

Recruitment of Subjects Into Clinical Trials for Alzheimer Disease

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Alzheimer disease is a devastating neurodegenerative disorder affecting millions of Americans. It reduces the ability of the individual to remain independent, places a burden on caregivers, and substantially increases healthcare costs. New treatments are being tested in numerous clinical trials with the goal of preventing or delaying the onset of Alzheimer disease, slowing or modifying the disease's course, or finding a cure for patients with the disease. Alzheimer disease research can successfully proceed only if individuals who have this illness are willing to participate in clinical trials. However, recruitment and retention of subjects in clinical trials for Alzheimer disease is a challenging task. Furthermore, because of reductions in decision-making capacities of individuals with Alzheimer disease, clinical trials also need to involve caregivers. The present article delineates unique hurdles encountered in the recruitment process for Alzheimer disease clinical trials. The article also identifies strategies for effective recruitment of subjects in Alzheimer disease clinical trials, including guidelines to help principal investigators and clinical research coordinators reach recruitment goals.

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Alzheimer disease, a severely debilitating condition that affects 5.3 million Americans,¹ is being vigorously investigated by researchers around the world. Despite US Food and Drug Administration (FDA) approval of medications that alleviate symptoms of Alzheimer disease, the quest for pre-

ventive, disease-modifying, and curative treatments continues. Randomized, placebo-controlled clinical trials are essential to establish the efficacy of medications designed to improve cognition and function in patients with Alzheimer disease.² Participation of human subjects in clinical trials is crucial to advancing our understanding of Alzheimer disease and to assisting in the development of better therapeutics.

Medical research would grind to a halt without volunteer subjects. Delays in the recruitment of subjects can adversely affect results of clinical trials³ in addition to increasing trial costs.⁴ Alzheimer disease clinical trials encounter unique challenges during recruitment of subjects.⁴ To improve subject accrual into clinical

trials, identification of these challenges and implementation of effective strategies to overcome the hurdles are important.⁵

Defining Challenges in Recruitment

Alzheimer disease clinical trials face some challenges in recruitment common to all clinical trials—most notably the potential risks and uncertainty of the intervention's benefits.⁴ Alzheimer disease clinical trials also have unique challenges as a result of the nature of the illness and the patient population. Challenges in subject recruitment for Alzheimer disease clinical trials are listed in *Figure 1*.

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and

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- ☐ Potential risks of intervention
- ☐ Uncertainty of benefits of intervention
- ☐ Protocol restrictions, including inclusion and exclusion criteria
- ☐ Comorbid conditions
- ☐ Subject's background (eg, education, culture, socioeconomic status)
- ☐ Need for caregiver participation
- ☐ Transportation problems
- ☐ Concern over study drug adverse effects
- ☐ Lengthy duration of trial
- ☐ Cynicism among minority groups
- ☐ Media influence (eg, negative portrayal of clinical trials)
- ☐ Lack of awareness of clinical trials

Figure 1. Challenges in recruiting subjects for Alzheimer disease clinical trials.

Related Disorders Association (NINCDS-ADRDA) criteria for recruitment have been accepted by Alzheimer disease researchers worldwide.⁶ The NINCDS-ADRDA criteria are usually used in tandem with the modified Hachinski Ischemic Index to reduce the probability of including patients with serious cerebrovascular disease in Alzheimer disease clinical trials.⁶ Mild to moderate severity of dementia has been defined by a range of scores on the Mini-Mental State Examination (MMSE),⁶ which is also considered by study recruiters.

Inclusion and Exclusion Criteria

Identifying a study's target population according to inclusion and exclusion criteria is the first step to meeting recruitment goals.⁷ The mantra is "know your audience."

Strict study protocol inclusion and exclusion criteria are fundamental barriers to enrollment of required numbers of subjects in Alzheimer disease clinical trials.^{4,8} Alzheimer disease is a progressive neurodegenerative disorder in which various stages of the disease are defined

by certain cognitive and functional characteristics. The characteristics of particular patients may either include or exclude the patient from study participation. For example, if the trial calls for patients with mild to moderate Alzheimer disease defined by an MMSE score of 13 to 26, individuals who score 12 or 27 on the MMSE would not be included. It should be kept in mind, however, that because of the nature of Alzheimer disease, mild variation of MMSE scores might be detected in a single individual if that individual is tested frequently.

Comorbid Conditions

The target population for Alzheimer disease clinical trials includes mostly adults aged 65 years or older.¹ Hence, comorbid medical conditions are inevitable in study participants.

Inclusion and exclusion criteria related to comorbid conditions may disqualify many potential subjects from participation in Alzheimer disease trials—thereby threatening the validity and generalizability of trial results.⁷ A pool of 100 potential subjects may yield only 3 or fewer qualified participants in a typical Alzheimer disease trial.³

Subjects' Backgrounds

Education, culture, family, neighborhood, and socioeconomic status also play large roles in determining who volunteers for, and who is qualified for, participation in Alzheimer disease clinical trials. The recruitment process begins as dialogue between the potential subjects and the researchers (ie, principal investigators and clinical research coordinators). Although widespread information about Alzheimer disease can be found in the mass media, a general lack of awareness about Alzheimer disease clinical trials exists among many families and patients affected by this disease.⁹ To increase the chance of success in the recruitment process, researchers need to consider the various backgrounds of potential subjects when discussing Alzheimer disease clinical trials with them.

Impaired Abilities of Subjects and the Roles of Caregivers

Subjects with Alzheimer disease have impaired decision-making capabilities

as a result of the progressive decline in cognition and daily function intrinsic to the disease.¹⁰ Alzheimer disease clinical trials require the commitment of not only the individual with the disease but also of a caregiver, who is usually a family member or a trusted friend of the subject. The caregiver usually accompanies the subject for study visits and assists in overall assessment of the subject's functioning.^{4,11}

The caregiver's contact and involvement with the subject, combined with the subject's lack of ability to report treatment responses themselves, make the caregiver an essential source of information in Alzheimer disease trials.¹¹ Caregiver responses to formalized questionnaires typically include such information as the level of burden they face (eg, the time they spend each day engaged in caregiving tasks), answers to questions about the subject's moods and behaviors, and their own assessments of the subject's functional abilities and cognitive status. These caregiver responses are usually considered as secondary outcomes in Alzheimer disease clinical trials.¹¹

Specifically, a battery of time-consuming cognitive functioning and neuropsychiatric assessments—such as the Alzheimer's Disease Assessment Scale-Cognitive Portion (ADAS-Cog), the MMSE, and the Neuropsychological Test Battery (NTB)—are performed with the subject. However, results of global assessments and assessments of activities of daily living—such as the Basic Activities of Daily Living (BADL), the Clinical Dementia Rating (CDR), the Dependence Scale, the Instrumental Activities of Daily Living (IADLs), and the Neuropsychiatric Inventory (NPI)—are obtained through the caregiver.^{2,6,12} Thus, as a result of the complexity of these assessments performed during study visits, participation in Alzheimer disease trials demands a high degree of cooperation from the subject as well as from his or her caregiver.^{11,13}

The caregiver's role combined with the subject's living situation can be determining factors regarding eligibility to participate in an Alzheimer disease clinical trial. Certain trials exclude subjects who are living in nursing homes or

assisted living facilities, and other trials may require the caregiver to see the subject at least three to five times a week to obtain comprehensive information about the subject's level of functioning.^{11,14} Thus, the necessity of a consistent caregiver may be an additional barrier to a subject's ability to volunteer for an Alzheimer disease clinical trial.

Transportation

Many patients with Alzheimer disease are dependent on their caregivers for transportation to the study site.^{9,11} Individuals with Alzheimer disease are typically older than 65 years¹ and, hence, caregivers—whether spouses, siblings, or adult children—may also be relatively old. Caregivers' personal circumstances, such as their health status or work schedules, may interfere with their decisions to enroll loved ones in clinical trials.^{4,9}

Study Drug Adverse Effects

Randomized, placebo-controlled clinical trials are necessary to establish the efficacy and safety of pharmaceuticals.^{2,5,6,15} However, the possibility of randomization to the placebo arm of a trial instead of the study medication arm can hinder a potential participant's decision to enroll in the trial.^{8,9} In addition, the risk of adverse effects from using a new treatment may affect a caregiver's decision to allow his or her loved one to be entered into a trial.^{7,8}

Duration of the Trial

The disease-delaying or disease-modifying effect of an investigational Alzheimer disease drug would most likely manifest itself as a change in cognitive, behavioral, or physical performance over a period of several months. Hence, the duration of Alzheimer disease trials typically ranges from 6 months to 2 years.¹² Consequently, an important issue in recruitment of older subjects involves their health status. The subject's risk of morbidity and mortality must be considered during recruitment because enrolled subjects need to be capable of completing all study visits in order to obtain valid results. In addition, a subject's limited functional abilities can be a serious barrier to compliance and adherence to the study protocol.⁸ Limited func-

tional abilities may also prevent the subject from completing all study visits.

Cynicism About Clinical Research

Another hindrance to recruitment can be skepticism and suspicion about the medical research process among certain ethnic groups. Despite federal regulations, such as the National Institutes of Health Revitalization Act of 1993, requiring clinical trials to include women and ethnic minorities as subjects, ethnic minority groups continue to be underrepresented in clinical studies, including those for Alzheimer disease.¹⁶ Among participants in four National Institute on Aging-funded Alzheimer's Disease Cooperative Study trials, only about 6% were African American and only about 4% were Hispanic.¹⁷ In the international database of clinical trials for the FDA-approved cholinesterase inhibitor donepezil hydrochloride, data reveal that of the 4301 trial participants, only 2.4% were African American and only 0.9% were Hispanic.¹⁷

It has been reported that many African American caregivers are reluctant to seek professional medical treatment for family members, preferring instead to take care of family members without outside assistance.⁹ One reason these caregivers might be reticent to participate in clinical trials is that they would have no control over the treatments offered in the studies. These caregivers may also harbor a distrust of medical research in general.^{9,13} The fact that a trial may not provide a direct benefit to the subject may further discourage participation in medical research among individuals from certain racial and socioeconomic backgrounds.⁹

Media Influence

Direct-to-consumer marketing of research studies consists of advertisements that are intended to be seen or heard by potential subjects to solicit their participation in a study. Such marketing may include newspaper, radio, television, Web sites, bulletin boards, posters, and flyers.¹⁸ Some of these advertisements may make implicit or explicit claims about the safety and efficacy of "investigational" drugs, including assertions that the study medication is known to be

equivalent to or superior to other medications. Such false representation would not only unduly influence prospective subjects, but it would also be a violation of federal regulations concerning the promotion of investigational drugs.¹⁸

Inaccurate news reports about clinical trials may mislead the "audience" for Alzheimer disease trials, further distancing researchers from their recruitment goals. For example, media reports that exaggerate a trial's findings of adverse drug reactions may contribute to an increasingly distrustful public, serving as a barrier to effective recruitment of subjects.⁵

Media portrayal of a new Alzheimer disease clinical trial may influence—positively or negatively—practicing physicians' referrals of potential subjects into the research project. For example, media reports may lead some physicians to view an Alzheimer disease trial as a worthwhile opportunity to offer patients who are interested in trying more than currently approved Alzheimer disease treatments. Alternatively, news reports may lead some physicians to believe that their patients should not be subjected to an Alzheimer disease study because of the patients' comorbid conditions or lack of decision-making capacity. Physicians may not even be aware of certain Alzheimer disease clinical trials because of little media coverage.¹⁹ This lack of awareness is obviously a barrier to effective recruitment of subjects.

Reasons for Subject and Caregiver Interest in Study Participation

The major factor influencing subjects' interest and involvement in clinical trials is the altruistic intent—the goal of finding better treatments and advancing science and medicine.⁹ Other factors encouraging subjects' participation in studies include hopes of finding a cure for themselves, access to the newest medications for their diseases, access to regular health checkups, and other monetary and non-monetary incentives.^{7,9}

Caregivers of patients with Alzheimer disease are interested in study participation based on altruistic motives toward other caregivers and patients, as well as personal motives for improvements in their own caregiving roles.¹¹

Other factors driving caregiver participation in Alzheimer disease clinical trials include support from clinical research staff and perceptions that they are not alone in their struggle with the disease.⁹ Many caregivers look at study participation as a two-way street. They assist research teams by reporting about subjects' functioning. In turn, they obtain state-of-the-art care for their loved ones, a chance to talk on an ongoing basis with Alzheimer disease experts, and up-to-date information about the disease and current research.⁹

Overcoming the Challenges

Successful recruitment of subjects into Alzheimer disease clinical trials requires a proactive attitude. Strategic and effective planning will bolster the recruitment efforts of clinical researchers. Once the recruitment strategy is defined, it serves as a guiding light for recruitment efforts. *Figure 2* displays steps in successful recruitment efforts.

Role of the Principal Investigator

The principal investigator should guide the study team to ensure that subjects are ethically enrolled in the Alzheimer disease trial. The principal investigator should use his or her clinical judgment to determine whether a potential subject is eligible for the trial based on the study inclusion and exclusion criteria.²⁰

Building awareness about clinical trials among potential participants and educating potential participants about the trials are keys to effective recruitment.²¹ The principal investigator can inform his or her patients about new studies during regular clinic visits, helping the patients understand the details of the studies.²⁰ Potential participants may have a variety of questions about any new trial. The principal investigator and the rest of the study team should be available to patients and well-equipped with answers for such questions. This sharing of information lays a foundation for a positive relationship between the subject and study team in the clinical trial.²¹

As previously discussed, recruitment for Alzheimer disease trials is a process that must be conducted with involvement of caregivers.¹⁰ Hence, the

principal investigator must reach out to the caregivers and provide them with information about the study design and protocol and the importance of participation in the trial. In many ways, the caregiver is essentially a "co-subject" in a clinical trial, as well as a crucial stakeholder and participant in every step of the trial process. Researchers who attend to the needs, concerns, and special circumstances of caregivers will achieve greater success with enrollment opportunities.

Encouraging Partnerships

Partnering with primary care physicians, neurologists, and psychiatrists in the community will enhance recruitment efforts for Alzheimer disease clinical trials. Educational seminars, letters to physicians, and professional networking Web sites serve as important means of communication with local practicing physicians. Concise educational material about a clinical trial can be used to promote discussion of trial participation in a time-efficient manner.¹⁹ For example, laminated cards listing trial inclusion and exclusion criteria can be sent to partnering physicians as a means of screening potential subjects.

Advertisements

After a patient and caregiver become interested in learning about a clinical trial, the principal investigator and research team must focus on educating the prospective trial participants. At the same time, the researchers must carefully avoid any efforts that would be perceived as manipulative or coercive to the potential study participants and their caregivers.²²

Advertising the clinical trial is one of the best ways to reach out to the public. Effective advertisements include those in newspapers and magazines and public service announcements on radio and television.⁸ Online social networking sites, such as Twitter and Facebook, could be considered to reach larger populations of potential subjects and caregivers.

Additional ways to increase the visibility of a clinical trial include the following: flyers displayed in physicians' offices and examination rooms; information posted on the study's Web site;

presentations given to local medical societies; and distribution of information through local, state, or national physician organizations through newsletters, monthly journals, and the Internet.⁸ A multifaceted approach to advertisements is best for spearheading recruitment efforts.

Role of Institutional Review Board

Because the "consenting process" for clinical research essentially begins with advertising and recruitment, the FDA requires that an institutional review board (IRB) have authority to approve or disapprove all research activities covered by IRB regulations.¹⁸ Regardless of the vehicles used for advertisements, the FDA expects IRBs to review all advertising materials to ensure that the materials are not unduly influential and do not make claims for treatment results or cures beyond what is outlined in the study protocol and consent form.^{18,22}

The IRB approval process may add to the study timeline and delay the beginning of recruitment. Thus, Alzheimer disease researchers must work with and educate the IRB members well before a protocol reaches them for review. Typical major concerns for IRBs include the abilities of study subjects to provide consent and the risk-benefit profile of the project. In many cases, the altruistic component of "benefits to future patients" is the driving force assuring IRB members that something good may come out of a clinical trial—even if it does not directly benefit the subjects and caregivers participating in the study.

Support Groups and Other Outreach to Potential Subjects

Other approaches to increase the likelihood of patients becoming subjects in Alzheimer disease clinical trials include collaboration with recruitment firms, which assist study investigators in receiving referrals. Partnership with national and local chapters of the Alzheimer's Association or other Alzheimer disease support groups will provide a vehicle to enhance recruitment efforts. The Alzheimer's Association offers a free online service, titled "TrialMatch," that enables individuals with Alzheimer disease and their caregivers, families, and

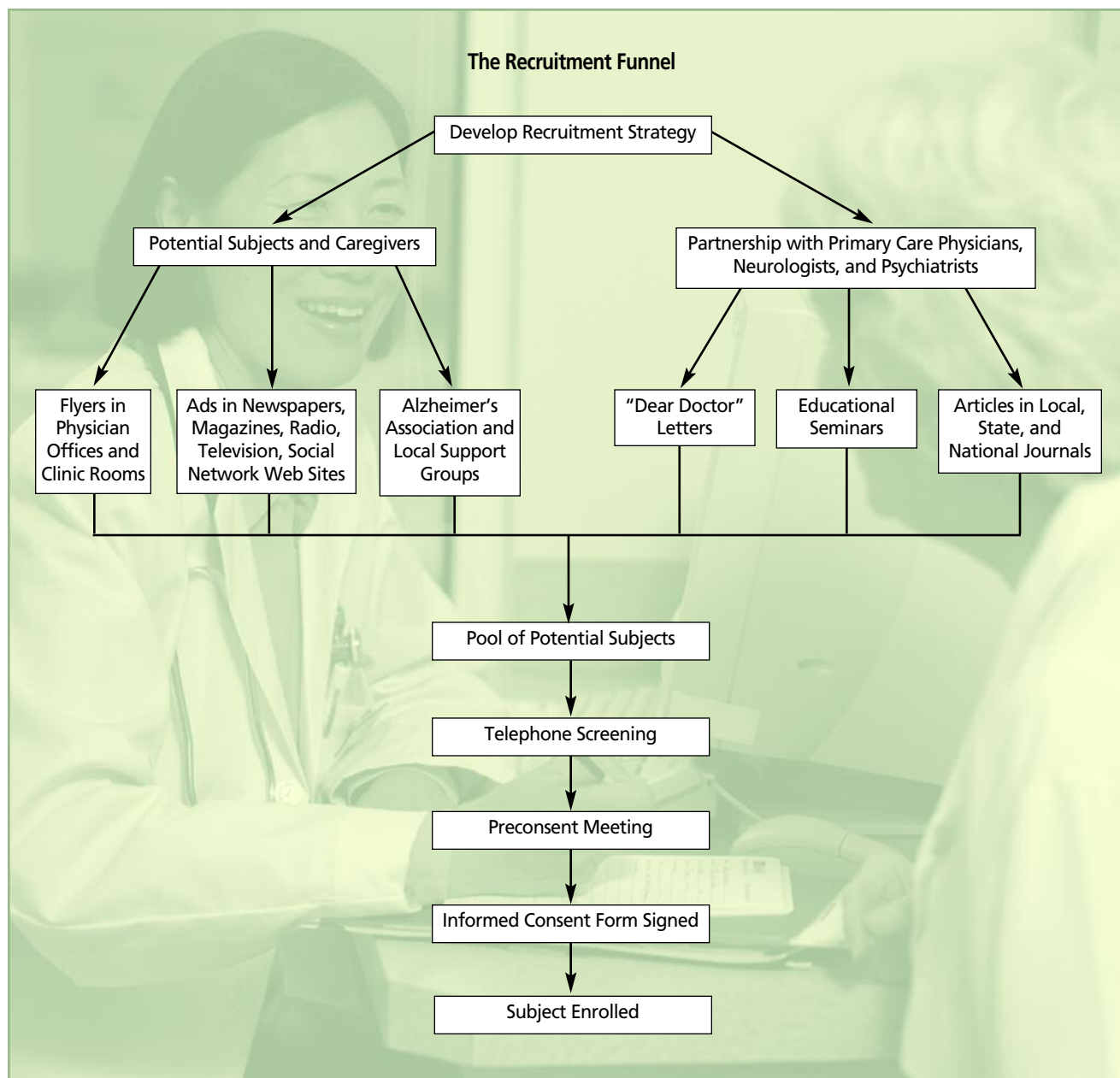


Figure 2. Steps involved in successful recruitment efforts for Alzheimer disease clinical trials.

physicians to find clinical trials based on personal criteria (eg, diagnosis, stage of disease, location).¹ Figure 3 lists Web site addresses for TrialMatch and other online resources with clinical trial information.

Educating all employees at the study site about trial requirements for subjects can further expand recruitment efforts. This is especially true if the study site is at an academic health science center with a large faculty and staff.

Lastly, word-of-mouth serves as a powerful tool to educate potential sub-

jects.⁹ Do not forget that publicity of Alzheimer disease trial information is the key to effective recruitment.

Telephone Screening and Preconsent Meetings

After potential participants are identified, telephone screening of these individuals provides an effective time-saving measure. Considering the requirements of the inclusion and exclusion criteria, phone screening can help to streamline the recruitment process. In addition, all contact information of screening failures

can be maintained in an electronic database for future study reference.

Another creative approach that may work well in recruitment—depending on the clinical research setting—is the use of “preconsent” meetings.²² Such meetings would involve inviting a targeted group of potential subjects and their caregivers to the clinic to discuss details of the Alzheimer disease clinical trial. Participants would greatly benefit from such an interactive presentation, which could serve as a forum for questions.

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- Alzheimer's Association TrialMatch
<http://www.alz.org/trialmatch/about.asp>
 - Alzheimer's Disease Clinical Trials Database
<http://www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials/>
 - Alzheimer's Disease Education & Referral Center—News and events, other information
<http://www.nia.nih.gov/Alzheimers>
 - Alzheimer's Disease Education & Referral Center—Search for clinical trials
<http://www.alzheimers.org/clinicaltrials/search.asp>
 - CenterWatch—Alzheimer disease clinical trials
<http://www.centerwatch.com/clinical-trials/listings/studylist.aspx?CatID=11>
 - ClinicalTrials.gov—A service of the US National Institutes of Health
<http://clinicaltrials.gov>

Figure 3. Online resources with information on Alzheimer disease clinical trials.

Importance of Informed Consent

The clinical trial's informed consent process begins with the subject's recruitment. The informed consent form is a document that is crucial to the involvement of human subjects in clinical research. The Belmont Report,²³ prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, discusses the voluntary nature of informed consent and explains that information provided to subjects in the informed consent document must be complete, understandable, and presented in an unhurried manner. Investigators are responsible for ensuring that subjects understand all the information presented in the informed consent document.

Subjects with Alzheimer disease and their caregivers should be given enough time to grasp the information presented to them and to ask any study-related questions. It is important to explain to subjects and caregivers about any foreseen and unforeseen adverse effects associated with the investigational drug. It is ethically essential to make subjects and caregivers aware of the fact that they may not derive any direct benefit from study participation, and that the study may help only future patients.²⁴ At any time throughout the trial, a subject or a subject's caregiver should be allowed to withdraw consent and to drop out of the study. It is essential that the subject and caregiver fully understand the voluntary

nature of study participation and that they are not unduly influenced by recruiters.²³

Subject Retention

After investing time and effort into the recruitment of subjects, it becomes essential to retain those subjects throughout the entire period of the trial. Retention of subjects in Alzheimer disease clinical trials, in which retention is affected by not only the subject but also the caregiver, is especially complex and demanding. The staff at the study site is responsible for ensuring that participation in the trial is a positive experience for subjects and caregivers. Study participants should be made to feel that they are more than just a number—that they are integral parts of the study and that their well-being is of utmost importance.

Alzheimer disease clinical trials can be complex, involving multiple study site visits and a variety of procedures and tests conducted at each visit.² The study staff must be proactive, guiding the subjects and their caregivers through the process to make it less taxing for them. For example, if an abnormal laboratory value is detected as part of a subject's routine study visit, the research staff must promptly follow up with the subject and caregiver regarding the meaning of the abnormal value.

Giving due respect to subjects and being thankful for their involvement in the trial boosts the subject-research staff

relationship and, in turn, encourages retention of subjects.⁹ Routine follow-up phone calls to stay in touch with caregivers are another way to continue to engage a subject's participation. The study team may even have to occasionally perform a home visit to continue to engage the subject and caregiver in the trial.⁴

Other effective ways to promote subject retention include the following: a welcoming, friendly, and caring principal investigator and study staff; reminders for each study visit; personal thank you notes; birthday cards; study calendars; and a newsletter that periodically reports the progress of the trial.²⁰

Conclusion

Recruitment of subjects into clinical trials for Alzheimer disease is a challenging though worthwhile endeavor. Successful recruitment is a joint venture that involves the principal investigator, the research coordinator, the study site staff, the caregiver, and the subject. The principal investigator and study team must ensure the ethical recruitment and treatment of subjects and caregivers. The principal investigator must discuss appropriate recruitment strategies with the study staff, identify resources needed to support the recruitment plan, and delegate roles and responsibilities to implement the plan.

Increasing awareness of study opportunities and delineating benefits from study participation among families affected by Alzheimer disease are crucial to recruitment and retention of subjects. Media advertising, word-of-mouth passing of information, liaisons between study sites and local Alzheimer's Association support groups, educational seminars, study brochures, and online networks are some methods of enhancing recruitment in Alzheimer disease trials.

Involving IRBs early in the study design process can help identify and address changing regulatory concerns and ethical issues. Addressing such matters can reassure subjects and caregivers that the researchers are on their side.

Clinical researchers must be well-prepared and knowledgeable to answer any study-related questions and to

explain details of the clinical trial in a way that is understandable to subjects and their caregivers.²³ The principal investigator and study staff need to respond to any misconceptions about the clinical trial and to promote volunteerism without coercion.

The principal investigator and research staff must remember to be amenable to and accommodating of the caregiver's schedule when planning study visits. Study participants should be treated as "valued partners" in the clinical trial, rather than as mere research subjects.

Overall, successful recruitment depends on trust and the integrity of the research team. Support, encouragement, and motivation from principal investigators and research teams will improve subjects' participation in Alzheimer disease clinical trials. This participation is an absolute necessity to advance our knowledge of Alzheimer disease and to find preventive, disease-modifying, and curative treatments for patients with this devastating illness.

References

1. Alzheimer's Association. 2010 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2010; 6(2):158-194. <http://www.alzheimersanddementia.com/article/PIIS1552526010000142/fulltext>. Accessed August 29, 2010.
2. Schneider LS. Drug development, clinical trials, cultural heterogeneity in Alzheimer disease: the need for pro-active recruitment. *Alzheimer Dis Assoc Disord*. 2005;19(4):279-283.
3. Keith SJ. Evaluating characteristics of patient selection and dropout rates. *J Clin Psychiatry*. 2001;62(suppl 9):11-14.
4. Karlawish J, Cary MS, Rubright J, TenHave T. How redesigning AD clinical trials might increase study partner's willingness to participate. *Neurology*. 2008;71(23):1883-1888. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2649726/>. Accessed August 29, 2010.
5. Sullivan J. Subject recruitment and retention: barriers to success. *Applied Clinical Trials Online Web site*. April 1, 2004. <http://appliedclinicaltrials-online.findpharma.com/appliedclinicaltrials/Patient/Subject+Recruitment/Subject-Recruitment-and-Retention-Barriers-to-Succ/ArticleStandard/Article/detail/89608>. Accessed August 29, 2010.
6. Knopman DS. Clinical trial design issues in mild to moderate Alzheimer disease. *Cogn Behav Neurol*. 2008;21(4):197-201.
7. Patel MX, Doku V, Tennakoon L. Challenges in recruitment of research participants. *Adv Psychiatr Treatment*. 2003;9(3):229-238. <http://apt.rpspsych.org/cgi/reprint/9/3/229>. Accessed August 29, 2010.
8. Fitzpatrick AL, Fried LP, Williamson J, et al; GEM Study Investigators. Recruitment of the elderly into a pharmacologic prevention trial: the Ginkgo Evaluation of Memory Study experience [published online ahead of print July 4, 2006]. *Contemp Clin Trials*. 2006;27(6):541-553.
9. Connell CM, Shaw BA, Holmes SB, Foster NL. Caregivers' attitudes toward their family members' participation in Alzheimer disease research: implications for recruitment and retention. *Alzheimer Dis Assoc Disord*. 2001;15(3):137-145.
10. Kim SY, Cox C, Caine ED. Impaired decision-making ability in subjects with Alzheimer's disease and willingness to participate in research. *Am J Psychiatry*. 2002;159(5):797-802.
11. Lingler JH, Parker LS, DeKosky ST, Schulz R. Caregivers as subjects of clinical drug trials: a review of human subjects protection practices in published studies of Alzheimer's disease. *IRB*. 2006; 28(3):11-18.
12. Mohs RC, Kawas C, Carrillo MC. Optimal design of clinical trials for drugs designed to slow the course of Alzheimer's disease. *Alzheimers Dement*. 2006;2(3):131-139.
13. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidemiol*. 1999;52(12):1143-1156.
14. Safety and cognitive function study of EVP-6124 in patients With mild to moderate Alzheimer's disease; ClinicalTrials.gov identifier: NCT01073228. <http://clinicaltrials.gov/ct2/show/NCT01073228?term=alzheimer%27s&rank=9>. Accessed September 16, 2010.
15. Drug study designs. Food and Drug Administration Web site. <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidanceInformationSheetsandNotices/ucm11787.htm>. Accessed September 16, 2010.
16. Alzheimer's clinical studies: clear guidance on recruiting volunteers. *Medical News Today Web site*. July 13, 2009. <http://www.medicalnews today.com/articles/157228.php>. Accessed August 29, 2010.
17. Olin JT, Dagerman KS, Fox LS, Bowers B, Schneider LS. Increasing ethnic minority participation in Alzheimer disease research. *Alzheimer Dis Assoc Disord*. 2002;16(suppl 2):S82-S85.
18. Recruiting study subjects-information sheet-guidance for institutional review boards and clinical investigators (recruiting study subjects). US Food and Drug Administration Web site. May 22, 2009. <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm>. Accessed August 29, 2010.
19. Galvin JE, Meuser TM, Boise L, Connell CM. Predictors of physician referral for patient recruitment to Alzheimer disease clinical trials. *Alzheimer Dis Assoc Disord*. 2009;23(4):352-356.
20. Frestedt J. The role and impact of the principal investigator. *The Monitor*. September 2008:31-34. <http://www.acrpnet.org/MainMenuCategory/Resources/TheMonitor/September2008/TheRoleandImpactofthePrincipalInvestigator.aspx>. Accessed August 29, 2010.
21. Harper B, Neuer A. A strategic formula to enhance subject enrollment and retention. *The Monitor*. February 2009:59-63.
22. Greco S, Bartilucci-Lotze DM. Approaches to ethical recruitment of research participants. *The Monitor*. December 2008:23-26.
23. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. National Institutes of Health, Office of Human Subjects Research Web site. April 18, 1979. <http://ohsr.od.nih.gov/guidelines/belmont.html>. Accessed August 29, 2010.
24. Kolata G. What to tell the patients after a trial goes awry. *The New York Times*. August 23, 2010. <http://www.nytimes.com/2010/08/24/health/24alzheimers.html>. Accessed August 29, 2010.

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