

# FPWR's Questionnaire Measures Important - But Often Overlooked - Concerns for Prader-Willi Patients and Caregivers

## FPWR Leverages Multiple CTTI Recommendations to Develop Patient-Centered Anxiousness and Distress Measurement Tool

### SUMMARY

The Foundation for Prader-Willi Research (FPWR) is a nonprofit organization with a mission to eliminate the challenges of Prader-Willi syndrome (PWS) through the advancement of research and therapeutic development. PWS is a rare genetic disorder that affects the brain's development, leading to a number of problematic symptoms like weak muscles, hormone imbalances, obsessive compulsive behaviors, insatiable hunger, and difficulty controlling emotions. This case study details how FPWR, in collaboration with an industry partner and RTI International, used a combination of CTTI recommendations and resources to create a questionnaire that measures anxiousness in PWS patients, a major complication of PWS for which there is no current treatment.

### GOAL(S)

When it comes to clinical research for rare diseases, scarcity of ongoing trials to inform new treatments is a ubiquitous challenge. Prader-Willi syndrome (PWS), which occurs in about one out of every 15,000 births, is no different — and nearly all the ongoing studies into the condition are focused on its hallmark characteristic, hyperphagia (excessive hunger). But around half of all caregivers for PWS patients also report anxiousness as a significant problem in their loved ones' day-to-day lives. So when a new study launched exploring the impact of carbetocin (a medication that mimics the action of oxytocin) on hyperphagia, patient communities hoped that the medication might positively impact anxiousness as well. However, due to the unique expressions of anxiousness in PWS, the study team had no existing measure to determine carbetocin's efficacy in treating this symptom. To address this challenge and bring new patient-centered insights to light, FPWR wanted to develop a tool that could capture the symptoms of both anxiousness and distress experienced by people with PWS.

### CHALLENGES

In creating a questionnaire to measure anxiousness and distress in PWS patients, FPWR and their collaborators were essentially developing a novel endpoint, which the organization had never attempted. But there was no doubt a new endpoint was needed. While the Diagnostic and Statistical Manual of Mental Disorders (DSM) contains a specific measure for anxiety, it is not well suited to PWS. Existing questionnaires for anxiety contained questions like, "Are you worried about your future?" or, "Do you fear public speaking?" These were not meaningful to PWS patients, whose anxiety is much more centered around adhering to a rigid schedule and knowing when meals are coming. Existing anxiety measures are also intended for self-reporting, which is not appropriate for PWS patients given varying levels of intellectual disability and deficits in self-awareness that might impact the accuracy of their responses. FPWR had a strong need and willing network of patients and caregivers but lacked guidance on where to begin in the development of a novel endpoint for use in clinical research.

### SOLUTION(S)

CTTI's [suite of recommendations](#) offers a range of advice and resources to optimize clinical research. They span topics from patient engagement to quality by design, diversity and inclusion to the appropriate use of digital health technologies, and more. Having been a long-term member of CTTI's Steering Committee with active engagement in numerous projects and related activities, FPWR's co-founder knew CTTI's portfolio of work could help FPWR achieve its goals.

### TAKING ACTION

With three key CTTI guidance documents in hand, the collaborative team began developing the PWS Anxiousness and Distress Behaviors Questionnaire.

**Patient Group Engagement:** To ensure the voices of patients and caregivers were reflected in the new questionnaire, the team heeded CTTI's [Patient Group Engagement Recommendations](#) to establish patient partnership at the beginning of a new clinical research effort. Upon crafting the initial draft of questions, the team's first action was to ensure the questionnaire's validity via in-depth interviews with 12 caregivers of children with PWS. The interviews aimed to understand the challenging emotions and related behaviors associated with PWS, the impact of these symptoms on both the patient and the caregiver, and the desired benefits of treatment. The feedback the team collected was pivotal in helping modify and improve the questionnaire.

**Novel Endpoints:** CTTI's [Novel Endpoints Recommendations](#) largely focus on the use of digital health technology in endpoint design, but FPWR still found them valuable in guiding the development of their questionnaire that was decidedly "low-tech". For example, FPWR made it a priority to consider the needs of each stakeholder throughout the development process. While regulators would like an endpoint to be fit for the purpose of evaluating a new drug or therapy, researchers want the endpoint to be suitable for implementation in their clinical trial, and patients want endpoints to reflect a clinical outcome that is important to them. FPWR's understanding that they needed to satisfy multiple audiences drove them to perform a thorough assessment to prove the questionnaire's merit. Via 400 registrants from the Global PWS Registry, FPWR looked at the questionnaire's performance, structure, and validity, as well as its ability to measure anxiousness and associated distress specifically in individuals with PWS. Registry participants were asked to complete these measures twice to evaluate test-retest reliability.

**Quality by Design (QbD):** Once the questionnaire was designed, the collaborative team took a critical look at each component of the tool, heeding [CTTI's QbD Recommendations](#) to embed quality principles and proactively identify issues at the outset of any research effort. Per QbD thinking, taking the time to challenge assumptions upfront and think critically to eliminate any unnecessary components of a research effort is essential to minimize participant burden and ensure the effort achieves its aim. For FPWR, that meant looking at each question to see if it got to the heart of what patients need to know. If a question was too vague or did not speak directly to the issue of anxiousness, it was eliminated from the questionnaire.

FPWR also ensured a diversity of perspectives beyond patients and caregivers vetted the questionnaire to confirm its utility. Not only was development of the measure spearheaded by three experienced researchers who are involved in the PWS community both professionally and personally, but the concepts of measurement and their observable nature were also endorsed by the Behavioral Outcome Measures Working Group of the [PWS Clinical Trial Consortium](#), composed of expert PWS clinicians and researchers.

## IMPACT

In semi-structured, qualitative interviews, the PWS Anxiousness and Distress Behaviors Questionnaire (PADQ) was found to successfully capture a constellation of behaviors indicative of anxiousness and distress as they are uniquely expressed in PWS, filling an important gap for families, caregivers, and the PWS research community overall. Feedback was positive from families participating in the interviews, who agreed that the questionnaire captured the concepts most important to them. Although the original carbetocin study was not a success, the PADQ has unlocked researchers' ability to assess new treatments for efficacy in reducing anxiousness and related distress among individuals with PWS. The development and psychometric validation of the PADQ [was featured](#) in the February 2023 issue of the International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) *Value in Health* journal.

Furthermore, in June 2023, a [separate study](#) published results showing that a 3.2-mg dose of carbetocin was well tolerated and associated with clinically meaningful improvements in hyperphagia as well as anxiousness and distress behaviors in participants with PWS. The PADQ was again used as a critical tool to determine the drug's efficacy.

## ADVICE

Don't let the perfect be the enemy of the good when it comes to the fit or applicability of CTTI's recommendations and resources. For example, FPWR feels they would have missed out on a considerable amount of important advice had they disregarded the Novel Endpoints Recommendations because they were initially created for use with digital health technologies. In fact, the recommendations were easily tailored to FPWR's purpose by just honing in on the insights that are generalizable to any endpoint design.

"My advice to any organization is to look across all CTTI recommendations and resources, even if they aren't intended specifically for your need or purpose," said FPWR's co-founder. "When we are designing trials and endpoints, so much of our work is interconnected, and CTTI's recommendations offer value across the entire research spectrum. Whatever your next research effort, go there first; you will almost definitely find hidden gems of insight that will ease the path to your ultimate goal."

## ORGANIZATION

Foundation for Prader-Willi Research

## CONTACT

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## ORGANIZATION TYPE

Patient

## IMPLEMENTATION DATE

2022

## TOPIC

Novel Endpoints, Quality, Patient Engagement

## RELATED CTTI PROJECT

[Quality by Design Patient Group Engagement Novel Endpoints](#)

## CTTI RESOURCES

[CTTI Recommendations: Effective engagement with patient groups around clinical trials](#)

[CTTI Recommendations: Developing Novel Endpoints Generated by Mobile Technology for Use in Clinical Trials](#)

[CTTI Recommendations: Quality by Design](#)

## ADDITIONAL RESOURCES

[The Prader-Willi Syndrome Anxiousness and Distress Behaviors Questionnaire: Development and Psychometric Validation](#)

[Intranasal Carbetocin Reduces Hyperphagia, Anxiousness, and Distress in Prader-Willi Syndrome: CARE-PWS Phase 3 Trial](#)