CDAD-DaySyms™: A new patient-reported outcome tool for *Clostridium difficile*-associated diarrhoea

PRM145

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INTRODUCTION

Background

- *Clostridium difficile* infection (CDI) is a growing global public health challenge, with dramatic increases in incidence, severity, mortality, and healthcare burden in recent years.[1,2] The incidence of cases of recurrent CDI following initial treatment is also rising.[2]
- Clinical manifestations of *C. difficile* infection range from diarrhoea of varying degrees of severity to colitis, systemic toxic shock, and even death.[3]
- Symptoms of *C. difficile*-associated diarrhoea (CDAD) are important because they impair patient functioning and quality of life.[4]
- Since the patient voice in the drug approval process is becoming more prominent,[5] clinical studies of new agents for CDAD should evaluate symptoms in addition to objective clinical assessments; however, no patient-reported outcome (PRO) questionnaire measuring symptoms is currently available.
- The 2009 Food and Drug Administration (FDA) PRO Guidance for Industry emphasizes the importance of documenting content validity, including evidence that the questionnaire is conceptually comprehensive, relevant, and understandable to patients with the disease.[6]

Objective

- Develop a symptom PRO for CDAD in accordance with the FDA Guidance

METHODS

Study design

- A cross-sectional, qualitative research study was undertaken consisting of 2 main phases (Figure 1):
  - Concept elicitation interviews of CDAD patients and nurses to better understand the patients' experience of their disease, and inform the development of the new PRO
  - Cognitive interviews (2 rounds) with CDAD patients to test the content validity of the draft PRO and revise it if required
- Before implementing qualitative work, a preliminary conceptual framework was developed to provide the initial PRO structure.
- Interviews with 5 clinical experts from Europe and the US informed the development of the study protocol and a semi-structured interview guide.

Participants

- Patients with CDAD meeting study eligibility criteria (Table 1) were recruited at 5 participating study sites in the US.
- All patients provided written informed consent.
- Nurses from the 5 participating sites who treated CDAD patients on a regular basis were recruited to participate in supplemental interviews in Phase 1.

Phase 1: Concept elicitation interviews

- Patients' spontaneously reported experiences with CDAD symptoms were gathered from patient interviews as well as supplemental interviews with nurses, who were asked about symptoms reported by patients.
- Once concept saturation was reached, the draft PRO, named the CDAD-DaySyms™, was developed with input from the panel of clinical experts.
- The draft PRO was reviewed by a translation expert to assess the ease of future translation to other languages and to determine lexibility (grade level and readability).

Phase 2: Cognitive interviews

- Patients with CDAD were interviewed by telephone in 2 iterative rounds, and asked to complete the PRO.
- Interviewers used a semi-structured interview guide to obtain feedback on:
  - Relevance, comprehensibility, acceptability, and compre- hensiveness of the questionnaire items
  - Interpretability and appropriateness of the instructions, response options, and recall period

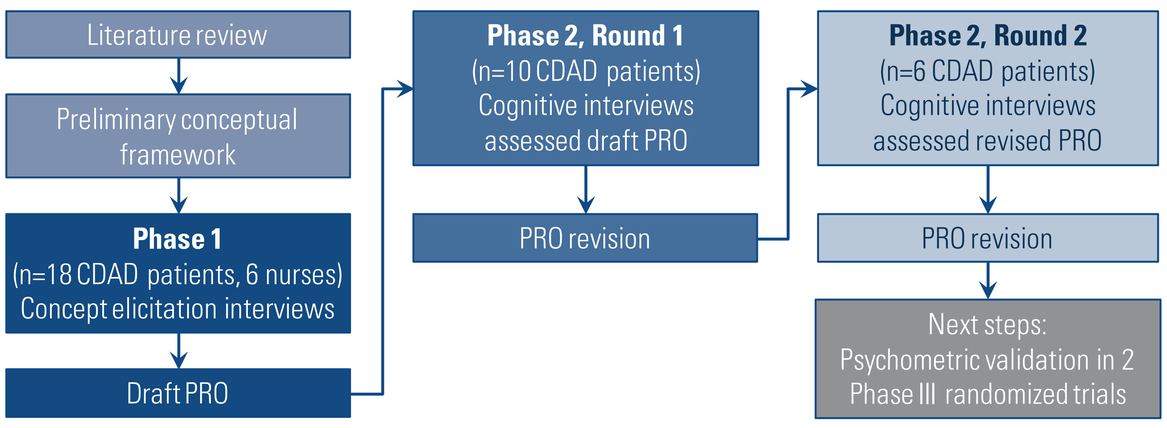

Figure 1. *Study flow*

CDAD: *Clostridium difficile*-associated diarrhoea; PRO: patient-reported outcomes (questionnaire)

Table 1. *Study eligibility criteria*

Inclusion criteria	Exclusion criteria
▪ Age ≥18 years ▪ Diagnosis of CDAD: charting of diarrhoea (≥3 unformed stools in ≤24 consecutive hours) and stool test positive for toxigenic *C. difficile* or its toxins ▪ First occurrence or first recurrence of CDI ▪ Able to speak/read US English ▪ Able to participate in 60-min telephone interview within active disease period	▪ Concurrent life-threatening condition ▪ Treatment with a medication (other than an antibiotic) likely to cause diarrhoea as a side-effect ▪ Any other clinically relevant and/or serious medical condition which would interfere with ability to participate in an interview ▪ Current participation in a randomized clinical trial ▪ Any active disease other than CDI that could cause diarrhoea

CDAD: *Clostridium difficile*-associated diarrhoea; CDI: *Clostridium difficile* infection

RESULTS

Participant sample

- A total of 34 patients and 6 nurses were recruited across both study phases.
- Patient characteristics are shown in Table 2. Recruitment targets were generally met, though there were fewer patients than anticipated with first-recurrence and hospital-acquired CDAD.

Table 2. *Recruitment targets and characteristics of study patients*

Characteristic	Recruitment target	Phase 1 (n=18)	Phase 2 (n=16)	Total (N=34)
Age, years, mean ± SD (range)	–	61.1 ± 17.1 (22–78)	67.4 ± 7.39 (57–88)	63.8 ± 13.6 (22–88)
Female:male, n (%)	No exact target apart from diversity	9:9 (50:50)	13:3 (81:19)	22:12 (65:35)
Race/ethnicity, n (%)	No exact target apart from diversity			
Caucasian		18 (100)	13 (81.3)	31 (91.2)
African American		0	2 (12.5)	2 (5.9)
Asian		0	1 (6.3)	1 (2.9)
Highest level of education, n (%)	No exact target apart from diversity			
Primary/elementary school		1 (5.6)	1 (6.3)	2 (5.9)
Secondary/high school		4 (22.2)	4 (25.0)	8 (23.5)
Some college/university		5 (27.8)	6 (37.5)	11 (32.4)
College/university degree		3 (16.7)	4 (25.0)	7 (20.6)
Post-graduate		4 (22.2)	0	4 (11.8)
Other		1 (5.6)	0	1 (2.9)
Missing		–	1 (6.3)	1 (2.9)
CDAD severity, n (%)				
Mild	< 10%	5 (27.8)	3 (18.8)	8 (23.5)
Moderate	40%–50%	9 (50.0)	5 (31.3)	14 (41.2)
Severe	40%–50%	4 (22.2)	8 (50.0)	12 (35.3)
Disease episode, n (%)				
First occurrence	50%–60%	14 (77.8)	14 (87.5)	28 (82.4)
First recurrence	40%–50%	4 (22.2)	2 (12.5)	6 (17.6)
Where acquired, n (%)				
Hospital	60%–70%	6 (33.3)	7 (43.8)	13 (38.2)
Community	30%–40%	12 (66.7)	9 (56.3)	21 (61.8)
CDAD medications, n (%)				
Any	–	17 (94.4)	16 (100)	33 (97.1)
None	–	1 (5.6)	0	1 (2.9)
Comorbid conditions, n (%)				
Any	–	8 (44.4)	12 (75.0)	20 (58.8)
None	–	10 (55.6)	4 (25.0)	14 (41.2)

CDAD: Clostridium difficile-associated diarrhoea

Phase 1

- Concept saturation was reached for 18 emergently reported CDAD symptoms, which included diarrhoea, abdominal pain, fatigue, and lightheadedness. Patients and nurses reported similar types of symptoms relevant to patients.
- Severity-based response options were chosen, using a 5-point Likert type rating scale with options of none, mild, moderate, severe and very severe.
- A 24-hour recall period was chosen because symptoms are variable day to day, may progress quickly, and may begin to respond to therapy within 1–2 days.[7]

Phase 2

- Patients reported that the symptoms in the PRO were relevant to their everyday experience with the disease.
- The formatting and phrasing of the PRO including the instructions, items and response options were clear and easy to understand, and patients were able to use the questionnaire as intended.
- Minor changes were made to the PRO following the first and second rounds of cognitive interviewing, as follows:
  - Revisions to the instructions to improve translatability
  - Rewording of 2 items for clarity
  - Reversing the order of 2 items for logical flow
  - Separation of an item into 2 due to patients perceiving the 2 items differently and clinical experts noting different underlying physiological mechanisms
- The revised PRO incorporates 5 hypothesized symptom sub-concepts (subdomains) comprising 13 items (Figure 2).

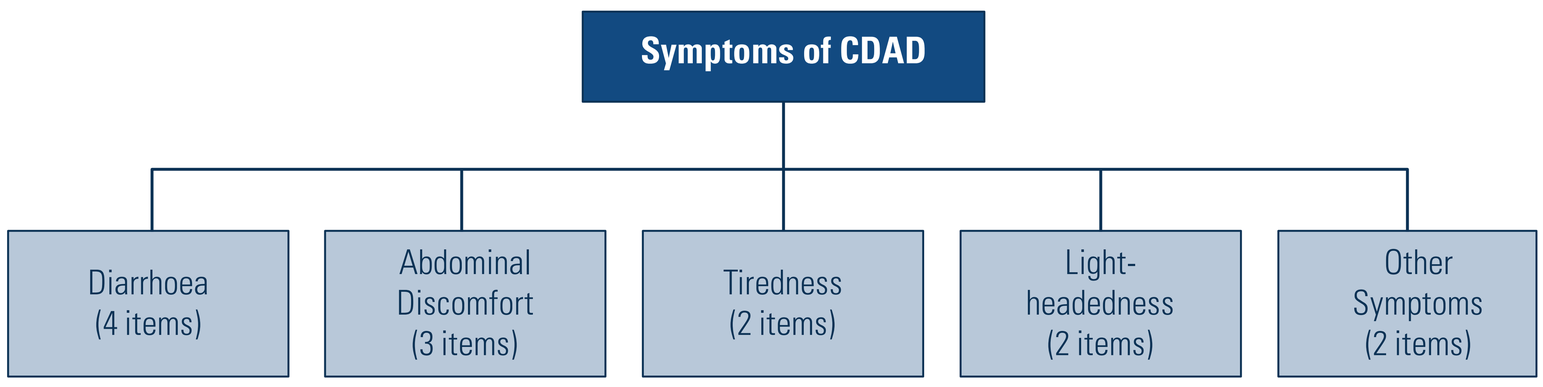

Figure 2. *Conceptual framework of the draft PRO questionnaire*

CDAD: *Clostridium difficile*-associated diarrhoea

CONCLUSIONS

- The patient perspective in CDAD is important.
- The CDAD-DaySyms™ was demonstrated to capture the patient voice as a comprehensive measure of CDAD symptoms, with data from initial qualitative research supporting its content validity in patients with varying severity of CDAD.
- The psychometric properties of the PRO must be evaluated before the questionnaire can be used in clinical practice or clinical studies; validation will be performed in two clinical trials.

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