

## Core B: Clinical Specific Aims:

The Clinical Core of the now well established Dominantly Inherited Alzheimer Network (DIAN) will continue to recruit and retain participants from ADAD pedigrees. The Core will continue to monitor longitudinal clinical evaluations including: clinical assessments, neuropsychological testing, imaging studies and collection of CSF and blood biomarkers.

Aim 1: The Clinical Core will emphasize the retention of current DIAN participants and continue to enroll 50 new participants for longitudinal assessment for a goal of 250 to achieve longitudinal follow-up to estimate the rate of change and inflexion of clinical, cognitive, biochemical and imaging measures. Based on estimates that 200 DIAN participants will choose to enter trials, we will enroll 50 new participants younger than their parental age of onset, with emphasis on those more than 15 years before the expected age of onset (see Figure 1). Current DIAN participants will be followed up either in year 1 (N=75) or year 2 (N=125) with the addition of 50 new participants in year 1. Thus, 125 participants will have assessments every other year, ensuring at least 3 assessments for all participants (including assessments obtained in this budget period for current participants).

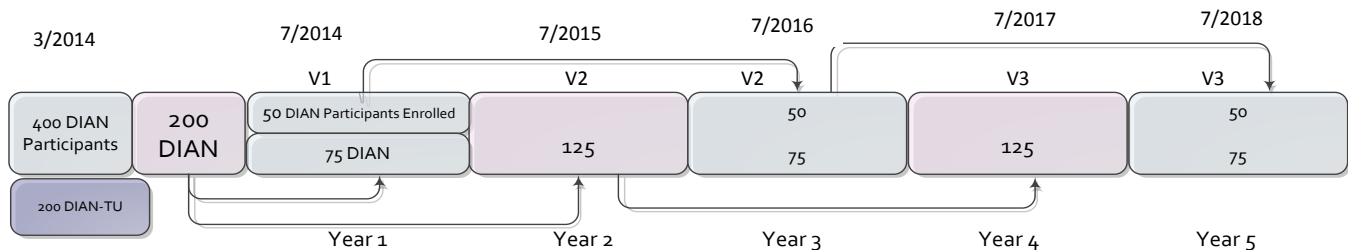


Figure 1

Aim 2: To coordinate the DIAN performance sites and the ADCS Clinical Coordinating Center (CCC) for implementation of protocols. Coordinate the 14 DIAN performance sites: London, Munich, Tübingen, Perth, Sydney, Melbourne, Boston, Indianapolis, Jacksonville, Los Angeles, New York, Pittsburgh, Providence and St. Louis. The Clinical Core also directs the sites and CCC for implementation of protocols, including clinical evaluation, psychometrics, LP, MRI, PET, and provisional consent for autopsy. Current procedures for site performance and monitoring will be continued, and regular reviews of enrollment, retention, attrition and completion rates will be made.

Aim 3: Ensure protection of sensitive and confidential genetic and research data while increasing accessibility to external researchers and offer clinical genetic counseling and testing to DIAN participants. Funds will be utilized to continue genetic counseling and testing for interested participants. Double blinding, data use agreements and limiting access of genetic status only to those researchers not in contact with participants will be continued. Data freezes with de-identified data are made available to qualified researchers with data use agreements. Data is also made available to multiple external and internal research groups for ADAD research, comparison to LOAD results (e.g., ADNI), and trial design planning.

Aim 4: Implement revised cognitive tests to enable longitudinal analysis and minimize burden. Evaluate the cognitive and clinical onset by multifactorial analysis including age, estimated years to onset (parental age of onset), ApoE4, average familial onset, genetic risk factors and biomarkers. Current cognitive tests that have low sensitivity and high burden (Reading Span, Paper Folding, Pair Binding, FAS, and Vegetable Naming) will be discontinued; all other original tests will be kept. In addition, CogState measures of the Chase Test, Groton Maze Learning Test, Identification Task, One Card Learning Test and International Shopping List Test will be incorporated because of the demonstrated sensitive metrics and use in multiple prevention trials (DIAN-TU, A4). These changes will reduce burden on participants by eliminating some of the most demanding measures.

Aim 5: Coordinate and manage transition of DIAN participants to and from the DIAN-TU trials. The DIAN Clinical Core will coordinate and manage DIAN participants who choose to join the DIAN-TU trial. The DIAN-TU trial began enrollment of participants in December 2012 (first patient dosed in March, 2013). In order to manage the departure of eligible DIAN participants to the DIAN-TU trial, participant records and follow-up intervals will be tracked and placed on hold for participants whom join the DIAN-TU trial. Of the expected 400 DIAN participants, up to 200 are expected to be eligible and join the DIAN-TU trial. Trial baseline (pre-drug exposure) clinical, cognitive and biomarker measures of prior DIAN observational participants participating in the DIAN-TU trial will also be utilized for longitudinal data analysis. After an appropriate wash-out period (6 months), DIAN-TU participants may re-join the DIAN observational study.

Aim 6: Transition Leadership of the Clinical and Administration Cores. Planned leadership transition of the Clinical Core Leader (Dr. Bateman) and the Administrative Core Leader (Dr. Morris) will occur during this grant renewal. With the transition, Dr. Bateman will serve as PI and Administrative Core leader and Dr. Morris will serve as Clinical Core leader and Associate Director. The leadership transition is expected to be seamless given their close working relationship and current involvement in both the Administrative and Clinical Cores.