

Refining Clinician- and Caregiver-Reported Outcome Measures for Evaluating Phelan-McDermid Syndrome

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Objective

To refine clinician- and caregiver-reported outcome measures for evaluating Phelan-McDermid syndrome (PMS) after their use in a phase 2 clinical trial of NNZ-2591

Key Takeaways

Iterative refinement of PMS-specific clinician- and caregiver-reported measures improved clarity and content validity, ensuring alignment with the unique needs of individuals with PMS

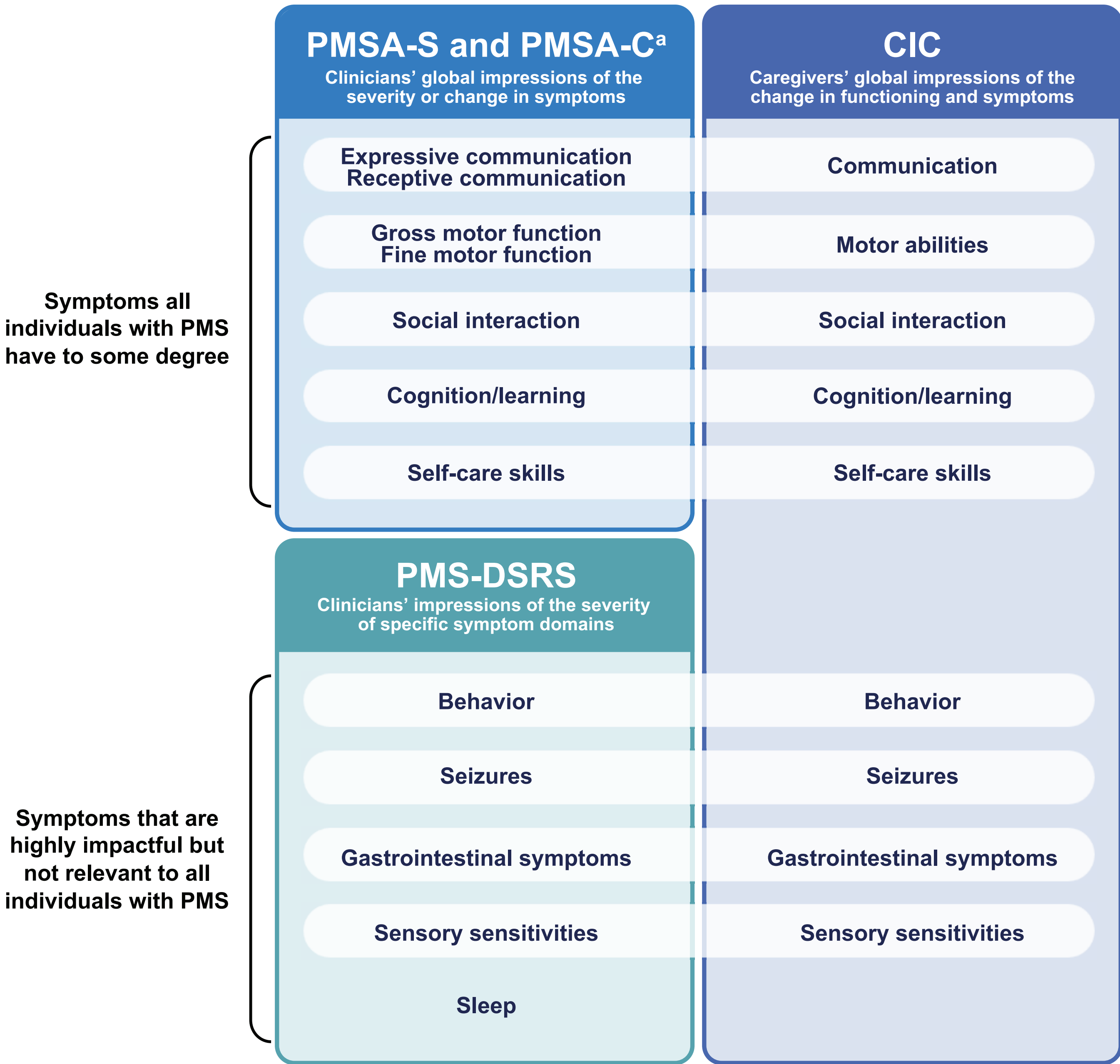
Measures were revised through a rigorous, collaborative process, including input from caregivers and clinicians through narrative data analysis, cognitive interviews, and input from experts

The refined PMS Assessments of Severity/Change and Caregiver Impression of Change will be used in upcoming clinical trials and will undergo further analyses to provide supportive evidence

Background

- Phelan-McDermid syndrome (PMS) is a rare genetic condition characterized by global neurodevelopmental delay with a complex, heterogeneous presentation^{1,2}
- No widely accepted outcome measures specific for PMS exist, making it difficult to evaluate treatment effects in clinical trials for PMS
- We developed PMS-specific instruments by adapting standard global impression scales (**Figure 1**)^{3,4}:
 - Clinician-rated PMS Assessment (PMSA) of Severity (PMSA-S) and PMSA of Change (PMSA-C)
 - Caregiver Impression of Change (CIC)
- An additional clinician-rated instrument, the PMS Domain-Specific Rating Scale (PMS-DSRS), was also developed (**Figure 1**)
- The measures were evaluated among children and adolescents with PMS in a phase 2 clinical trial of NNZ-2591, a synthetic analog of the IGF-1 metabolite cyclic glycine proline⁵
- Here we describe the multi-step refinement of the global clinician- and caregiver-reported outcome measures following their use in the clinical trial⁶

Figure 1. PMS-Specific Outcome Measure Domains



CIC, Caregiver Impression of Change; PMS, Phelan-McDermid syndrome; PMS-DSRS, PMS Clinician Domain-Specific Rating Scale; PMSA-C, PMS Assessment of Change; PMSA-S, PMS Assessment of Severity.
^aFormerly referred to as the PMS-Specific Clinical Global Impression of Severity and of Improvement, respectively.

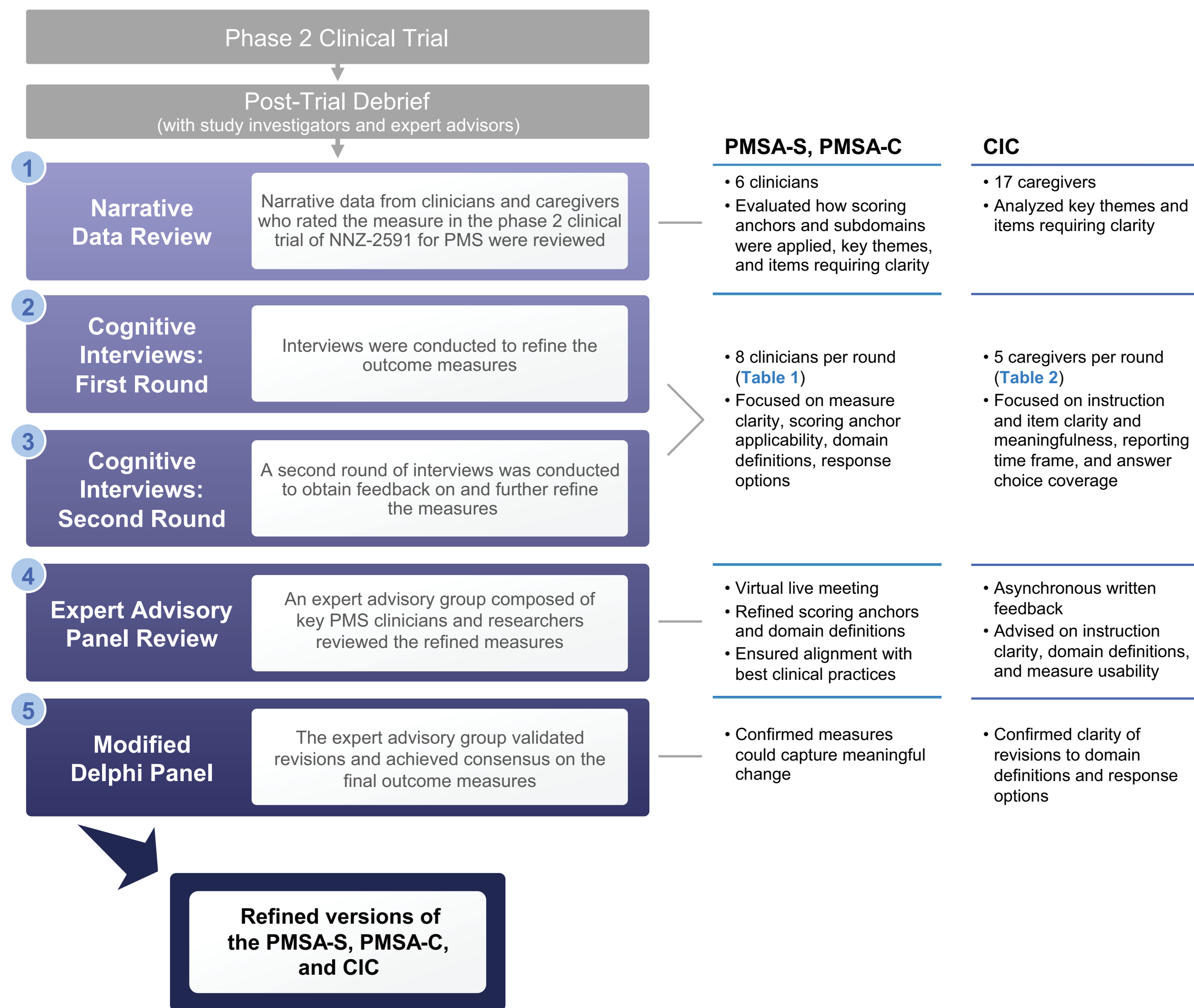
Methods

Multi-Step Refinement Process

- An iterative, multi-step, mixed-methods refinement process was applied to the PMSA-S, PMSA-C, and CIC (**Figure 2**)
- The goal of measure refinement was to ensure clarity, relevance, and ability to capture meaningful change in people with PMS

Methods (cont'd)

Figure 2. PMS-Specific Outcome Measure Refinement Process



CIC, Caregiver Impression of Change; PMS, Phelan-McDermid syndrome; PMSA-C, PMS Assessment of Change; PMSA-S, PMS Assessment of Severity.

Table 1. Clinician Demographics: Cognitive Interviews

Characteristic	First Round Interview n = 8	Second Round Interview n = 8
Interview length, minutes, median (range)	57 (50, 115)	64 (46, 88)
Age, years, median (IQR)	53 (40, 67)	53 (40, 64)
Female, n (%)	5 (63)	5 (63)
Time working with neurogenetic/neurodevelopmental disorders, years (IQR)		
<i>Clinic/healthcare</i>	30 (12, 36)	27 (14, 30)
<i>Clinical trials</i>	20 (4, 22)	18 (7, 21)
<i>Non-clinical trial research</i>	20 (10, 36)	18 (10, 30)
Time working with PMS, years (IQR)		
<i>Clinic/healthcare</i>	10 (7, 15)	10 (1, 15)
<i>Clinical trials</i>	4 (2, 15)	2 (0, 15)
<i>Non-clinical trial research</i>	10 (2, 15)	5 (1, 15)
Age of individuals with PMS seen by clinician, years, range	0, 50	1, 45

IQR, interquartile range; PMS, Phelan-McDermid syndrome.

Table 2. Caregiver Demographics: Cognitive Interviews

Characteristic	First Round Interview n = 5	Second Round Interview n = 5
Interview length, minutes, median (range)	67 (51, 114)	63 (51, 118)
Age, years, median (IQR)	45 (33, 54)	45 (38, 53)
Female, n (%)	4 (80)	4 (80)
Parent or guardian to someone with PMS, n (%)	5 (100)	5 (100)
<i>Age, person with PMS, median (IQR)</i>	9 (6, 21)	9 (3, 18)
<i>Female, person with PMS, n (%)</i>	2 (40)	4 (80)

IQR, interquartile range; PMS, Phelan-McDermid syndrome.

Analytical Rigor

- Rigorous methodologies to ensure validity and reliability included member checking, source triangulation, and collaborative analysis with multiple researchers
- Revisions were tracked in item-level matrices and analyzed using a framework approach
- The measure refinement approach followed principles outlined in the FDA guidance for outcome measure development⁶

Revisions

PMSA-S and PMSA-C

- The “**cognition/learning**” domain was revised to the “**attention/awareness**” domain to better reflect the constructs assessed within the domain
- Scoring anchors** were updated to follow a **developmental hierarchy** and improve consistency and ease of use; **redundant categories were collapsed** to improve clarity
- Clinicians supported **maintaining domain-level ratings separate from the global impression rating**

CIC

- Instructions** were clarified to ensure **direct observations** as well as **information from other sources** (eg, teachers, therapists) were considered when rating
- A “**not applicable**” response option was added to allow for more flexibility in response
- Practical examples** were provided to improve clarity (eg, attention span, facial expressions)

Implications

PMSA-S and PMSA-C

- The revised PMSA-S and PMSA-C will allow clinicians to provide comprehensive, consistent, and meaningful assessments of PMS severity and improvement across key symptoms
- Revisions to improve clarity, relevance, and usability position the PMSA-S and PMSA-C to enhance data quality and support robust conclusions when applied in clinical trials

CIC

- The revised CIC will allow caregivers to document their perceptions of meaningful changes in individuals with PMS
- Revisions, including clear instructions and expanded response options, ensure greater reliability and engagement from caregivers and support measure use in clinical trials

Future Directions

- The revised PMS-specific outcome measures may undergo additional evaluation of psychometric properties and will be used within future clinical trials

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