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The BrainHealthRegistry.org: Using the Internet for identification, assessment, screening, recruitment, and longitudinal monitoring of subjects for neuroscience and Alzheimer's disease studies

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The major obstacle preventing development of effective treatments for Alzheimer's disease (AD) is the high cost of conducting clinical trials. The use of the Internet for the identification, assessment, screening, recruitment, and longitudinal monitoring of subjects for neuroscience and AD studies is one promising approach towards lowering this cost and thereby accelerating successful trials. To this end, we developed the BrainHealthRegistry.org.

Currently, there are no treatments that have been shown to slow the progression of AD. During the past decade a number of large, costly Phase 3 registration trials aimed at reducing amyloid beta in the brain have failed to meet their primary endpoints. There are many reasons for these failures, perhaps not least that treatments may not have been effective. Each of these trials is estimated to cost over $100 million, a major barrier preventing the majority of the dozens, if not hundreds, of candidate treatments developed in basic science, and effective in experimental animals, from being studied in humans. How, then, can we make clinical trials more efficient and reduce their cost, thereby reducing the time to successful completion?

Currently, there are a number of problems associated with enrollment of subjects into AD clinical trials. Trials primarily enroll “Early AD” subjects who meet established clinical criteria for dementia due to AD. Because such subjects experience functional impairment and have memory complaints or problems, they frequently seek out treatment at memory or Alzheimer's centers. If new and existing patients at these centers meet trial criteria, they can be enrolled as trial subjects. In addition, subjects are recruited through advertising of all types including public relations (newspapers, radio, and TV features), and posting of advertisements to bulletin boards, and on the Internet. These advise subjects to call a recruiting center and schedule appointments. Subjects then visit the center, sign informed consent forms, answer screening questions, and often have memory testing and blood tests. However, a large fraction of subjects responding to these advertisements do not meet

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screening criteria. These screen fails ultimately slow trial enrollment and add to the overall cost of the study.

Recently, clinical trials have increasingly enrolled subjects with “prodromal AD” or mild cognitive impairment (MCI) due to AD. Although some of these MCI patients are referred to clinics, many are not seeking medical help and are likely not aware of clinical trials aimed at them. Even more difficult to identify are subjects for the very recently launched “prevention trials” which are enrolling cognitively normal elders with no or minimal symptoms. These subjects are unlikely to be seeking treatment, and therefore recruitment, through memory clinics; even advertising is ineffective. The identification and recruitment of these critical subjects is an additional challenge and cost to AD clinical trials.

Recruitment costs are also impacted by the lack of cooperation and communication between clinical trials funded by different sponsors. Clinical trial recruitment funded by one sponsor usually does not help a future clinical trial funded by another sponsor. For example, a clinic might recruit subjects for a clinical trial funded by sponsor A, but will not enroll screen fails, who in turn might be useful for a clinical trial funded by sponsor B, enrolling at a different clinic in the same city.

Another challenge in subject recruitment is the frequent lack of prior record of standardized cognitive measurements, as subjects often are being seen for the first time or have not previously undergone these tests at their clinic. The identification of subjects undergoing cognitive decline is extremely useful in clinical trials aimed at preventing this decline. A number of factors predict future cognitive decline including age, APOE4 status, baseline cognition, brain atrophy, brain amyloid load, and the rate of prior cognitive decline. Therefore, it would be desirable to obtain data on prior rates of cognitive decline from subjects who are candidates for future clinical trials.

One approach to the problems outlined above is to use the Internet to create a registry of subjects who: 1) consent to be involved in research, 2) provide the type of information usually obtained by clinical screening questions, 3) take both baseline cognitive tests and future tests to measure cognitive change. This is the overall goal of the BrainHealthRegistry.org.

Internet registries for clinical research and clinical trials are not new and registries exist for all types of diseases. For example, PatientsLikeMe is a for-profit company registry for clinical trials of all types. Specifically aimed at AD studies, the Internet-based registry pioneered by The Alzheimer's Prevention Initiative and sponsored by the Banner Institute in Phoenix, Arizona has had great success in enrolling potential clinical trial subjects. What, then, makes the BrainHealthRegistry.org unique?

First, the BrainHealthRegistry.org is not uniquely focused on recruiting subjects for AD trials. By emphasizing “Brain Health” rather than “Alzheimer's disease” in our name, we hope to attract many individuals and their families who might not otherwise go to a website focused on AD. My personal focus as an AD researcher is to use the BrainHealthRegistry.org for AD trials, and we hope that other investigators will use our site for this purpose. But in addition, the BrainHealthRegistry.org may facilitate all types of

neuroscience clinical research including studies on stroke, Parkinson's disease, frontotemporal dementia, sleep, depression, traumatic brain injury, and cognitive effects of surgery and medications, to name just a few.

Second, the BrainHealthRegistry.org requires that, immediately after joining, the subject electronically sign an Informed Consent Form approved by the Institutional Review Board of the University of California San Francisco. This allows the investigators of the BrainHealthRegistry.org and our collaborators to examine the data, contact subjects for further information, and to enroll them in future studies.

Third, in contrast to most other registries, the BrainHealthRegistry captures a plethora of information that will be extremely useful to academic investigators and companies in the selection of clinical trial subjects. The information is of two types, self-report questionnaires and online neuropsychological tests. We have developed a self-report battery based on that used for enrolling subjects in the Alzheimer's Disease Neuroimaging Initiative (ADNI). This is very similar to those used for AD clinical trials in general, and captures information including age, gender, family history of AD, current medications, past medical history, memory complaints, mood (depression/anxiety), alcohol and substance use and abuse, and sleep problems. The questionnaires are divided into a short battery required of all newly-joining subjects and a more comprehensive battery completed by subjects after they join the registry. Participants are asked to complete two separate online neuropsychological tests; The Cogstate brief battery (Cogstate LTD, Melbourne, Au) and the Lumos Brain Performance Test (Lumos Inc., San Francisco, CA). After 6 months they are prompted by email to return and answer follow-up questions, and retake some tests that capture longitudinal data.

Fourth, we intend to share the BrainHealthRegistry.org data and subjects with qualified academic investigators and companies conducting neuroscience studies, including AD clinical trials. We are seeking partnerships and collaborations to help investigators and companies enroll qualified subjects in clinical trials across the USA, and ultimately internationally.

Our website became “live” in early January 2014. After a test period, we started to advertise our website and we have grown to over 7,000 registrants predominantly locally in the San Francisco Bay Area. We hope to grow our enrollment, initially in this region, and also to expand further afield by advertising more widely. Our early results, including the Cogstate brief battery results, are very promising and with time we will gather longitudinal data on many of our subjects. This has the potential to detect cognitive decline, possibly even in subjects whose cognitive tests are in the normal range and who would be of great interest for recruitment into AD prevention trials.

It should be emphasized that after initial start-up costs, operating a registry website like the BrainHealthRegistry is not expensive. Internet registries are very “scalable”. We believe that Internet registration of subjects for clinical trials will be much more cost effective than the conventional approaches where subjects are scheduled for office visits and in-person interviews. BrainHealthRegistry.org will not replace the need for office visits and in-person

interviews; rather it will allow the identification of highly suitable and willing subjects who could then be contacted for in-person assessments. However, the possibility of doing some research, including treatment trials, completely online is being discussed.

Two papers in this issue of the Journal of Alzheimer's Prevention concern Internet-based patient registries. The first, entitled “Arizona Alzheimer's Registry: strategy and outcomes of a statewide research recruitment registry” by Saunders, et al., (1) concerns the Arizona Alzheimer's Consortium (AAC) which created the Arizona Alzheimer's Registry, a screening and referral process for people interested in participating in AD-related research. The goals of this registry were to increase awareness of AD research and accelerate enrollment into AAC research studies. A total of 1,257 people consented, 1,182 underwent an initial cognitive screening, and 301 were referred to AAC sites. These methods were found to be effective at prescreening individuals for studies, which facilitated AAC research recruitment. This registry served as the prototype for the Internet-based Alzheimer's Prevention Registry, a national registry focusing on AD prevention research. The second paper, entitled “Alzheimer's Prevention Education: If We Build It, Will They Come?” by Isaacson, et al. (2), concerns the usability of, and user perceptions about AlzU.org, an online AD education research platform. Isaacson, et al. also sought to identify whether users of social media interested in AD would participate in online education about AD prevention. Over two-weeks, there were 4,268 unique visits to AlzU.org and 412 users completed at least one beta-testing site. These two papers strongly support the idea put forward in this Editorial that better use of the Internet will greatly facilitate AD research and lead to faster, more efficient development of disease-modifying or preventive treatments.

In conclusion, the major obstacle towards finding effective treatments for AD and other neurological disorders is the high cost of clinical trials. Using the Internet for the identification, assessment, screening, recruitment, and longitudinal monitoring of subjects for neuroscience and AD studies has many advantages over conventional methods. The early success of the BrainHealthRegistry.org helps to demonstrate the feasibility of such approaches.

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