

Review

Patient Engagement: The Fundació ACE Framework for Improving Recruitment and Retention in Alzheimer's Disease Research

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Abstract. Alzheimer's disease (AD) research is at a critical time. The global society is increasingly aware of the frightening rate of growth of the human and financial burden caused by this condition and of the urgent need to halt its progression. Consequently, the scientific community holds great responsibility to quickly put in place and optimize the machinery necessary for testing new treatments or interventions. In this context demand for participants for AD research is at an all-time high. In this review, we will focus on a methodological factor that is increasingly recognized as a key factor that shapes trial populations and affects validity of results in clinical trials: patient engagement, recruitment, and retention. We outline specific problems relevant to patient engagement in AD including recruiting enough participants, difficulties in participant retention, ensuring the recruited sample is representative of the general AD population, the burden of screening failures, and new challenges related to recruiting in preclinical disease. To address the urgent need for more research studying the applicability and cost-effectiveness of different recruitment strategies across different settings and nationalities, we describe the Models of Patient Engagement for Alzheimer's Disease (MOPEAD) project, a public-private partnership promoted by the Innovative Medicine Initiative (IMI), which will provide a large multinational quantitative analysis comparing different innovative recruitment models. We also discuss strategies that address each problem and draw on the experience of Fundació ACE to argue that focusing resources on comprehensive AD centers that offer coordinated clinical and social care and participate in basic and clinical research, is an effective and efficient way of implementing many of the discussed strategies.

Keywords: Alzheimer's disease, clinical trials, community outreach, Fundació ACE, MOPEAD, patient engagement, recruitment, retention

INTRODUCTION

Global Alzheimer's disease (AD) research is at a critical time. AD is the first cause of dementia

worldwide. The 2015 World Alzheimer Report estimates that the 46.8 million people worldwide living with dementia will almost double every 20 years [1]. The global society is increasingly aware of the frightening rate of growth of the human and financial burden caused by this condition, increasing from 604 billion in 2010 to 818 billion US\$ in 2015, and of the

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urgent need to halt its progression. In the wake of this increased sense of urgency, society is calling for increased action and governments worldwide are responding by recognizing dementia as a public health priority and drafting national plans that increase funding and define strategies to defeat AD [2, 3].

Consequently, the scientific community holds great responsibility to quickly put in place and optimize the machinery necessary for testing new treatments or interventions. Of the many methodological factors that can be improved in AD trials, we will focus on patient engagement, recruitment, and retention. This issue has perhaps garnered less attention than other topics such as study design, establishing effective outcome measures, or incorporating biomarkers but it is increasingly recognized as a key factor that shapes trial populations and affects validity of results [4, 5]. The demand for participants for AD research is at an all-time high. Data from the Alzheimer's Association trial match service [6] shows there are more than 250 studies currently looking for volunteers. A recent editorial warns that patient recruitment is the most important rate limiting factor delaying therapy development and is poised to derail the first goal of the National Plan to Address Alzheimer's Disease: to prevent and effectively treat Alzheimer's Disease by 2025 [7]. It describes a meeting in which key stakeholders including the Alzheimer's association, academics, government agencies, and industry outlined an action plan to address this problem. Another recent report from the EU/US task force noted that AD research is faced with unreasonably long periods of recruitment, small proportion of patients recruited per center, and unacceptably high drop-out rates and called for increased research focused on understanding why patients choose or refuse to participate and quantifying the impact of different inclusion criteria and strategies on recruitment [8].

In the following pages, we will outline specific problems relevant to patient engagement in AD (Table 1) including recruiting enough participants, difficulties in participant retention, ensuring the recruited sample is representative of the general AD population, the burden of screening failures, and new challenges related to recruiting in preclinical disease. We will also discuss strategies (Table 1) that address each problem and draw on the experience of Fundació ACE [9] to argue that focusing resources on comprehensive AD centers that offer coordinated clinical and social care and participate in basic and clinical research, is an effective and efficient way

of implementing many of the discussed strategies. Fundació ACE Institut Catala de Neurociències Aplicades, herein after ACE, has developed an integrated multidisciplinary care model in Barcelona (Spain) following the guidelines of the "Catalan Model for Cognitive and Behavioral Disorders in Social Health Care [10]" that includes diagnosis, therapy, follow-up care, daycare, and a day hospital in the context of an active research program. Since its start in 1996 up to 2016, ACE has performed 21737 diagnoses, evaluated 17642 families, and participated in 128 phase I, II, and III clinical trials.

INCREASING THE NUMBERS OF POTENTIAL PARTICIPANTS

The first challenge is increasing the pool of potential participants. The demand for participants in AD research is at an all-time high. Based on data from clinicaltrials.gov, the National Institute on Aging (NIA, USA) counted more than 150 open studies calling for more than 70,000 participants which could require screening of more than 700,000 potential volunteers [11]. Furthermore, the recent trend of focusing efforts in preclinical and prodromal AD will require more subjects and longer follow-up time to demonstrate treatment effects [12]. Low trial awareness and unfavorable attitudes toward participation are factors that negatively influence recruitment which affect patients, referring doctors, and the society at large. Studies in the US [13] and Europe (IMPACT study, [14]) suggest that the majority of primary care doctors are not aware of AD trials in their area. Patients and families generally depend on their health care providers for information about available clinical studies and doctors who are not specialized in cognitive disorders or aging may understandably not be aware of all the studies recruiting in their area. Reports suggest that willingness to participate depend more on attitudes toward research than caregiver burden [15–17]. Specific concerns regarding the potential harm of treatments and diagnostic tests, the logistical and time consuming burden, or the futility of participation can cause unfavorable attitudes toward participation in patients, care-givers and doctors alike [14, 18–20]. Primary care physicians also cite lack of time and availability of appropriate diagnostic tools to screen for cognitive impairment as significant barriers to referral to AD studies. These factors probably also contribute to poor detection of cognitive impairment in primary care settings, 20%

Table 1
Problems and remedial strategies in patient engagement for AD research

Problems and remedial strategies in patient engagement for AD research

Increasing the pool of potential participants

- *Increase awareness and improve attitudes towards research via advertising, education, and community outreach campaigns.
- *Maximize referrals through coordination with primary care and other local medical centers and establishment of best practice guidelines for screening for cognitive impairment.
- *Increase potential pool of participants by expansion and coordination of existing participant registries.
- *Increase the number of recruited subjects by expanding the number of recruiting sites.

Improving participant retention

- *Target outreach and adapt trials to the needs of care-givers, especially non-spousal care-givers.
- *Make participation more rewarding and foster a sense of purpose by improving communication and giving regular feedback to participants.
- *Evaluation of patients' social circumstances and support resources to direct them to appropriate studies and trials.
- *Establish a relationship of trust through integrated and continued clinical and social care.

Ensuring representativeness of the recruited sample

- *Implementation of community based participatory research methodology.
- *Combining community outreach with increasing recruitment efforts in "satellite clinics" which primarily attend minority populations generally due to their geographical location.

The burden of screen failures

- *Ensure availability of appropriate diagnostic tests and clinical expertise in the recruiting center by:
- *Recruiting from the same center where patients are diagnosed and followed
- *Recruiting at centers that participate in basic and clinical research programs

Recruiting for prevention trials

- *Requires far-reaching strategies that act upon multiple levels to engage a primarily non-memory clinic population.
- *Large informative campaigns directed at the general public explaining the urgency of halting AD's progression and the importance of early diagnosis and research to achieve this goal.
- *Innovative initiatives that facilitate the arrival of cognitively intact individuals to memory clinics (such as the Open House Initiative).
- *Existence of registries of cognitively healthy individuals who are potentially willing to participate in research studies.
- *Existence of observational cohorts with available biomarker data in which participants are asked upon entry about their willingness to enroll in clinical trials in the case of positivity.

of dementia and 60% of MCI cases by some reports [21]. Finally, due to a combination of restrictive inclusion criteria (age restrictions, minimum MMSE score, level of education, requirement of a study partner, etc.) and elevated prevalence of comorbidity and poly-pharmacy, a surprisingly small proportion of AD patients are actually eligible for trials, 27% and 10–13% of AD patients from research [22] and clinical [23, 24] settings, respectively.

Expanding the number of recruiting sites could be a forthright way of increasing recruitment; however, there is insufficient evidence to direct its implementation. Studies recruiting from multi-national sites face difficulties derived from differences in patient populations, cultural practices, and regulatory agencies [5] and existing research suggests there are significant differences in patient sample characteristics and efficiency depending on the setting (memory clinic versus community [37–39]) or nature (academic versus commercial [40, 41]) of the recruiting center. We need more studies that compare the success and cost-effectiveness of recruiting from different sites including memory clinics, primary care centers, residential homes, and other non-traditional settings

such as community centers, or web-based portals. These gaps in knowledge motivated the design of the Models of Patient Engagement for Alzheimer's Disease (MOPEAD) study [42]. Its objective is to understand the obstacles to early diagnosis and treatment faced by AD patients in various European communities and to develop and evaluate innovative models to overcome them. MOPEAD is a multinational European public-private partnership promoted by the Innovative Medicine Initiative (IMI) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) that will be carried out by 14 partners including academic centers and industry. Four screening models will be tested simultaneously in five European countries to evaluate cost-effectiveness for identifying subjects with early AD in community settings with different cultural and socioeconomic conditions. The screening models that will be evaluated include online cognitive testing preceded by an online marketing campaign, a memory clinic evaluation preceded by a publicity campaign (Open house model [37]), primary care physician screening based on short cognitive tests and dementia risk score calculation [43], and a similar screening

procedure undertaken at a specialist outpatient clinic where subjects present elevated risk of dementia: a diabetes clinic in a tertiary care center.

Coordination with primary care and other local medical centers is essential for maximizing referrals. ACE has a contract with the Health Ministry of the Government of Catalonia designating it as a referral center for evaluating cognitive impairment that supports referrals from the districts of greater Barcelona. ACE has received 7,327 new referrals since 2013. Evidence supporting screening for cognitive impairment in the general population is still inadequate [34]; however, publication of best practice guidelines regarding when and how to screen for cognitive impairment or when to refer to the nearest memory clinic could be of great help to primary care and other non-dementia specialists. The professionals at ACE have contributed to best practice guidelines of dementia care [35] and perform teaching activities at primary care centers promoting communication and coordination between centers. The expansion and coordination of existing participant registries has been proposed as a method to increase enrollment [11]. However this remains a challenging task as registries can differ in scale (multinational: European Prevention of Alzheimer's Consortium [EPAD], Global Alzheimer's Platform [GAP]; national: Alzheimer's Prevention Registry, Alzheimer Association's TrialMatch; local institute-specific registries at academic and research centers), model (disease-specific versus general recruitment), and type of data contained (contact information, medical data) and little research is available for guidance [36]. Besides increasing the quantity and speed of recruitment, recently started multinational initiatives such as EPAD and GAP will play a major role in increasing sustainability of AD research. Traditionally, the majority of AD trials result from the uncoordinated efforts of various private companies and a considerable part of their huge costs can be ascribed to the requirement of having to reconstruct multiple resources for each trial. Costly tasks such as creating registries, establishing the network of sites and individual site preparation, preparing IRB and other administrative documentation, establishing evaluation and data collection protocols, and training personnel are repeated for each trial. The purpose of these initiatives is to build and maintain a structured resource (by coordinating multinational registries) that will allow continued access to patients and to establish a harmonized trial protocol and network of trial ready sites that will improve the logistical

burden, cost-efficiency, and comparability of future research.

Education and advertising campaigns could be effective for increasing awareness and improving attitudes toward participation. Some research suggests that investing in community-based education and outreach is more effective than educating primary care providers [18, 25] and that direct mailings are more effective than newspaper ads or community outreach [26] but more research is clearly needed comparing effectiveness of targeting different populations (i.e., primary care doctors, residential homes inhabitants and staff, patient support groups, community center members, or the general public) and using different mediums or campaigns including lectures, ground campaigns and pamphlets, and ads in newspapers, radio, television, or internet. Planning and executing these campaigns requires personnel and resources typically available only to large centers. For example, the NIA funded AD Research Centers (ADRC) have education cores in charge of outreach programing. Similarly, ACE counts with an outreach team in charge of maintaining a website and monthly electronic magazine, of interacting with social networks and the media (in 2016 the news generated by ACE reached an estimated audience of more than 60 million people) and organizing community outreach activities (La Nit de l'Alzheimer [27], Regala Memòria [28], Dia Mundial de l'Alzheimer) to raise awareness. The expenses generated by the ACE outreach team account for about 4% of the total annual expense. Activities such as the Open House Initiative (OHI) [29], offering free cognitive evaluations once a month (452 evaluations in 2016), the Estimul' Art program [30], which organizes visits to art museums for patients and families, diverse teaching and support activities [31], and publication of multiple books and guides [32, 33] promoting age-specific AD education and awareness are based on the principles of "social responsibility" and "giving-first" that foster a relationship of respect and trust with the community.

INCREASING PARTICIPANT RETENTION

Improving retention of study participants is a challenge of vital importance. Participant drop-out is a key contributor to selection bias which poses a great threat to the internal validity and generalizability of results in clinical trials [4, 5]. More research analyzing the reasons participants' drop-out of AD trials and evaluating different remedial strategies is urgently

needed given the long follow-up periods required for trials aimed at preventing progression or development of cognitive impairment in MCI and healthy populations respectively [44]. Analysis of one recent trial in MCI with a 30% drop-out rate showed that being non-white, not reaching university level education, reporting greater depressive symptoms, having a non-spousal study partner, and recruitment by a commercial non-academic center were associated with higher risk of drop-out [40]. A survey conducted by the Center for Information and Study on Clinical Research Participation [45] suggests that participants who drop-out are more likely to report difficulty understanding the consent form, un-satisfaction with the answers to their questions in the consent form interview, and described the site visits as “stressful.” They were also less likely to report self-motivation as the primary reason for participation.

The factors contributing to poor retention and the strategies needed to address them partly overlap with those pertaining to initial recruitment. In particular, increasing outreach, education, or advertisements targeting health care providers, patients, caregivers, and the general public could help improve poor motivation and unfavorable attitudes towards research that affect recruitment and retention alike. Targeting outreach and adapting trials to the needs of care-givers, especially non-spousal care-givers, seems especially important given that participants with non-spousal study partners are less willing to participate [15] and twice as likely to drop-out [40]. One study suggests that reducing travel inconveniences, increasing the probability of assignment to a treatment group, and educating about the risks of participation could increase care-givers willingness to participate [16]. Contrary to what some may expect, a recent review reports that disease severity, trial length, or placebo group placement did not clearly affect drop-out rate [5] suggesting that other factors affecting participants’ subjective experience such as the quality of care and the information received or the sense of purpose, of being part of a larger enterprise, are more important determinants of study completion. The finding that subjects recruited by commercial centers are twice as likely to drop-out also supports this idea [40]. Interviews of AD research participants show they value the access to diagnosis, care, emotional support and up-to-date information about new treatments [17] that come with participation in clinical research. It follows that improving communication and establishing a relationship of trust with patients and care-givers is paramount to increase adherence.

Offering regular feedback via written reports or personal meetings and organizing periodic research participant gatherings are examples of activities that could be implemented. Offering continued care, from both clinical and social perspectives, instead of discontinuing visits in advanced stages of disease or at the end of a trial is essential for participants to feel supported instead of utilized. Furthermore, knowledge of patients’ social circumstances and support resources can help direct them to appropriate studies and trials increasing the probability of study completion. Patients and families seek out and trust in ACE because of this type of integrated care. At first visit, every patient receives a clinical and social evaluation. Follow-up medical (18,545 visits since 2013) and social care (9,898 families evaluated and followed up between 2006–2015) [46] is also always offered and many patients (5,291 since 1991) participate in day care and cognitive [47] stimulation programs.

ENSURING REPRESENTATIVENESS OF THE RECRUITED SAMPLE

The recruited sample should be representative of the general population presenting the studied condition to ensure external validity and generalizability of trial results. However, this is usually not the case in AD trials [24]. One of the main reasons is that many trials exclude subjects with significant comorbidities or taking multiple medications making the majority of AD patients followed in clinics ineligible for trials [23, 24]. In our experience, around 10% of patients diagnosed with AD at ACE are eligible for trials and the main reasons for exclusion are advanced severity of disease, comorbidities, poly-pharmacy, and absence of a study partner. It is also well documented that research participants tend to be of higher educational and socioeconomic levels than the general population [48]. There are probably multiple interrelated causes of this phenomenon including increased health awareness and confidence in science and research institutions in individuals of higher sociocultural levels. With respect to AD research in particular, differences in conceptualization and attitude towards the disease across different social groups may also be a relevant factor [46]. It is noteworthy that ethnic and racial minorities are systematically underrepresented in clinical trials and observational studies. A 2007 review showed that in the US only 3.2% of the subjects included in clinical trials promoted by industry were non-

white [49]. Possible causes are distrust toward the medical establishment and research institutions, barriers to access medical services, language barriers, logistic and financial burden, lack of similarity and cultural empathy between researchers and potential participants [11, 50]. This over representation of white participants supposes a dangerous bias for AD research, especially since there is evidence showing that minority groups could have increased risk of presenting AD [51] and the US Census Bureau estimates non-Hispanic whites will make up less than half of the population by the year 2044 [52].

Different strategies have been proposed and tested with the objective of recruiting representative samples for clinical trials and increasing research participation in racial and ethnic minorities. Community outreach is a useful strategy in which direct contact is established with a specific community via alliances with its leaders or representative associations. Inviting community leaders and members to lectures or informative seminars regarding disease management and research opportunities are usual practices. The concept of community based participatory research (CBPR) defines a structured and bidirectional methodology of community outreach that endeavors to reduce the distance between researchers and a community by establishing a forum of mutual communication and learning [53]. Investigators inform of research results with the objective of causing a positive impact in the health of the community and so its members understand the importance of scientific research and the principles it is based on. Likewise, researchers receive feed-back from community members regarding their preferences and opinions as potential participants, allowing them to adapt research methodology to “real world” community needs. In this manner the community becomes an active player in the research process and a relationship of mutual trust is generated [54, 55]. Instead of attributing the absence of individuals from a specific community to their distrust of scientific and medical institutions, this methodology helps scientists take an active role in studying the role of the scientific community in creating and reducing this distrust. CBPR methods have been used successfully for recruiting minorities in AD research [56, 57]. For its success, it is necessary that researchers establishing contact understand specific aspects about the culture of the community and maintain direct and stable contact which typically requires research centers to designate personnel and resources specifically to outreach activities. Promoting the “retooling” of staff scien-

tists to learn how to build community partnerships could be an effective strategy for success of community outreach activities. Another strategy that has also proved useful when combined with community outreach methods [58, 59] involves concentrating recruitment efforts on “satellite clinics” which primarily attend minority populations generally due to their geographical location.

THE BURDEN OF SCREEN FAILURES

Screening accuracy has profound effects on the number of participants required and the cost and length of recruitment. A failure in screening in AD trials generally denotes a participant who does not meet the inclusion/exclusion criteria after undergoing lengthy (possibly >10 h) and expensive (>8000 US\$ per subject) procedures including clinical and cognitive evaluations, blood and CSF analysis, and MRI and PET brain scans. Screen failure rate has been worryingly high in AD trials and inclusion of subjects without AD is often cited as one of the main reasons of failed trials in the past [60]. The introduction of AD biomarker inclusion criteria has helped identify subjects with putative AD; however, it has introduced the new problem of predicting which subjects will be amyloid PET or CSF positive and screen failure rate has sky rocketed to 70–90% in recent trials of prodromal AD (MCI with positive AD biomarkers) [61]. The younger age of participants in prevention trials comes with lower prevalence of some causes of screen failure such as co-morbidity and poly-pharmacy however the probability of biomarker positivity indicating brain amyloidosis is also lower making the reduction of screen failure rate an even greater challenge in trials of preclinical AD (cognitively intact subjects with positive AD biomarkers).

Improving screening accuracy starts early in the trial design phase. The selection of inclusion/exclusion criteria requires substantial prior knowledge and planning to identify a target population which is feasible to recruit with the available resources. The ability to perform accurate and reliable clinical diagnoses is also essential to reduce screen failures and crucially depends on the availability of appropriate diagnostic tests and clinical expertise in the recruiting center. Recruiting from the same center where patients are diagnosed and followed entails that the same team of expert clinicians is involved or at least in frequent and close communication with the professionals in charge of recruiting.

Active participation in basic and clinical research programs and longitudinal studies adds further expertise that benefits screening accuracy. The use of sample enrichment and targeted clinical trial designs hold great potential for reducing recruitment requirements by increasing the power of finding treatment effects in heterogeneous conditions such as AD [12, 62]. These techniques are based on the idea that the treatment under study might benefit a subset of patients in the population in particular [63]. In AD trials this may entail enriching a MCI sample with subjects that are likely to show early significant decline or randomizing only subjects with positive brain amyloidosis biomarkers to receive an anti-amyloid medication. Since these techniques rely critically on the challenging task of reliably identifying a subset of patients, errors in implementation can result in elevated rates of screening failure. This is yet another reason that supports concentrating recruitment activity in comprehensive AD centers that run basic and clinical research programs besides offering diagnosis and continued care. For example, by developing its own neuropsychological battery and normative data that allow calculation of sensitivity and specificity for detecting dementia [64], ACE is able to identify a subset of MCI in which 70% of subjects convert to dementia in less than 2 years [65]. Similarly, active genetic [66], CSF biomarker, neuroimaging [67, 68], and longitudinal aging [69] research programs provide the tools and knowledge of how to classify patients according to genetic, CSF, neuroimaging, and clinical features and contribute to the low screen failure rate at ACE (72 out of 384 patients, 19%, in 2016).

IMPLICATIONS OF RECRUITING FOR PREVENTION TRIALS

Preventive clinical trials are gaining importance as the scientific community realizes it may be necessary to intervene at earlier stages of AD for treatments to be effective [70]. Different levels of prevention have been defined in the context of the establishment of preclinical AD as a nosologic entity [71]. Primary prevention targets healthy subjects with the objective of preventing the biologic processes associated with the disease whereas secondary prevention is directed at cognitively intact subjects that present preclinical AD [72], which refers to biologic evidence of AD in the form of deterministic genes or positive biomarkers. Primary and secondary prevention trials present

many common features but there are also important differences that can affect recruitment.

A common feature is that the target population of preventive trials is generally not found in the usual clinical settings. Cognitively intact individuals typically make up only a small proportion of the population attended by memory clinics. These individuals are generally younger than those with MCI or dementia and are usually active members of the workforce with little availability for multiple visits and medical procedures. Another common feature is that the probability of short term cognitive decline is lower in this population requiring an elevated number of participants or longer follow-up periods to ensure enough power to detect statistically significant treatment effects [73]. Sample size and trial length are especially large in primary prevention trials [74, 75] because, in the absence of biologic evidence of AD, the expected rate of progression is similar to that of the general population. In this case, an often employed strategy is “enrichment” of the sample with AD risk factors such as older age [76], APOE carriers [77], or other modifiable risk factors [78]. Though the expected rate of progression is faster, secondary prevention trials present their own significant logistic and ethical challenges [79]. In this case, cognitively intact individuals are told they have an increased risk of developing cognitive impairment and dementia (possibly without a clear time-frame) and are offered to participate in a complex trial consisting of multiple time-consuming visits, medical procedures which are not always innocuous, and exposure to an experimental treatment. All of these circumstances complicate the recruitment process. In our experience at ACE, the time necessary for informed consent is significantly longer and the proportion of individuals who decline trial participation is much higher than in MCI or AD trials. Adding positive biomarkers to inclusion criteria also complicates recruitment. Biomarker analysis is not part of the typical work up in cognitively intact subjects and predicting a positive result based on clinical evaluation is very challenging which can lead to high screen failure rate due to biomarker negativity [36].

These difficulties related to recruiting for AD prevention trials necessitate far-reaching strategies that act upon multiple levels to engage a primarily non-memory clinic population [73]. Large informative campaigns directed at the general public explaining the urgency of halting AD’s epidemic progression and of the importance of research to succeed in this enormous challenge. The global society needs to

understand that dementia and AD are partially preventable by intervening upon modifiable risk factors and that these conditions begin with a long preclinical stage in which interventions are potentially more effective. In this manner it is foreseeable that the number of asymptomatic people who decide to undergo a “cognitive check-up” and enroll in research programs will grow.

Memory clinics can implement certain initiatives with the objective of facilitating the arrival of cognitively intact individuals. Since 2008, ACE carries out an Open House Initiative (OHI) as part of its corporate social responsibility program in which a local publicity campaign invites anybody over the age of 50 to come to the memory clinic for a “cognitive check-up” free of charge and without the requirement of being referred by another medical professional [37]. Subjects meeting inclusion criteria for any ongoing research studies are invited to participate on a later date. Since its start, the OHI has attracted almost two-thousand (approximately 300 in 2016) cognitively intact individuals which would probably not have come to the memory clinic otherwise and many of these individuals have enrolled in clinical trials or observational studies [69]. On average, each evaluation includes 40 minutes of a neurologist or neuropsychologist’s time for performing the cognitive evaluation, 20 minutes of administrative paperwork, and 15 minutes of nurse-time. It is of note that the setting and mode of recruitment can affect sample characteristics. There is evidence showing that cognitively intact subjects recruited from memory clinics show higher rates of AD biomarker positivity than those recruited from the community [39, 80]. Thus recruiting from non-memory clinic settings gives access to a larger pool of potential participants but may result in lower prevalence of positive AD biomarkers and higher rates of screen failure [37].

Registries of cognitively healthy individuals who are potentially willing to participate in research studies could be a valid source of participants for preventive clinical trials. Proper coordination between multiple registries and a network of centers that are geographically close to potential participants and offer the possibility of participation is necessary to maximize efficiency of this strategy [55]. However, in the case of secondary prevention trials that require positive biomarkers, most subjects in the registry would probably not be eligible and many may not accept enrollment into a trial of an experimental drug. In this case, an intermediate option that could facili-

tate recruitment of individuals with preclinical AD is the existence of observational cohorts with available biomarker data in which participants are asked upon entry about their willingness to enroll in clinical trials in the case of biomarker positivity and the consequent increased risk of developing cognitive impairment [81].

CONCLUSION

The goal of this article was to highlight the critical role of patient engagement in the challenge of developing treatment and prevention strategies for AD. We outlined specific problems and discussed various remedial strategies that can be implemented by comprehensive AD centers. To increase the pool of potential participants we considered the possibility of expansion of recruiting sites, coordination of participant registries, coordination with primary care and other local medical centers, and increasing awareness and improving the general public’s attitude towards participation in research through advertisement and outreach. Targeting outreach and adapting trials to the needs of caregivers, improving communication and offering regular feedback, and building a relationship of trust through continued clinical and social care could improve participant retention in trials and longitudinal studies. Implementation of community based participatory research methodology could help improve diversity and representativeness of the recruited sample with respect to “real-world” AD patients in the population. Focusing recruitment in the same centers that diagnose and follow patients and that participate in research helps guarantee availability of the clinical expertise and technical resources that are necessary to reduce screening failure rate. Finally, specific challenges relating to recruitment in the preclinical AD population were discussed.

Recruitment and retention is increasingly recognized as one of the most important rate limiting factors delaying therapy development and key stakeholders in AD research world-wide are designing work groups and action plans to address this urgent difficulty. We provided an overview of specific difficulties related to patient recruitment and retention and strategies to address these problems drawing from our experience at ACE. There is an urgent need for research studying the applicability and cost-effectiveness of different recruitment strategies across different settings and nationalities. In this line, we described the Models of Patient Engagement for

Alzheimer's Disease (MOPEAD) project which will provide a large multinational quantitative analysis comparing different innovative recruitment models. The specific methods and organization of ACE are likely not generalizable to all parts the world, however the success of ACE shows that a model of integrated clinical and social patient-centered care with a built-in research emphasis and an active outreach team can effectively implement strategies that increase patient engagement in the local community.

DISCLOSURE STATEMENT

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/17-0866r1>).

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