WORLDWIDE
CLINICAL TRIALS

10 STEPS TO BETTER ALZHEIMER'S DISEASE RESEARCH

UNCOMMON TENACITY NEEDED
FOR PROGRESS IN CLINICAL TRIALS

CONTENTS

Introduction

For 40 years, the experts at Worldwide Clinical Trials have contributed their time, talent and uncommon tenacity towards improving the lives of patients suffering from the ravages of Alzheimer's disease. Advances to date have been hard won, but Alzheimer's research is at a tipping point. Standing firm in our commitment to win the fight against this perplexing disease, here we offer the benefits of our lessons learned with 10 steps to improve Alzheimer's disease research.

A HISTORY OF STRUGGLE IN ALZEIMER'S DISEASE RESEARCH NEARS TIPPING POINT

The facts and figures are daunting – calling for uncommon tenacity.

— An unusually high

99.6%

failure rate in Alzheimer's clinical trials *(Cummings, 2014)*

47

million people suffer from dementia – a number with no signs of slowing down *(Alzheimer's Disease International)*

60% to 80%

of these patients are diagnosed with Alzheimer's disease *(Alzheimer's Association)*

— Complex pathogenesis and multifactorial etiology

— Few new drug submissions for market authorization, despite an unprecedented flow from discovery to development

These facts are familiar and daunting. But did you know Worldwide Clinical Trials has been on the front lines of this struggle since the advent of cholinesterase inhibitors as a cognitive therapeutic in the late 1970s? And we're not about to give up now.

Worldwide brings 40 years of passion, expertise, and experience to Alzheimer's disease research

After 40 years toiling in the perplexing field of dementia – in partnership with innovative companies and with the support of patients and their families – Worldwide brings an uncommon blend of passion and hard-won expertise and experience that is shaping the future of Alzheimer's disease and related dementia research.

Despite historical trends, there are positive signs that Alzheimer's disease research is close to a tipping point where a deeper appreciation of pathophysiological mechanisms, innovative clinical trial design, and operations excellence from industry experts such as Worldwide will deliver the next generation of therapies.

The optimism is apparent in this eBook, which summarizes

WORLDWIDE'S UNCOMMON APPROACH

to the following clinical trial challenges:

- Recruiting and engaging Alzheimer's patients and caregivers who face an array of barriers to participation
- Reducing the high rates of screen failure that are common due to difficulties in evaluating early stage and pre-symptomatic trial volunteers
- Limiting high variability in the selection, administration, and scoring of cognitive assessment tools.

If you, too, are working against this formidable foe, make it a point to engage with the diverse group of Worldwide staff members who are uncommonly committed to improving the the lives of the 47 million people living with dementia today.

WORLDWIDE CLINICAL TRIALS

WORLDWIDE'S CONTRIBUTIONS
TO ALZHEIMER'S DISEASE RESEARCH

NEURO-DEGENERATION

- Accelerating CNS Drug Development (Cutler, Sramek, Kurtz, 1998)
- ADAS development (Stanford CRC; Murphy)
- Alzheimer's Disease: Optimizing Drug Development Strategies (Cutler, Veroff, Sramek, 1995)
- Commercial, computerized NP assessments (Veroff et al, 1991)
- Commercial CSF/plasma PK/PD modeling (Gobburu et al, 2001)
- Commercial 24-36 hour continuous CSF acquisition (Cutler)
- Critical Pathways to Success in CNS Drug Development (Cutler, Sramek, Murphy, 2010)
- Drug Studies in the Elderly: Methodological Concerns (Cutler, Narang, 1986)
- First in human "bridging" concept (Cutler et al, 1996)

- Industry-sponsored multicenter trial - esterase inhibitor (Murphy, 1989-1992)
- Industry sponsored conversion trials (multiple)
- Linkage ADAS - caregiver burden (Murphy; Clipp and Moore, 1995)
- fMRI semantic memory in AD (Saykin and Riordan, 1999)
- Understanding Alzheimer's Disease (Cutler and Sramek, 1996)

INTERVENTIONS

- Nutriceuticals / Phytoceuticals
- Precursor loading strategies
- Esterase inhibitors
- Muscarinic agonists (various receptor subtype specificities)
- Nootropic agents and supplements
- Partial nicotinic agonists
- Monoaminergic MOA based compounds
- H3 inverse agonists
- 5HT6 antagonists
- Anti-inflammatory agents
- Anti-fibrillogenic agent
- Alpha secretase enhancers
- Beta secretase inhibitor
- Gamma secretase inhibitors
- Gamma secretase modulators
- Antibodies for passive immunization
- Tau protein aggregation inhibitors
- PKC isozyme activator (α and ϵ)
- Other interventions (including devices)

RECENT MILESTONES

- Immunotherapy aimed at alpha synuclein in early PD
- Multinational study in FTD progranulin mutation / largest FTDbv
- Industry-sponsored MSA (Multiple System Atrophy) study, PET as outcome
- Multicenter implementation of several imaging methodologies
- PET microglial activation in MSA 11C PBR28
- PET Amyloid burden for inclusion purposes and outcome
- PET Tau (THK-5351) burden for eligibility and outcome
- 18FFDG-PET for eligibility and as an outcome measure
- DTI (Diffusion Tensor Imaging) in AD studies
- DAT for eligibility and outcome in PD study
- PTI-125 for safety, tolerability, and PK

1 ENGAGE WITH STRATEGIC PARTNERS WHO CAN BRIDGE THE BENCH-TO-BEDSIDE GAP

Early-phase clinical research in Alzheimer's disease creates and crosses critical inflection points in product development. Creating a bridge carefully in order to cross it quickly and efficiently becomes a challenge in translational clinical research.

Data derived during animal-to-man transitions, first in human studies, target engagement, and proof of concept studies either greatly enhance an asset or accelerate its demise. In this environment, turnkey clinical operations bereft of real-time scientific and medical oversight by both sponsor and contract research organizations (CROs) are anathema (Murphy, 2017).

A limited number of patients evaluated, signal detection across multiple assessments (biochemical, physiological, clinical), and the evolving database of product attributes (e.g., safety, exposure, biodisposition) affect the resulting clinical program.

Having established tools, processes, and infrastructure no longer provide differentiation for a CRO but are essential business attributes. It is the value-added activity from integrated, highly functional project teams and a visionary approach to clinical research that are foundational to today's successful business relationships.

Bridging the gap from discovery to development, from bench-to-bedside, starts with an appreciation of the drug discovery processes informing a clinical program, especially in earlier phases when few patients and single points of data inordinately drive decisions for program development.

Access to clinical trialists – individuals steeped in trial methodology – who also have relevant basic research and drug development experience becomes an essential perspective to permit exploitation of product attributes within the initial phases of clinical research.

When proposed indications, such as disease modification for Alzheimer's, have few precedents, staff cognizant of evolving regulatory sentiments and professional knowledge of international standards of care become invaluable.

The partner that offers this unique combination of experience and expertise increases the odds that your clinical trial program will achieve the desired results.

IT'S CHESS, NOT CHECKERS

Historical relationships between sponsors and CROs in Alzheimer's disease research can be characterized by an analogy to the game of checkers - a predictable, slow, capacity-driven business model with rare jumps and primarily transactional exchanges.

Modern research and development efforts, by contrast, are closely aligned with chess – intuitive, strategic, and cognizant of multiple downstream events. It's essential in today's environment to deploy CRO services that are commensurate with this new paradigm.

FOUR QUESTIONS TO EVALUATE A PARTNER FOR ALZHEIMER'S DISEASE TRIALS

When exploring strategic research partnerships consider the following questions.

Q1

How does the company's experience delivering innovation and differentiated services in the perplexing field of dementia research help it create integrated and highly effective project teams for strategic program development?

Q2

Considering the overall success rate of 0.4% (99.6% failure) in Alzheimer's disease clinical trials, how can you combine flawless execution to predictable milestones and timelines with good assay sensitivity to derisk the drug development process?

Q3

Given the mosaic of possible measures and outcomes, what constitutes the proper balance between hypothesis testing versus generation for illnesses with complex physiology?

Q4

Is the development pathway created for mild-to-moderate Alzheimer's disease applicable to other indications under the umbrella of dementia?

2 INNOVATE CLINICAL TRIAL OPERATIONS TO SMOOTH TRANSITIONS BETWEEN STUDIES

The global impact of Alzheimer's disease (AD) continues to increase, affecting an estimated 60%-80% of the 46.8 million people now living with dementia, a number expected to reach 131.5 million in 2050, according to Alzheimer's Disease International and the Alzheimer's Association. Despite more than a decade of frustration in finding effective disease-modifying therapies, there are new opportunities to reduce the time and risk of AD drug development through improvements in trial design (Cummings, 2016).

For example, there has been an effort led by the innovative Alzheimer's disease researchers of Worldwide Clinical Trials and others to ensure a seamless transition from single to multiple dose cohorts of patients (SAD-MAD) within a single study, often consisting of up to 10–12 cohorts across as many sites. Of note, some sites may be engaged early on in the enrollment process while others are activated in a staggered approach.

Unlike studies seeking to enroll healthy volunteers at a single site, the majority of early-phase cohort studies in patient populations are conducted across multiple sites, with the number of sites being dependent upon sample size, length, and complexity of the study and the recruitment potential of the indication of interest.

"Virtual waiting room" enables proactive management of early-phase Alzheimer's study tasks.

In an effort to increase the predictability of timelines, stabilize enrollment fluctuations, master the timing and unpredictability of complex cohort designs, fight recruitment fatigue, and ensure that all eligible patients who can be randomized actually are randomized, Worldwide's researchers created a technology-assisted "virtual patient waiting room" in partnership with the study sponsor (House, 2017).

This virtual waiting room permits investigators in Alzheimer's disease research to recruit patients on an ongoing, rolling basis in a "next in line" approach that permits multiple sites to simultaneously enroll patients into a single cohort, while continuing

to recruit for the upcoming cohorts. Patients recruited who meet eligibility criteria when randomization is closed for a specific cohort are simply placed in the virtual patient waiting room while screening activities continue for the subsequent cohorts. This simple maneuver stabilizes recruitment efforts and patterns such that sites do not have to be shut down and started back up multiple times.

Technology ensures all eligible patients are enrolled and there is no over-enrollment.

By utilizing this strategy, the appropriate enrollment of each individual cohort can be more easily managed simply by proper programming of the interactive response technology to ensure that all eligible patients are randomized, that there is no over-enrollment within the cohort, and that the time between cohorts is minimized. Importantly, forecasting important metrics, such as last patient visit in each cohort, can be easily achieved.

CONCLUSION

In summary, the technology-assisted cohort optimization strategy outlined at left results in faster progression through cohorts in Alzheimer's disease research while preserving study data integrity in early phase multi-center studies, **saving both time and money.**

3 EMBRACE NEW RESEARCH FRAMEWORK TO FACILITATE USAGE OF BIOMARKERS
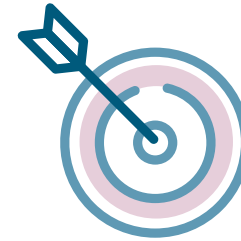
Biomarkers offer one of the most promising paths to diagnosing Alzheimer's disease before the symptoms emerge. As such, they represent a key ingredient necessary to identifying preventative agents.

Here's the problem: Although imaging and cerebrospinal fluid (CSF) biomarkers have long been incorporated into Alzheimer's disease research and have a robust body of supporting literature, a gulf remains between their scientific value and their actual use in clinical practice (Tricarico, 2017).

The good news: A new research framework may begin to bridge that gulf.

Biomarkers, not symptoms, define Alzheimer's

The National Institute on Aging (NIA) and the Alzheimer's Association (AA) are finalizing a revised framework that modernizes the diagnosis of Alzheimer's disease. The previous update was released in 2011.

In this iteration of the framework, biomarkers alone define the presence of Alzheimer's disease. Symptoms would merely help stage the disease.

The framework focuses on three biomarkers:

- β-amyloid deposition (Plaques formed when protein pieces – β-amyloids – clump together.)
- Tau pathology (Accumulation and aggregation of the microtubule-associated protein tau are hallmarks of neurodegenerative disorders, including Alzheimer's disease.)
- Neurodegeneration (A broad term that refers to progressive loss of structure or function of neurons.)

Implications for clinical trials and clinical practice

Validated biomarkers allow researchers to better identify candidates to enroll in Alzheimer's clinical trials. They're also more accurate than cognitive assessment tools in measuring disease progression; this means fewer participants and less time required to demonstrate efficacy, which reduces costs (Alliance, 2017, CLN, 2012).

Using biomarkers also allows for a precise approach to trials that target specific pathways. And, perhaps less measurable but just as important, the use of biomarkers can improve an investigator's confidence in the diagnosis.

Biomarkers approach needs to be validated

Significantly, this research framework is not intended for clinical practice – at least not yet; it's just for Alzheimer's disease research. The framework's approach to biomarkers needs to be validated and possibly modified before it is ready for the clinical setting.

Work is already underway on the clinical side, however. For example, the Alzheimer's Biomarkers in Daily Practice (ABIDE) project seeks to identify what biomarkers mean for clinical practice, what patients think about biomarkers, and how to engage patients to determine which biomarkers to use.

CONCLUSION

With the new NIA-AA research framework, biomarkers have the potential to transform Alzheimer's clinical studies and clinical practice, from enrollment of the first patient to, perhaps eventually, a cure.

NIA-AA RESEARCH FRAMEWORK ADOPTS SIMPLIFIED BIOMARKER CLASSIFICATION

Scheme categorizes multidomain biomarker findings at the individual person level in a format that is easy to understand and use.

Various imaging and CSF biomarkers are widely used in AD and brain aging research. As part of the 2018 NIA-AA Research Framework to Investigate the Alzheimer's Disease Continuum, the drafting committee followed recommendations from a recent position paper that reduces complexity by outlining a descriptive classification scheme for biomarkers used in AD and cognitive aging research.

Summarized in Table 1, the scheme is labeled ATN to recognize three general groups of biomarkers based on the nature of the pathophysiologic process that each measures (Jack, 2016).

Biomarkers of β-amyloid plaques or associated pathophysiologic process (labeled "A)" are cortical amyloid PET ligand binding or low CSF Aβ42.

Biomarkers of aggregated pathologic tau or associated pathophysiologic processes (labeled "T") are elevated CSF phosphorylated tau (P-tau) and cortical tau PET ligand binding.

Biomarkers of neurodegeneration or neuronal injury (labeled "N") are CSF total tau (T-tau) FDG PET hypometabolism and atrophy on MRI.

New unbiased descriptive classification scheme for biomarkers is intended to simplify Alzheimer disease research.

Table 1 - ATN Biomarker Grouping (NIA-AA, 2017)

A/T/N Classification	Pathophysiological Process	Specific Biomarkers
A	Aggregated β-amyloid or associated pathophysiology	CSF Aβ 42, or 42/40 ratio Amyloid PET
T	Aggregated tau (neurofibrillary tangles) or associated pathophysiology	CSF phosphorylated tau Tau PET
N	Neurodegeneration/neuronal injury	Anatomic MRI FDG PET CSF total tau

4 ENHANCE CLINICAL SITE PRODUCTIVITY THROUGH STRONGER RELATIONSHIPS

With the continuing trend toward patient-centric trials in Alzheimer's disease research, clinical sites and investigators are increasingly left out of the process and need to be re-engaged (Underwood, 2017). It is crucial for sponsors and contract research organizations (CROs) to balance patient-focused activities with increased site engagement to forge and maintain strong relationships with those site study teams on the ground.

CROs and sponsors should aim to engage more closely with sites, as they are carrying out the work and can provide valuable input. Most sites relish the opportunity to be more involved, offering insights on operational issues throughout a trial, which, if used effectively, can improve protocol development and assessment, as well as data quality.

There are several factors that can improve site relationships, including structured processes, consistent interaction and engagement, and purposeful communication.

Bringing structure to the relationship process

Building and maintaining site relationships should be a structured process starting with early engagement with site leaders. A solicitation meeting should take place first, where a mutual confidential disclosure agreement (CDA) can be put in place, followed by a face-to-face meeting with the main study coordinators to agree upon lines of communication and potential pain points.

Next, high-level processes need to be set for the following items to ensure collaboration at all levels:

- Pre-award input: How is the sponsor/CRO going to reach out to get a site's input on protocols, rather than just issuing a survey?

- Site identification: How will the site become one of the sponsor's/CRO's preferred sites and vice versa?

- Issue escalation: How will this be handled without undercutting the CRA?

- Communication: Frequency is key, but it should also have a purpose, so how will this be managed?

Today, relationships often are forged via email, Skype, etc., and although technology has clear benefits in terms of time and cost efficiencies, one cannot underestimate the value of building relationships with face-to-face communication. In addition to the importance of consistent communication, sponsors and CROs must also manage the frequency and quality of communication – you should be communicating with purpose. You should work to ensure that you are clear in all communication about any response that is needed or expected, as well as changes in processes, goals, or timelines.

CONCLUSION

By communicating with purpose, engaging with sites throughout Alzhiemer's disease clinical trials and operating with clear processes, sponsors and CROs can make it easier for sites to conduct trials with improved data quality. To achieve this, investigator sites must be considered as true partners.

5 ADOPT ADVANCED STRATEGIES TO ENGAGE WITH ALZHEIMER'S PARTICIPANTS AND CAREGIVERS
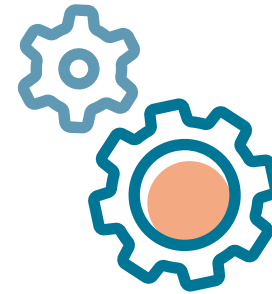
Participant recruitment and retention are critical to the success of any clinical trial program. However, there is added urgency with Alzheimer's disease, given the competitive landscape, restrictive eligibility criteria tailored to specific patient subsets, and comparatively high screen failure and dropout rates.

In addition, primary care physicians' lack of capacity and resources to assess cognition and refer patients to research; barriers to participation for underserved communities; and the use of invasive procedures, such as lumbar punctures or brain imaging, can all be hurdles for recruitment efforts.

With this in mind, innovative recruitment strategies are required to find the right patients, reduce screen failure rates, and enhance patient retention over the long term (Zupancic, 2017). Getting access to these patients requires that researchers first identify suitable sites and build a strategy for fostering and maintaining good relationships with these sites.

Ideally, sites will have access to targeted subjects with neuropsychological/ cognitive and biomarkers data and have identified subjects that fulfill diagnostic criteria for either pre-clinical,

mild cognitive impairment (MCI) or dementia due to Alzheimer's disease. Studies within the MCI classification, for example, will require a very specific recruitment strategy as well as retention plan, so it is important for researchers to work with study partners that are armed with the knowledge and ability to do this.

Caregiver partners are as vital as patients to trial success

In addition to fully understanding the disease and its progression, a critical component of engaging patients and their caregivers is understanding them and what they go through on a day-to-day basis. Typically serving in the role of study partner, the caregiver is instrumental to trial success: they ensure informed consent, assist in protocol and medication compliance, and serve as an informant on trial outcomes. Moreover, the study partner is critical to the decision whether to enroll. No effective strategy can be developed without understanding caregiver needs.

For example, caregivers can help influence AD patients who may be unable to handle long doctor's visits, are frightened of loud waiting areas, will become quickly frustrated and irritable if asked to undergo certain procedures (such as neuroimaging, which they perceive as painful), are more sensitive to sensory input, or can't understand compound sentences and abstract concepts. Being cognizant of such things as partner work schedules and transit time to clinics can help with this understanding.

It is crucial for study teams to reach out to the medical community and organizations supporting patients and caregivers within each community. By engaging with neurology departments in hospitals, private practices and clinics, memory clinics and mental health departments, etc., researchers can increase awareness of the clinical study among all relevant health care professionals.

CONCLUSION

By working with strategic partners who have the expertise and experience in designing and delivering these trials and the passion to address unmet clinical needs, researchers can implement effective patient-centric trials that will meet the unique demands of this clinical population.

6 UNDERSTAND WHICH PATIENTS ARE MORE LIKELY TO QUALIFY BEFORE FORMAL SCREENING BEGINS

Failures in Alzheimer's disease (AD) research have been attributed to multiple factors, including an inadequate understanding of mechanisms of action and poor target engagement; however, other issues such as poor study design, wrong stage of AD matched to a particular drug, limited statistical power of endpoint measures, and inclusion of ineligible participants also contribute (Babic, 2016).

In fact, failure to meet entry criteria in randomized controlled studies focusing on cognition improvement is a fundamental barrier to study execution, leading to protracted timelines and increased costs.

Appropriate study design and optimization of recruitment/screen failure rates in Alzheimer's disease research are proving increasingly important as the field focuses on putative disease-modifying agents and patients that are early in the disease spectrum – studies that have notoriously high screen failure rates (with averages upward of 85%) and low recruitment rates (with averages of 0.19 patients per site per month).

Evaluate predictable reasons for screen failure in Alzheimer's disease research before patient consent

To address these screen failure rates, Worldwide Clinical Trials recommends an uncommonly proactive approach to understand which patients are more likely to qualify by evaluating the predictable reasons for screen failure before patient consent.

These predictable reasons include medical history, medical status, dementia history and diagnosis, con-medications, Mini-Mental State Examination (MMSE) range, study benefits and complexity, patient and caregiver wishes and expectations as well as their external pressures.

Though good clinical practice (GCP) guidelines recommend no formal screening actions take place before patient consent, leading memory centers in Alzheimer's disease research are able to pre-qualify patients based on the predictable dimensions noted above. Given familiarity with a clinical trial protocol, a few highly sophisticated clinical sites in Europe can offer this data. Notably, screen failure rates in Alzheimer's disease research at these clinical sites are much lower than average.

PREDICTABLE CAUSES OF SCREEN FAILURE

- Medical history
- Medical status
- Dementia history and diagnosis
- Con-medication
- MMSE range
- Study benefits
- Study complexity
- Patient's and caregiver's wishes and expectations
- Logistics
- External pressures

Worldwide's proactive approach to limiting screen failure evaluates these measures for potential issues before consent.

7 IMPROVE SCREEN FAILURE WITH A HIERARCHICAL APPROACH TO ELIGIBILITY AND STATISTICAL TOOLS
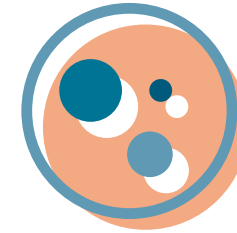
In terms of screen failure, the development of symptomatic treatment in mild to moderate Alzheimer's disease (AD) has been associated with rates ranging between 15-35%. Although this range is manageable, it is not uncommon for trials to have twice the fail rates in early AD populations, with high rates also characteristic of many disease modification studies (Babic, 2016).

To ameliorate these, a hierarchic approach to patient's eligibility factors may be used, which takes into account all known and estimated, or semi-predictable, screening variables. This hierarchy should be based on how costly and cumbersome various screening procedures are, with less costly and complex procedures occurring first. Following such a hierarchical procedure has been shown to reduce screen failures in an ongoing study from 80% to less than 50%.

Predicting the presence of amyloid/tau or diagnostic conversion to Alzheimer's disease

It is more difficult to reduce failure rates caused by non-predictable factors such as amyloid level on CSF, amyloid-PET, or safety brain MRI indicating Amyloid Related Imaging Abnormalities (ARIA). However, one promising technique utilizes statistical tools that predict the presence of amyloid/tau or even the eventual diagnostic conversion to AD. Typical techniques involve using multiple regression analyses to predict the presence or absence of beta amyloid or tau on imaging or in CSF, based on scores on earlier-obtained and easier-to-acquire screening measures such as demographics, cognitive test scores, genetic status, clinical signs/symptoms, and structural MRI findings.

Another method has been proposed to minimize the cost of trials without compromising statistical power. Utilizing an adaptive design for data acquisition exploits harmonic analysis of a band-limited signal on a graph whose node corresponds to participants with the goal of fully recovering a multivariate signal on the nodes, given the full set of lower-cost features and a partial set of more expensive measurements.

Analytical techniques offer the opportunity to predict which subjects will qualify for study participation in an adaptive manner, with each additional piece of screening information adding to the success of final predictions based on biomarkers.

CONCLUSION

These methods, along with an increased familiarity of patient clinical status and the use of a hierarchical approach to screening, should help to minimize screen failure rates, improving overall recruitment rates in these notoriously difficult-to-enroll trials.

WORLDWIDE SCREENING ASSESSMENT PROCEDURES RESCUE PRODROMAL ALZHEIMER'S DISEASE RESEARCH STUDY

Worldwide Clinical Trials was retained to intervene in a Phase IIb, multinational, randomized, double-blind, placebo-controlled study on subjects with progressive cognitive decline compatible with the diagnosis of prodromal Alzheimer's disease (AD).

For this highly complex study, the original CRO had failed to meet enrollment expectations due to inadequate vetting of site capabilities for this unique diagnostic category, which required the use of multiple, sophisticated screening assessments that served as "gatekeepers" for patient eligibility.

The study had been launched in over 30 centers by the sponsor with virtually no patient enrollment prior to Worldwide's engagement.

The solution

- Dedicated a Worldwide neuropsychologist to oversee clinical monitoring, site selection and enrollment.

- Structured the sequence of test applications for compatibility with protocol design and standard of care.

- Re-evaluated site attributes and rater qualifications for administration of a battery of neuropsychological tests, many of which required specialized training in a highly codified sequence.

The results

Worldwide's conceptual, operational, and assessment services oversaw the study's extension into neighboring countries.

Supervision and training by the Worldwide therapeutic specialist on measures that affected patient eligibility accelerated patient randomization, enabling the study to complete one week prior to the original target date.

As acknowledgment of Worldwide's material contribution to concepts, analysis, and implementation of the study, Worldwide scientific staff are co-authors in an accepted article in the Journal of Alzheimer's Disease.

8 CONSIDER COGNITIVE COMPOSITES TO REDUCE FALSE POSITIVES

As Alzheimer's disease research moves to investigate earlier stages of the disease, there is a need for more sensitive and specific cognitive assessment tools to capture subtle clinical decline, identify individuals with minimal symptoms, and discern treatment effects among participants with earlier stages of the disease.

The relative insensitivity of traditional cognitive outcome measures to describe the more subtle and selective cognitive impairment associated with mild cognitive impairment/prodromal Alzheimer's disease, as well as track treatment-related changes, has resulted in a recent boom in cognitive composite measures (Riordan, 2017). Composites are typically created in an effort to reduce Type 1 error (false positives) by reducing the number of outcome measures to a more manageable level and ultimately improve signal detection by being more sensitive to disease state and treatment effects while reducing sample size.

Composite endpoints characteristically have several other advantages, including being more highly correlated with putative biomarkers,

such as neuroimaging and CSF measures, and being better at predicting disease progression.

Only rarely are composite measures employed to guarantee that appropriate cognitive domains of interest are sampled in a practical and efficient manner, ensuring adequate psychometric properties (such as sufficient reliability and avoiding celling/floor effects), or employed as a method to characterize the cognitive profile of a drug in an a priori fashion that is associated with a disease state longitudinally and/or with treatment intervention.

Composites capture the variability in multiple cognitive domains caused by cognitive enhancers.

Although it is relatively easy for many clinical trialists to acknowledge that specific cognitive domains are more likely to be associated with particular CNS conditions, few appreciate that even widely recognized cognitive enhancers typically affect multiple cognitive domains: preferentially improving some domains while possibly causing impairments in others, even against a backdrop of improved overall cognitive function. One method for ensuring that this variability is adequately captured is through the proficient construction and

analysis of cognitive composite measures.

One of the most notable novel composites is based on data obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and applies psychometric methods to various cognitive tests utilized across approximately 800 subjects in a series of studies.

The ADNI authors reviewed the entire baseline ADNI neuropsychological battery to identify items that could be considered indicators of either executive function (EF) or memory (MEM), both known to be important in diagnosing early AD.

Importantly, the authors then compared ADNI-EF with individual component measures in 390 subjects with mild cognitive impairment (MCI) with respect to the composite's ability to detect change over time; to predict conversion to dementia; to be correlated with MRI-derived measures of structures involved in frontal systems; and with cerebrospinal fluid (CSF) levels of amyloid β1–42, total tau, and phosphorylated tau. The ADNI-EF composite showed the greatest changes over time, followed closely by the component category fluency measure, but notably, the ADNI-EF composite required a 40% smaller sample size to detect change.

CONCLUSION

Including these new cognitive probes may result in a better understanding of early disease trajectory as well as the relationship of specific measures to clinically meaningful symptoms and signs *(Alsen, 2015)*.

9 INTRODUCE CENTRALIZED ELIGIBILITY REVIEW TO IMPROVE ENROLLMENT DECISIONS

One implication of the trend in researching pre-symptomatic stages of Alzheimer's disease is that it relies more on subjective judgement in order to evaluate patients for clinical trial enrollment. This has extended the focus from the early clinical sign of cognitive impairment measured with neuropsychological tests to the purely subjective report of cognitive decline in unimpaired elderly individuals, placing a heavy burden on clinical judgement (Jessen, 2014).
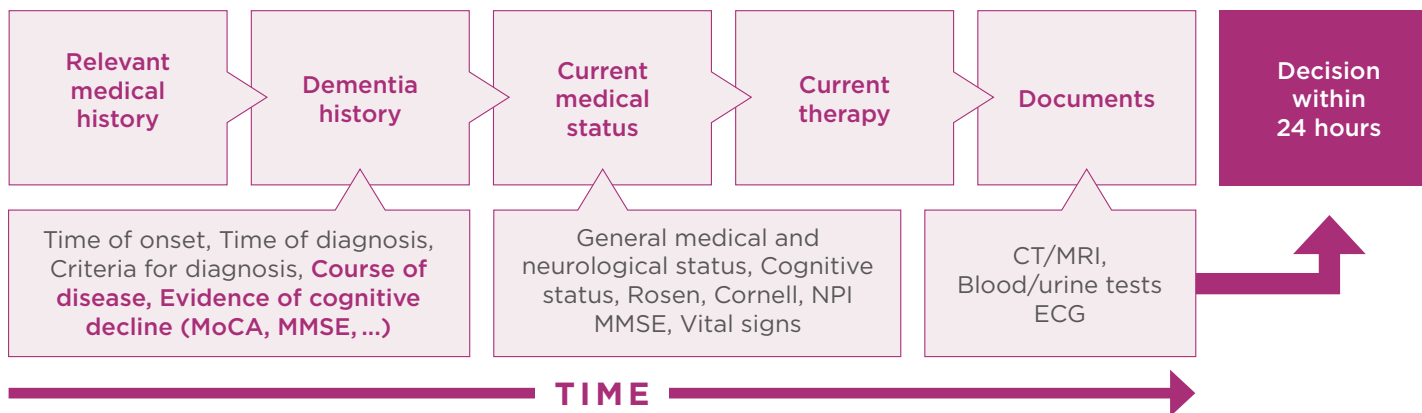
In some cases, this means that patients who pass successfully through screening are later deemed to be ineligible for randomization. Though focused on ensuring a high quality patient pool and protocol compliance, investigators often interpret inclusion criteria differently, enrolling patients who might not have otherwise qualified for a trial. Different levels of risk tolerance cause variability across trial sites which becomes more pronounced in global Alzheimer's disease research due to country– or region-specific approaches to diagnosis.

To reduce this variability, Worldwide recommends a central eligibility review team of physicians and experienced clinical scientists who collect key diagnostic and medical data just after patient screening then review the data as a group.

Eligibility concerns are discussed with the sites and investigators who make the final decisions, and subjects are withdrawn or randomized if additional clinical history is supplied to support eligibility.
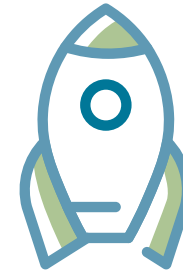
CONCLUSION

Because the centralized review system leaves the final randomization decision in the hands of the treating physicians it has been an accepted and vital part of limiting variability across clinical sites and reducing screen failure in Alzheimer's disease research.

Centralized teams provide comprehensive review of eligibility data and rapid delivery of randomization decisions.

Relevant medical history → Dementia history → Current medical status → Current therapy → Documents → **Decision within 24 hours**

Time of onset, Time of diagnosis, Criteria for diagnosis, **Course of disease, Evidence of cognitive decline (MoCA, MMSE, ...)**

General medical and neurological status, Cognitive status, Rosen, Cornell, NPI MMSE, Vital signs

CT/MRI, Blood/urine tests ECG

TIME

10 CONDUCT RATER TRAINING AND SURVEILLANCE TO BOOST ALZHEIMER'S DISEASE ASSESSMENTS

The inclusion of Alzheimer's patients with prodromal disease or mild cognitive impairment (MCI) in clinical trials allows individuals to be treated earlier in their illness and, hypothetically, at a time when some drugs may be more effective than they would be at a later stage (Schneider, 2014).

However, it is difficult to recruit for MCI trials due to lack of interest in higher-functioning subjects and demands on time and resources imposed by study participation.

In addition, raters must be highly skilled when screening subjects because many subjects may meet criteria for Alzheimer's dementia or may have deficits that do not suggest specific memory and cognitive disturbances.

Case study: The operational oversight necessary to address challenges with rater training is illustrated by Worldwide's involvement in a multinational study evaluating an investigational drug within subjects with MCI phenotype, (Friedmann, 2010).

Notably, a high screen failure rate (33%) occurred at numerous sites due to strict inclusion criteria for neuropsychiatric testing in which subtle differences in scoring and/or implementation of free and cued recall disqualified the subject from consideration.

As a result of the unexpectedly high screen fail rate and the potential for misapplication of assessments, a team of psychologists and monitors visited all sites to ensure understanding of concepts and techniques. Additionally, regular teleconferences and web-based seminars reinforced conventions.

Twenty-eight centers in six European countries were trained and certified at one of two investigators' meetings. The therapeutic team contacted each center again either in person (weeks 7-8) and/or by web-based teleconferences (weeks 14-18) during the course of the trial for refresher training. The methods to be applied in neuropsychiatric testing, particularly for screening, were emphasized during these meetings, and the impact of this

additional professional intervention on subject enrollment was evaluated.

The number of subjects randomized increased from 9 to 40

Both site visits and 5 weeks of teleconferences focusing on correct neuropsychological techniques greatly increased the number of subjects from 9 to 40 randomized. Randomization of subjects temporally correlated with the interventions activity affecting subject enrollment.

Diagnostic specificity and rater reliability improved.

Direct supervision and ongoing training of raters at the sites by the therapeutic team resulted in better diagnostic specificity and rater reliability. This produced an increase in enrolled subjects due to improved adherence to protocol and scale-specific instructions.

The use of regular teleconferences following on-site training had a beneficial effect, as enrollment continued to increase after the series of calls was discontinued.

CONCLUSION

The lessons from this case study can be applied to other multi-site MCI studies that may screen subjects too strictly or inappropriately due to raters' inexperience with assessment instruments, which are gatekeepers to randomization.

In these instances, ongoing supervision and refresher training by a therapeutic team can aid subject recruitment.

ASK THE EXPERTS

Worldwide Clinical Trials experts are renowned for their uncommon accessibility, therapeutic expertise and operational excellence. We invite you to reach out to our experts to discuss any challenges you may have with your current or upcoming clinical trial.

eBook Contributors

Michael Murphy, MD, PhD
Chief Medical and Scientific Officer

ASK ME A QUESTION

Tomislav Babic, MD, PhD
Vice President, International Neuroscience

ASK ME A QUESTION

Hank Riordan, PhD
Executive Vice President, Medical and Scientific Affairs

ASK ME A QUESTION

Barbara Zupancic, MBA, MSc
Director, Patient Recruitment and Retention

ASK ME A QUESTION

Alzheimer's Disease Experts – Standing by to Take Your Questions

Stephen Coates
Executive Director, Franchise Leader, Alzheimer's Disease & Dementias

ASK ME A QUESTION

Tamara Ast
Vice President, Global Project Management, Neuroscience

ASK ME A QUESTION

Nancy Cameron
Senior Director, CPM Leader, Global Project Management, Neuroscience

ASK ME A QUESTION

Jeff Zucker, MS
Senior VP, Global Clinical Operations

ASK ME A QUESTION

Allison House
Therapeutic Strategy Lead, Neuroscience

ASK ME A QUESTION

Natalia Drosopoulou
Director, Global Project Management, Neuroscience

ASK ME A QUESTION

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Corporate LiveWire recognized Worldwide as "Best in Neuroscience Therapeutics" in its 2016 Healthcare & Life Sciences Awards, which recognize the pinnacle of business achievement and organizations that have made a difference in patient lives.

This prestigious award recognizes Dr. Michael Murphy's exceptional contributions and his consistent history of service and dedication to the clinical research industry throughout his career.

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