wcg

Finding the Right Partner

Delivering CNS Trials Requires Specialized Clinical Knowledge

We need to improve the conduct of CNS trials. The failure rate of CNS drugs in phase 2 and 3 clinical trials is around 85%, second only to oncology.[1] Because of this failure rate, many large pharmaceutical companies are exiting the space. At the same time, the need for CNS therapies has never been more acute and there is a pressing need for both disease modifying and symptomatic treatments.

Estimates vary, but we know that over 10 million people live with Parkinson's disease globally. In the US alone at least 5.5 million people live with Alzheimer's disease. Anxiety disorders, the most common psychiatric disorder in the US, affect around 40 million adults each year. These are just three of many examples.

To meet this growing demand for treatments, we must carefully evaluate the areas most often associated with trial execution that lead to poor outcomes. Avoidable trial failure not only deprives patients of a new treatment they desperately need, it also compounds the cost of the failed trial, the cost of all prior trials and the lost opportunity cost of not pursuing viable alternatives.[2] These costs of failure become particularly acute for smaller sponsors who may lack the financial safety net to survive this failure.

TO IMPROVE TRIAL DESIGN, ACCOUNT FOR SUBJECTIVITY

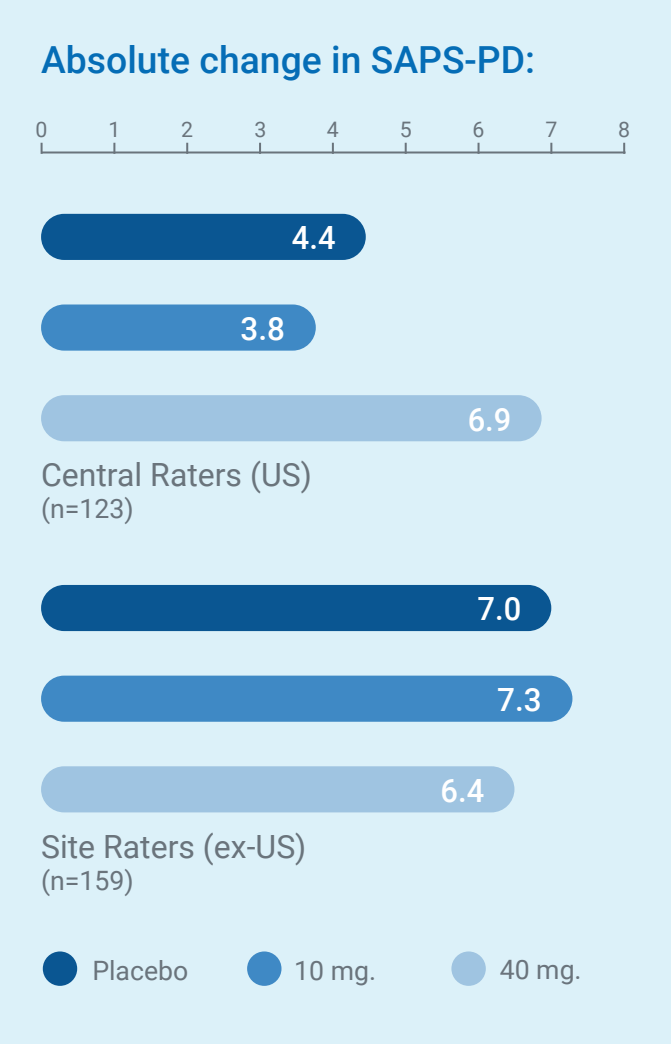
Poor study design is the number one reason for trial failure.[2] We know trial design and endpoint protection are crucial choices that directly impact success, and both present challenges for CNS trials.

The endpoints in CNS trials are usually subjective. We rely on the reporting of symptoms by the trial participant and on observational reporting by the clinical investigator. In some diseases, such as Alzheimer's and pediatric illnesses, we also rely heavily on the caregiver for their assessment of how the trial participant is thinking, feeling and acting.

Endpoint protection is a crucial part of study design, and WCG MedAvante-ProPhase (MAPP) is a specialized provider who can provide trial design advice and then support assessment of your trial endpoints in a way that eliminates bias and variability that can lead to erroneous conclusions.

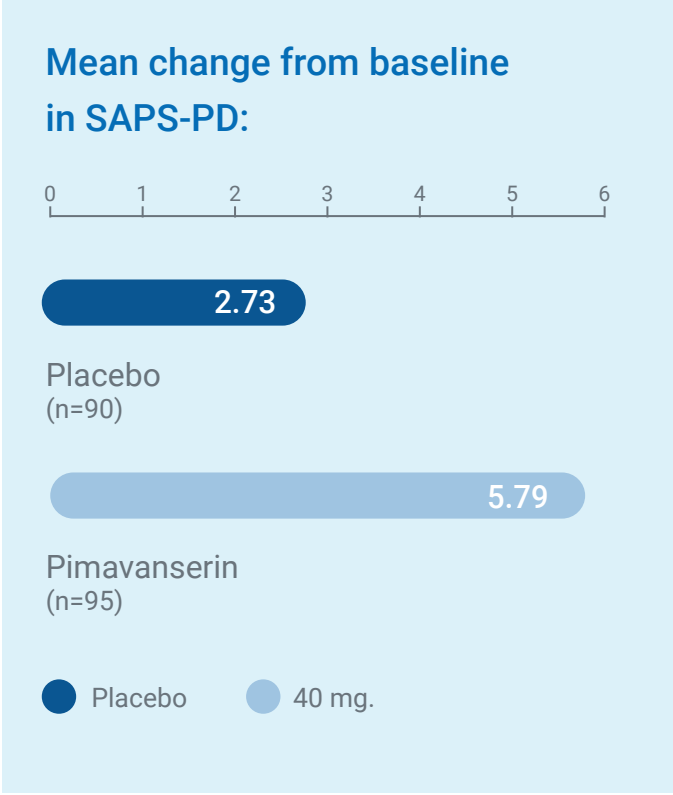
In 2009, Acadia conducted a trial in Parkinson's disease psychosis using MAPP central raters in the USA for the SAPS-PD scale but used site raters ex-USA. *The results are shown in the left-hand column on the following page*

The USA MAPP central raters found statistically significant separation for the 40 mg dose at week two and a trend towards significance at week 6, but the ex-USA site raters found no separation at any dose.[3]



MAPP central raters globally for its phase 3 trial and they saw strongly positive efficacy signals across multiple measures – most importantly, primary endpoints and prospectively defined secondary endpoints. Thus, they eliminated a potential false negative and showed separation of test drug and placebo. *The results are shown to the top right.*

Based on these compelling results, FDA cancelled the need for a confirmatory phase 3 trial and fast-tracked the submission based on the robust centrally rated results.



Placebo response represents another issue in CNS trial design. The presentation of a strong placebo response—subjects who psychologically believe they are receiving benefits from the investigational drug even though they are unknowingly assigned to the trial's placebo arm—can adversely affect results. Placebo response in CNS trials appears to be increasing over time.[1]

"The placebo response is more a problem in clinical [trials] with subjective endpoints rather than objective endpoints," explains Nathaniel Katz, Adjunct Associate Professor of

Anesthesia, Tufts University School of Medicine, and founder of WCG's Analgesic Solutions[1].

At WCG, we spearheaded training for trial participants that educates them how to self-report the relevant symptoms in a consistent way. Katz pioneered such training courses, and they have been used to train more than 50,000 trial participants. In this way, we minimize placebo response and increase the likelihood of an accurate trial outcome.

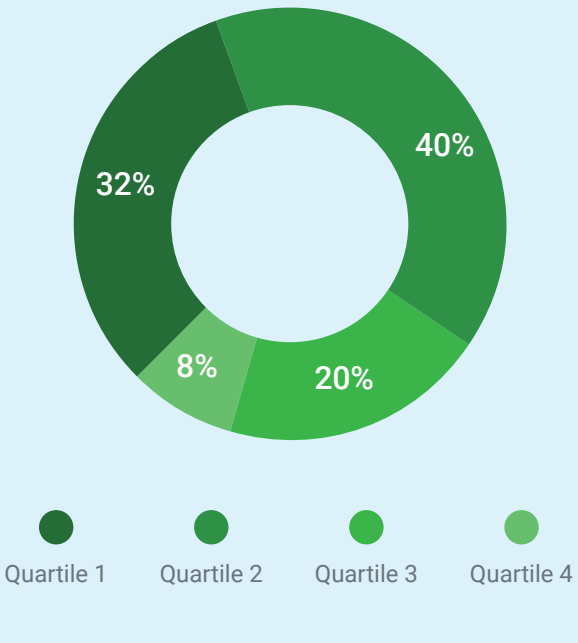
SITE SELECTION: A DELICATE BALANCE

Ineffective site selection is the second contributor to trial failure,[2] and again, CNS trials face unique challenges. Sponsors need to achieve a balance between sites that have extensive CNS trial experience and those who have less experience. Extensive trial experience may be an indicator for success but has the risk of competitive trials and trial participants who may have participated in multiple trials ("professional patients") or may even be participating in multiple trials ("trial shopping"). Less experienced sites may need more support but have untapped patient pools and fewer competitive studies.

To find the sites that fit the development sponsor's needs, we tap into the WCG Knowledge Base® with over 180,000 global investigators; this database contains proprietary information on over 93% of industry-sponsored studies, benchmarks and competitive performance data, as well as subscription and open-source data. We can also access our database of almost 3,000 US hospitals and independent sites that perform research - sites with whom we have close relationships.

To demonstrate how WCG can enhance study enrollment through evidence-based site identification, we conducted a retrospective analysis of a completed phase II trial for major depressive disorder. In this US study of 250 participants, actual enrollment was 0.76 participants per site per month and took 13.24 months to complete using 25 sites. When we analyzed these sites, 28% were historically low performers based on being in the lowest two quartiles for performance (quartiles 3 and 4). *The site distribution that the sponsor used is shown in the figure below.*

Distribution of sites used by the sponsor in this Major Depressive Disorder trial:



Based on historical performance from the WCG Knowledge Base® we identified the top 25-enrolling sites. Using only 18 of those sites, enrollment would have been completed in the same period of 13.24 months because they would have accrued at 1.32 patients per site per month. Reducing the number of sites to 18 would have resulted in cost savings of around $400,000 ($50,000 per site initiated). Alternatively, the sponsor could have utilized 25 top performing sites and reduced the enrollment period.

With WCG's proprietary tools, we can point sponsors to the sites most likely to succeed.

We provide data to ensure that the sponsor can make the best site selection decisions, including:

- Data on sites presented by quartile, based on past trial performance, which allows the sponsor to see which sites are the most likely and least likely to perform.
- Intelligence about competitor studies at the sites which enables a sponsor to make an informed decision about the likely competitive situation.

We can personally introduce sponsors to sites that have clear potential to enroll and are looking to expand their trial footprint. WCG's dedicated site identification and feasibility team provides the expert guidance and hands-on support companies need to find these sites. Our experts interpret the data and customize it to each sponsor's specific needs, accelerating the study startup process and maximizing the likelihood of success.

CNS TRIAL COMPLEXITY PUTS UNDUE PRESSURE ON SITES AND PARTICIPANTS

Poor recruitment, the third leading cause for trial failure,[2] also presents special challenges for CNS trials. "For Alzheimer's disease studies alone, there might be more than a dozen different technology platforms that investigators and staff would be asked to use for one study," the President of Independent Sites at WCG Clinical, told CenterWatch.[1] Because of the stringent protocol criteria "it's become impossible to find those patients."

In the face of this complexity, as well as growing internal and external site pressures, how can we help sites to manage our CNS studies and the CNS trial participants who may need more assistance than other groups to navigate the trial?

WCG ThreeWire, with global reach, provides experienced clinical research coordinators (CRCs) to augment site staff and provide dedicated focus on a single sponsor's clinical trial. This resonates especially well at busy sites where there are many trials competing for site staff time or at less experienced sites who need more support in navigating clinical trials processes. Additionally, these CRCs can focus on assisting trial participants to navigate the often complex pathway through the trial. This support is fully customized to the needs of each individual site and the needs of the trial.

CNS trial participants and their caregivers need exceptional support to enter and remain

in clinical trials. WCG ThreeWire site augmentation services offer participants a personalized experience and can be on hand to walk them through the trial processes and procedures, as well as supporting all recruitment activities.

In pediatric studies and other studies with a caregiver, retention truly starts with recruitment and our experience shows that parent/caregiver inclusion in every aspect of the process is key. If the participants and caregiver are not recruited correctly, then the rest of the downstream process is flawed, and the trial will not recruit successfully. This is exemplified by the amount of time that, in this case, the CRCs spent on chart review and physician referral outreach and communication, to find the best fit trial participants with caregivers who were willing and able to return for study visits and provide reliable feedback.

Clinical trial sites are under increasing pressures. In quarter 1 of 2021 the rate of trial starts rose with over 300 phase 1-3 trials started in March, exceeding pre-COVID-19 pandemic levels. Yet the number of available sites continues to decline. This increased work volume comes at a time when sites have lost staff and have not been able to replace them. All biopharma companies doing clinical research are affected by this, but the impact on smaller sponsors is greatest as they struggle

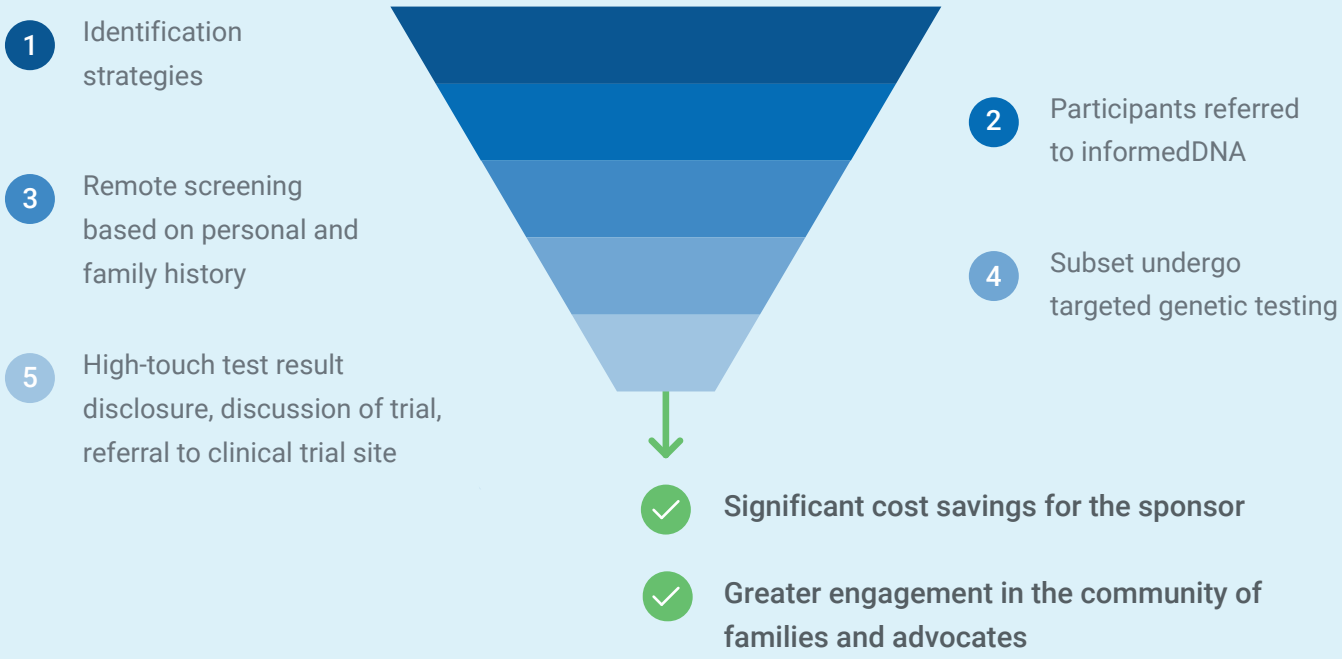
most to ensure that their trials receive the attention they deserve and need. Site augmentation support by WCG ThreeWire CRCs has been shown to effectively ameliorate these issues.

Another recruitment-related challenge is related to genetics. As the number of personalized medicine trials in the CNS area grows, so does the need for patients with specific genetic mutations. WCG, in partnership with InformedDNA offers genetic support services for those trials.

InformedDNA provides expert genetic advice throughout the trial process and through registration, as well as support for trial participants and family members. Hereditary conditions often affect entire families. In an autosomal dominant condition, any sibling, parent, or child of an individual with this disease has a 50% chance of sharing the genetic mutation. Family member outreach with cascade testing is a highly efficient method of identifying additional family members with the condition. Also, identifying at risk family members provides an opportunity for early detection and improved clinical outcomes.

For trials with a genetic component, InformedDNA can provide support from identifying those with the necessary genetic mutation through to referral to the clinical trial site, including counseling. *The process is shown below.*

informedRECRUIT™ Screening Process



HELPING DESPERATELY NEEDED CNS DRUGS MAKE IT TO MARKET

CNS trials present specific needs and challenges, but with specialized expertise and support, sites and sponsors can overcome them to help ensure an optimal trial outcome.

The reliance on subjective endpoints poses a significant challenge. Using centralized rating for completion of scale assessments and training to mitigate placebo response can positively affect outcome. Site selection remains a balance between experience, competition, and site resources. Being able to access a large selection of sites, understand their prior experience and success in delivery, and know the competitive landscape at those sites, are key to making informed site selection decisions.

Furthermore, we need to help alleviate the burden on both sites and trial participants due to the complex nature of CNS trials. Sites find it increasingly difficult to keep up with the demands that sponsors place on them, resulting in delays recruiting patients and processing trial data, as well as inadequate time to support participants, which hurts retention. Trials with a genetic testing component compound this situation. Augmenting site resources and the use of specialized genetic counseling support can overcome these obstacles.

Over the past decade, many larger pharmaceutical companies divested their CNS research because of the low rate of success in bringing those products to the market. It now falls to small and mid-size biopharma companies to fill this void, and we must do all we can to ensure that every CNS drug has the best opportunity the reveal its true therapeutic benefit.

NEED SUPPORT FOR AN UPCOMING OR ONGOING CNS STUDY?

Speak to an expert

REFERENCES

[1.] Salzman, S. CNS Trial Failures Problematic but Fixable, Experts Agree. The CenterWatch Monthly Vol 26 issue 06.

[2.] Fogel, DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. Contemporary Clinical Trials Communications 11 (2018) 156-164.

[3.] Friedman, JH (2009). Pimavanserin Phase III PDP Results ACP-103-012. Presented at AAN 2010 Conference, Toronto, Canada.

WCG is the world's leading provider of solutions that measurably improve the quality and efficiency of clinical research. Comprised of two segments, Ethical Review and Clinical Trials Solutions, WCG enables biopharmaceutical companies, CROs, and institutions to advance the delivery of new treatments and therapies to patients, while maintaining the highest standards of human participant protection.

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