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Short Report

Adherence/Retention Alzheimer's Prevention Initiative Colombia Plan

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Abstract

Background: The Alzheimer's Prevention Initiative Colombia Trial is a collaborative project involving the Neurosciences Group of Antioquia, Genentech/Roche, and the Banner Alzheimer's Institute, studying whether crenezumab can delay or prevent the clinical onset of Alzheimer's disease in cognitively unimpaired individuals who carry the *PSEN1 E280A* mutation. In an effort to optimize participant compliance and adherence and maintain interest in the trial for its duration, the Neurosciences Group of Antioquia developed an "Adherence/Retention Plan." This plan identifies potential barriers to trial adherence related to characteristics of the participants and study partners, protocol design, sponsors, investigators, environmental factors, and characteristics of this population in general and identifies potential solutions to these barriers.

Methods: Neurosciences Group of Antioquia designed and implemented a number of strategies including a) a prescreening process that emphasized detailed and staged informed consent involving the participant and family and/or friends, b) a schedule of visits and assessments designed to minimize burden while achieving the trial's aims, c) appointment reminders, d) reimbursement for transportation and missed work, e) meals during study visits, f) birthday cards, g) quarterly newsletters, h) annual in-person feedback meetings, i) a supplemental health plan to participants, and j) a social plan to support family members. All the methods used in this plan were approved by local ethics committees.

Results: By the end of the fourth year of the trial, participant retention was 94.0%, with most participants reporting that they felt "very satisfied" with their participation in the trial.

Discussion: The Adherence/Retention Plan plays a crucial role in maintaining adherence and compliance needed to achieve the ambitious goals of the Alzheimer's Prevention Initiative-Colombia Autosomal Dominant Alzheimer's Disease Trial and may offer guideposts for other prevention trials.

Conflicts of interest: S.R-R., N.A-B., L.M-Z., F.L., and L.L. report participation in other projects financed by the National Institutes of Health, Comité para el Desarrollo de la Investigación, and Colciencias. W.C. is a full-time employee of Genentech, Inc. and a member of the Roche Group. He also owns stock in Roche and is one of inventors on a crenezumab patent. H.S. and L.J. report no conflicts. J.B.L. has received consulting fees from Biogen and Lilly. E.M.R. has received consulting fees from Alkahest, Alzheon, Biogen, Denali, Pfizer, United Neuroscience, and Zinfandel Pharma. He received research support from Avid/Lilly, Genentech/Roche, and Novartis/Amgen, the National Institute on Aging, the National Institute of Neurologic Disorders, Banner Alzheimer's Foundation, Alzheimer's Association, GHR Foundation, FBRI, NOMIS Foundation, Flinn Foundation, and the State of Arizona. P.N.T. has received consulting fees from Acadia, Abbott Laboratories, AbbVie, AC Immune, Auspex, Boehringer-Ingelheim, Chase Pharmaceuticals, Eisai, GliaCure, Insys Therapeutics, and Pfizer. He has received consulting fees and research support from AstraZeneca, Avanir, Biogen, Eli Lilly, Lundbeck, Merck & Co., Inc., and Roche and research support only from Amgen, Avid, Elan, Functional Neuromodulation (f(nm)), GE Healthcare, Genentech, Novartis, and Targacept. P.N.T. has received other research support from the National Institute on Aging, Banner Alzheimer's Foundation, Alzheimer's Association, GHR Foundation, FBRI, NOMIS Foundation, Flinn Foundation, and Arizona Department of Health Services and holds stock options in ADAMAS.

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1. Background

Clinical trials in Alzheimer's disease (AD) face difficulties in recruitment and retention similar to those faced by other clinical trials of interventions with potential risks and uncertain benefits [1]. Furthermore, AD clinical trials have unique challenges [1], including the potential for impaired decision-making capabilities as a result of progressive cognitive decline and the requirement of study partners [2]. Recruitment and retention of a sufficient number of participants in trials are critical, particularly for randomized clinical trials and cohort studies. Failure to recruit and retain participants in a study may lead to invalid or inconclusive results, extend the clinical trial, or result in premature trial termination for operational futility [2–4].

In the current AD clinical trials era, there has been a significant shift toward preclinical and prodromal stages of the disease. Several secondary prevention clinical trials are underway, targeting cognitively unimpaired individuals with genetic predisposition to the disease or with biomarker findings indicating increased risk of cognitive decline and AD pathology [5–8], as well as studies of tertiary prevention in individuals with mild cognitive impairment and early treatment of people with mild AD dementia [9]. There is hope for primary prevention trials in the future, which will require novel strategies for outreach, recruitment, enrollment, adherence, and retention.

The Alzheimer's Prevention Initiative is a collaborative international project among the Neurosciences Group of Antioquia (GNA), Genentech/Roche, the Banner Alzheimer's Institute (BAI), and other key partners, studying whether crenezumab, a monoclonal antibody directed against toxic amyloid β species [10,11], can delay or prevent the clinical onset of AD in cognitively unimpaired individuals who carry the *PSEN1 E280A* mutation. The "API Colombian Autosomal Dominant AD (ADAD) trial" is described elsewhere [12] (NCT01998841). This trial requires people without cognitive impairment, with and without the *PSEN1 E280A* mutation, to commit to a trial lasting at least 5 years. Extensive evaluations and experimental treatment are required in a community with little research experience. To optimize chances for operational success, GNA developed and implemented a trial-specific Adherence/Retention Plan that we describe here.

2. Methods

2.1. Identification of influential factors and barriers

GNA identified possible factors, positive and negative, that could affect adherence and retention (Fig. 1). Consideration was given to socioeconomic, demographic, cultural, and regional characteristics of the study population in Colombia, relying on GNA's experience working with families with the *PSEN1 E280A* mutation for more than 3 decades. Potential factors and barriers included participant and study partner circumstances, aspects of protocol design, sponsor and investigator characteristics, and cultural, political, and social factors.

One important participant factor is that the age range (30–60 years) represents a time of life during which there may be interest, likely to vary over time, in having children, as well as reluctance to comply with strict contraception requirements: both could have a marked impact on compliance and retention during a lengthy trial. Low education level and low income [3] may predispose to instability at work, more frequent job changes, and changes in work locations, relationships with employers, and responsibilities, factors that, in the aggregate, may be associated with high withdrawal rates. Young adults and single mothers are more likely to withdraw from clinical trials [3]. Physical and psychological characteristics, such as chronic illness, fatigue, substance use, and lack of interest/motivation can also lead to study withdrawal [3]. Depression, a common manifestation of AD, is one of the strongest predictors of nonadherence to treatment, possibly resulting from associated pessimism, cognitive disturbance, social, and impaired motivation [13]. Impaired language skills, difficulty understanding risks, benefits, and requirements of the protocol, as well as cognitive deterioration related to AD, may also contribute to attrition [13]. The fact that the trial requires being blinded to one's own genetic risk for AD and the fact that a proportion of participants do not carry this risk may influence adherence and/or retention. Progression to a symptomatic stage of AD will likely impact motivation of participants and/or family members to continue in the trial.

A reliable study partner is an important factor for adherence and/or retention of the primary participant. Study partners provide information about cognitive, psychological, and functional status, compliance, and physical well-being of participants: this represents a significant time commitment. If symptoms of AD emerge in the participant, the study partner may become the participant's legal representative and caregiver, which would entail even more commitment and responsibility [1].

Protocol complexity and burden [3], including long treatment duration (5–8 years), biweekly visits for study drug administration, lengthy research visits every 6 months at the main site in Medellin, and repeated blood tests, lumbar punctures, and neuroimaging (magnetic resonance imaging and positron emission tomography scans), can threaten adherence and retention [12]. Protocol complexities can also lead to frustrating scheduling challenges, especially if rescheduling is required due to technical or operational problems at the site