Short Communication

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Implementing a Memory Clinic Model to Facilitate Recruitment into Early Phase Clinical Trials for Mild Cognitive Impairment and Alzheimer's Disease

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Abstract

BACKGROUND: The recruitment challenges for MCI and AD subjects into clinical trials are well known, and this is particularly true for early phase studies. Currently, only 10-20% of all patients who are referred for research from the community are trial eligible (Grill and Karlawish, 2011). Due to the limited and specific study objectives in early phase study designs, these rates drop to approximately one patient every two months. Barriers to research recruitment are multi-factorial, involving patient centered factors, issues related to caregiver/study partner participation, and aspects related to the involvement of their treating physicians. To address this challenge, we implemented a Memory Clinic within PAREXEL's Early Phase Clinical Pharmacology Unit. Our objective was to significantly facilitate recruitment into AD clinical trials by providing resources and education to patients, their treating physicians, and caregivers in the community.

METHOD: The Clinic's primary goals were to increase research visibility and partnerships with local organizations and referring physicians. Members of the research team co-sponsored community outreach events with local organizations, thereby increasing awareness about the services of this memory clinic. Secondly, physician outreach was expanded to include those who were not previously amenable to clinical trial referrals. Finally, Memory Clinic patients were given clinical evaluations, free of charge and the results were discussed with the patients and their caregivers. If the patients were interested in hearing more about possible research opportunities, they were referred to the early phase unit for a screening visit.

RESULTS: We found that new referrals for research participation significantly increased as a result of this new paradigm. In 2016, 12 patients diagnosed with MCI or AD per protocol, were referred to a research study and 3 were randomized. In 2017, 98 patients were referred and 16 were enrolled In addition, our referral network increased with 30 physicians over a 20 mile radius. Collaborations with national non-profit organizations also increased, thereby increasing public awareness about the importance of research participation in the development of new treatments for Alzheimer's Disease.

CONCLUSIONS: In summary, community engagement and providing referring physicians with a clinical service improved recruitment significantly for our phase 1 unit. Resource education, staff training, and dedicated medical professionals can significantly improve awareness about clinical research participation and provide additional participants over and above traditional recruitment methods and trial registry enrollment in a large urban area.

Key words: Enrollment, recruitment, early phase, clinical trials, Alzheimer's disease

Introduction

The prevalence of Alzheimer's Disease (AD) is expected to reach 1.1 trillion by 2050, in the absence of effective pharmacological interventions (1). The last novel treatment approved for AD was in 2003, despite the fact that there are currently 105 candidates in development across all phases of clinical trials (2). To address the challenge, a call to action by politicians, industry and academic leaders is ongoing, but even with the recent scientific advances in biomarker development, translational research, and clinical trial methodology, issues with AD recruitment hinder drug development (3, 4). Only 10-20% meet criteria for participation when they are referred for research, resulting in a national enrollment rate of one patient per research site every two months (4). Issues associated with eligibility are multi-factorial and involve patient-centered factors (e.g., comorbidities, concomitant medications, randomization to placebo), caregiver/study partner participation (e.g., availability), and limited involvement of their treating physicians (e.g., awareness about available trials).

A number of recruitment approaches exist to attract participants (e.g. appealing to previous research participants) (5). There are also significant initiatives to create patient database registries to facilitate recruitment among community-dwelling elders (6). However, there is limited evidence to suggest that these efforts successfully translate to enrollment into clinical trials. In response to the ongoing crisis facing patient recruitment, the National Institute of Aging and the Alzheimer's Association

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funded programs to address this unmet need. One such example is the Outreach, Recruitment, and Education Core (ORE) through the Alzheimer's Disease Research Center (ADRC) across the United States. Each ORE has a specific goal to educate the public about aging, Alzheimer's Disease, cognitive health, and research participation through different outreach initiatives, expert lectures, and avenues for expert patient care and evaluation. This resulted in the successful enrollment in some areas, proving that such models are effective and efficient ways of increasing patients' access to research and clinical care in their communities (7).

Although ORE's success is proven in academic settings and large teaching hospitals, the model had not been tested in commercial settings to evaluate its success in early phase (Phase I and IIa) clinical trials, where there is hesitation about research participation. Some reasons relate to the focus on safety, pharmacokinetic and pharmacodynamics, with minimal therapeutic benefits to the patient. Early phase studies also tend to be more burdensome due to more frequent visits (or longer inpatient stays) and complex procedures (e.g. lumbar puncture, neuroimaging, cognitive testing) (8). These studies are also associated with higher risks, thereby excluding many older adults with common co-morbid medical conditions from participating. As such, traditional recruitment methods of advertising and database mining, fail to make these studies attractive to patients and their families. A more targeted and personalized approach to recruitment is required to overcome these hurdles and a model such as ORE can bridge the gap between recruitment targets and actual enrollment rates in early phase studies.

To test the model set forth by ORE, the PAREXEL Los Angeles Early Phase unit established a Memory Clinic, the goals of which were to facilitate recruitment by providing comprehensive neuropsychological evaluations to interested patients, perform consultation services to physicians, pre-identify appropriate patients for studies, and conducting educational activities about research participation. The Memory Clinic also provides information about resources available to the patient and their caregivers as it relates to healthy aging, dementia, and Alzheimer's disease.

Methods

The Memory Clinic is a pilot program modeled after ORE which focuses on community events, self-referrals and increased physician outreach. Patients are eligible for an evaluation free of charge, in exchange for hearing about clinical research and the overall goals of the clinic. There is no obligation to participate in research studies. Community outreach is done in a two-stage approach. First, a clinician or other member of the research team provides a lecture or a seminar on topics of interest such as healthy aging and dementia. At the completion of each lecture, psychometrists are on-site to administer questions regarding cognition and everyday life. This information is then reviewed by a clinician and an invitation for a comprehensive Memory Clinic evaluation is extended, if the complaints represented a marked decline from their previous level of functioning. Patients are also seen at the clinic through self, caregiver, or treating physician referral. An important aspect of the clinic is to establish relationships with physicians in the community, educate them on the Memory Clinic goals and provide information on the utility of neuropsychological testing for clinical care. Once they became familiar with the concept, they refer patients with the hope of obtaining cognitive test results to assist with differential diagnosis and treatment planning. Physicians are also provided with information about potential research opportunities for their patients.

During the evaluation the patient, or their surrogate, is provided with an informed consent and educated about the overall goals of the memory clinic. The patient is given a comprehensive clinical evaluation including a review of their medical history, current medications, and a semi-structured interview to obtain collateral information. Patients are also administered tailored neuropsychological batteries, depending on the nature of the evaluation or referral question by the physician or family member. The neuropsychological battery included tests assessing attention/processing speed, working memory, learning and memory, visuospatial ability, language, executive functioning and mood, using the Wechsler Test of Adult Reading (WTAR), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Trail Making Test (TMT), Controlled Oral Word Association Test (COWAT), and Geriatric Depression Scale (GDS). The WTAR is a norm-referenced standardized measure of premorbid intelligence in English-speaking individuals 16-89 years of age (9, 10). The RBANS is a brief neuropsychological battery that consists of ten subtests which yield five index scores related to different cognitive domains (10). The TMT is a neuropsychological test of visual attention and task switching which provides information about speed of processing, cognitive flexibility, and executive functioning and found to be significantly related to functional decline in dementia (11). The COWAT is a verbal fluency test found to have significant age related effects (12). The GDS is a 30-item self-report assessment administered to screen for depressive symptoms in the elderly (13). Functional impairment is established using semi-structured clinical interviews. If additional tests are needed to further elucidate cognitive impairments, they are incorporated into the battery as appropriate. The tests are scored, interpreted, and written into a report that is shared with the patient and his or her medical provider upon request. Patient performances were discussed during interdisciplinary team conferences where they were diagnosed by consensus. If the patient meets

Table 1. Patient Characteristics for Age, Education, and RBANS Standard Scores

	Age	Education	Immediate Memory	Visuospatial	Language	Attention	Delayed Memory
AD (n=6)	76.76±6.52	12.94±5.61	66.57±14.56	88.16±25.45	76.14±19.19	79.71±17.34	53.00±11.37
MCI (n=17)	71.26±9.13	15.44±2.73	80.71±20.98	98.29±18.90	85.29±17.78	87.00±21.29	84.00±19.67
HNE (n=17)	66.26±9.19	14.78±2.78	97.72±16.52	102.65±13.59	93.06±11.68	99.50±11.80	101.81±10.56

AD=Alzheimer's Disease; MCI= Mild Cognitive Impairment, HNE=Healthy normal elderly or cognitively normal.

criteria for Mild Cognitive Impairment or Alzheimer's disease, they were subsequently invited for a feedback session to review their results with a clinician and discuss possible recommendations (14, 15). At the conclusion of the visit, participants were offered opportunities to screen for clinical research studies and if they were interested, a member of the project specific research team would meet with them individually. If patients did not meet criteria, they were still presented with opportunities for research participation as a member of another population (i.e. healthy older adults, healthy normal volunteers, Parkinson's disease, etc.)

Results

Approximately 169 individuals were referred through community outreach services targeting those with memory loss or their treating physicians. Of all those who were evaluated through the Memory Clinic, 52 were found to have MCI, 40 had AD, and 30 were determined to be cognitively normal. 47 patients were found to have cognitive impairments as a result of other etiologies (e.g. non-AD dementia, psychiatric impairments, traumatic brain injury, epilepsy, etc.). 110 patients were referred for research and the overall pool was ethnically and linguistically diverse. Approximately 60 patients spoke English and the neuropsychological characteristics of those who completed the neuropsychological battery in English (n=40) are provided in Table 1. Those who were non-English speaking, (e.g. Korean, Spanish, and Arabic) were administered a flexible neuropsychological assessment and a clinical interview in their native language. A total of 19 patients were eventually enrolled in a clinical trial. Other goals of the clinic were achieved by increasing the referral network to over 30 physicians within a 20 mile radius from the Memory Clinic location. Collaborations with national non-profit organizations also increased, thereby increasing public awareness about the importance of research participation in the development of new treatments for Alzheimer's disease and other related disorders.

Discussion

The findings from the Memory Clinic suggest that a model adopted in academia can be translated into a commercial clinical research setting with the proper clinicians and resources, resulting in increased awareness about clinical research and enrollment. Comprehensive neuropsychological assessments are costly, have limited insurance coverage, and the scarcity of clinical resources can lead to waiting lists delaying a diagnosis and access to care. Physician engagement in the research process increased as they became more aware of the importance of participation in clinical trials and the availability of research opportunities for their patients. Connecting caregivers and their families with resources in the community was also an added incentive and the cross-referrals between professional organizations and the Memory Clinic proved to be a mutually rewarding collaboration. As such, the Memory Clinic addressed common methodological challenges needed to improve recruitment and retention in AD clinical trials (3).

Our community outreach activities increased exponentially through the Memory Clinic. Perceptions about clinical trials shifted as organizations were more inviting, as a result of the service to the community, as opposed to using their event as a platform solely for recruitment. Educational seminars included information about the importance of research to the development of new treatments, as well as the medical and regulatory protections that are made on the patient's behalf. When patients and their families observed the relationship between members of the Memory Clinic and trusted organizations, they were more likely to request an appointment for an evaluation.

Caregiver resources were also addressed during Memory Clinic visits. Families were taught about lifestyle changes and modifiable risk factors to improve cognition and prevent the progression of dementia. Education related to the influences of caregiver distress on health and psychological functioning was discussed and caregivers were given information about how to seek respite to reduce their burden. Recommendations to help improve daily function and communication with the patient were also provided. Consistent with reported findings in the literature, caregiver access to this information through the Memory Clinic addressed an unmet need in the AD community and also increased overall interest in research participation (16).

An unintended benefit of the Memory Clinic, was the opportunity to evaluate patients from other neurologic populations and add them to the research database for future studies. Due to the fact that the Memory Clinic was available as a community resource, patients with a wide range of cognitive impairments across different etiologies were invited for an assessment. This was done primarily to increase our contacts with other patient

populations for other future research opportunities.

While the Memory Clinic was useful in increasing our patient interactions and identifying people for research participation, many were still reluctant to participate in early phase clinical trials. Of those who were, the selection criteria within the individual research protocols were prohibitive (e.g. many did not qualify based on the fact that they were recently diagnosed and subsequently not stabilized on their medications, or they had several comorbid conditions or medications that were prohibitive, or they were simply above the age limit). Future research of our Memory Clinic data will include evaluating how the clinical diagnosis given as part of the clinical neuropsychological assessment differs from the criteria set forth by common AD protocols. Moreover, strategies for recruitment will center on the importance of evolving patient engagement as outlined by other initiatives in the AD community (17).

Another common barrier to research participation was the requirement of invasive procedures as part of the early phase research studies. Even if the patient was willing to engage in these procedures, their caregivers were reluctant to let them continue. While innovative biomarkers serve as important pharmacokinetic and pharmacodynamic measures of signal detection in early phase trials, they also pose a challenge to recruitment. As the knowledge within the scientific community evolves, consideration may be given towards creating adaptive protocol designs to accommodate a patient's level of comfort with the procedures and facilitate recruitment.

Existing literature shows that attitudes towards research are the strongest predictors of willingness to participate (18). A significant number of non-English speaking patients, were referred for research studies. Utilizing multi-lingual staff with training in culturally competent neuropsychological testing increased the patient's and their caregiver's willingness to engage in the evaluation and hear about opportunities for research (19, 20). This has previously been proposed as a necessary component of improving recruitment rates in AD and future endeavors for the Memory Clinic will include expanding the ethnic subgroups to increase the heterogeneity of our overall research samples.

In summary, the Memory Clinic proved to be a useful model of recruitment within the setting of a commercial early phase research unit. Addressing significant barriers to patient enrollment such as individual patient factors, caregiver influences, and involvement of their treating physicians was instrumental in the assessment of individuals interested in participation and subsequent research participation. The Memory Clinic is a relatively recent concept in the unit and some of the original patients are returning for their annual follow-up visit. Further work will be done to assess the patients' longitudinal cognitive status and determine if attitudes towards research participation changes as a function of dementia severity.

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Ethical standards: Patients and/or legal proxies signed informed consent for the evaluation.

References

1. Alzheimer's A. 2016 Alzheimer's disease facts and figures. Alzheimers Dement. 2016;12(4):459-509.
2. Cummings J, Lee G, Mortsdorf T, Ritter A, Zhong K. Alzheimer's disease drug development pipeline: 2017. Alzheimers Dement (N Y). 2017;3(3):367-384.
3. Vellas B, Hampel H, Rouge-Bugat ME, et al. Alzheimer's disease therapeutic trials: EU/US Task Force report on recruitment, retention, and methodology. J Nutr Health Aging. 2012;16(4):339-345.
4. Grill JD, Galvin JE. Facilitating Alzheimer disease research recruitment. Alzheimer Dis Assoc Disord. 2014;28(1):1-8.
5. Grill JD, Karlawish J. Addressing the challenges to successful recruitment and retention in Alzheimer's disease clinical trials. Alzheimers Res Ther. 2010;2(6):34.
6. Williams DE, Vitiello MV, Ries RK, Bokan J, Prinz PN. Successful recruitment of elderly community-dwelling subjects for Alzheimer's disease research. J Gerontol. 1988;43(3):M69-74.
7. Bachman DL, Stuckey M, Ebeling M, et al. Establishment of a predominantly African-American cohort for the study of Alzheimer's disease: the South Carolina Alzheimer's disease clinical core. Dement Geriatr Cogn Disord. 2009;27(4):329-336.
8. Watson JL, Ryan L, Silverberg N, Cahan V, Bernard MA. Obstacles and opportunities in Alzheimer's clinical trial recruitment. Health Aff (Millwood). 2014;33(4):574-579.
9. Duff K, Patton D, Schoenberg MR, Mold J, Scott JG, Adams RL. Age- and education-corrected independent normative data for the RBANS in a community dwelling elderly sample. Clin Neuropsychol. 2003;17(3):351-366.
10. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol. 1998;20(3):310-319.
11. Marshall GA, Rentz DM, Frey MT, et al. Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease. Alzheimers Dement. 2011;7(3):300-308.
12. Rodriguez-Aranda C, Martinussen M. Age-related differences in performance of phonemic verbal fluency measured by Controlled Oral Word Association Task (COWAT): a meta-analytic study. Dev Neuropsychol. 2006;30(2):697-717.
13. Yesavage JA. Geriatric Depression Scale. Psychopharmacol Bull. 1988;24(4):709-711.
14. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263-269.
15. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):270-279.
16. Jennings LA, Reuben DB, Evertson LC, et al. Unmet needs of caregivers of individuals referred to a dementia care program. J Am Geriatr Soc. 2015;63(2):282-289.
17. Vellas B. Recruitment, retention and other methodological issues related to clinical trials for Alzheimer's disease. J Nutr Health Aging. 2012;16(4):330.
18. Grill JD, Raman R, Ernstrom K, Aisen P, Karlawish J. Effect of study partner on the conduct of Alzheimer disease clinical trials. Neurology. 2013;80(3):282-288.
19. Chow TW, Ross L, Fox P, Cummings JL, Lin KM. Utilization of Alzheimer's disease community resources by Asian-Americans in California. Int J Geriatr Psychiatry. 2000;15(9):838-847.
20. Perales J, Moore WT, Fernandez C, et al. Feasibility of an Alzheimer's disease knowledge intervention in the Latino community. Ethn Health. 2018:1-12.