studies related to vitamin supplements in AD. This story generated more than 250 inquiries.

2.4 Direct Mailings for Prevention Trials

This is clearly the best source of subjects with 90% of participants coming through mailings; many investigators have found this to be an excellent potential source of participants.[4-9] Mailings have been done using Centers for Medicare and Medicaid Services (CMS) but these mailings have become much more restricted since the Healthcare Information Portability and Accountability Act (HIPAA) regulations took effect. Nevertheless, these mailings can be facilitated through commercial mailing companies.

For example, at the Sun City site for ADAPT, 236 471 Medicare recipients were mailed information on the trial. The total cost of mailing was $US179 851.75. Three thousand four hundred respondents returned information by mail and another 170 responded by phone (total response 2%). This resulted in 364 enrolled participants; this translates to 463 Medicare recipients mailed to each subject enrolled. The total mailing cost, at $US0.76 per mailing piece (total cost including brochure, mail house and postage excluding labor), equalled $US352.29 per enrolled subject. For ADAPT, the cost per enrolled subject from site to site ranged from under $US400 to more than $US1500 with an average cost of $US1000 per enrolled subject.[10] This is much higher than the estimates of Tarlow and Mahoney[11] who noted that substantial time, money and personnel need to be budgeted for recruitment efforts. In their study, the average cost was $US101 per patient enrolled.

The majority of responses to CMS and other direct mailings come through response cards with postage paid, business reply envelopes. Some recipients of mailings may call with angry and unusual responses; they may feel harassed by direct mailings thinking that they are promotional material (i.e. telemarketing). It is also important to be aware of seasonal influx/efflux of the target population as in several metropolitan areas, retirees leave to spend summer or winter elsewhere. It is recommended to mail to primary service areas (i.e. areas principally served by the hospital or medical center) during peak season but to avoid mailing around holiday times. Strategically, mailings should be tied to news articles.

2.5 Alzheimer's Association Referrals for Treatment Trials

Research studies should be used as a 'product or service line' that Alzheimer's disease associations can offer to their clients. It is recommended that investigators work closely with their Alzheimer's disease association representative/case manager.

2.6 Private Practice Physicians for Treatment Trials

In our experience, private practice physician (primary care and specialist) referrals can be a sustained source of potential subjects. Other investigators have also suggested that this is a reliable source.[12,13] Our Alzheimer's Disease Cholesterol Lowering Trial (ADCLT) serves as an example. Most referrals for the ADCLT came from news announcements, physician referrals, and referrals from other AD researchers. By contacting local neurologists and geriatricians and encouraging referrals, we had 457 inquiries about the study with the best yield in terms of subjects enrolled per referral coming from a memory disorder clinic. One hundred and thirty eight did not qualify by telephone prescreening and 336 were sent information about the study. Ninety-eight signed a consent form and 65 were ultimately randomized. This means that there were 4.5–inquiries/consent and 7 inquiries per subject enrolled (14%).[14] These findings are consistent with those of Treves et al.[15] who noted that 13% of patients screened ended up in AD treatment trials and higher than the rates cited by Levy et al.[16] (8%) and Williams et al.[17] (11%).

3. Medium-Yield Strategies for Prevention and Treatment Trials

Call centers (a central office staffed by screeners contracted to screen calls and participants for studies) appear to be less effective and are far more expensive than response cards (post-cards with return reply and minimum screening information that are mailed back). The Alzheimer's Disease Cooperative Study (ADCS) used a call center as part of its recruitment campaign for their mild cognitive impairment (MCI) protocol. Of the 52 722 calls to the call center, 2303 were referred to the sites that resulted in 162 enrolled subjects. The total cost of the call center was $US485 992; the cost per enrolled subject was approximately $US3000. This cost did not include the cost of the public relations work that resulted in the calls. The ADCS MCI study coordinators were subsequently polled to determine their level of interest, satisfaction, and need for the centralized screening. While many of

the study coordinators received the majority of their enrolled patients through local clinics and local media and community outreach efforts, the majority also recognized the value of the call center. Overall, the centralized screening provided a value-added service (i.e. benefited the study recruitment overall) to the study sites and staff, but the cost probably outweighed the benefits because of the low referral rate (Jacqueline Bochenek, personal communication).

Dining with local physicians provides an opportunity to appeal directly for referrals to treatment trials. Physician endorsement, support or approval, either tacit or active, is critical for buy-in for treatment trials. It is important that centers are not perceived as an invader or a competitor to local physicians. It is also important to reinforce to physicians the study center priorities about safety so they will not discourage patients from participation.

Several other strategies seem to yield some patients; however, many of these strategies are difficult to quantify. Strategies include brochures in senior centers and community education centers; taped information while 'on-hold' when calling the hospital; presentation to physicians and other healthcare providers at grand rounds; television news pieces (often too brief to absorb); support groups and local talks to retired health professional groups; and participants' referrals.

4. Low-Yield Strategies for Prevention and Treatment Trials

Several strategies seem to yield relatively few patients given the amount of time and effort involved. Unlike the experience of Adams et al.,[13] in our experience, local talks to general audiences yield less than one enrollee per presentation. Nevertheless, they foster good will in the community and enhance visibility. When doing these talks, on-site sign up should be considered.

Direct mailings to physician offices may not achieve the intended benefit, perhaps because they are treated as junk mail. Placing pamphlets in physician offices usually does not result in recruiting subjects unless they are given by the physician to the potential subject. Similarly, placing posters in different locations rarely generates interest. Display tables at health fairs are generally a low-yield activity. This can be improved by encouraging on-site sign up with attainment of contact information.

Paid advertisement intuitively would appear to be a good source of reaching prospective subjects; some investigators have achieved successful recruitment in gerontological trials as a result.[9,18,19] However, the yield in this category is likely to vary greatly and our experience suggests that paid advertisements are expensive for their yield. For example, in the ADCLT, two advertisements were placed in the Arizona Republic at a cost per advertisement of $US600, resulting in three inquiries and none enrolled. For the Health Aging Memory Study (HAMS) sponsored by the Alzheimer Disease Cooperative Study, advertisements were placed in minority specific newspapers (the Valley India Times and the Asian American Times). The cost per advertisement was $US150 and resulted in 0 inquiries/enrollments. For the ADAPT study, seven paid advertisements were placed (in the Daily News Sun, Arizona Republic, Sunlife Magazine, Wickenburg Sun, Asian American Times, Valley India Times). The average cost per advertisement was $US866 ($US120–3200) and resulted in six inquiries and one enrollment. It is unclear how variables such as the size of the advertisement, placement, context of the message, or reading level of the audience influenced interest of the reader.

Despite these seemingly low-yield strategies, these strategies may be of indirect benefit by increasing exposure of the study and the institution. This may in turn make it more likely that potential participants will respond to other means of contact (e.g. mailings or physician referrals).

5. Unproven But Potential Strategies

Targeting physicians who have minority dense practices could be important. Ideally, these physicians could serve as ambassadors for recruitment of minority subjects. Alternatively, offering service-based clinics in minority communities may be useful. Paid advertisements in minority-oriented or local ethnic newspapers appear to have a low yield but this strategy is unproven. Ballard et al.[20] pointed out challenges of minority recruitment (African-Americans) and that the barriers can be overcome by a referral network specific to this population, patient education, and staff sensitive to the needs of African Americans. Connell et al.[21] noted that African-American caregivers are skeptical of research; however, this could be overcome by personal contact with research staff, information about health status changes, and sharing results of the studies. Some barriers to participation of minority subjects could be overcome by home visits.[22]

Satellite sites are used by some institutions to increase subjects' recruitment at geographically distant locations. Though they are feasible, they tend to be expensive to operate and difficult to manage. Satellite sites break up staff time and add logistical challenges.

Memory screenings are often considered a potential source of subjects. Our experience of a memory screening where 103 people attended suggested that depression was more common than memory impairment and that most people with memory impairment had not sought care or evaluation. Thus, memory screening could be useful to identify prospective subjects with the understanding that

these subjects may need a complete evaluation and diagnosis prior to enrollment.

Other ideas that may be associated with some yield but remain unproven include the following: posters and brochures in the doctor's lounge at nearby hospitals; interdepartmental mailings to other faculty and departments; informing medical center departments and physicians of studies through bulletins and e-mail; and enlisting institutional board members as ambassadors. Enticing physicians to have lunch at the institute/research center may reduce suspicion or increase cooperation, as physicians often do not have an understanding of the clinical research process. Unfortunately, physicians may be reluctant to visit because of time constraints.

6. Screening, Consenting, and Withdrawals

First impressions are extremely important. Careful prescreening by phone assists a higher enrollment rate and fewer screen refusals. Saving money on low budget staff to do screening will lose many subjects and may increase labor costs over time (i.e. screen failures). People call with many questions. Thus, it is important to hire someone with good phone skills and a medical background. For example with telephone prescreening for ADAPT, 85% of patients assessed at the eligibility visit were enrolled. Thus, time is not wasted on ineligible participants. An Institutional Review Board (IRB)-approved detailed screening interview form should be used when performing the phone prescreening.

Dowling and Weiner[23] noted three roadblocks to recruitment to AD clinical trials: caregiver resistance, provider resistance, and mismatch of disease characteristics with protocol requirements. Participation in clinical trials is driven by caregiver's and subjects perception of risk which may be influenced by interaction between the investigator and patient/caregiver.[2,24] Cohen-Mansfield reported that in dementia treatment trials, reasons given for withdrawal of consent include: caregivers perception of a threat to the participant's stability; the perception that an increase in adverse events will result; other medications would work better; or no reason is given at all.[2]

Reluctance to provide consent for study participation has been identified as a potential roadblock to recruitment into gerontological studies.[25] To avoid caregiver resistance, the consenting process should not be rushed because subjects or caregivers may become anxious and suspicious. Potential subjects and their caregivers are often very suspicious when signing consent. Knowledgeable educated staff need to take the time to explain the protocol, background, study process, subject involvement, and medication used in the study in detail. Consenting potential participants takes time and requires a knowledgeable person to do this. It improves patient understanding of the study, compliance and retention. Staff should explain expected outcomes in order to adjust expectations of the study. Realistic outcomes based on disease progression must be stressed whenever there is a blinded placebo arm in the study design. Our standard practice is to give the subjects or caregivers the consent to read and discuss any concerns prior to attaining a signature. Subjects and legally authorized representatives must be given time to read, understand, and have all questions answered prior to consenting to study participation as mandated by the US FDA.

As noted by others,[16,23] most potential subjects who do not meet screening standards in studies at SHRI do so because of a number of reasons, such as stated inclusion/exclusion criteria, comorbid medical conditions, or unanticipated exclusionary laboratory abnormalities.

Subjects withdraw for several reasons. The most commonly stated reasons are summarized in table III. There is a strong tendency for many participants to blame every health complaint on the study drug regardless of whether it is related or not.

7. Retention

Mastwyk et al.[26] explains the reasons people participate in studies including "helping a relative feel better, contributing to medical science, and hoping for a cure. Caregivers rely on research staff for support and may recommend trials to others". At our site, some of the reasons for participating in a primary prevention trial mentioned are: "afraid to get diagnosis"; the subject witnessed a loved one with the diagnosis and was frightened by the experience; or "doing this for my children". Reasons given for participating in treatment trials include: "hope to stop progression", "cure disease", or "improve symptoms". Expectations are always unrealistic. Surprisingly, few enroll for 'the good of research and mankind'.

Gifts such as pens and appointment books may build good will. Remuneration may influence participation in studies although its

Table III. Reasons most commonly stated for subjects withdrawing from a study

No longer wanting to take the study medication
Want to take medications restricted by the study criteria (i.e. open label)
Health-related reasons
Adverse effects
Lack of family support or change in opinion of the family regarding ongoing participation in the study
Having high expectations (i.e. positive therapeutic benefit) that do not materialize

effect in AD trials is not well studied. However, some IRBs restrict financial remuneration to participants. When possible, alternate incentives to compensation should be used (e.g. meals, calendars, fuel cards, parking validation). This cost should be built into your budget. For physician referrals, yearly acknowledgments (e.g. gift baskets) will sustain interest and show your appreciation. 'Finders fees' are efficacious but may be restricted by IRBs and may encourage physicians to refer for the financial rewards.

Subjects and physicians should be contacted and involved when adverse events and abnormal laboratory results occur so they understand that the clinical research staff is considering safety first. The subject or caregiver should be called when laboratory results are abnormal in addition to facsimiling them to their primary care physician with appropriate consent given. The significance of the laboratory results should be reviewed with the participant and copies of results given if they request them. Explaining to the participant what the results mean and where to go next is vital to building trust with the subject and their family. In addition, letters to subjects' physicians when a subject starts a study and ends a study with information on the outcome of the study provided will improve relationships with local physicians.

8. Conclusion

The strategies for recruitment for primary prevention studies and treatment trials differ and often differ from study to study. A corporate mentality for recruitment should be adopted as the importance of successful recruitment translates into increased revenue, salary support, public awareness, and reputation. Often a '1, 2, 3 punch' is necessary (news articles followed by local talks followed by mailings) as potential participants may not reply until the third or fourth exposure. This has also been suggested by others.[1,9] It is recommended that your audience is exposed to information in a variety of ways.

Organization and communication between study team members (your media relations department should be considered as part of the study team) is the key to productive and successful enrollment and retention of subjects. Consistent patient-friendly core staff can develop relationships with subjects that may improve 'customer satisfaction'. To increase patient satisfaction, time needs to be allowed for staff to relate to patients/subjects and make participant satisfaction a priority.

Knowing your environment and community is important including demographics, population density of prospective subjects, education levels, and ethnic diversity and population influx/efflux. Also important is knowing key medical personnel (i.e. physicians) in the community. For example, in the Sun Cities, our site monitors demographics routinely (e.g. ethnicity, education levels, seasonal migration). Our site also identifies where minority groups are and tailors recruitment strategies for those communities.

Present and future challenges to recruiting are abundant. They include increased competition as new clinical research companies continue to open in large metropolitan areas. Because of HIPAA guidelines, direct mailing may become more difficult. Health Maintenance Organization (HMO) plans for Senior Citizens might allow direct mailing to members if access to these lists were available to the investigator. However, this may also be restricted by HIPAA guidelines. Additionally, mailing to senior-oriented communities or residential facilities could be promising. Getting the message about your research to potential consumers and having them trust clinical research studies will always be a perennial problem.

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