Optimizing Prader-Willi Syndrome Clinical Trials

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Prader-Willi syndrome (PWS) is a rare disease caused by genetic mutation(s) on chromosome 15 and affects an estimated 1 in 20,000-30,000 individual worldwide1. During infancy, the affected individuals have severe hypotonia and poor feeding. From early childhood the individuals develop hyperphagia (excessive hunger) which very often leads to dramatic obesity. Additionally, other symptoms such as short stature, aggressive behavior, sleep disorders, and cognitive impairment are very frequent in PWS patients. These symptoms persist throughout the life of the individuals.

Clinical trials in PWS

While recombinant human growth hormone, the only FDA-approved treatment specifically for PWS, provides some benefits to patients2, it does not address hyperphagia, one of the core features of the disease.

There are currently no approved therapies to treat the hyperphagia and some other aspects of the disease (e.g., sleep disorder, aggressive behaviors, metabolic disorders). However, there are currently seventeen PWS clinical trials, either ongoing or about to recruit (source: Clinicaltrials.gov).

Recently, diazoxide choline (DCCR), developed by Soleno Therapeutics, showed some promising benefits on hyperphagia and other symptoms, and has been granted Breakthrough Therapy Designation by the FDA as well as Orphan Drug Designation for the treatment in the U.S. and EU3. In August 2024, the FDA has accepted for filing its NDA and granted NDA priority review. The regulatory review is still ongoing

While the success of a clinical trial resides in the safety and efficacy of the investigational product (IP), determining safety and efficacy can be hindered by factors

such as placebo response, expectation biases, and other critical factors, including the quality of the ratings, the training provided to the caregivers – who often provide most of the data - and the site staff–participant interactions. If not properly controlled, these factors may cause the failure of a trial, despite the potential efficacy and safety of the IP.

Important Factors for Paving the Path to Success

Rater training

> The path to a successful clinical trial, without any ambiguity in the interpretation of the results, starts with ensuring highly accurate assessments.

Our expertise in PWS and other rare diseases is the foundation of our state-of-the-art approach to Rater Training and Qualification. We draw upon our relationships with PWS KOLs in the field as well as our full-time leadership teams in Science and Medicine and Digital Health Sciences groups. Carefully selected raters, by the means of a robust qualification methodology established in collaboration with the sponsor, are trained on the protocol-relevant scales and their understanding can be further assessed by the mean of quizzes or mock interview-skills proficiency demonstrations. For detailed information see our other blog on this topic, "5 Reasons to Prioritize Rater Training."

Electronic Clinician Ratings

> While carefully selected and thoroughly trained raters are key to providing excellent data, data variability can be further reduced by using electronic scales.

Paper-based scale administration introduces opportunities for diminished data quality as a result of:

- Omitting a scale item
- Circling a score on the wrong line
- Inadvertently selecting two responses for one item
- Transcription errors

Electronic scales are designed to reduce rater burden thereby increasing compliance and, particularly for ePROs, participant retention.

Signant's enhanced Electronic Clinician Ratings solution and electronic Caregiver-Reported Outcomes, part of our Electronic Outcomes Assessment (eCOA) platform, improve the quality of the data by helping to remove these types of errors, thus reducing data variability.

> We have successfully implemented the electronic versions of the 9-Item Hyperphagia Questionnaire for Clinical Trial (HQ-CT), Food Safe Zone Questionnaire (FSZQ), and many other scales routinely used in PWS clinical trials.

In-trial data quality monitoring

Data consistency and reliability are key to success. Signant's Blinded Data Analytics helps study teams proactively review clinical assessments and ensure timely and collegial remedial actions to help limit impact on the quality of the data and prevent recurring errors.

> We have invested in and developed proprietary algorithms specific to PWS scales that have been successfully applied in PWS clinical trials.

Placebo response mitigation training for sites and caregiver/participant

Another important, often disregarded factor influencing clinical trials outcomes is the placebo response. Heightened placebo response and expectation bias is a major challenge for rare disease trials, including PWS trials. It is associated with failed clinical trials and significant financial loss. Increased placebo response has been observed in past PWS clinical trials[4,5,6,7].

At Signant, we see the complexity of this phenomenon as a call to action requiring increased knowledge and concrete, attainable mitigation strategies to improve the likelihood of study success. The most effective mitigation strategies include providing sites with culturally adapted approaches to placebo response mitigation and education of caregivers and participants.

For detailed information, see our recent blog on this topic, "Placebo Response in Clinical Trials: Challenges and Mitigation Strategies."

If you want to take the next step in advancing PWS drug research and are interested in better understanding Signant Health's extensive experience in PWS and other rare disease clinical trials, **please contact our team**.

REFERENCES

About the Authors

Joan Busner, PhD, has more than 35 years of experience as an academic psychiatric researcher and psychopharmacology principal investigator and founded and directed two university psychiatric clinical trials units. Dr. Busner served continuously on University Institutional Review Boards for 20 years. At Signant she has scientific and clinical responsibility for studies in mood, anxiety, pediatrics, and rare/orphan diseases. Dr. Busner is currently Affiliate Associate Professor of Psychiatry at Virginia Commonwealth University.

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