Fortrea

Effective planning to address unmet needs in Prader-Willi Syndrome trials.

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Prader-Willi Syndrome (PWS) is the most common genetic cause of life-threatening obesity. Occurring in close to one out of every 15,000 births, PWS currently has no cure and consists of chronic overeating, mild to moderate intellectual impairment and compulsive behavioral problems. These challenges create difficulties in providing care, and effective treatments have had inconsistent success in recent years. However, multiple assets are currently being studied in hopes to fulfill this unmet need, and treatment paradigms continue to be improved in practices all around the globe to enhance patient well-being. This white paper discusses best practices for operationalizing PWS trials and engaging PWS patients and their families, including:

- Operational factors to be addressed in protocols and study designs
- Treatment considerations from our recent experience in PWS trials
- Using appropriate scales and questionnaires for endpoint accuracy
- Patient-centric considerations to make trials appealing for the patient and family
- Finding and recruiting PWS patients
- Working with advocacy groups in the PWS space
- Incorporating decentralized trial methods to reduce PWS patient burden

The clinical research field is in an optimal position to support the PWS population and develop effective treatments to improve their lives. The strong coalition of patient advocacy, clinical and industry experts, using lessons learned from ongoing provider support, family and caregiver input and recently completed clinical trials, allow us a set of unique perspectives to continue building a crucial paradigm of support and care.

Understanding Prader-Willi Syndrome

PWS is a complex genetic condition associated with one of the most common forms of syndromic obesity. Caused by missing or nonworking genes on chromosome 15, most cases are not inherited and occur randomly. A definitive diagnosis is usually made with a "methylation analysis," which detects more than 99% of cases, including all of the major genetic subtypes of PWS. Symptoms starting at infancy include hypotonia, difficulties with feeding, short stature/growth failure and delayed development. A hallmark in presentation also includes development of hyperphagia in early childhood, leading to chronic overeating and contributing to obesity. PWS typically involves mild to moderate intellectual impairment, learning disabilities and compulsive behavioral problems. Caregivers often note behavioral challenges and hyperphagia to be the most burdensome limitations to providing care.

There is no cure for PWS currently. Treatments focus on managing co-morbidities; however, various pharmacotherapies for hyperphagia and behavioral issues have had limited use. To date, the clinical trials environment has seen an increase in the number of studies and compounds. There are at least six ongoing or recently completed clinical trials for PWS, with a number of other molecules that have not succeeded in providing a crucial therapy for this population.

Operationalizing PWS trials

At Fortrea, our team has seen a wide range of strengths and weaknesses across these recent trials and potential treatments for PWS. While challenging, clinical research in PWS is essential to develop safe and effective management options for these patients, however, trials involving PWS patients must walk a tightrope of clinical efficacy and patient satisfaction.

The management of PWS is a multi-disciplinary approach involving endocrinologists, primary care providers, nutritionists, behavioral health specialists, child life and social workers. This team is an integral part of overall care of the PWS patient, and coordination between practitioners becomes a vital planning piece for a clinical trial. Other operational factors observed in trials include:

- **Comorbidities.** Several comorbid conditions exist for PWS patients outside of obesity including osteoporosis, growth hormone deficiency, sleep apnea, type 2 diabetes and behavior concerns. During clinical trials, treatment for these conditions, as well as appointments to the varied specialists, need to be considered when scheduling study visits.

  Often, the burden of extra visits can limit participation in a clinical trial. For example, certain studies may look at bone mineral density given the propensity of PWS patients having osteoporosis. This is most often assessed through the utilization of DEXA scanning. These scans often require spending additional time at the site, or even an additional site visit, increasing a PWS patient's discomfort. Ensuring availability of DEXA imaging capabilities, and staff members well versed in the scan to allay concerns from the patient, allows such comorbidities to be assessed with minimal barriers to the patient and family.

  Location of the various specialists should also be reviewed at each site in order to provide logistics coordination for patients and families. Logistics can come in the form of visual maps of facilities, a personal guide to walk to different specialists or other creative solutions that may help minimize stress and burden.

- **Pediatric/adolescent patient consent.** Patient consent/assent can be time-consuming and potentially burdensome for both the patient and family. Managing consent correctly creates a positive first impression of the trial, and having a variety of methodologies to reduce concerns and support successful informed consent improves recruitment. These methods should include age-appropriate consent and assent forms, adhering to country and site-specific parent/guardian consent requirements, and proactively discussing site informed consent form (ICF) processes to avoid any activation delays.

  Specific materials to incorporate for appropriate assent of younger age ranges can include video-based supporting education materials, interactive electronic assent forms and illustrations within traditional assent forms. As young children grow into young adults, forms should be no higher than a 7th grade readability level. Study staff should always allow adequate time for a pediatric patient to read an assent form thoroughly, ask questions and provide an environment that supports open engagement. Study staff should also be prepared for discussions with these patients and their parents/caregivers when they say no to assent and participation.

- **Primary endpoints and questionnaires.** The use of questionnaires to determine efficacy is common in PWS trials. However, in both clinical practice and research trials, existing PWS scales have challenges that should be accounted for prior to use. Even questionnaires that have been previously used for a pediatric population typically require modification and validation for use in a PWS population. This may include proxy versions, reduced frequency, or taking into consideration recall periods to ensure accuracy. Should questionnaires require completion by a caregiver, study eligibility criteria must ensure the caregiver is available to complete all questionnaires through the course of a study.

  Additionally, many commonly used measures are self-reported, and traditionally designed only for patients at least 18 years of age. These should be reviewed and adjusted as needed to include a caregiver-report or to be streamlined for the PWS patient. It may be more useful to assess a wider range of health-related quality-of-life metrics like mobility, self-care, usual activities, pain/discomfort and anxiety/depression, to replace more standard measures. Additionally, we recommend evaluating caregiver burden due to its direct impact on patient care. Furthermore, consider utilizing specific questionnaires related to behavioral difficulties, as well as those focused on food and environment, as they offer essential details on PWS patient health metrics during a trial.

- **Treatment considerations.** Treatments currently being studied for potential use in PWS include oxytocics, diazoxide choline and cannabinoids. Many of these treatments necessitate specific protocol and ICF components to satisfy regulatory bodies and other agencies. As early as possible, discussions with regulatory bodies should be undertaken to not only understand the risk/mitigation processes for the specific treatment under review, but also ensure the appropriate pathway is in place for regulatory agency interactions including submission and follow-up meetings. Understanding any government policies and requirements that regulate storage, dispensing and administration of any restricted drugs will also be critical.

Treatment considerations – a case study

Fortrea recently helped a sponsor developing a Schedule I drug for PWS. Internally, the team developed a set of questions that were key considerations prior to study start which were likely to avoid potential known issues. Working with both the sponsor and sites, we created a set of mitigation plans as described below:

Risk	Mitigation
Can the site securely store and keep study drug to comply with the US Drug Enforcement Administration (DEA) requirements?	• Ensured securely locked, substantially constructed cabinet • Stored drug by clinical study and by DEA registration number • Kept study drugs in separate box, container or shelf • Upgraded systems so study drug handling follows DEA requirements • Maintained a separate physical count of all controlled substances on hand
Do the sites have the necessary licenses and training for the Schedule I study drug?	• Selected sites with investigators who had licenses/registrations already in place • Tracked study drug expiration dates in the clinical trial management system • Developed logistics for any proposed satellite facility requiring additional registration • Provided intensive site/CRA (clinical research associate) training regarding recordkeeping, accountability and reporting requirements • Provided site study drug manual and created study-level clinical trial supplies plan • Trained investigators on the process of obtaining their DEA research licensure if they didn't already have one
How can the study drug be distributed and returned without DEA violation?	• Used interactive voice response system (IVRS) to distribute study drug/supplies • Trained study personnel to follow the DEA recording process when dispensing drug to the patient • Sought DEA waivers to permit investigators to receive study drug returns from patients • Determined what constituted a "significant loss" of study drug • Inputted "significant loss" into protocol to ensure consistency and to better evaluate any occurrences as possible adverse events
What would be the best method for drug depot implementation?	• Developed early communication plans and work streams between Fortrea, the sponsor and the drug depot • Set up quality agreement specifying depot responsibilities, including status reporting and escalation procedures • Inspected depots to ensure they can handle a controlled investigational medicinal product (IMPs) • Reviewed quality agreement with IMP contractor and each of the depots • Instituted single points of contact at each depot along with a RACI matrix for critical activities • Developed an early warning feedback mechanism in the event of a disruption (e.g., transportation labor strike)

Along with a dedicated communication pathway between Fortrea, the sponsor and depots, the team also developed work streams for site initiation, vendor review and contracting and budget finalization; with both the sponsor and Fortrea keeping up-to-the-minute contact about timelines. We also incorporated members with specific pediatric experience across these work streams to provide added expertise and advocacy for the needs of the patient.

PWS patient considerations for study visits

Enrolling a specific PWS patient population requires additional care and sensitivity to the patient and family. In practice, multiple visits for multiple co-morbidities increase burden on families and patients and require careful planning and preparation. Often patients in the clinic need distraction methods and quick visits to ensure completion and to prevent distraction from food-seeking behaviors. Scheduled breaks and rewards are also vital to prevent frustration of both the patient and their family. Subject retention in a clinical trial requires an adequate support of site staff, patients and patients' families, as well as active engagement of investigators and patients/parents throughout the study.

Across our PWS studies, Fortrea found the following methods to be most helpful.

- **Supporting the patient visit.** Involvement in PWS trials requires multiple clinic visits and undergoing difficult procedures. Patients are sensitive to changes in their daily routine, and unusual procedures can be a challenge for some of these children. Electrocardiogram (ECG) sensors can feel "sticky" or unpleasant, blood draws are frightening and DEXA scans require sitting very still for short amounts of time in unfamiliar surroundings. These may be more difficult for these children, depending on each individual's ability, and can drastically reduce retention and study visit success. Key facets to help children through these procedures include:
    - Pictorial or video-based guides of each visit and what procedures are involved or walk-throughs with demonstrations of the equipment and how it will be used on them can help relieve anxiety and fear of the unknown
    - Activity books to distract the patient during waiting times in the clinic, including puzzles and word searches that play to the strengths of what is typically seen in PWS
    - Stickers or other reward mechanisms to celebrate when each procedure is completed and to help indicate what still needs to be done
    - Development of a separate, child-specific ICF (assent) with supportive materials to ensure understanding of the studies
    - Pediatric-experienced staff, especially phlebotomists or study nurses, should be at every study visit to reduce discomfort
    - Additional supplies like EMLA cream (numbing medication), Buzzy® (a device combining cold and vibration) or VR (virtual reality) headsets, as well as comfort kits, should be considered to reduce pain and anxiety if blood draws and invasive procedures are required

- **Collaborating with sites, patients and families.** In our experience, close contact with the family and a strong collaboration between site, family and clinical research staff yields lower dropout rates. Provider consistency throughout visits helps prevent discomfort from routine change, especially as PWS patients are often very familiar with the staff and facility that are present at their follow-up visits. Sites should incorporate the following to help the family continue in research, including:
    - Providing useful information on their progress of the disease
    - Having referring physicians informed of patients' treatment, progress and adverse events, so they can help provide emotional support to patients and answer their questions
    - Outlining projected visit schedule with parents/patients during recruitment and during study contact to confirm availability; scheduling subsequent visit(s) at the early end of the visit window; and providing a calendar with visual reminders of each visit and any special requirements such as fasting, and including approximate length of each visit
    - Ensuring the family keeps study staff informed of any potential delays in site visits, including vacations, out-of-city/state/country travel, etc.
    - Reducing wait times for any difficult study procedure or assessment
    - Streamlining complex visits wherever possible to minimize time commitment and burden. (The site should assess and determine the best order in which procedures should be completed.)
    - Providing 24/7 support capabilities for trial-related questions

- **Highlighting the full involvement of the family.** Enrolling the family is an approach and concept that is critical in pediatric research. Parents and caregivers provide support and commitment, and are needed at every clinical trial visit. Educating the patient's family on the importance of clinical research and the safety of the product for their child is crucial. An additional focus on the parents or caregivers, and ensuring their comfort and interest is a key driver to study success. Clear instructions of what is required of both the caregivers and the child should be provided, and additional focus can involve:
    - Parents/patients and caregivers should be asked to call the site if they notice any changes in the disease state or symptoms. This should include other forms of real-time communication such as text or app-based feedback to allow site contact where making a phone call is not available or private.
    - Ensuring study buy-in/assent from the PWS patient, even if the parent/caregiver is providing consent. This is critical for a child of assent age who does not wish to participate, as they cannot be enrolled without assenting. Conducting procedures on these patients can be extremely challenging and stressful for not only the patient but also the parent/caregiver and study staff. Avoiding excessive anxiety, fear and disruption early in the trial process is extremely important in this population.
    - Ensuring up-to-date phone numbers/email addresses are collected for all parents/patients and reviewed at each visit to ensure no changes have occurred, or to update if needed.
    - Facilitating reimbursement for travel and meals (if not provided) to reduce family burden.
    - Consideration of paying a stipend to the parent/caregiver to compensate for time visiting the site.

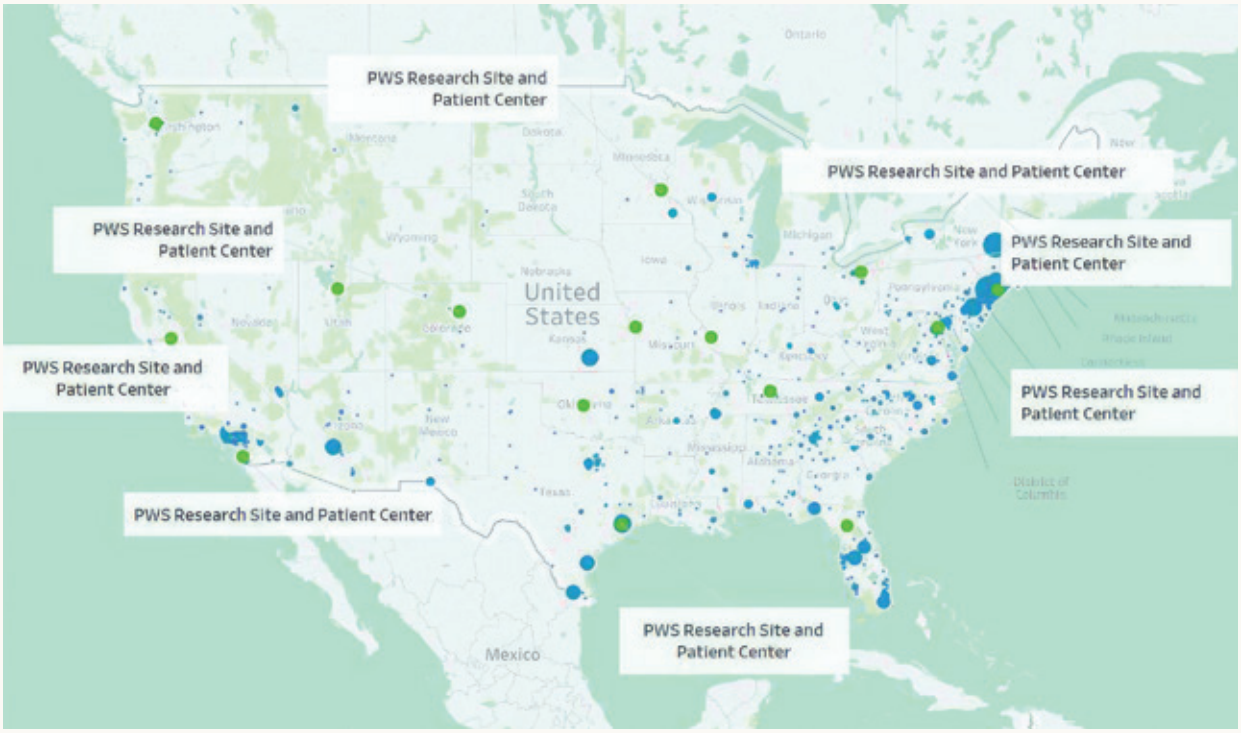
Most importantly, clinicians, investigators and their staff form long-term relationships, as observed in practice, with both the PWS patient and their family. This bond should be fostered as part of the study and sites will be encouraged to have regular contact with parents/patients to ensure they remain motivated to continue study participation.

Finding PWS patients

Developing a strong study design, while minimizing patient and family burden, is only one piece of the overall puzzle. Identifying sites with the necessary expertise, including applicable licenses (if needed), DEXA scanning equipment and existing recruitment and retention pathways for PWS patients, expedites the process and helps mitigate risk from startup issues. Qualified sites can immediately serve as strong recruiters and advocates for a PWS trial.

Most companies working in the PWS space have site relationships developed by medical and operational teams. At the same time, PWS patients and their families are likely to be known to local and national advocacy groups, which also provide site outreach and collaboration.

Another useful method for site identification is to incorporate laboratory testing values to hone in on PWS patient locations. As PWS requires a genetically confirmed diagnosis to define the appropriate patient population, DNA methylation tests or fluorescent *in situ* hybridization tests can be reviewed to highlight PWS patient locations. Using ICD diagnosis coding, mapping with concentrations of Angelman/PWS methylation assays can be developed and, where available, overlaid with the locations of experienced PWS sites from previous or ongoing trials (see map below). These data can augment an existing investigator list to create a full picture of sites, such as those noted on the map, that have the greatest potential for reaching out to known PWS patients.



Benefiting from advocacy group collaboration

Outreach to advocacy group chapters to reach PWS patients already working with their local support group is an often untapped method of collaboration. As advocacy support is vital for many patients, providing not only education about available disease management options but also the benefits of clinical trial participation, patients and families are likely to be intertwined with the groups that support them. Liaising with multiple advocacy groups, such as the Prader-Willi Syndrome Association, the Foundation for Prader-Willi Research and the International Prader-Willi Syndrome Organization, only bolsters the potential for patient identification and trial success. With these groups, it is best to:

- Engage in early discussions to share plans and obtain agreement to cooperate
- Determine points of mutual benefit and interest to highlight the trial within the advocacy groups' promotional materials
- Obtain permission to post study information on the advocacy/support groups' websites
- Provide direct-to-patient information regarding the study
- Provide regular follow-up information about the trial, enrollment benefits and any available results to facilitate continued relationships with the groups

Many key opinion leaders belong to one or more of these advocacy groups. Working with them to present at conferences, meetings and sponsor engagements, highlights a strong relationship with PWS patients, investigators and families. This additional expertise and feedback can augment the value of a protocol, and build and maintain a crucial reciprocal relationship across a drug development process.

Incorporating decentralized trial components

Routine is a key part of PWS management. The less a PWS patient goes outside of their routine, the better. The pandemic added uncertainty to clinical trial conduct, but also helped accelerate innovative solutions that have allowed PWS patients to complete trial objectives away from traditional sites. It is vital to integrate decentralized trial components with patient applications, home health nurses and devices to directly capture source data from patients, and tele-visits to better coordinate schedules and reduce travel time to traditional study sites. Providing fewer on-site visits, less interaction with "unfamiliar" faces and fewer "out of the norm" activities can improve the PWS patient experience and ensure trial retention. An example of an integrated technology platform to optimize study outcomes could include:

- **Site/patient application.** A fully integrated platform which connects patients to sites remotely and supports investigator workflow forms the backbone of a decentralized solution. The study team can conveniently screen, enroll and capture patient data in a user-friendly format and for remote patient monitoring. The application at the site level can be integrated into other systems such as interactive response technology (IRT) or electronic data capture (EDC) to minimize disruption to the site's activities. The application for the patient should focus on the patient experience, be versatile with different mobile device platforms and potentially include wearables for direct data capture. Connecting patients to sites remotely, and allowing the necessary measures to be completed off-site, results in higher satisfaction. The application should also configure patient visit schedules, and provide notifications, alerts and reminders based on the schedule of assessments by push notification, email and/or SMS.

- **eConsent.** The potential for success using eConsent (electronic consent) solutions for PWS trials is also high. An eConsent solution can incorporate video, PDF or questionnaires to support specific study design and needs, easily diagram the informed consent, and scale to allow consent and assent from both patient and family. It can support electronic signatures on tablets or mobiles phones, and signed documents can be converted to PDF and shared with sites and patients. Coordinating with the site or patient application to review consent and record digital signature with patients provides real-time tracking and report generation and incorporates family or caregiver signature and approval as well.
- **Tele-visits.** Application functionality should also connect patients and sites together for increased communication and collaboration. It should allow for secure virtual visits, distribution and completion of questionnaires to increase communication, and medical resolution of any issues as needed, along with completing routine assessment reviews for adverse events (AE) and serious adverse events (SAE), as well as medical assessments, etc. A solution should quickly and easily facilitate tele-visits with principal investigators in conjunction with home nursing visits. Site contact and technical support information should also be preloaded on both patient and site devices to provide 24/7 support.
- **Home health nursing.** Providing in-home ambulatory care services can be a vital piece in patient burden reduction. These services are extremely helpful with PWS patients as the nurse can support the family in dispensing medication, recording medical histories and measuring vital signs. For an added level of patient convenience, the family can book at-home lab appointments when convenient, and a home health nurse will come to their home and collect samples. The samples are then sent directly to the lab for testing. This system should integrate with any site or patient application to ensure patient visit schedules and detail provided is up to date.

Although some PWS patients may not easily adapt to these technologies, parents, caregivers and sites can support completion of questionnaires, lab assessments and other key protocol requirements. Sites and contract research organizations (CROs) have incorporated these techniques in other pediatric trials, and can work together to make the necessary adjustments for a given PWS study.

Incorporating lessons learned

Both in practice and in trial research, finding the most effective treatment paradigm for PWS patients should be a priority to address the current unmet need for this population. Pediatric endocrinologists see PWS patients in their individual practices, and operational teams maintain dedicated relationships with investigators, advocacy groups and communities, each seeking to improve the lives of PWS patients every day.

With limited options for symptom management, implementing new and innovative technologies and treatments brings hope to the patients who so desperately need them. By incorporating lessons learned, and driving new innovative tools, data resources and medical and operational knowledge, our industry's PWS expertise can guide new therapies through the drug development process, and help bring these crucial treatments to market.

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