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The CDI-DaySyms: Content Development of a New Patient-Reported Outcome (PRO) Questionnaire for Symptoms of *Clostridium difficile* Infection

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ABSTRACT

Objectives: To develop a patient-reported outcome (PRO) questionnaire for symptoms of *Clostridium difficile* infection (CDI) following the US Food and Drug Administration PRO guidelines. **Methods:** Patients' experiences of CDI symptoms were elicited in open-ended discussions with patients and nurses at five US sites (stage 1). A draft PRO measure was developed after demonstration of concept saturation. Two rounds of cognitive interviews were conducted with patients at three US sites (stage 2), with revision of the draft measure after each round. All patients were 18 years or older, with confirmed CDI. The study was conducted with input from a panel of five CDI experts in Europe and North America. **Results:** Stage 1 included interviews with 18 patients and supplementary interviews with 6 nurses; 16 additional patients were interviewed in stage 2. Patients were representative of the general CDI population and were diverse in age, sex, and disease severity. Concept saturation was reached in stage 1. Items were organized in a draft conceptual framework with five hypothesized domains: diarrhea, abdominal discomfort, tiredness, lightheadedness, and other symptoms. Stage 2 demonstrated initial content validity of the 13-item draft daily diary (CDI-DaySyms). Participants reported that the questions were clear, relevant, and comprehensive. They were able to use the instructions to complete the diary correctly and considered the 24-hour recall period appropriate. **Conclusions:** The CDI-DaySyms captures symptoms relevant to patients undergoing CDI, demonstrating initial content validity. Final content and psychometric validity are being evaluated in a substudy comprising patients from two ongoing international clinical trials (ClinicalTrials.gov identifiers NCT01987895 and NCT01983683).

Keywords: CDAD-DaySyms®, *Clostridium difficile*–associated diarrhea, *Clostridium difficile* infection, health-related quality of life, patient-reported outcomes, symptoms.

Introduction

Clostridium difficile infection (CDI) is a global public health challenge not only in the inpatient setting, but is also increasingly recognized in the community [1]. Diarrhea is a component of the case definition for the typical presentation of CDI [2]. Henceforth in this article, "CDI" refers to confirmed infection with *C. difficile*, clinical manifestations of which may range from asymptomatic carriage to fulminant (and potentially fatal) pseudomembranous colitis [2]. Patient-reported symptoms of CDI include reduced appetite, abdominal pain, loss of control over bowel function, lack of energy, and fatigue [3].

Current evaluation of CDI severity relies on clinician assessment via history-taking, physical examination, laboratory tests, imaging, and colonoscopy [2,4]. Clinical studies have focused on physician-reported assessments such as cure, treatment failure, and recurrence, supplemented by objective outcomes such as mortality [5]. Nevertheless, only patients themselves can directly

Conflicts of interest: L. Kleinman is an employee of Evidera. G. H. Talbot has received consulting and scientific advisor fees from Actelion Pharmaceuticals Ltd. E. Hunsche and R. Schüler are employees of Actelion Pharmaceuticals Ltd. and have stock options or bond holdings in the company. C. E. Nord has received scientific advisor fees from Actelion Pharmaceuticals Ltd. G. H. Talbot and C. E. Nord were Steering Committee members on the IMPACT study program, which comprises two phase III studies comparing the efficacy and safety of cadazolid versus vancomycin.

Portions of this work were previously presented at the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, on September 6, 2014; the International Society for Pharmacoeconomics and Outcomes Research 17th Annual European Congress, Amsterdam, The Netherlands, on November 11, 2014; and the 13th Biennial Congress of the Anaerobe Society of the Americas (ANAEROBE 2016), Nashville, TN, on July 14, 2016.

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report how they experience the symptoms of CDI. This is increasingly being recognized and the patient voice is becoming more prominent in the drug approval process [6]. In 2009, the US Food and Drug Administration (FDA) issued guidance on the development of patient-reported outcome (PRO) instruments to measure symptoms from the patient perspective [7]. Because currently no PRO instrument exists that appropriately assesses CDI symptoms, the objective of this study was to develop a disease-specific questionnaire according to the FDA PRO guidance requirements, including establishing its content validity, that is, documenting that the structure and content (items) of the new PRO instrument capture the connection between the intended measurement concepts and the way patients from the target population understand and discuss these concepts [8].

Methods

Overview

A multicenter, qualitative PRO research study was undertaken following the iterative process recommended in the FDA PRO guidance, with full documentation of all stages of questionnaire development [7]. As shown in Figure 1, a literature review was performed to determine whether an adequate PRO instrument already exists to assess CDI symptoms, and to identify any previous qualitative studies conducted in this patient population to gather evidence on patient-reported CDI symptoms. At the outset of the research, a preliminary conceptual framework for CDI symptoms was developed on the basis of findings in the literature as well as additional input from a Clinical Expert Advisory Group comprising five clinicians from Europe and the United States specializing in the treatment of CDI, who also provided guidance for the development of the study protocol for the qualitative research. In stage 1, concept-elicitation interviews were conducted with patients, and supplementary interviews were conducted with nurses, to generate items relevant to patients with CDI and inform the drafting of a new questionnaire with input from the clinical experts. Stage 2 of the qualitative research consisted of two rounds of cognitive interviews to ensure understanding and completeness of the draft questionnaire, with revisions of the draft PRO after each round. The research was implemented following the FDA PRO guidance [7] and was consistent with the FDA's roadmap to patient-focused outcome measurement in clinical trials [9], the International Society for Pharmacoeconomics and Outcomes Research Clinical Outcomes Assessment—Emerging Good Practices for Outcomes Research Task Force [10], and the International Society for Pharmacoeconomics and Outcomes Research PRO Content Validity Good Research Practices Task Force [8,11].

This qualitative research preceded psychometric validation of the new PRO instrument, which is forthcoming.

Literature Review

A literature review was performed to search for any existing CDI-specific PRO questionnaires as well as instruments covering symptoms of general diarrhea and gastrointestinal symptoms and to search for evidence regarding symptoms of CDI to inform the qualitative research, including the development of the conceptual framework. The date range for the literature search was 2006 to 2011 (the date of study initiation). Because no existing PRO questionnaires were identified that could be adapted to adequately assess symptoms of patients with CDI, qualitative research proceeded to develop a new questionnaire.

Stage 1

After the drafting of a preliminary conceptual framework with evidence from the literature review and input from the Clinical Expert Advisory Group, concept-elicitation interviews were conducted in patients with active CDI at five study sites in the United States. Patient eligibility criteria are presented in Table 1. Recruitment targets, presented in Table 2, aimed to achieve diversity of patients and to be generally representative of the CDI population seen in clinical practice and likely to be recruited in future clinical trials, including diversity of participant clinical factors such as CDI severity, type of disease episode (i.e., first occurrence or first recurrence), and where participants acquired CDI (i.e., hospital or community). Study sites were selected to ensure geographical diversity. The approval from an institutional review board was obtained for all sites, and all patients provided written informed consent.

One-on-one patient concept-elicitation interviews were conducted by telephone from the end of 2011 through 2012 using open-ended questions to elicit symptoms of CDI experienced by patients, including information about symptom frequency, intensity, and variability, as well as to ask about patients' experiences with CDI symptoms identified in the literature review, in interviews with the clinical experts, and in previous patient interviews conducted in this study (i.e., symptoms elicited in interviews were queried in subsequent interviews). Telephone

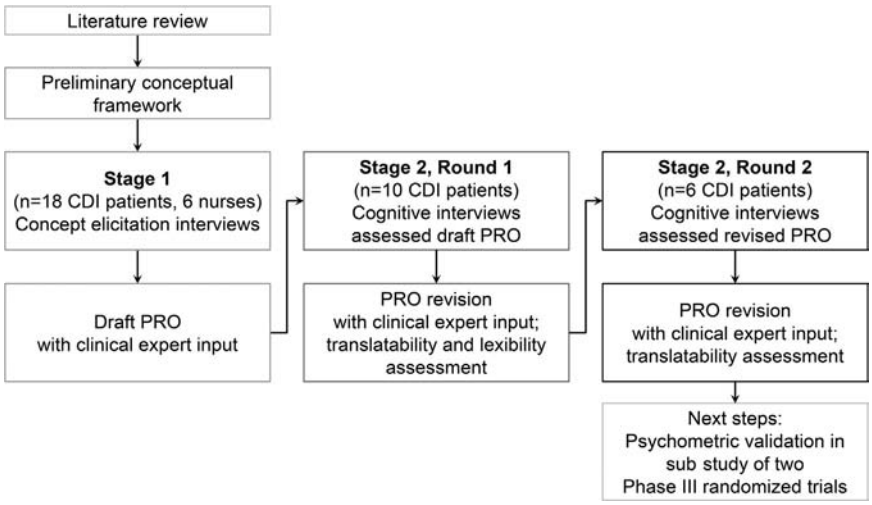

Fig. 1 – Study flow. CDI, *Clostridium difficile* infection; PRO, patient-reported outcome.