



# PRADER-WILLI SYNDROME

## Patient Listening Session

Summary of June 17, 2021 Meeting



# Patient Listening Session on Prader-Willi Syndrome Clinical Trial Challenges

June 17, 2021, by Zoom

On June 17, 2021 representatives from the Foundation for Prader-Willi Research (FPWR), the Prader-Willi Syndrome Association USA (PWSA|USA), and experts in the field of Prader-Willi syndrome (PWS) research met with the FDA's Center for Drug Evaluation and Research (CDER) to discuss issues related to PWS clinical trials.

The purpose of this meeting was to promote dialogue between and members of the PWS patient community to ensure that FDA has a full understanding of the unique challenges of PWS. FPWR and PWSA|USA shared information on the dire unmet medical need, the community's tolerance for risk and uncertainty of benefit as it relates to new treatments, and the impact of the COVID-19 pandemic on PWS clinical trials. We also discussed the PWS community's perception as to what constitutes meaningful changes in addressing hyperphagia and other behavioral aspects of PWS, the unique challenges of performing clinical trials in the PWS population, and in light of those concerns, discussed how to efficiently advance new medical products that may be safe and effective for PWS.

This meeting was patient-led; after an opening statement from FDA, FPWR and PWSA|USA led the discussion, sharing the perspectives and concerns of the PWS community, with time for questions and discussion with FDA staff on specific topics of interest.

## Summary of Topics Discussed

During the meeting, FDA staff had the opportunity to hear input from the PWS community on the following areas:

- [Review of patient experience data from the PWS community](#)
- [Summary of the perspective of individuals with PWS](#)
- [Impact and meaningfulness of modest improvements in PWS-associated behaviors](#)
- [Impact of COVID-19 pandemic and lockdown on PWS families and implications for clinical trials](#)
- [Discussion of how PWS patient experience informs clinical trial conduct and interpretation; feasibility challenges for future PWS trials](#)

**Disclaimer:** *Discussions in FDA Rare Disease Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects FPWR's and PWSA|USA's account of the perspectives of patients and caregivers who participated in the Rare Disease Listening Session with the FDA. This report is not meant to be representative of the views and experiences of all individuals with PWS and their families, or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.*

## Attendees:

### On behalf of the PWS patient community (FPWR and PWSA|USA):

- Elisabeth Dykens (Professor of Psychology & Human Development, Psychiatry and Behavioral Sciences and Pediatrics, Vanderbilt University)
- Susan Hedstrom (PWS Parent, Executive Director, Foundation for Prader-Willi Research)
- Rob Lutz (PWS Parent, Board of Directors, Prader-Willi Syndrome Association | USA)
- Paige Rivard (PWS Parent, CEO, Prader-Willi Syndrome Association | USA)
- Elizabeth Roof (Senior Research Specialist, Vanderbilt University)
- Lauren Schwartz-Roth (PWS Parent, Clinical Psychologist, Foundation for Prader-Willi Research)
- Theresa Strong (PWS parent, Director of Research Programs, Foundation for Prader-Willi Research)
- Caroline Vrana-Diaz (FPWR: note taker)
- John Walter (CEO, Foundation for Prader-Willi Research)

### More than 60 FDA staff attended, representing the following centers, offices and divisions:

- Center for Drug Evaluation and Research
  - Office of the Center Director
    - Professional Affairs and Stakeholder Engagement
- Office of New Drugs
  - Office of Neuroscience
    - Division of Psychiatry
- Office of Compliance
- Office of Translational Sciences
  - Office of Biostatistics
    - Division of Biometrics I
  - Office of Clinical Pharmacology
    - Division of Pharmacometrics
- Office of the Commissioner
  - Patient Affairs Staff
- Office of Regulatory Affairs
- Center for Biologics Evaluation and Research
  - Rare Disease Liaison
  - Patient Engagement Program

## Opening Statement from the FDA

FDA staff thanked FPWR and PWSA|USA for contacting the Agency to hold this meeting. The Agency stated that meetings like this are very important to help the FDA understand the priorities of the community and consider how this information can be incorporated in treatment decisions. FDA assured meeting participants that patient and family perspectives are carefully considered in regulatory decisions, to enable the availability of both safe and effective therapies. FDA staff thanked PWSA|USA and FPWR for providing the meeting materials, including personal stories, and stated that the meeting brings visibility to the needs of PWS patients and caregivers.

## Review of patient experience data from the PWS community

The meeting began with a brief overview of PWS, with a review of the information provided on the PWS patient experience (see Appendix), including the family perspective severity of disease, unmet medical need, treatment preferences, and risk tolerance.

- PWS is a rare, highly complex neurodevelopmental and metabolic disorder, caused by a well-defined genetic aberration. The symptoms impact multiple systems in the body and are highly intertwined.
- The two features that pose the biggest challenge for most people with PWS and their family are the change in appetite over time (difficulty feeding and failure to thrive in infancy, hyperphagia beginning in childhood), and the behavioral profile of PWS. Alterations in appetite, metabolism, cognition and behavior have profound impacts on daily functioning as well as long term ability to achieve goals and gain independence. (1)
- Individuals with PWS need 24/7 supervision to maintain food security, and any breakdown in that system can cause the child or adult with PWS to gain weight rapidly.
- Challenging behaviors are often present, including anxiety, obsessive compulsive behaviors, rigidity, and temper outbursts. These behaviors are often extreme – for example, debilitating anxiety with repetitive questioning hundreds of times a day, and temper outbursts that continue throughout adulthood, and can include destruction of property and extreme aggression to themselves and others. (2)
- The combination of difficult behaviors and food restrictions severely limit opportunities for the person with PWS – it often becomes too difficult to participate in community activities or even go to family functions, isolating the individual and their family.
- Caregiver burden is strikingly high in this population (3). The high degree of caregiver burden is reflective of the severity of the disease, and many caregivers are themselves at risk for mental health problems. Relief is needed for the whole family so that the person with PWS can thrive. A second study shows that higher hyperphagia scores are associated with higher caregiver burden (4).
- An online survey capturing the input of more than 750 PWS families (5) demonstrated the profound impact of PWS, as well as the tremendous unmet needs in the community. It is clear that current treatments are not adequately addressing the challenges of PWS. The open text responses highlighted the broad scope of challenges in PWS.
- Hyperphagia is rated by caregivers as the most important aspect of PWS to treat, but other PWS-associated behaviors including anxiety and temper outbursts also rated very highly (5, 6). The most important symptom to treat can change over time, and different families may have different priorities. We believe a diverse portfolio of treatments will likely be needed to fully manage PWS.

- In terms of the benefit: risk analysis for any new treatment for PWS, it is important to note that our families live with risk every day. If the food environment is not controlled, individuals with PWS will become morbidly obese. However, even when there is food security and individuals with PWS are at a healthy weight, hyperphagia is still present and individuals may be at risk for accidents related to trying to acquire food and/or episodes of excessive eating. PWS is life-threatening. The reported mean age of death in PWS has not changed substantially over the past 40 years, despite earlier diagnosis and better education.
- Families are struggling to manage behaviors, with many individuals taking multiple psychiatric medications. These drugs have never been evaluated in the PWS population for safety or efficacy.
- Caregivers are willing to accept significant risk in a new treatment for PWS, even if it leads to only a modest reduction in hyperphagia (7). Families are willing to accept significant risk if it would mean a more manageable life.
- Based on feedback from our community, families are also willing to accept some uncertainty of benefit. Families would like the opportunity to work with their doctors and access new treatments that have been looked at in large studies of PWS participants, where the benefit and risk are reasonably well-known.

## The Perspective of Individuals with PWS

Dr. Elisabeth Dykens presented the results of a study (8) to gain insight into the perspective of individuals with PWS themselves, which the FDA has indicated is an area of interest for them. Dr. Dykens and her team performed semi-structured interviews with 21 adolescents/young adults with PWS to better understand how young people with PWS view themselves and future clinical trials. Among the questions discussed: “How does having PWS affect you in your everyday life?”, “What sorts of things do you need help with, because of PWS?”, and “What are your ideas for new medications for PWS, for clinical trials, and how these might help you?”.

### Three key findings of the interviews were discussed.

- Despite purposely selecting individuals the team thought would be appropriate for the interview, 6 of the 21 participants weren’t able to meaningfully respond to the questions asked. These 6 individuals did not differ from those who could respond in terms of their age, genetic subtype, or IQ. Their inability to convey their perspective may be due to limited insight or capacity to self-reflect; inattention; or problems recalling, organizing or expressing information. Therefore, in high-stakes clinical trials, it is risky to assume every individual with PWS can provide meaningful self-report clinical data, or to use cognitive functioning as a proxy for their ability to do so. Caregiver and clinician reporting in clinical trials is appropriate.
- The second key finding is that all participants indicated that they struggled with hunger, food, and eating daily. They described very negative impacts of hunger on relationships and life choices and their goals. Fewer talked about their struggles with weight loss, and many reflected that their parents helped them with weight, using food security measures. The second dominant theme was struggling with anxiety, stress, and outbursts. This anxiety and stress could relate to schedule changes, being denied food, other triggers. School emerged as a stressor, even for those participants who were no longer in school.
- The third key finding is related to new medicines. All participants endorsed the need for new medications, and all participants wanted to be in future clinical trials. Just like parental priorities for clinical trials, participants wanted new medicines that targeted their hunger, anxiety, and outbursts. They envisioned the downstream effects of improving these areas, such as less stress at home, improved relationships with their families and friends, and ability to meet life goals. They anticipated that effective medications could let them live in an apartment, go into job training programs, and do things that they could not do now.

Dr. Dykens discussed the “dignity of risk”, which is a key principle among self-advocates in the disability community, that people with intellectual and developmental disabilities have an inherent right to learn from risky ventures, just like the rest of us do, including participating in clinical trials. She also discussed that in both the frequency and tone of their remarks, participants emphasized that hunger urges were omnipresent, regardless of their weight, and locking the cabinet or being constantly supervised didn’t make their hunger go away, reinforcing the use of hyperphagia as an endpoint in clinical trials. Finally, Dr. Dykens again emphasized the need for caregiver and clinician-reported endpoints in clinical trials.

## Impact and meaningfulness of modest improvements in PWS-associated behaviors

The next area of discussion focused on how families view the changes that might happen with a new treatment, emphasizing that even modest improvements in hyperphagia and/or PWS-associated behaviors would be valued by families and are expected to have meaningful impacts on functioning and quality of life. The parent of a young woman with PWS expressed this perspective:

*My daughter is a 21-year-old woman with Prader-Willi Syndrome. To help provide context about Prader-Willi Syndrome and the decisions you will be making about potential treatments for the disorder, I thought it would be helpful to describe my daughter’s life and what drug treatments to reduce the impacts of PWS might mean to her and to our family. Every individual with PWS is unique but I will try to share what I believe are common elements of the PWS experience. My daughter no longer lives at home with us. But she is far from independent. She has a caregiver overseeing her every day for 12 hours a day. I am not aware of any Prader-Willi adult who lives completely independently— they either live with their parents or in a group home or some other supported-living situation. A caregiver is necessary in part to unlock access to food and provide appropriate food quantities to prevent my daughter from getting morbidly obese. The care is also there to help her manage through behavioral issues which often stem from food and from social gatherings where food may be present (a BBQ, an evening at the movies, a pool party, a sporting event, etc.).*

*Food is everywhere in our culture— work, school, friend’s houses, the mall— so constant vigilance is required. My daughter has no money of her own. If she did, she would find ways to sneak to a restaurant or supermarket to buy food. My daughter has stolen money from her family and her teachers and her caregivers to try to get food. So, we have to monitor her and prevent her from stealing or having money. My daughter loves horses and horseback riding. Most individuals with PWS have a passion. However, they can’t always pursue their passion. My daughter would like to be around horses and working with them all day long. Unfortunately, her food-seeking and food-related behaviors get in the way. Barns are not set up to have food security. Barns are dangerous places where a tantrum is a danger to my daughter and to others. My daughter dreams of being a veterinarian or a vet tech— but she can’t fulfill that dream today with her PWS limitations.*

*My daughter’s food is well controlled. It is unlikely she will die of obesity. She’s relatively healthy. But it’s clear PWS has a SIGNIFICANT impact on her quality of life due to the food seeking and food-related behaviors. How would you feel as an adult if you had to have someone watching you 12 hours a day? How would you feel if you had no money and needed to ask someone else to pay for everything you bought or did? How would you feel if you couldn’t go out with your friends without a chaperone to watch you? How would you feel if you couldn’t do the things you loved to do the most and couldn’t pursue your dreams?*

*I am not suggesting that treatments to reduce hyperphagia and hyperphagia-related behaviors from Prader-Willi will immediately allow my daughter to pursue her dreams and live independently. But I am confident that safe treatments will give her a better chance. She might get more autonomy and control over her adult*

*life. She might be able to eat a few more calories every day and therefore reduce her anxiety and anger over every meal and social occasion. She might have more friends and social engagements. She might find someone she loves who loves her back. She might resent me less because I wouldn't have to limit her and control as many aspects of her life.*

*I think I speak for all Prader-Willi parents when I say that even a small improvement in food seeking and food-related behaviors would be valuable for those with Prader-Willi and their families. We implore you to consider the effect a drug may have for my daughter and those like her as you examine the risks and benefits of drug treatments for Prader-Willi. Thank you.*

## Impact of COVID-19 pandemic on PWS families and implications for clinical trials

FPWR/PWSA|USA discussed the challenges of clinical trials during the COVID-19 lockdown. Data from the Global PWS Registry survey has previously been shared with FDA and indicated that most families experienced more stress, but impacts were varied and unpredictable. We expect that the lockdown had confounding effects on data collected in ongoing clinical trials; parents were with their kids 24/7 after schools and vocational sites closed, and people with PWS were not able to do any activities. We are also concerned looking ahead at the uncertainty and change associated with coming out of the COVID pandemic. Uncertainty and change are particularly challenging for individuals with PWS, so we anticipate there will be stress and impact moving forward.

## Discussion of how PWS patient experience informs clinical trial conduct and interpretation (benefit: risk profile); feasibility challenges for future PWS trials

The final area of discussion was the challenges of doing clinical trials in this rare disease population, and concerns about feasibility of completing multiple large clinical trials in PWS. Our population faces the typical challenges for participating in clinical trials (disruption of work schedules, travel difficulties, etc.), but the unique challenges of PWS make it very difficult for families to participate. FPWR/PWSA|USA shared stories to illustrate some of the specific problems encountered when participating in PWS clinical trials, including food seeking during travel, in hotels and while in clinics, resistance to change in routine, and issues with medical procedures (e.g., fasting blood draws). PWS families are incredibly stressed already, with many 'hanging on by a thread', so adding clinical trial participation is often too much. FPWR/PWSA|USA encouraged FDA to consider the challenges PWS families face in completing clinical trials and to employ all available flexibility in considering clinical trial findings.

## Closing statement

The FDA thanked PWSA|USA and FPWR for sharing their experiences with this rare disease. FDA conveyed that these lived experiences help FDA staff understand better how to evaluate the data that companies present, how to interpret it appropriately, and whether or not the treatment effect shown matters to the community. FDA expressed a strong desire for treatments that impact our loved one's lives in a way that matters.

## Appendix: Information Provided to the FDA as Part of the Patient Listening Session Briefing Document

- 1. PWS across the Lifespan** – This film developed by the PWS Clinical Trials Consortium, illustrates the complexities and challenges of living with PWS, from the perspective of three families (infant, child, adult with PWS).
- Schwarz L et al. **Behavioral Features in Prader-Willi Syndrome (PWS): Consensus paper from the International PWS Clinical Trial Consortium** (<https://jneurodevdisorders.biomedcentral.com/articles/10.1186/s11689-021-09373-2>)  
This paper presents consensus definitions and descriptions of key PWS behaviors, from a group of international PWS academic investigators and clinicians who are part of the PWS Clinical Trials Consortium. Behavioral features including hyperphagia, temper outbursts, anxiety, obsessive–compulsive behaviors, rigidity and social cognition deficits are discussed.
- Kayadjanian et al **High levels of caregiver burden in Prader-Willi syndrome.** PLoS One, 13(3):e0194655, 2018. Using a validated measure of caregiver burden (Zarit Burden Interview), primary caregivers of those with PWS show high levels of caregiver burden, with highest scores among those who are caring for adolescents and young adults. Caregivers also indicated negative impacts on employment, mood, sleep and romantic relationships.
- Kayadjanian et al., **Characteristics and relationship between hyperphagia, anxiety, behavioral challenges and caregiver burden in Prader-Willi syndrome.** PLoS ONE 16(3): e0248739, 2021. High levels of hyperphagia are associated with increased caregiver burden in PWS; caregiver burden and hyperphagia scores are stable over a 6-month period. Caregivers also rated symptoms that impact the person with PWS, as well as the symptoms and tasks that have the biggest impact on caregivers.
- PWS Perspectives: Summary of the Impact of PWS on Individuals and Their Families and Views on Treatments: Results of an International Online Survey.** (<https://www.fpwr.org/pws-patient-voices>) The findings of an online survey of >750 PWS families, addressing issues such as the most challenging PWS symptoms, impact of PWS, characteristics of an ideal treatment and attitudes towards clinical trials; includes open text comments.
- Tsai et al **Caregiver priorities for endpoints to evaluate treatments for Prader-Willi syndrome: a best-worst scaling.** J Med Econ. 1230-1237, 2018. Based on input from more than 450 caregivers, this study found that finding new treatments for hyperphagia is the highest priority for families. However, there was variability across ages (of the person with PWS), and treatments addressing anxiety, temper outbursts and cognition were also valued.
- Tsai S, et al. **Measuring Meaningful Benefit-Risk Tradeoffs to Promote Patient-Focused Drug Development in Prader-Willi Syndrome: A Discrete Choice Experiment** (MDM Policy and Practice, in press) A discrete choice experiment was used to show caregivers (n=468) have significant tolerance for risk when considering a treatment to reduce hyperphagia in the person with PWS.
- Dykens et al, **“The cure for us is a lot of things”:** How young people with Prader-Willi syndrome view themselves and future clinical trials (submitted manuscript). Semi-structured interviews with twenty-one adolescents/young adults with PWS captured their perspective on PWS, and thoughts about clinical trials and possible treatments for PWS.
- Lavell et al., **Quantifying the burden of hyperphagia in Prader-Willi syndrome using quality adjusted life years (QALYs)** (Clinical Therapeutics S0149-2918(21)00228-9, 2021. doi: 10.1016/j.clinthera.2021.05.013.). Time-trade-off (TTO) and visual analog scale (VAS) were used to elicit PWS caregivers’ values for three fixed health states, which demonstrated that reducing hyperphagia will reduce the burden of PWS.
- Vrana-Diaz et al, **Variability and change over time of weight and BMI among adolescents and adults with Prader-Willi syndrome: a 6-month text-based observational study.** Orphanet J Rare Dis, 15:233, 2020. A study of 161 individuals with PWS, age 12 & up, monitoring weekly change in weight and change in BMI over six months, in the ‘real-world’ setting.

### Additional Resources:

#### Natural History Study of Serious Medical Events in PWS (PATH for PWS)

<https://clinicaltrials.gov/ct2/show/NCT03718416>

<https://pathforpws.com/study-information/>

**Impact of COVID on the PWS community** – blog of survey results: <https://www.fpwr.org/blog/pwsregistry-data-impact-of-covid-19-on-pws-families-infographic>