Perfect Platform

The Washington University DIAN-TU platform can be used as a standard for what represents clinical trial best practice today. Following these guidelines can greatly affect research into Alzheimer's disease prevalence and financial impact

Graham Wylie at MRN

"Today, 47 million people live with dementia worldwide, more than the population of Spain. This number is projected to increase to more than 131 million by 2050, as populations age. Dementia also has a huge economic impact. The total estimated worldwide cost of dementia is US$818 billion, and it will become a trillion dollar disease by 2018" (1).

Because of the social impact of this chronic neuro-degenerative disease, it has become a major target for new therapies and, together with Parkinson's, accounts for approximately a third of all neurological trials initiated over the past five years (2). Despite this, the success of new medicines in the area is poor. At present, the only products on the market are Cholinesterase inhibitors and N-methyl-D-asparate (NMDA) antagonists, providing symptomatic therapy. Consequently, the drive for disease-modifying treatments is huge, and, despite major setbacks for drugs in trials to date, in 2016, 51 Alzheimer's trials were initiated compared to five in 2002 (3,4). Dominantly Inherited Alzheimer Network Trial (DIAN-TU) represents a new frontier for assessing the impact of disease-modifying drugs as it targets patients with a genetic predisposition and starts treatment prophylactically.

Patient Centricity

The design element of a trial could be defined as 'patient-centric', ensuring anything that makes it easier or more desirable for a patient to choose to participate in a trial is facilitated. Patient-centric activities have been analysed for some time to understand and improve on them. They can be categorised as design elements that:

- Reduce the overall workload for the patient
- Make participating more convenient or simpler for the patient
- Reduce the invasive nature of the investigations
- Provide a benefit to the patient
- Are considerate of the patient's requirements and lifestyle

DIAN-TU

In 2008, the DIAN was established as an observational, longitudinal study and registry of individuals with or at-risk for Autosomal Dominant Alzheimer's disease (ADAD). In 2011, a public-private partnership (DIAN-TU [Trials Unit]) was formed to facilitate collaborative discussion between the pharmaceutical industry, families affected by ADAD, the Alzheimer's Association, US National Institute on Aging (NIA), the FDA and EMA regulatory agencies, philanthropic foundations, and researchers (5). In 2012, a Phase 2/3 double blind, randomised, pooled placebo-controlled two year biomarker trial began by testing two leading investigational drugs (6). The trial transitioned within the DIAN-TU platform to the Adaptive Prevention Trial in 2014 as a four year Phase 3 cognitive endpoint trial to determine whether amyloid beta antibody administration demonstrating central nervous system biomarker target engagement is able to prevent cognitive decline in cognitively normal individuals. DIAN-TU is now operational in six countries (Australia, Canada, France, Spain, the UK, and the US), with 24 sites utilising three languages. In 2015/16, the design was adapted to incorporate additional drug arms and utilise a novel statistical design to detect cognitive and clinical changes earlier with fewer participants, thus becoming the Next Generation (NexGen) prevention trial within the same DIAN-TU platform (7). In 2017, a third leading investigational drug was added to the DIAN-TU trial platform.

This adaptive trial was designed to follow principles of trial scientific integrity, safety, reduced subject workload or burden, balanced assessments across arms, streamlined operations, efficiency, and patient confidentiality. It is a global trial testing multiple drugs in a rare patient population, with very few patients close to a participating site fully equipped to make the full spectrum of safety and efficacy assessments. Overall, the trial has taken a very patient-centric approach to design. Specific elements of note are:

- Use of the DIAN Observational Study platform and associated organisations to promote discussion with all relevant parties, including patients and their families, about what they want from clinical trials in this condition, using surveys, webinars, and an annual ADAD family conference
- A DIAN expanded registry facilitates electronic communication with families and caregivers
- A design allowing patients to participate without being informed of their gene mutation status. In this study, patients were given access to genetic counselling and related information at no cost. The DIAN-TU team have published elsewhere that the provision of genetic information is often unwelcome, but, if knowing

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the status is necessary to enter a trial, many patients who previously reported preferring not to know then changed their mind (8)

- Adaptive design: The trial is able to add additional drug arms. All subjects will be treated with active drug or placebo in a 3:1 ratio. The pooled placebo group has been carefully designed to allow comparison to each active group, reducing the overall study numbers by 50% compared to separate placebo groups, therefore increasing the chances of a patient receiving active drug and significantly enhancing recruitment and retention of subjects
- Patient referral: The ability for other sites and investigators who do not have the facilities or resources to conduct the study, but wish to give their patients the chance to participate to refer patients to the DIAN-TU 'host' sites
- Significant safety and efficacy assessments are included, but at a frequency (quarterly specialised MRI, annual PET scans, and lumbar punctures, as well as complex biomarker assessments) that limits their impact on the patient burden and reduces assessment fatigue while maintaining scientific integrity. An MRI can be set up in a 'nonhost' site (if required) as close as possible to the patient's home to maximise convenience
- In the third arm, they are also piloting the use of an electronic smart phone app on which no information is as yet available for publication
- Home trial support: First, the use of general local nurses specially trained in Good Clinical Practice and the study details to visit the patients in their own homes to conduct screening post consent and monthly visits for administration. This also requires the use of centralised pharmacies and cold chain logistics to deliver the investigational medicinal product direct to the patient's home. Second, a specialised team of travelling nurses conducting six monthly visits, having had specialised training to complete the abbreviated cognitive assessment, additional safety assessments, and taking and spinning samples for further blood testing

An article by *Aisen PS et al* clearly displays the detailed design of the operational logistics of the study (6).

The study has been successful in completing enrolment for the first two drug arms in 2015 in a rare patient population. Enrolment in the third drug arm has begun with nearly half of the targeted number of participants ready and waiting to join the trial.

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Trial Design

In other trial designs, additional tools are available for ease of participation. These should also be relevant to trials in chronic neuro degenerative disease, such as use of an expenses system to reimburse patient's (and carer's) costs (travel, etc), patient portals to provide information, and texting systems or other means of providing reminders to the patient and carer about visit schedules and preparations are also commonly used.

In Alzheimer's disease, trial recruitment is often a joint decision between a primary carer and the patient. In 2008, Karlawish, Cary, Rubright, and Tenhave reported in *Neurology* the results of conjoint analysis to determine the impact of various elements of trial design that contributed to a decision to consent by the patient: carer dyad for 108 patients across eight clinical trials (9). Home visits had the strongest impact on willingness to consent, raising willingness from 17% to 27% of patients. When coupled with a low-risk trial and a higher probability of getting an active drug (rather than placebo), this rose to 60%. The worse the cognitive function of the patient, the stronger these correlations became. It is also worthy of note that Karlawish, Casarett, Klocinski, and Sankar reported in 2001, also in *Neurology*, that, for those who agreed to participate, both the carer and the patient tended to agree on participation, whereas in those who refused to participate more commonly the carer refused, yet the patient desired to participate (10). This implies that tools to aid the carer – often the need for convenience, reduction in expenses, and the ability to be seen out of hours or at weekends – are critical and may explain the strong impact of home visits in these therapeutic areas, where, otherwise, it may be felt that the patient is less concerned about convenience, making this a particularly important component of the patient-centric design in this therapeutic area.

Care and Consideration

Clinical trials will run faster and better if the patient's and carer's needs and wants are taken into account. This benefits all the stakeholders, not just the patient. Recognising this generated the concept of patient-centric design elements in trials. Such design elements have several subgroups, knowledge of which can be used to guide design of trials in this therapy area and has been illustrated with this case history. Based on regular surveys of their patients, DIAN-TU has designed this study to reduce the patient workload, reduce the invasive nature of the investigations, and to be considerate of the patient's requirements. The approach has led to significant success in recruitment and retention in a rare and complex disease that is usually difficult to study.

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About the author

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