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FACILITATING ALZHEIMER'S DISEASE RESEARCH RECRUITMENT

Joshua D. Grill, PhD¹ and James E. Galvin, MD, MPH²

¹Mary S. Easton Center for Alzheimer's Disease Research, Department of Neurology, David Geffen School of Medicine at UCLA

²Alzheimer's Disease Center, Departments of Neurology, Psychiatry and Population Health, New York University Langone Medical Center, New York

Abstract

Alzheimer's disease (AD) research faces challenges to successful enrollment, especially to clinical trials and biomarker studies. Failure to recruit the planned number of participants in a timely fashion threatens the internal validity and success of clinical research, raising concerns about external validity and generalizability of results, and possibly leading to disparities in disease treatment. Methods to improve recruitment exist, but require varying levels of staff effort and financial resources and evidence of effectiveness is often lacking or inconsistent. In this review, we summarize some of the available methods to improve AD research recruitment, the available literature to support or refute these strategies, and some of the experiences at the authors' AD Research Centers. We discuss the use of community-based participatory research principles and participant registries as a means to enhance research enrollment and increase diversity of research samples.

Keywords

Alzheimer's Disease; Recruitment; Registries; Clinical Trials; Community-Based Participatory Research; Research Participation

Introduction

Recruitment to Alzheimer's disease (AD) clinical trials is often slow and sometimes fails to enroll the specified number of participants. Failure to meet recruitment goals delays treatment advances, threatens internal validity, raises concerns about generalizability of results, and possibly leads to disparities in disease treatment.

AD trial recruitment faces many challenges (Table 1).¹ AD is a disease of the elderly and older patients take higher numbers of prescription medications and frequently suffer from medical and psychiatric comorbidities, which can be exclusionary. Studies examining rates of eligibility find that only 10–27% of AD patients are trial eligible.^{2–5} Only a portion of AD patients are aware of research opportunities and many are unable or unwilling to participate. Many older adults live alone and may not have access to someone who can accompany them to study visits. Indeed, AD trials require not one but two participants: the patient and a study partner.

Send Correspondence to: Joshua Grill, PhD, Mary S. Easton Center for Alzheimer's Disease Research, Department of Neurology, David Geffen School of Medicine at UCLA, 10911 Weyburn Ave, Suite 200, Los Angeles, CA 900095, jgrill@mednet.ucla.edu.

The patient's primary caregiver typically fulfills the role of study partner. The study partner is instrumental to trial success: they ensure informed consent, assist in protocol and medication compliance, and serve as informant on trial outcomes. Moreover, the study partner is critical to the decision whether to enroll.⁶ Logistical burden on the caregiver may impact their willingness to participate,⁷ while caregiver desire for patient benefit may serve as a primary motivation for enrollment.^{6, 8} Though most AD patients lack a spouse,⁹ roughly two thirds of AD trial participants enroll with a spousal study partner.¹⁰ Nonspousal caregiver-patient dyads may therefore face additional barriers to trial participation and attempts to improve recruitment may need to focus on both the patient and the caregiver and consider means to reach adult children and other nonspousal care providers.

Similarly, AD trial participants tend to be younger, more educated, and more often Caucasian than is typical for the general AD population. For example, a 2007 review found that greater than 90% of NIH-supported and 97% of industry-supported AD trial participants were non-Latino Caucasians.¹¹ The older adult population in the US is becoming increasingly diverse and AD research samples must diversify in parallel. In 2006, 19% of adults age 65 or older were non-Caucasian. By 2050 it is estimated that the proportion of elder Americans who are African American, Latino, or Asian American will increase to 39%.¹² In addition to expediting AD trial recruitment, enrollment of more representative samples is imperative.

Two action items (1.B.2 and 1.B.3) in the National Plan to Address AD aim to increase enrollment to AD clinical trials.¹³ Current trials aim to enroll AD patients with dementia, mild cognitive impairment (MCI), and preclinical AD.^{14–16} Improved methods to increase enrollment for all types of AD trials and other forms of aging and dementia research are needed. In this review, we discuss methods of patient recruitment to AD research (Table 2). Though we focus on clinical trials, the methods discussed are applicable to recruitment strategies for other patient-oriented research projects including biomarker and longitudinal studies and caregiver research. We provide an overview of the literature on this topic, as well as experiences toward enhancing recruitment at two AD Research Centers (ADCs). The National Institute on Aging funds a network of approximately 30 ADCs nationwide. The purpose of these ADCs, at least in part, is to follow a cohort of AD patients (along with MCI and normal control participants) who can be recruited to other research studies, including clinical trials. Even at these Centers, however, clinical trial recruitment is often inadequate, necessitating additional recruitment from outside sources. Outreach programming, interventions, and the establishment of collaborations to increase outside referrals to ADC trials are often performed by or through a core mandated in each ADC, the Education Core. We address a number of strategies that can be implemented by Education Cores or by investigators outside of the ADC system, but focus on techniques that have recently gained traction in AD research, the use of community-based participatory research (CBPR) methods^{17–18} and participant registries.

Methods to improve AD trial recruitment

Appeal to current participants

Barriers to AD trial participation may be lowest among previous participants. These individuals have demonstrated eligibility for trial entry criteria, as well as motivation to participate. Indeed many participants are eager to enroll in subsequent studies after trial completion or stoppage. Most protocols will exclude participants in previous trials within a given time frame (e.g. 6 months). More and more frequently, however, protocols for particular treatment modalities (e.g. immunotherapies) specify that previous participants in trials of agents in the same treatment class be excluded altogether. Participants in some trials (e.g. vaccines and neurosurgical interventions) may be excluded from all subsequent studies

of potential disease modifying therapies. Since minority participation in trials is so low, this strategy will not improve the diversity of trial samples.

Increase clinical referrals

The number of memory care clinics operating in the United States is increasing and many are not affiliated with medical schools or Universities. The concentration of a large number of AD patients with an established relationship to a clinic may make an ideal recruitment site.¹⁹ Referrals to trials from other health care providers not associated with a research site, however, are infrequent. Studies from the Alzheimer's Association²⁰ and the Important Perspectives on Alzheimer's Care and Treatment (IMPACT) survey in the United Kingdom²¹ suggest that most primary care providers are not aware of AD trials. Community physicians may be willing to refer participants, however, if awareness is increased and barriers to referral are overcome. For example, 98% of European physician respondents to the IMPACT study who were aware of AD trials stated that they would be willing to refer patients. In the US, 52% of community providers positioned to refer AD patients to trials responded that they were likely to do so in one study.²² Barriers to referral included concerns about the impact of participation on patient health and inadequate time to discuss research. The likelihood of referral was predicted by respondents' proximity to an AD Research Center and physicians' perceived importance of AD research. Thus, education may provide an avenue to improve physician attitudes toward referral.

Physician education

Studies of physician education as a means to improve research referrals have yielded mixed results. In a partnership between National Institute on Aging-funded ADCs and the Pri-Med Institute, more than 2,800 primary care health providers in five US cities received AD education from national experts in dementia research. Educational sessions included the need for increased referrals to clinical research at ADCs and local site information. Long-term outcomes for these programs were not collected, but confirmed referrals were extremely low. A study by Carr and colleagues at the University of Kentucky ADC found that an investment in primary care physician education yielded 0 research referrals, compared to an equal investment in a community education model that resulted in 69 new research participants.²³ The ineffectiveness of the physician education program was despite a targeted approach, inviting health care providers in "the referral area." In contrast, the Washington University ADC conducted a physician education program in which rural physicians were paid \$200 and provided 20 CME credits for their successful completion. This program resulted in a 52% (30–40 participants) increase in rural participants in longitudinal research but not necessarily in AD clinical trials.²⁴ One difference that could account for the discrepant outcomes is the length of the programs. The Kentucky program examined effectiveness 4 months after the intervention, while the Washington University program had been occurring for 9 years when results were reported. Efforts directed at professional education may be less likely to result in immediate improvements in referral but long-term programs may have delayed benefits.

Mailing lists

Mailed recruitment materials can identify new volunteers and have been used most frequently to support enrollment to AD prevention clinical trials. Screen failure rates are lower for prevention trials,²⁵ but the sample sizes of these studies are necessarily larger, as a low proportion of participants will go on to develop AD or MCI and trials must be powered to demonstrated drug impact on the rates of such progression. Since, by definition, eligible participants do not suffer from cognitive problems, recruitment from clinical sources is ineffective. These trials have used mailing lists as primary, supplementary, or post-hoc means to recruit participants.²⁶ In the AD Anti-inflammatory Prevention Trial (ADAPT),

more than 3.5 million mailings were sent to Medicare beneficiaries. The trial enrolled 2,518 volunteers at six sites over 44 months. Across trial sites, the efficiency of mailings ranged from 0.4 to 1.9 participants per 1,000 mailings.^{27–28} The Ginkgo Evaluation of Memory (GEM) study supplemented recruitment from the Cardiovascular Health Study with brochures mailed to four unique lists, including purchased lists, voter registration lists, and university lists (total = approximately 243,000 recipients). When permitted by the local Institutional Review Board, sites followed-up with phone calls to mailing recipients. Among those eligible to be called, 83% were reached of which 25% (or 1.3% of those initially sent brochures) were enrolled.²⁹

Mailing lists can also be used to recruit cognitively impaired volunteers. Andersen and colleagues mailed a questionnaire examining self-reported cognitive function to more than 11,000 community residents in Norway.³⁰ Thirty one percent responded to the questionnaire, of whom 438 met criteria for cognitive impairment and 292 were willing to undergo clinical evaluation. Thirty-one respondents met criteria for MCI, 15 had cognitive impairment not due to AD, and 113 met criteria for probable AD. Compared to a cohort recruited clinically, the authors found that those recruited from the community mailer were more likely to be male and to have higher scores on the Mini-Mental State Exam.

Purchasing mailing lists can be costly and information is not always up-to-date. Sending information through bulk mail may be cheaper, but is more likely to be unopened or discarded as “junk mail.” Electronic mailing (e-mail) may be a more cost-effective way of disseminating study information but also may be sorted into junk folders.

Advertising

Although local and national advertisements in newspapers, television, and radio, as well as public service announcements, have been used in a large number of clinical trials, few peer-reviewed publications examining the success rate or cost-effectiveness of these methods are available. Lines and colleagues reported that an advertising campaign inviting individuals age 65 or older who have memory complaints to call a toll free number resulted in 16,988 respondents as part of the recruitment to the *Prevention of AD in Society's Elders* study of rofecoxib.³¹ Callers were screened for inclusion criteria and then administered a category fluency test (CFT; animals) and the modified Telephone Interview for Cognitive Status (TICS) to exclude those unlikely to meet MCI criteria. Of responders, 8742 passed initial CFT criteria and 5223 met TICS criteria. Only 14% of callers (n=747) were seen in clinic and 324 (2%) met MCI criteria. These participants represented ~25% of total trial sample. It is likely that the sponsor of the study incurred substantial cost associated with the advertising campaign itself, which supported recruitment across multiple national regions, and the central call center, which employed 10 trained operators.

Site press releases to attract stories in local news outlets such as affiliate television and radio stations or local papers may provide free advertising. Universities often have media relations offices that can partner with investigators on press releases or attempts to garner media attention related to a new study. Media outlets, especially television, may prefer human-interest stories regarding participants in trials. Appearances in local media may be as effective at generating interest in studies as are paid advertisements, though the experiences of the authors regarding responses to both free and paid advertising have been inconsistent.

Community outreach

Outreach to the surrounding community at large, including strong partnerships with community organizations, is a traditional mechanism to increase AD recruitment. This often takes the form of providing community lectures and seminars. The effectiveness of

community outreach is dependent upon the strength of the outreach plan. Even with substantial planning, however, interventions may not result in increased recruitment rates and any benefits gained may be delayed. Austrom and colleagues at the University of Indiana ADC partnered with the Alzheimer's Association in a pilot project that aimed to recruit through the Association's helpline.³² Researchers trained staff and volunteers who answered the helpline to discuss four open-to-enrollment research studies, including two clinical trials. Over 6-months, the helpline received calls from 818 individuals deemed eligible to receive study information. Of these, 257 were given information about studies, 4 followed-up with the research team, and 2 were enrolled. The authors noted that research coordinators in the study felt that the recruitment rate would have been improved if they had been able to initiate contact with callers to the helpline.

Community outreach has also provided mainstay of attempts to improve minority participation rates. Minority research recruitment faces a wide range of challenges including differing access to care and therapy,^{33–34} gaps in the knowledge of AD among certain racial and ethnic groups,^{35–37} differences in perceived risk for AD,³⁸ and long-standing (and well-founded) skepticism toward research.^{39–40} A significant literature exists regarding the need for awareness of the culture, partnership with community leaders, staff who can relate to the population to be recruited, and continued presence in the community in order to be successful.⁴¹ We address some of these points below.

Satellite clinics

To address structural, linguistic, and cultural barriers to recruiting non-Caucasian elders, a number of ADCs recruit minority participants from satellite clinics. Differential access to care means that recruitment methods beyond providing clinical service to the target community are necessitated.^{42–44} Faculty and staff of similar background to the target population being recruited are key to success in satellite research programs.^{45–46} Successful programs incorporate community outreach and social marketing strategies as well as partnerships with community leaders and organizations to augment recruitment.^{45, 47} Of note, satellite clinics are not always successful. Well-planned, well-funded community outreach efforts have been shown to efficiently recruit minority cohorts to clinical research at academic medical centers.⁴⁸ The opportunity to participate away from universities, however, may overcome some of the logistical and attitudinal barriers to enrollment. Importantly, no method has demonstrated efficacy at improving trial enrollment of underrepresented minority patients.

Community-based participatory research methods

Community coalitions and partnerships are being recognized as important strategies for addressing health disparities.⁴⁹ They provide a means to develop and sustain innovative approaches to affect community health, particularly that of older adults. Guided by principles of CBPR, these partnerships bridge the social divide between academic researchers and communities by providing a forum for mutual learning and education.¹⁸ CBPR partnerships create synergy by pooling expertise, resources, and perspectives of diverse stakeholders. CBPR is characterized by three essential elements: participation, education, and social action.

In CBPR, community members are active participants in the design, conduct, and evaluation of research.⁵⁰ Results are used formatively to inform partnership planning. A high degree of satisfaction, trust, collaborative decision making, understanding of CBPR, and positive perceptions of community-academic partnership are essential.¹⁸ Built on mutual trust and respect for the partners' different perspectives and expertise, this is a process whereby community partners are exposed to research findings and evidence-based programming and

learn to understand the elements involved in the implementation process, while the academic partners benefit from the “real world” insights offered by the practice community. The overall goal is to enable community partners to become “research-ready” to fully engage in the process of generating and implementing evidence-based health information.

The Tri-Ethnic Center for Prevention Research’s Community Readiness Theoretical Model⁵¹ posits nine stages of community readiness for moving the community to a higher level of readiness to engage in evidence-based health research. At the heart of this for AD research participation are four basic tenets: (1) learn about the people who live in your community; (2) educate your community about AD and its consequences; (3) engage your community by creating community advisory boards and co-hosting events with community partners; and (4) recruit your community into research projects after establishing trust and equity.

CBPR principles can be used effectively in AD research recruitment. Etkin and colleagues partnered with community organizations such as neighborhood, and faith-based organizations and caregiver support groups to distribute advertisements and study fliers and successfully recruited 327 strained sedentary caregivers of whom 34% were minorities.⁵² O’Bryant and colleagues employed CBPR methods to recruit more than 400 Mexican Americans to a study of normal aging, MCI, and AD that included genetic testing.⁵³ Morhardt et al used members of five *low English proficiency* cultural groups (Assyrian, Arabic, Bosnian, Hindi, and Urdu), identified from a previous study, to recruit and then conduct interviews (after training from investigators) with ten caregiver participants each to better understand the groups’ conceptualization of dementia and cognitive impairment.⁵⁴ This study is a good example of the bidirectional learning that exists between researchers and community members in CBPR. Though the investigators originally proposed focus groups of the ethnic populations of interest, community partners from the ethnic groups urged the performance of interviews instead, based on fear that cultural constraints might prevent participants from discussing personal and private information in front of others.

A potential weakness of the CBPR approach is that identified individuals may be relied upon to follow-up with the research site. One way to enhance study enrollment of individuals who express interest in research in a community setting is by first enrolling them in a registry of potential participants.

Potential participant registries

Registries of older individuals who are willing to consider participating in studies provide an opportunity to reach out to a large number of volunteers immediately upon study initiation, rather than serially enrolling participants. Persons enrolled in such registries have already expressed a willingness to participate in research, may have defined the types of studies they are (and are not) interested in participating in, and can be quickly contacted upon IRB approval of a new protocol, thus expediting enrollment.

IRBs may offer specific approval processes for local registries, distinct from the process of submitting a new human subjects study. Registries can usually be processed as a minimal risk activity and may be eligible for expedited review with some IRBs. Regulatory applications should outline how individuals will provide informed consent to enroll in the registry. Paper forms may be used simultaneously to demonstrate informed consent and collect registry information. Alternatively, a stepwise procedure may be implemented in which individuals sign an approved *consent-to-be-contacted* form and are then verbally consented into the registry during a telephone follow-up. Electronic enrollment through Internet-based platforms may be permitted by some IRBs. For registries in which only self-reported medical information is collected, signed HIPAA approval is not necessary in most

instances. For more sophisticated registries, securing a signed HIPAA form may enable researchers to ensure data validity by linking to an electronic medical record (EMR).⁵⁵ The regulatory needs for national registries that enroll from and refer to a network of sites is more complex, though approval is typically through a single IRB. Protection of volunteer confidentiality must be ensured and systematic evaluation of whether participants wish to learn more about a particular study prior to the sharing of identifying information with researchers is advised.⁵⁶ One unique aspect of registries that should be outlined in initial applications is the length of “participation.” It is foreseeable that a large portion of individuals who enroll in the registry may never be contacted about a study. A timeline should be established, according to which participants will be removed from registry or re-contacted to renew consent to participate. At UCLA and NYU, this time frame is 5-years.

In Table 3, we provide an example of the type of data that can be collected through a self-report registry. Investigators may wish to go beyond clinical and demographic information collected in the registry. For example, the Banner Institute’s Alzheimer’s Prevention Registry invites enrollees to provide saliva samples for apolipoprotein E (APOE) genetic testing.⁵⁷ Registries may also create a data element for the number of contacts made with registrants.⁵⁵

Once a registry is established, it can enhance research recruitment, including to clinical trials.⁵⁸ Each study that recruits from the registry must gain separate IRB permission to do so. This may require listing the registry as a source of participants and using approved general recruitment tools (e.g. flyers or phone scripts) or developing specific recruitment tools (e.g. investigator letters to the members of the registry). Queries of the registry (to the extent that data permit) can limit communications to viable candidates based on diagnosis, age requirements, and a variety of exclusionary criteria (e.g. use of prohibited medication), potentially limiting screen failures and enabling more efficient use of study coordinator time.

When used, consent-to-be-contacted forms can enhance recruitment from both clinical and community sources. Clinicians (e.g., physicians, nurses, neuropsychologists), as well as study coordinators and other recruitment staff, can administer the forms. Research or volunteer speakers in community venues can also collect forms, providing an approved means for members of the research team to follow-up with interested attendees. This may be especially effective when combined with targeted outreach aiming at minority communities.^{46, 48} The dual advantage of this approach is to increase research recruitment and provide objective measures of outreach success.

National registries include disease-specific models, such as the Alzheimer’s Association’s TrialMatch® (http://www.alz.org/research/clinical_trials/find_clinical_trials_trialmatch.asp)⁵⁹ and the Alzheimer’s Prevention Registry (www.endalznow.org, accessed 04/04/13), and general research recruitment registries, such as ResearchMatch (<https://www.researchmatch.org>), developed at Vanderbilt University.⁵⁶ National registries have a variety of strengths, including the potential for greater publicity through national campaigns. For example, the Alzheimer’s Prevention Registry is partnering with the NIA and the Alzheimer’s Research Forum (www.alzforum.org) to increase exposure. National registries also may utilize clinical networks such as the institutions receiving Clinical Translational Science Awards. This is the model employed by ResearchMatch, which has enrolled more than 34,000 volunteers (<https://www.researchmatch.org> accessed 03/27/13). Similarly, TrialMatch® can utilize the Alzheimer’s Association’s more than 200 chapters (<http://www.alz.org/apps/findusall.asp>, accessed 03/27/13) to facilitate enrollment. The interactions between enrollees and researchers, however, are minimized in national registries, which may result in decreased

efficiency. For example, in the first year of operation, TrialMatch enrolled 11,744 volunteers but only 1.4% were confirmed to enroll in a research study, in part due to a high proportion of caregiver and healthy volunteer enrollees.⁵⁹

Local registries may be more effective at ensuring that viable research participants are enrolled in studies. At NYU, the ADC collaborated with the CTSA to create a community-based registry to recruit older adults for a cross-sectional positron emission tomography-magnetic resonance (PET-MR) biomarker study with a recruitment goal of 75 older adults. The registry collected the names of 590 individuals, of whom 147 expressed initial interest. Fifty-five individuals were telephone screened and 30 were scheduled and completed neuroimaging in the first two months of enrollment. Another 84 individuals agreed to review the study's informed consent; 40 of these individuals agreed to participate. Complete enrollment is anticipated within 6 months of initiating the study. Additionally, 40% of enrollees are from underrepresented minority groups. Of the 25 individuals who were not eligible for the PET-MR study, 6 were recruited to related studies. To date, approximately 12% of those in the NYU Aging Registry have enrolled in at least one study.

At UCLA, recruitment through a registry has boosted enrollment to many studies. Since inception in 2010, 567 individuals have signed consents-to-be-contacted. Of these, 282 have enrolled in the registry and 45 (16%) have enrolled in research studies. Twenty-four percent of these individuals have participated in biomarker studies (primarily neuroimaging), 27% have participated in longitudinal natural history studies, 22% have participated in clinical trials, and 27% have participated in other studies such as interview studies of barriers to prevention clinical trial participation.⁶⁰

Registries do have limitations. A thorough screening process remains necessary for each individual study recruiting from the registry. If the registry collects self-reported clinical data, that data may not always be reliable. This may be improved by linking to medical records, but the logistical and regulatory burden is increased for these registries. Alternatively, registries could incorporate validated self-rating scales such as the AD8⁶¹ that can detect the presence of cognitive impairment. Because AD is a progressive disease and registries typically collect static information, there remains the possibility that individuals eligible for specific trials at the time of registry enrollment may not be eligible at the time of trial recruitment. Systematic updates of registry information may minimize this concern but increase the burden on the research team. Successful registries also require resource support. The amount of resources will depend on the type and methods of the registry. To this point, the registries at UCLA and NYU have used telephonic and paper-based data collection, respectively, requiring staffing resources to collect data, complete queries, and contact participants.

The Internet and other technological approaches to improving recruitment

The recent rapid increases in computer and Internet availability in US homes may lend opportunities to facilitate research recruitment. In particular, online social networks may provide a means to improve awareness of trials. For example, one randomized trial found that peer leaders, communicating through Facebook groups, were effective at increasing HIV screening participation among at-risk minority men.⁶² On-line groups of caregivers might therefore provide a means to perform grass roots recruiting for AD research, though, to our knowledge, no studies have attempted this in a formal or controlled way.

Another aspect of technological advance that may support trial recruitment is the wide scale adoption of EMR. Such systems introduce the possibility of alerting physicians that their patient may be eligible for a trial and request that they discuss the study or refer the patient

appropriately.⁶³ Alternatively, such tools may be able to identify sufficient numbers of eligible participants to conduct studies.⁶⁴

Remaining gaps in the literature

Though a large variety of interventions aimed at improving recruitment to trials have been attempted, controlled comparisons of strategies are lacking. Moreover, the cost-effectiveness of strategies is rarely examined. Thus, investigators have little guidance in choosing how to use often extremely limited budgets toward trial recruitment.

Few studies have demonstrated effective strategies at improving minority participation, especially to trials. It is likely that unique strategies will be needed for different racial and ethnic groups, but here too, studies that compare attitudinal or logistical burdens among distinct minority populations are lacking.

One potentially effective strategy for improving minority participation rates in AD trials would be to increase enrollment of AD patient participants who lack a spouse. Minority AD patients are more likely than Caucasians to have a nonspousal caregiver.^{65–66} In a series of six ADCS trials, though only 10% of participants were minority race or ethnicity, nearly half of the minority participants enrolled with a nonspousal study partner.¹⁰ Specific interventions for improving participation rates among nonspousal caregivers are lacking, but preliminary data suggest that the attitudes of these caregivers, not the burden of their role, may be responsible for their low participation rates (Cary et al., *submitted*).

Summary and conclusions

Traditional means of recruiting eligible AD research participants are often inadequate and improved methods are required. Among viable recruitment strategies, shifting toward community-based participatory methods and maintaining pools of potential participants that can be called when initiating new studies may expedite trial enrollment. While national registries may be associated with large media campaigns, local registries may provide particularly valuable tools to investigators conducting clinical research in AD. Local registries may vary in their sophistication, but even straightforward paper-based data collection under an IRB-approved protocol may enhance research recruitment into a variety of AD-related research projects, ranging from clinical trials to biomarker studies to caregiver surveys. An example of a coordinated model that could be explored is for national groups to facilitate enrollment to local site registries. We recommend that all ADCs consider implementation of a community-based research registry. Among NIA-funded ADCs, this might be conducted through Education Cores or in collaboration with CTSA or Geriatric Education Centers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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