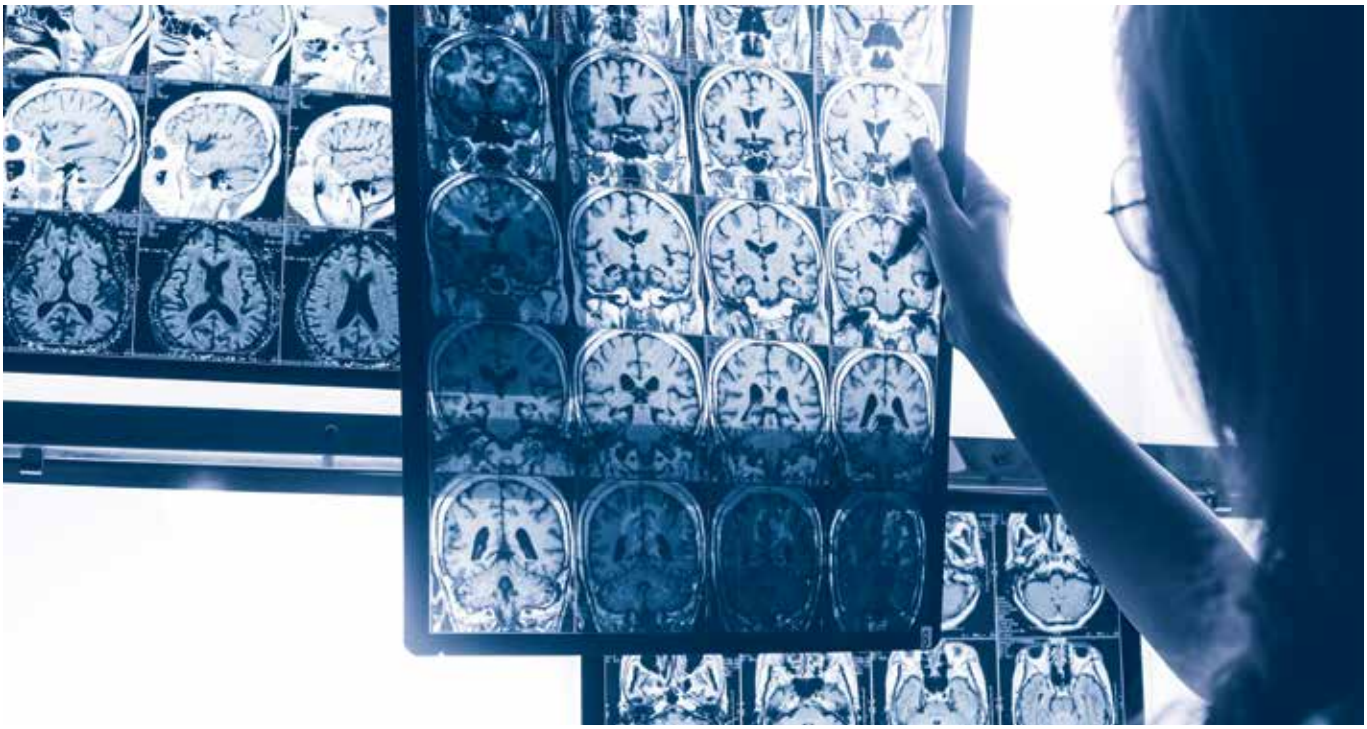

# Improving Subject Selection And Endpoint Management In Alzheimer's Trials

## Executive Summary

**The rapidly growing burden of Alzheimer's disease (AD) worldwide, and the high attrition rate in trials of disease-modifying drugs for AD, call for better-designed clinical research, particularly in terms of selecting the right patients and making sure that endpoints are clear, transparent and well-supported.**

**This is all the more crucial as drug development transitions from the late to the more challenging early stages of AD. Disease-modifying studies with Alzheimer's drugs must demonstrate significant decline over time in the placebo arm, determined by reliable cognitive and functional endpoint measures. This can be particularly difficult when the disease trajectory is relatively slow and some trial participants may not even have Alzheimer's.**

**WCG has years of expertise in helping AD trial sponsors to design effective protocols, identify and recruit the most appropriate participants, and collect consistent, accurate, reliable endpoints. Our Virgil electronic data-capture platform ensures that trial inputs and outcomes produce definitive positive or negative data to inform next steps in drug development.**

**With our systems active at more than 2,000 sites conducting Alzheimer's studies worldwide, and implemented by a coordinated network of clinicians across multiple markets, we can exercise centralized clinical oversight to help usher in new treatment paradigms for this most intractable of diseases.**

Alzheimer's disease is one of the most daunting and intractable challenges facing health, social-care and economic systems worldwide. As things stand, some 30 to 35 million people around the world have Alzheimer's, while as many as 50 million are living with dementia, according to the World Health Organization. With populations aging rapidly, the number of people with dementia could triple to 152 million globally by 2050.

This represents an enormous burden of care. In raw cost terms, the World Economic Forum warns that the global economy will lose $1 trillion dollars in 2018 and $2 trillion by 2030 unless more is done to manage dementia.

We must also factor in the enormous psychological, physical and emotional costs for patients, families and health- or social-care providers, and the challenge to long-established notions of social solidarity. All in all, the need for truly effective disease-modifying therapies in Alzheimer's disease is considerable and urgent.

## High Rates Of Attrition

To date, drug development in this field has been hampered by high rates of attrition and complications including multiple pathologies and risk factors; slow patient recruitment for clinical trials; and inadequacies both in clinical diagnoses of AD and in demonstrating and measuring pharmacological effects. A review last year by Jeffrey Cummings of the Cleveland Clinic, published in the US journal Clinical and Translational Science, found that the failure rate for Alzheimer's drug development was 99.6% between 2002 and 2012, and had continued at the same high level since then.

These problems underline the importance of two key drivers in clinical trials for Alzheimer's disease: careful screening to ensure that trials select appropriate patient cohorts; and effective, informed endpoint adjudication, so that trial outcomes are clear, transparent and well supported. Getting subject eligibility and endpoint measurements right are all the more crucial as drug development transitions from late- to early-stage Alzheimer's disease, including secondary-prevention trials.

"In Alzheimer's disease we're aware that amyloid buildup in the brain can begin 15 or more years before the onset of clinical symptoms," points out Dr Chris Randolph, Chief Scientific Officer at WCG.

## Trial Challenges

Designing and implementing trials in preclinical Alzheimer's presents additional challenges, such as length of follow-up and finding surrogate endpoints for clinical outcomes, such as positive tests for beta-amyloid or tau proteins. Since Alzheimer's is progressive, disease-modifying studies must be able to demonstrate significant decline over time in the placebo arm, as determined by reliable cognitive and functional endpoint measures. This is necessary if clinicians are to identify any treatment effects in slowing disease progression.

For example, in Merck's recently discontinued Phase III EPOCH trial of its BACE1-inhibitor verubecestat, the drug reduced from around 30% to 10% levels of beta-amyloid deposits associated with Alzheimer's in the 90% of patients with mild-to-moderate disease who were amyloid-positive. Yet while the EPOCH placebo group showed "very robust" clinical decline in dual cognitive and functional endpoints over an 18-month period, the verubecestat arm declined at exactly the same rate on both endpoints, with "no glimmer" of a treatment effect, Dr Randolph notes. "So that was a negative study, but a very definitely run negative study that didn't leave any room for doubt."

A further complication is that the disease trajectory in AD is relatively slow. Combined with high error rates in the measurement of clinical endpoints, this can compromise sponsors' ability to detect signals that the drug is viable.

Moreover, some trial participants may not even have Alzheimer's disease. Recent sub-studies with amyloid imaging found that 25-35% of subjects in trials for dementia due to Alzheimer's did not have brain evidence of amyloids denoting AD. This becomes even more problematic in the earlier asymptomatic or prodromal phases of the disease, where diagnosis is much more tentative.

## Applying Expertise

As was noted last year in a feasibility review in the journal Alzheimer's & Dementia, the design of secondary-prevention trials in AD has been handicapped by a lack of proximal cognitive outcome markers. The cognitive tests currently used to describe Alzheimer's are largely derived from comparisons of people with or without dementia, who are by definition unsuited to preclinical studies, observed Marion Mortamais et al.

In response, a growing number of studies are combining biological, neuroimaging and cognitive biomarkers in large cohorts to determine whether sequential cognitive changes follow on from biomarker changes, or may be detected at an earlier stage using conventional testing. The authors found ample evidence that cognitive changes could be detected in preclinical AD but also that the changes "only partially map" to current brain biomarker studies.

While some existing testing procedures have provided very early signal detection (notably episodic and semantic memory), other areas such as executive functioning are measured in too wide a variety of ways, and subsume too many other cognitive abilities, to be meaningfully interpreted, Mortamais et al cautioned. They called for the development of more region-specific cognitive measures, which were likely to be most effective within a longitudinal rather than a crosssectional study design.

Last year also, the Horizon 2020/IMI European Prevention of Alzheimer's Dementia (EPAD) project issued a consensus statement recommending appropriate cognitive-outcome measures in studies for preclinical AD. In February 2018, the European Medicines Agency's Committee for Medicinal Products for Human Use adopted a revised guideline for clinical studies in Alzheimer's, including use of new diagnostic criteria, biomarkers

and outcome measures. In the same month the US Food and Drug Administration issued guidance for industry on diagnostic criteria and outcome measures for early AD.

At WCG we can apply years of expertise in clinical research for central nervous-system disorders to help trial sponsors design effective protocols, select the right participants, and collect consistent, accurate, reliable endpoints in AD trials. We are currently engaged in around 30 Alzheimer's trials, spanning the preclinical, prodromal and dementia stages of the disease.

Using our Virgil electronic data-capture (EDC) platform, clinicians can ensure that inputs and outcomes in AD studies generate definitive positive or negative data to inform the next steps in drug development. "We can't make a drug work that's not going to work," Dr Randolph comments. "But we want to be able to tell you whether it works or it doesn't."

As Dr Randolph observes, clinical-outcome assessments in Alzheimer's "have a fair amount of subjectivity built into them. We try to improve the reliability of those measurements, primarily by using an EDC system we have built on tablet computers. The tablets have a lot of built-in guidance, they have consistency checks and a calculator in them, so they really help steer site-based clinicians through those assessments."

*With a global network of clinicians who train as a group, follow the same trial-review parameters and speak English as a second language, we can exercise centralized clinical oversight on a worldwide scale.*

## Error Reduction

WCG was the first company to implement electronically based clinical outcome assessments with clinical guidance built into the system. Its tablet-based technology also enables clinicians to audio-record, or in some cases video-record, endpoint assessments.

Previously, the whole process was paper-based. Clinicians logged the data into an EDC system manually on site, which in itself left a wide margin for errors. Judged on four key outcome measures, the Virgil system is capable of reducing error rates in Alzheimer's trials by anything from 50% to 85% compared with paper-based management of study data.

These benefits carry all the more weight as AD studies become necessarily larger, longer and more global, taking in anything up to 700 sites per trial. WCG's systems are active at more than 2,000 clinical-trial sites conducting Alzheimer's studies worldwide. With a global network of clinicians who train as a group, follow the same trial-review parameters and speak English as a second language, we can exercise centralized clinical oversight on a worldwide scale. In this most demanding of research segments, WCG's science-based technologies, capabilities and human resources are helping to clear a path through better-calibrated clinical development to much-needed new treatment paradigms in Alzheimer's disease.

**Christopher Randolph, PHD**
Chief Scientific Officer, WCG
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*Dr. Randolph has extensive experience in CNS clinical trials work, as an investigator, consultant and creator and supervisor of rater training programs for a large number of Phase II and Phase III multinational studies in Alzheimer's disease and other neurodegenerative conditions; schizophrenia; stroke; hepatic encephalopathy; and traumatic brain injury.*

*He also has a strong background and interest in psychometrics and neurocognitive assessment, having worked for over 20 years as a consultant on test development, including the revisions of the Wechsler intelligence and memory scales. He is the author of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a brief neurocognitive battery used widely around the world.*

*Dr. Randolph is Clinical Professor of Neurology and Director of the Neuropsychology service at Loyola University Medical Center and is board-certified in clinical neuropsychology. He has authored more than 90 peer-reviewed articles on a variety of research interests, including Alzheimer's disease, Huntington's disease, Parkinson's disease, traumatic brain injury, sport-related concussion, Tourette's syndrome, schizophrenia and hepatic encephalopathy.*

*Dr. Randolph received an undergraduate degree from Vanderbilt University, and MS and PhD degrees from Rutgers University/University of Medicine and Dentistry of New Jersey. He completed an Intramural Training Award fellowship at the Clinical Brain Disorders Branch of the NIMH, and worked as a senior staff fellow in the Experimental Therapeutics Branch of the NINDS.*