Editorial

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Recruitment of At-Risk Participants for Clinical Trials: A Major Paradigm Shift for Alzheimer's Disease Prevention

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A major goal of the United States National Plan to Address Alzheimer's Disease is to prevent and effectively treat Alzheimer's disease (AD) by 2025. The advancement of biomarkers such as amyloid PET imaging over the last two decades broadened the focus of AD research to include prevention, targeting asymptomatic individuals at high-risk for AD for interventional treatment. AD prevention trials now routinely incorporate biomarker tests (e.g., amyloid PET imaging, cerebrospinal fluid tests, apolipoprotein E (APOE) genotyping) as risk assessment to identify preclinical AD participants who would derive maximum benefit from preventative therapy.

One of the biggest challenges facing our field is a transformation in the target therapeutic population, from a clinical population with an existing diagnosis of mild cognitive impairment (MCI) or dementia associated with AD to cognitively normal individuals at high risk in the community. It is imperative for our field to alter the conceptual framework surrounding recruitment science in AD prevention trials. In order to do this, we must increase public awareness to engage, educate, and identify potentially high-risk individuals for participation in AD prevention trials.

This paradigm shift presents several recruitment obstacles for clinical trials. The first is the engagement of large segments of cognitively normal older people to learn more about their risk. The creation of an AD prevention trial ready cohort demands that we educate the public about Alzheimer's detection and prevention. One of the key components for this educational framework is media engagement, on both local and national levels. Coordinated local online and print media campaigns featuring trial sites along with a national media strategy regarding Alzheimer's awareness, prevention, and research participation, will be essential to engage enough people to fill recruitment needs. The promotion of citizen science, a call to the public to serve in the fight against Alzheimer's, will be an integral component of achieving the goal of preventative treatment by 2025.

The use of online registries for recruitment and retention of a research-ready cohort has been a critical element for success at our site. We began the Butler Alzheimer's Prevention Registry in April 2016, and found that the maintenance of a database of potential research participants has been an important recruitment tool to engage and educate our local community about Alzheimer's research. Larger national registries, such as the Alzheimer's Prevention Registry (APR) coordinated by Banner Health, and the Brain Health Registry, have helped our site by referring interested participants in our catchment area for research participation. As a field, we must adopt a collaborative approach to recruitment science. Efforts to harmonize recruitment through data standardization in local and national registries to harness public momentum gained through education and media engagement will be vital for AD prevention recruitment success.

Additionally, local community outreach has become a necessity for recruitment. Holding educational events targeting individuals and building a network of community organizations is an effective recruitment strategy. For example, an educational event at a local senior enrichment program resulted in the recruitment of 60 individuals for research at our site. National advertisement in a widely-circulated senior citizen newsletter and a featured piece in a nationally circulated newspaper advice column have been successful recruitment tools for the A4 study. Developing online recruitment capacity will be a key tool for recruitment science moving forward. Collaboration with experts in public health, marketing, public relations, and information technology to develop and assess the effectiveness of recruitment strategies for clinical trials should become a common practice in the AD prevention field. We will need to reach out to potential participants via collaboration with primary care providers, satellite memory clinics, and mobile units, which could be especially useful in areas with little or no access to memory care and/or dementia specialists. Sites need to make a long-term commitment to building trusting relationships with key community organizations. Enlisting prominent community leaders to educate their networks about AD prevention research will be an important tool for community engagement, especially

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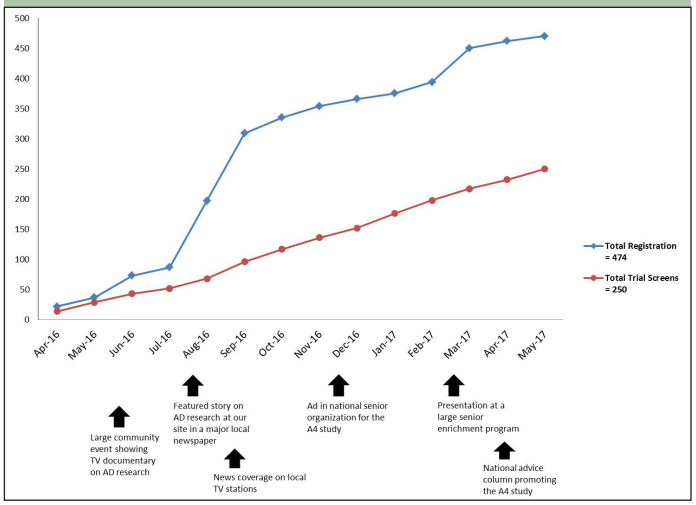
for recruitment of diverse populations. Receiving this education from a trusted source resonates with the public.

Another thing that resonates with the public is media coverage of the AD prevention research experience. Our site has benefited from both local and national media coverage, leading to a substantial increase in enrollment in our prevention registry. Figure 1 indicates increases in the Butler Alzheimer's Prevention Registry enrollment over time, corresponding to media coverage and community educational events, in particular a featured report on AD research at our site in a major local newspaper in August 2016. A 2014 feature article in the same newspaper led to a similar increase in clinical trial participation. Figure 1 also shows a commensurate increase in number of AD prevention trial screens, highlighting the essential role of media and community engagement and education in recruitment for AD prevention trials.

Figure 1. Butler Alzheimer's Prevention Registry recruitment by media and community events



The blue line shows the increase of total registrants for the Butler Alzheimer's Prevention Registry and the red line shows the number of screens for prevention trials over a one year period. There is a noticeable uptick in recruitment and screening following a featured article on AD research at our site in a major local newspaper. Local and national media and community outreach has significantly increased AD prevention trial screening and enrollment over a one year period.

The second challenge created by this paradigm shift is that biomarker tests are invasive and expensive, and the majority of participants screen fail due to negative results on biomarker tests. Our site has experienced a 10-20% randomization rate for AD prevention trials, meaning that to randomize 100 eligible participants, we need to screen 500-1000 individuals. Given the number of prevention trials currently underway or in the active planning stages, more than 100,000 cognitively normal, older individuals will need to be screened world-wide in the next few years to reach the current randomization goals.

Additionally, risk assessment and disclosure of biomarker test results has become a new feature of Alzheimer's prevention research. Trial sites must have a vision for recruitment science, investing in clinician scientists and perfecting the process of risk assessment and disclosure. One example of this is performing APOE genotyping to identify at-risk participants. We currently offer APOE genotyping and disclosure as part of the Butler Alzheimer's Prevention Registry, which is being carefully implemented and has become useful for identifying high-risk participants for prevention trials, leading to lower screen failure rates.

An important goal in prevention trial recruitment science is the development of an AD risk algorithm to predict a positive result on biomarker tests such as amyloid PET, to reduce the screen failure rate and cost of AD prevention trials and to generate an enriched sample for preventative interventions. Biomarker research has expanded dramatically in the last two decades, and there is currently a push for the development and validation of non-invasive, inexpensive biomarkers to identify early and pre-symptomatic stages of AD. The discovery and validation of novel, inexpensive biomarkers that could indicate or rule out possible preclinical AD is essential to this effort. Burgeoning work examining relatively novel biomarkers such as tau PET, retinal imaging, and blood biomarkers that could contribute to this risk algorithm must be a top research priority.

These recruitment challenges must be met with the prioritization of Alzheimer's prevention research by state and national governments. Funding for AD prevention research must be on par with other major diseases, such as heart disease and cancer, to support the scale of operations required to meet recruitment goals. Most clinical trial sites lack the capacity in funding, operation, outreach, facility or research staff to support or sustain the scale of effort required for efficient recruitment into AD prevention trials. More resources should be directed towards the development and execution of a strategic plan for capacity building and recruitment science in AD prevention research. Investment in clinical trial sites is required from state and federal governments, pharmaceutical companies, AD advocacy groups, health insurance companies, and philanthropic foundations to provide the research infrastructure to meet our ambitious recruitment goals. The AD research community must create a bold vision to engage, educate, and identify an at-risk AD cohort and to refine recruitment science for AD prevention trials. This is essential to meet the US National Plan 's goal to prevent and effectively treat AD by 2025.

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Ethical Standard: The Butler Alzheimer's Prevention Registry was approved by the Butler Hospital Institutional Review Board and all registrants have signed informed consent.

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