Mindful Measures: Assessing Content Validity of Patient-Reported Outcomes for Major Depressive Disorder in Clinical Trials

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Background and objective

- New treatments for major depressive disorder (MDD) are largely evaluated using clinician-reported outcome measures[1]
- As MDD is primarily a subjective experience, the use of patient-reported outcomes (PROs) is important for assessing the overall impact of treatment on patients' quality of life and symptom relief from the patient perspective
- Established US Food and Drug Administration guidance has emphasized the importance of demonstrating content validity for PROs used in clinical trials, stating that PROs should measure:

> ***"What is important to patients and comprehensive with respect to patient concerns relevant to the concept being assessed"***[2]

- To demonstrate that a PRO is content valid in the target patient population (TPP), evidence that it measures what matters most to patients in ways that are understandable to them should be established through qualitative research
- This research evaluated the inclusion and content validity of PROs in MDD Phase 2-3 clinical trials

Methods

Clinical trial search

A search of ClinicalTrials.gov was conducted to identify Phase 2-3 clinical trials focused on MDD conducted between 2004 and 2024

Trials were reviewed for use of PROs designed to assess:

Depression symptoms and/or their dimensions (e.g., severity, frequency)	The impact of these symptoms on daily life

Gap analysis

Following PRO identification, a gap analysis was conducted to assess whether the PROs were developed using key content validity activities **(Figure 1)**

Results

- The search identified 173 clinical trials initiated between June 2004 and March 2024. Of these, 162 were included, and 11 were excluded due to a primary focus outside of MDD
- Of the 162 included trials, 83 (51.2%) used PROs. Further evaluation identified 9 PROs specifically assessing depression symptoms/impacts, which were found in only 28 of the included trials **(Figure 2)**
  - Most of these trials (n=24/28, 85.7%) positioned the identified PROs as secondary endpoints, with only four trials including them as primary endpoints
- Results of the gap analysis showed the following evidence in the available literature across the identified PROs:
  - **Concept-focused literature** evidence was found for the Quality of Life in Depression Scale (QLDS) and the Center for Epidemiologic Studies Depression Scale (CES-D)
  - Evidence of **clinical expert input** in the TPP was identified only for the 16-Item-Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR16). Full or partial evidence was found in a related patient population (but not specifically for MDD) for the Patient Health Questionnaire (PHQ) and the Symptoms of Depression Questionnaire (SDQ)
  - **Patient concept elicitation interview** evidence was identified for the Beck Depression Inventory-II (BDI-II), QLDS, and the Hospital Anxiety and Depression Scale (HADS)
  - Among the identified PROs, only the PHQ had available and identifiable evidence of **concept saturation** in the literature
  - The activity with the strongest evidence in the available literature was **questionnaire debriefing interviews**, with evidence identified for the QLDS, BDI-II, PHQ, CES-D, and Montgomery–Åsberg Depression Rating Scale Self-Report (MADRS-S)
  - No PRO development included all five content validity activities **(Table 1)**

Figure 2. Breakdown of depression-specific PROs (n=9) across 28 trials

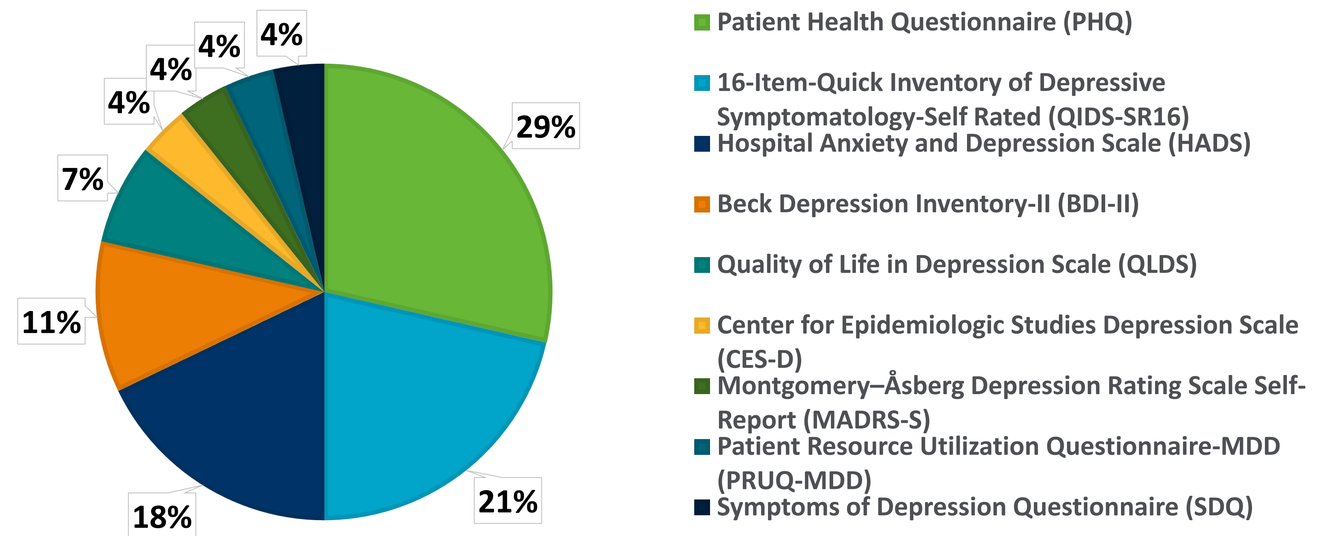

Figure 1. Key content validity activities

Table 1. Content validity gap analysis

Assessed PROs	Concept elicitation research				Content evaluation research
	Concept-focused literature review	Clinical expert input	Patient concept elicitation interviews	Concept saturation	Questionnaire debriefing interviews
PHQ	GAP	O	GAP	✓	✓
QIDS-SR16	GAP	✓	GAP	GAP	GAP
HADS	GAP	GAP	✓	GAP	GAP
BDI–II	GAP	GAP	✓	GAP	✓
QLDS	✓	GAP	✓	GAP	✓
CES-D	✓	GAP	GAP	GAP	✓
MADRS-S	GAP	GAP	GAP	GAP	✓
PRUQ-MDD	GAP	GAP	GAP	GAP	GAP
SDQ	GAP	O	GAP	GAP	GAP

✓ Evidence identified in the reviewed literature
GAP Evidence not identified as part of this review
O Full or partial evidence found in a related population

Conclusions

- This research highlights the **limited implementation of PROs** in Phase 2/3 clinical trials for MDD treatments.
- Among the nine PROs that evaluated depression symptoms or impacts in these trials, the majority were developed with **little to no input from patients with MDD**.
- **None of the PROs** were developed using all key content validity activities, resulting in **limited qualitative evidence** to support that these tools measure concepts of interest that are relevant to the TPP.
- **Increased patient involvement** in the PRO development process is recommended to enhance the reliability and validity of instruments used in future clinical trials for MDD.

References

1. Guidance for Industry: Major Depressive Disorder: Developing Drugs for Treatment Draft Guidance. 07/2018, 2018.
2. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health. *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Office of Communications, Division of Drug Information; 12/2009.

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