Case Study: The Role of the Caregiver and Clinician in Endpoint Development for Rare Disease Trials

Alison Skrinar, PhD

VP, Endpoint Development and Strategy

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Externally-Led Patient-Focused Drug Development Meetings

The PFDD initiative started in 2012 as part of FDA's commitments under PDUFA V.

- FDA-led PFDD meetings
    - FDA recognized there are many more diseases/conditions than can be addressed in a reasonable time by FDA.
- To help expand the PFDD initiative, FDA introduced externally-led (EL-PFDD) meetings in 2015.
    - Planned and hosted by patient organizations with input of FDA staff

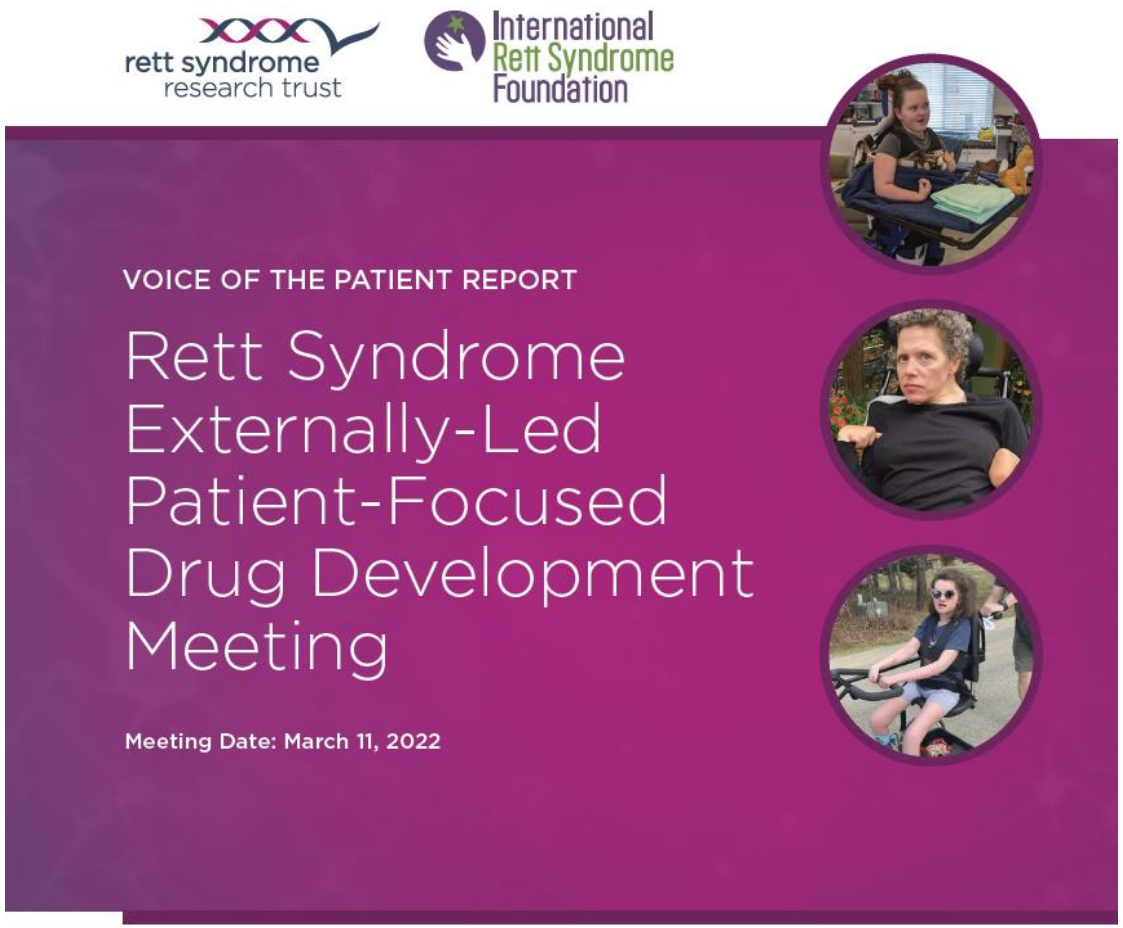
PFDD meetings target diseases with the following characteristics:

- Identified need for patient input
- Chronic, symptomatic, affect daily function
- Have aspects that may not be recognized or formally captured in trials
- Have no/limited therapies impacting how a patient feels, functions, or survives
- Have a severe impact on identifiable subpopulations

PFDD Meeting Format

- Town hall where patients and caregivers discuss their perspectives
  - Two panels followed by open discussion
    - Patients and caregivers share their stories before audience members and online participants provide input
    - Open discussion intended to provide diverse perspectives
- Panel 1 covers symptoms and impacts of the condition
- Panel 2 covers current treatment options and expectations for a new treatment, including benefit-risk assessment and clinical trial participation
- Following each PFDD meeting, FDA summarizes the discussion in a “Voice of the Patient” report that is made public
  - For EL-PFDD meetings, the patient group(s) are responsible for generating the report

EL-PFDD Meeting For Rett Syndrome



Key Insights from Rett Syndrome EL-PFDD Meeting

- Rett syndrome is characterized by a long and diverse list of symptoms and most families deal with 8 or more symptoms at any one time.
- Individuals living with Rett syndrome are cognitively aware, yet are unable to effectively act on their desire to communicate or participate in conversations and are often misunderstood
- Rett syndrome interferes with virtually all ADLs, including one's ability to feed, toilet and care for themselves.
- A cure and treatments for Rett syndrome are urgently needed and not currently available*
- Burden of both Rett syndrome and the therapies to address symptoms is tremendous, not only for individuals living with Rett syndrome, but on their caregivers and families
- Functional improvements in communication/speech and hand use are the aspects of Rett syndrome ranked as most important targets for a novel therapy.
- Additional areas of unmet need include clinical trials and therapies for males, therapies that result in functional improvements and more meaningful endpoints for trials.

* Daybue (trofinetide),developed by Acadia Pharmaceuticals, was approved by FDA for the treatment of Rett syndrome in March 2023

Most Common Symptoms from Perspective of Caregiver

- Communication/speech impairment
- Impaired hand use or repetitive hand movements
- GI issues (acid reflux, bloating, constipation, air swallowing)
- Mobility or balance difficulties (walking, crawling, weight bearing for transfers)
- Seizures
- Eating or swallowing difficulties
- Sleep disturbances
- Emotional/behavioral problems
- Breathing difficulties (hyperventilation, apnea, breath holding)
- Spine conditions (scoliosis, kyphosis)
- Movement disturbances (tremors, spasms, eye movements)
- Dental issues (teeth grinding, dental procedures)
- Muscle tone abnormalities (high tone, rigidity)

Areas of Highest Impact from Perspective of Caregiver

- Rett Syndrome impacts every area of life and all ADLs
- The inability to communicate is the most frequently reported AND most concerning Rett Syndrome-related health concern.
- Other impacted areas include*:
  - Activities involving use of their hands
  - Socializing with peers/siblings
  - Activities on feet (walking and participating in recreational activities and events)
  - Traveling and vacationing
  - Eating by mouth
  - Attending school/having a job

* See Voice of Patient report for comprehensive list

RSBQ (Rett Syndrome Behavioral Questionnaire)

- Developed based on input from caregivers on the behavioral impact of Rett Syndrome
- 45-item caregiver-reported rating scale that assesses the following domains:
  - General mood
  - Breathing problems
  - Hand behaviors
  - Repetitive face movements
  - Body rocking/facial expression
  - Nighttime behaviors
  - Fear/anxiety
  - Walking/standing
  - Other
- Caregiver rates items as 0 = not true, 1 = somewhat or sometimes true, 2 = very true
- Scores range from 0 to 90 with higher scores representing more significant impairment

Rett CGI-S (Clinical Global Impression of Severity)

Domain	CGI-S = 1	CGI-S = 2	CGI-S = 3	CGI-S = 4	CGI-S = 5	CGI-S = 6	CGI-S = 7
Language/ Communication	Normal	Generally appropriate. May have unusual features such as perseveration/echolalia. Reading disability/dyslexia	Phrases-sentences. May have conversations although echolalia may be present	Words (<5) Babbles Makes choices 25-50%	No Words Babbles Makes choices <25%	No words Vocalizations Occasionally screams Only rarely makes choices	No Words No Vocalizations May scream No Choices
Ambulation	No impairment	Normal, may have slight evidence of dystonia/ataxia/dyspraxia	Walks, able to use stairs/run. May ride tricycle or climb	Walks Independently, unable to use stairs or run	Walks with Assistance	Stands with support or independently May walk with support Sits independently or with support	Cannot sit Doesn't stand or walk
Hand Use	Completely normal, no impairment	Normal, may have slight fine motor issues	Bilateral Pincer grasp. May use pen to write but has some fine motor issues like tremor	Reaches for objects, raking grasp or unilateral pincer. May use utensils/cup	Reaches No Grasp	Rarely to Occasionally Reaches No Grasp	Does not reach for objects
Social (Eye Contact)	Normal	Occasional eye gaze avoidance	Appropriate eye contact, >30 sec	Eye Contact <20 secs	Eye Contact <10 secs	Eye Contact, Inconsistent 5 secs	No eye contact
Autonomic	None	Minimal	No or minimal breathing abnormalities and Warm, pink extremities No cyanosis.	Breathing dysrhythmia <50% No cyanosis Cool, pink UE & LE	Breathing dysrhythmia 50% No cyanosis Cool, pink UE & LE	Breathing dysrhythmia, 50%-100%, maybe with cyanosis Cold LE or UE, may be Blue	Constant breathing dysrhythmia, with cyanosis Cold UE & LE Mottled/Blue
Seizures	None	None or very well controlled	None or very well controlled seizures	Monthly-Weekly	Weekly	Weekly-Daily	Daily
Attentiveness	Entirely normal	Occasional inattention	Attentive to conversation and follows commands	50-100% of Time	50% of Time	Less than 50% time	0%

CGI-I (Clinician Global Impression of Improvement)

- The CGI-I is rated by clinicians and assesses how much the affected individual's symptoms and impacts of Rett Syndrome has improved or worsened relative to baseline on a 7-point scale.
- CGI-I ratings assigned based on symptoms and impacts assessed by CGI-S
- Training conducted to standardize CGI-I and CGI-Severity ratings using anchors and clinical case vignettes
  - Fidelity was established using "gold standard" ratings established by panel of experts
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CGI-I Guidelines

1 =	**Very much improved** — nearly all better; good level of functioning; minimal symptoms; represents a very substantial change
2 =	**Much improved** — notably better with significant reduction of symptoms; increase in the level of functioning but some symptoms remain
3 =	**Minimally improved** — slightly better with little or no clinically meaningful reduction of symptoms. Represents very little change in basic clinical status, level of care, or functional capacity
4 =	**No change** — symptoms remain essentially unchanged
5 =	**Minimally worse** — slightly worse but may not be clinically meaningful; may represent very little change in basic clinical status or functional capacity
6 =	**Much worse** — clinically significant increase in symptoms and diminished functioning
7 =	**Very much worse** — severe exacerbation of symptoms and loss of functioning

Adapted from Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 1997;73(3):159–71.

Caregiver and Clinician Input Used to Design LAVENDER*: Phase 3 Study that Led to FDA Approval of Daybue (Trofinetide)

- Randomized, double-blind, placebo-controlled trial
- 187 females 5-20 years of age with confirmed diagnosis of Rett Syndrome
- Patients randomized to receive Daybue (N=93) or matching placebo (N=94) for 12 weeks
- Co-primary endpoints of caregiver-reported RSBQ (Rett Syndrome Behavioral Questionnaire) and clinician-reported CGI-I (Clinician Global Impression of Improvement)
- RSBQ
  - At Week 12, Patients receiving DAYBUE had a decrease in RSBQ total score of 4.9 points vs 1.7 points in the placebo group
- CGI-I
  - At Week 12, 38% of patients on DAYBUE had improvement in symptoms vs 15% in the placebo group

* LAVENDER clinicaltrials.gov NCT 04181723

EL-PFDD Meeting Request

- FDA requires a Letter of Intent (typically 3-4 pages) that addresses:
  - The importance of the meeting in the context of the disease area
  - Meeting goals, key areas of learning, discussion questions, patient engagement plans and proposed method for disseminating the results
  - Requests for specific FDA attendees who may attend remotely
- The LOI should be submitted approximately 1 year before the expected meeting date
- If approved, FDA recommends holding the meeting in conjunction with an annual conference or symposium to maximize attendance and get more diverse feedback
- Information contained in the LOI, including the name of your organization and a point of contact, is shared on the FDA website
- For more information on requesting a PFDD meeting patientfocused@fda.hhs.gov

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Questions?

Thank You