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Development of a real-time patient-reported outcome measure for symptom assessment in patients with functional dyspepsia using the experience sampling method

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Abstract

Background: Patient-reported outcome measures (PROMs) are used to assess symptoms in patients with functional dyspepsia (FD). Current end-of-day questionnaires have several limitations including sensitivity to recall and ecological bias. The experience sampling method (ESM) is characterized by random and repeated assessments across momentary states in daily life and therefore less sensitive to these limitations. This study describes the development of a novel PROM based on ESM technology.

Methods: An initial draft of the PROM was developed based on literature. Focus group interviews with FD patients according to Rome IV criteria, and an expert meeting with international opinion leaders in the field of functional gastrointestinal disorders were conducted in order to select items for the PROM. Cognitive interviews were performed to evaluate patients' understanding of the selected items and to create the definitive PROM.

Key results: A systematic literature search revealed 59 items across four domains (ie, physical status; mood and psychological factors; context and environment; and nutrition, medication, and substance use). After patient focus group interviews and an international expert meeting, the number of items was reduced to 33. Cognitive

interviews resulted in some minor linguistic changes in order to improve patients' understanding.

Conclusions and inferences: A novel digital ESM-based PROM for real-time symptom assessment in patients with functional dyspepsia was developed. This novel PROM has the potential to identify individual symptom patterns and specific triggers for dyspeptic symptoms, and optimize treatment strategies.

KEYWORDS

(functional) dyspepsia, experience sampling method, patient-reported outcome measure, symptom assessment

1 | INTRODUCTION

Functional dyspepsia (FD) is a common functional gastrointestinal disorder with an estimated prevalence of 8%-12% in the general population.¹⁻³ Symptom presentation of dyspeptic patients is heterogeneous although four core symptoms have been defined according to the Rome IV criteria: postprandial fullness, early satiation, epigastric burning, and epigastric pain.^{4,5} These symptoms lead to impaired quality of life, reduced work productivity, and increased healthcare costs, which underlines the need for (development of) effective treatment options.⁵⁻⁷

Functional dyspepsia is a symptom-based diagnosis, and patient-reported outcome measures (PROMs) are used to assess treatment efficacy.⁸ In a recently published systematic review, 20 available retrospective outcome measures were described for the evaluation of dyspeptic symptoms.⁹ However, these outcome measures do not fulfill all criteria for adequate psychometric validation, as defined by regulatory authorities.

Moreover, several limitations of retrospective end-of-day questionnaires are apparent. Firstly, retrospective outcome measures are prone to recall bias as retrieval of information is based on autobiographical memory.¹⁰ Secondly, dyspeptic symptoms vary over time due to the influence of certain circumstances and triggers (eg, food intake and psychosocial factors).^{11,12} Lack of ecological validity may occur when questionnaires are completed in another environment or situation, compared with situations in which symptoms were triggered.¹³ Thirdly, noncompliance is a major limitation of retrospective paper questionnaires, and this could potentially be eliminated by use of an electronic sampling method.¹⁴ These limitations of available retrospective questionnaires together with the lack of a single universally accepted PROM underline the need for development of a novel PROM.

The experience sampling method (ESM) is an attractive electronic method for real-time assessment of symptoms, which may overcome some of the limitations of retrospective questionnaires.¹³ Random, repeated assessments are used for several consecutive days to capture symptom variability over time, and this takes into account contextual, social, and psychological factors,

Key Points

- Functional dyspepsia is a symptom-based diagnosis, and patient-reported outcome measures (PROMs) are used for symptom assessment. However, current available retrospective PROMs have several limitations including recall bias.
- A novel digital PROM for momentary symptom assessment, based on the experience sampling method (ESM), was developed.
- The developed ESM-based PROM has the potential to assess real-time FD symptoms, identify symptom triggers, and optimize (individualized) treatment strategies. Moreover, this novel PROM may overcome several limitations of retrospective outcome measures.

which might influence dyspeptic symptoms.¹³ Although ESM has been applied in several disorders (eg, mental disorders), use in patients with functional gastrointestinal diseases is currently limited to two studies in patients with irritable bowel syndrome (IBS).¹⁵⁻¹⁷ Both studies reported higher symptom scores in end-of-day diaries when compared to day-average scores of momentary assessments with ESM.^{16,17}

However, the ESM has not been previously applied in patients with functional dyspepsia. In this report, we describe the development of a novel PROM based on ESM technology for real-time assessment of symptoms in patients with functional dyspepsia.

2 | METHODS

Development of a novel ESM-based PROM for symptom assessment in patients with functional dyspepsia was undertaken in several stages according to the FDA guidelines for the development of PROMs.⁸

2.1 | Phase I: Item selection

A conceptual framework of theoretical constructs was developed for assessment of symptoms in patients with functional dyspepsia. For development of this framework, an extensive systematic literature search was performed to obtain available retrospective questionnaires for selection of FD-specific items.⁹ Moreover, ESM-specific constructs (ie, psychological status, social, and contextual factors) were derived from previously used ESM questionnaires at the departments of Gastroenterology and Hepatology, and Psychiatry and Psychology of Maastricht University Medical Center (MUMC+).^{17,18}

2.2 | Phase II: Focus group interviews

2.2.1 | Selection of participants for focus groups

Consecutive ambulatory patients between the age of 18 and 75 years with a diagnosis of functional dyspepsia were recruited at the outpatient department of Gastroenterology and Hepatology at Maastricht University Medical Center (MUMC+). Patients were diagnosed with functional dyspepsia according to Rome IV criteria, and an upper gastrointestinal endoscopy was performed up to 12 months prior to the focus group interview in order to exclude organic abnormalities.⁵ Patients with FD and a comorbid diagnosis of irritable bowel syndrome (IBS) were not excluded due to the considerable overlap of both disorders and to acquire a representative sample of the general population. Participants spoke Dutch as their mother tongue as focus groups were conducted in Dutch. All participants gave written informed consent, and the study protocol was approved by the medical ethical committee of Maastricht University Medical Center (METC 17-4-056).

2.2.2 | Conducting and moderating focus group interviews

Patient focus group sessions were organized in order to identify a relevant set of items for symptom assessment in functional dyspepsia and discuss practical issues of the ESM procedure.

Eligible participants were invited to participate in a focus group meeting which took approximately 90 minutes. Focus group interviews were planned and continued until saturation of input was achieved.¹⁹ Preferably, five to ten participants were included per focus group, in order to obtain the full spectrum of perspectives.^{19,20}

After an introduction about the aim of the study, one moderator (FS) and one assistant moderator (LV) guided the focus groups with use of a power point presentation to ensure adequate consistency in interview content. In order to minimize the probability of bias induced by the moderator, the first part of the focus group consisted of an open discussion in which participants were questioned about which items they considered to be essential in an outcome measure for dyspeptic patients. This section of the focus group aimed to (a) acquire information about experiences of gastrointestinal symptoms, (b) obtain information about the influence of symptoms on

daily life, and (c) identify which factors or triggers influence dyspeptic symptoms.

During the second part of the focus group, 59 items selected from previously used outcome measures and ESM questionnaires were presented on the power point presentation, and participants were asked to criticize these items. They were asked to consider which items were relevant in a real-time symptom assessment method for functional dyspepsia and which items could be excluded. Moreover, patients were asked to identify incomprehensible items and provide alternative terms or descriptions. Care was taken to obtain feedback from all participants on each item, and the number of participants that considered each item relevant was assessed. At the end of each domain, open-ended questions were asked to evaluate whether additional symptoms required mentioning.

Fatigue and sleeping problems are frequently mentioned by patients with functional gastrointestinal complaints. Assessment of sleep and fatigue is, however, not suitable for repeated assessment over the day. In line with the recently developed ESM-based IBS PROM, we intended to include a "morning" questionnaire for assessment of sleep once a day.

Besides evaluation of items to be included in an outcome measure for assessment of dyspeptic symptoms, several practical components of the ESM procedure were discussed. The proposed 11-point (0-10) Numeric Rating Scale (NRS), which is currently recommended for use as endpoint in clinical trials of patients with IBS, was discussed.²¹ Secondly, the number of assessments during the day and the time spent for completing each assessment (ie, 3-5 minutes) were discussed to assess the feasibility and burden of the ESM-based outcome measure. Random and repeated symptom assessment is the key feature of ESM. Ten times a day, a beep signal is produced by the application on the smartphone between 07.30 and 22.30 hour. Auditory cues are submitted in 90-minute blocks, and the minimum interval between two beeps is 15 minutes. Beeps occur completely random without relation to meal intake in order to prevent anticipation of symptom assessment.

2.3 | Phase III: Expert meeting

After conducting the focus groups, a teleconference meeting was organized with international experts in the fields to discuss the relevance of the individual items that were selected from the systematic literature search and patient focus groups. Experts criticized the items regarding their relevance and suitability for a real-time symptom assessment method. Based on this discussion, a definitive draft with questions for the ESM-based outcome measure was developed.

2.4 | Phase IV: Cognitive interviews

Interviews focused on cognitive understanding were performed to evaluate patients' grasp of the items included in the definitive draft. Again, native Dutch-speaking patients with functional dyspepsia according to the Rome IV criteria were included, but who had not previously taken part in the focus group interviews. The definitive ESM

draft was presented to the participants on paper. Participants were asked to read the items, speak them out loud, and consider whether the meaning of the items was clear (ie, *verbal probing*).²² Moreover, participants were asked for recommendations to improve the outcome measure. Cognitive interviews were performed on a one-to-one basis and were continued until additional cognitive interviews did not lead to substantial suggestions or recommendations from the participants.

2.5 | Data analysis

2.5.1 | Analysis of focus group data

Focus groups were recorded by a voice recorder, and notes were taken by both the moderator and assistant moderator. Immediately after the focus group sessions, a debriefing was performed between the moderator and assistant moderator to review and summarize the acquired information and observations.^{19,20} In addition, voice recordings were transcribed verbatim and summarized in a database together with the moderators' notes. This database was used to identify saturation of input, which is achieved when the core symptoms discussed in the sessions are stable, and subsequent focus groups only produce repetitive information.^{19,23} Finally, the database

was used to decide which items should be included in the definitive draft instrument.

2.5.2 | Analysis of cognitive grasp interviews

For the analysis of interviews focusing on cognitive grasp, a database was constructed to transcribe and summarize participants' statements, in order to facilitate comparison of interpretations for all individual items. This information was used to decide whether any modification of items was necessary.²²

3 | RESULTS

3.1 | Phase I: Item selection

Based on a systematic literature search and collection of previously used ESM questionnaires, 59 items were included in the initial ESM instrument. These items were divided into four domains: (a) physical status; (b) mood; (c) context and environment; and (4) nutrition, medication, and substance use (Figure 1). The "physical status" domain could be divided into three categories: (a) upper gastrointestinal symptoms, including symptoms of dyspepsia, gastroesophageal reflux disease, and other disorders (eg, nausea, belching, and

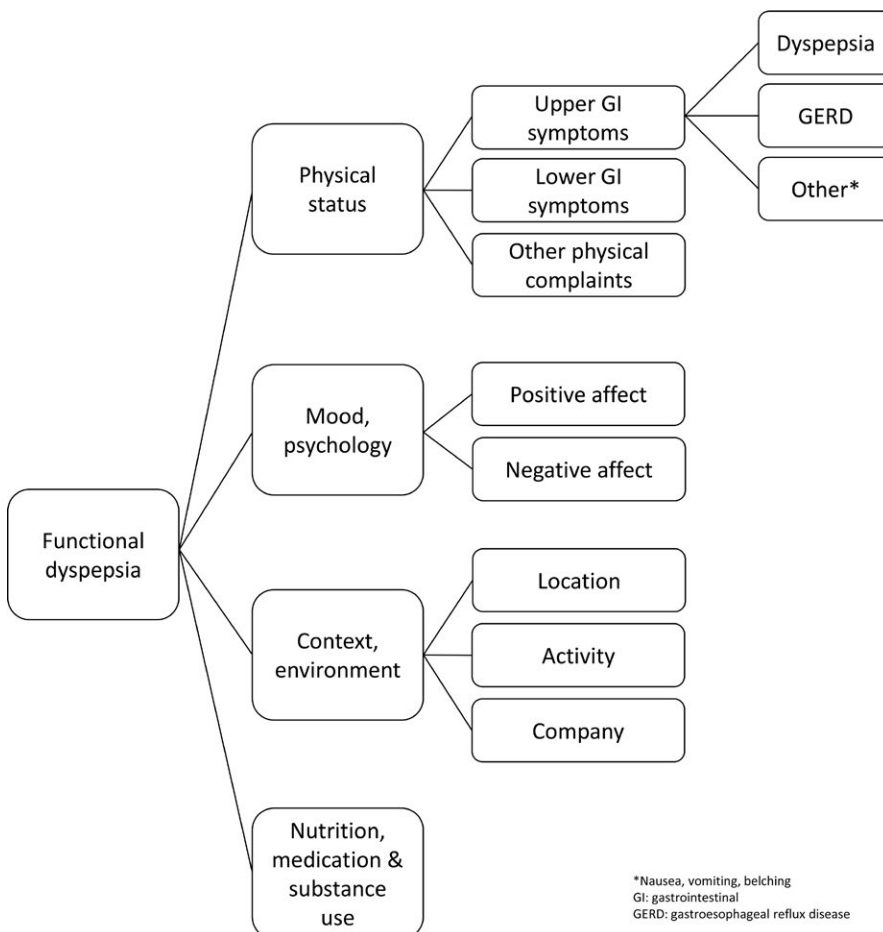


FIGURE 1 Conceptual framework for development of a novel patient-reported outcome measure using the experience sampling method

vomiting); (b) lower gastrointestinal symptoms; and (c) general physical complaints.

3.2 | Phase II: Focus groups interviews

3.2.1 | Study population

Forty-four patients with functional dyspepsia according to Rome IV criteria were invited for the focus group meetings. Eighteen patients confirmed their participation, and fourteen patients were present during three different focus group meetings (group 1: $n = 6$; group 2: $n = 3$; and group 3: $n = 5$). Family circumstances ($n = 2$) and lack of time ($n = 2$) were reasons for cancelation. Patient characteristics are described in Table 1.

3.2.2 | Focus group interviews

Physical status

Upper abdominal symptoms Postprandial fullness, early satiation, epigastric pain, and epigastric burning were considered important symptoms and were described by the majority of patients (86%, 64%, 64%, and 86%, respectively). Participants considered two aspects essential for real-time symptom assessment of pain: (a) pain severity and (b) location of pain. Assessment of pain severity using an 11-point NRS was considered adequate. To localize pain, participants suggested to add a schematic picture of the abdomen in which study subjects could select separate abdominal regions. In addition, several participants suggested description of the character of the pain (eg, cramp-like and dull) using multiple-choice options.

In addition to the four core FD symptoms, participants agreed on the importance of scoring additional frequently occurring upper gastrointestinal symptoms including bloating (86%), nausea (100%), and belching (93%). The open discussion revealed that bloating was sometimes considered equivalent to postprandial fullness. After clarification of the meaning of bloating (ie, an unpleasant sensation of gaseous distension), patients considered this an essential item for real-time symptom assessment separate from postprandial fullness. Not only bloating, but also nausea required

some further explanation as several participants correlated nausea with general malaise, instead of a desire to vomit. Heartburn was described by 12 patients (86%) and was considered distinct from epigastric pain.

Lower abdominal symptoms In addition to upper gastrointestinal symptoms, four participants reported lower abdominal pain and three patients had a comorbid diagnosis of IBS according to the Rome IV criteria. As a consequence, assessment of lower abdominal pain, defecation frequency, and consistency was considered important by four and three patients, respectively.

General complaints Several nonabdominal complaints were considered relevant by the majority of participants including palpitations, sweating, shortness of breath, and dizziness. Moreover, fatigue was reported by all participants and was considered an essential question. However, due to the often long-lasting nature of fatigue, this item was considered not eligible for repeated assessment. However, assessment of sleep with a "morning" questionnaire once a day was considered important by participants. Complaints reported by individual subjects were headache, weight loss, and fainting.

Mood and psychological factors

Assessment of psychological factors was considered important by all subjects, as they often experienced an association between psychological factors and gastrointestinal symptoms. "I feel anxious" (79%), "I feel irritated" (79%), and "I feel stressed" (100%) were considered important negative emotions, whereas "I feel relaxed" (100%) was considered a relevant positive affect. Participants discussed the item "I feel excited" as several patients found this item too positive and preferred "I feel good right now."

Context and environment

Contextual and environmental factors were considered relevant as these might influence the presence and/or severity of gastrointestinal symptoms. Questions with regard to location ("Where am I?"), activity ("What am I doing?"), and company ("Who is with me?"), with multiple-choice answers, were considered important by all participants. In addition, the majority of patients (86%) found it important

TABLE 1 Baseline characteristics of patients which participated in focus group interviews and cognitive interviews

	Participants focus group interviews (n = 14)	Participants cognitive interviews (n = 6)
Age in years, median (range)	64 (39-73)	47 (27-58)
Female, n (%)	10 (71)	5 (83)
FD subtype based on Rome IV criteria, n (%)		
FD-PDS ^a	1 (7)	3 (50)
FD-EPS ^b	6 (43)	1 (17)
Mixed subtype	7 (50)	2 (33)
Comorbid diagnosis of IBS, n (%)	3 (21)	1 (17)

^aFD-PDS: functional dyspepsia of the postprandial distress subtype.

^bFD-EPS: functional dyspepsia of the epigastric pain subtype.

to ask whether participants were restricted in their daily activities by current complaints.

Nutrition, medication, and substance use

Participants stressed that dietary factors and medication use should be taken into account when assessing dyspeptic symptoms. Two components of nutrition were considered essential, namely (1) type of food products and (2) amount of food intake. All subjects agreed on the question "Since the last beep I used" with categorical answers (ie, breakfast, lunch, dinner, or a snack). As several types of food and substance use can trigger symptoms, the question "What did you use since the last beep?" with categorical answer options (ie, coffee, tea, nicotine, drugs, medication, and carbonated beverages) was considered appropriate to all participants. In patients who took medication, a categorical answer option was preferable (ie, painkillers for abdominal pain, painkillers for another cause, acid-suppressive medication, anti-emetics, or something else). Although early satiety is a core symptom of FD, assessment of the amount of food intake is difficult. We suggested "I was able to finish a normal sized meal," which was appropriate for participants.

Practical issues

Several practical issues relating to the ESM procedure were discussed. An 11-point NRS was considered adequate and appropriate to grade the presence and severity of individual symptoms. Divergent opinions were present with regard to the proposed number of 10 measurements per day. A subgroup of participants indicated that 10 assessments per day would be quite burdensome and suggested that five to six measurements per day would be more acceptable. However, other participants considered it an investment in order to get additional information about their disorder and potentially optimize treatment.

Moreover, participants indicated that a 3- to 5-minute period was acceptable for completing each questionnaire. In order to reduce the time needed to complete the questionnaires, several participants suggested the use of an algorithm, in order to skip questions if possible. For instance, if participants answer "0 times" on the question "How many times did you defecate since the previous assessment?" then the question with regard to stool consistency could be omitted.

3.3 | Phase III: International expert meeting

All items resulting from the previous phases of the project were discussed by international experts in the field to assess the relevance for inclusion of individual items in an ESM-based FD-PROM.

With regard to upper gastrointestinal symptoms, several items were excluded as they were considered not relevant for inclusion in an FD-specific questionnaire (eg, dysphagia) or were not eligible for repeated assessments (eg, loss of appetite). In addition, some nuances were added for several items. For instance, patients in focus group interviews could not agree whether "I am having a full feeling" and "I am having a heavy feeling" were considered as identical or separate symptoms. Therefore, experts suggested to include both items

and evaluate them in a future validation study. Moreover, experts decided to merge "nausea" and "the feeling that I have to vomit," and recommended that a schematic pictogram of the abdomen should be given to patients before the start of the ESM questionnaire, in order to define the "upper" and "lower" abdomen.

Inclusion of items related to the lower gastrointestinal tract was extensively debated, as opinions of the international experts were heterogeneous. Although the goal was to develop an FD-specific PROM, considerable overlap is present between FD and IBS, which was also demonstrated in the patient focus groups, as 21% had a comorbid diagnosis of IBS. As it was supposed that it would be beneficial to evaluate the (potential) relation between upper and lower gastrointestinal symptoms with this ESM principle, experts agreed with inclusion of the most important lower gastrointestinal items (ie, lower abdominal pain, number and consistency of bowel movements, and incomplete evacuation).

The international experts agreed on inclusion of general physical complaints, as previous studies found associations between dyspeptic symptoms and somatic complaints.

Selection and inclusion of psychological items was extensively discussed as these ESM psychological items have not been validated before in patients with gastrointestinal disorders. Item selection was therefore performed based on a recent publication evaluating psychometric validation properties of the ESM in patients with mental disorders, the previously developed ESM-IBS questionnaire, together with patients' opinion in focus group interviews.^{18,24}

Contextual items were discussed as well, but no changes were made. Moreover, experts agreed that nutritional items were of special interest with regard to dyspeptic symptoms. Although patients in the focus groups mentioned specific kinds of food as triggers for dyspeptic symptoms (eg, onions and spicy food), evaluation of associations between dyspeptic symptoms and specific kinds of food was considered beyond the scope of this project.

In conclusion, focus group interviews and an international expert meeting resulted in a reduction of the number of included items from 59 to 33, categorized in the before-mentioned four domains.

3.4 | Phase IV: Cognitive grasp interviews

Demographic characteristics of the participants are shown in Table 1. One participant had a comorbid diagnosis of IBS according to Rome IV criteria. Only a few minor modifications were suggested to improve patients' understanding with the items. For instance, the wording of items regarding dyspnea and chest pain was modified.

The final ESM-based instrument for repeated symptom assessment is shown in Table 2. In addition, the morning questionnaire for assessment once a day is shown in Table 3. Content validity was assessed according to the following items: (a) development of a conceptual framework; (b) extensive item generation by a systematic literature search and organization of patient focus group interviews in the target population of FD patients according to Rome IV criteria with use of open-ended questions, continuation until saturation of input was achieved, and verbatim transcription; (c) discussion of

TABLE 2 Definitive set of items for the ESM-PROM

		Answer scale
Physical status—Upper abdomen		
1	I am having a full feeling in my upper abdomen	0 (none) - 10 (very much)
2	I am having a heavy feeling in my upper abdomen	0 (none) - 10 (very much)
3	My abdomen feels bloated	0 (none) - 10 (very much)
4	I am having pain in my upper abdomen	0 (none) - 10 (very much)
5	I am having a burning feeling in my upper abdomen	0 (none) - 10 (very much)
6	I am having pain in my lower abdomen	0 (none) - 10 (very much)
7	I feel nauseous	0 (none) - 10 (very much)
7a	Since the last beep, I have actually vomited.. time(s)	0, 1, 2, 3, 4, 5, more than 5 times
8	I am suffering from bothersome burping	0 (none) - 10 (very much)
9	I am having a burning feeling behind the breastbone	0 (none) - 10 (very much)
10	I am bringing up stomach contents into the mouth and/or nose	0 (none) - 10 (very much)
Nutrition, medication, and substance use		
11	I have eaten... since the last beep	Breakfast, lunch, dinner, a snack, none of these
11a	I ate... ago	Less than 15 min., 15-30 min., 30 min.-1 hour, more than 1 hour
11b	I am able to finish a normal sized meal	0 (none) - 10 (very much)
12	Since the last beep I have used...	Caffeine (coffee)/theine (tea), nicotine (smoking), alcohol, drugs, medication, carbonated beverages, milk products, fruit juices, none of these
12a	This was medication for:	abdominal pain, other pain relief, stomach acidity, nausea, diarrhea, constipation, something else
Physical status—General complaints		
13	I am having palpitations	0 (none) - 10 (very much)
14	I am sweating	0 (none) - 10 (very much)
15	I am short of breath	0 (none) - 10 (very much)
16	I feel dizzy	0 (none) - 10 (very much)
17	I have pain on my chest	0 (none) - 10 (very much)

(Continues)

TABLE 2 (Continued)

		Answer scale
18	I feel tired	0 (none) - 10 (very much)
19	Since the last beep, I have had the feeling that I had to open my bowels ... time(s)	0, 1, 2, 3, 4, 5, more than 5 times
20	Since the last beep, I have actually opened my bowels ... time(s)	0, 1, 2, 3, 4, 5, more than 5 times
20a	It looked like this:	Bristol Stool Form Scale
20b	I had to strain	0 (none) - 10 (very much)
20c	It feels like my bowels are not completely empty	0 (none) - 10 (very much)
Psychological aspects		
21	I am feeling good	0 (none) - 10 (very much)
22	I am feeling relaxed	0 (none) - 10 (very much)
23	I am feeling low	0 (none) - 10 (very much)
24	I am feeling anxious	0 (none) - 10 (very much)
25	I am feeling irritated	0 (none) - 10 (very much)
26	I am feeling stressed	0 (none) - 10 (very much)
27	I am worried	0 (none) - 10 (very much)
Context and environment		
28	Where am I?	At home, at someone else's home, work/school, public place, on my way, somewhere else
29	What am I doing (just before the beep)?	Resting, work/school, household work/shopping, hygiene/self-care, eating/drinking, relaxing/recreation, sports, travelling, something else
30	I feel (un)comfortable doing this	-5 (extremely uncomfortable) - +5 (extremely comfortable)
31	My symptoms are limiting my current activities	0 (none) - 10 (very much)
32	Who is with me?	Partner/children, friends, housemates, colleagues, family (other than those who live in your house), acquaintances, strangers/others, no one
33	I find this company (un)pleasant	-5 (extremely unpleasant) - +5 (extremely pleasant)

practical issues of the novel ESM-based PROM during focus group interviews (eg, digital mode of data collection, number of assessment per day, duration of data collection per day, recall period, and response scale); (d) teleconference with international experts in the field of functional dyspepsia and ESM; and (e) cognitive interviews in order to assess the participants' understanding of the PROM and evaluate the comprehensiveness of content.

4 | DISCUSSION

The current study was conducted in order to develop a novel PROM for assessment of symptoms in functional dyspepsia based on the experience sampling method.

Development of the novel ESM-based PROM was executed according to FDA guidelines over four executive phases. A systematic literature search, patient focus group interviews, and international expert meeting led to a novel ESM-based PROM, containing 33 items. Interviews were performed to confirm patients' understanding, although adequate briefing before use of the novel PROM remains necessary as variable interpretations of the meaning of the terms nausea and bloating were reported during focus group interviews. In the future, addition of pictograms in the digital ESM-based PROM may be useful to improve comprehension of verbal symptom descriptors, as previously demonstrated by Tack et al.²⁵ Moreover, forward-and-backward translation with additional cognitive interviews is necessary to verify patient understanding with the developed items in each language.

In line with the Rome IV criteria, the four core FD symptoms were described by the majority of patients. Additional frequently reported symptoms were bloating, nausea, and belching. These symptoms were also reported by a substantial subgroup of FD patients during previously performed focus group interviews, cognitive interviews, and validation studies (eg, bloating 86%-93%, nausea 40%-73%, and belching 27%-69%).^{26,27} Moreover, bloating was considered the most important symptom for improvement with effective therapy during development of the "Functional Dyspepsia Symptom Diary".²⁷ As the FDA states that the effect of treatment should be measured at the level of each symptom in order to ensure that treatment does not negatively affect symptoms, we suggest that a PROM should, as a minimum, evaluate the four FD core symptoms and the three frequently occurring additional symptoms.⁸ Food intake, medication use, and psychosocial factors were considered important triggers for generation and/or severity of gastrointestinal symptoms, which is in line with previous studies.^{26,28-30} Repeated assessment of dyspeptic symptoms, together with symptom triggers, offers the potential to optimize and individualize treatment strategies, and this is a potential advantage of the novel ESM-based PROM, compared with the recently developed "Leuven Postprandial Distress Scale" (LPDS) and "Functional Dyspepsia Symptom Diary".^{27,31}

Besides dyspeptic symptoms, lower gastrointestinal symptoms were studied, as evidence has been found for an increased prevalence of IBS in patients with FD.^{3,32} In our patient focus groups, 21% of patients had a comorbid diagnosis of IBS according to the Rome IV criteria, and this subgroup recommended inclusion of questions with regard to lower abdominal pain and defecation pattern. Although we intended to develop a disease-specific PROM for functional dyspepsia, the substantial overlap with IBS and potential implications for individualized therapy led to incorporation of IBS core symptoms (ie, lower abdominal pain and defecation pattern) in the newly developed PROM.

Psychological factors such as anxiety and depression are associated with functional gastrointestinal disorders and may precede or exacerbate symptoms.³³⁻³⁵ One of the main advantages of ESM compared with retrospective questionnaires is the fact that ESM offers the opportunity to improve ecological validity by taking into account these psychological factors.²⁴ However, one point of discussion during the international expert meeting was the fact that no validated psychological ESM items are currently available. In clinical trials, the Hospital Anxiety and Depression Scale (HADS) is often used to screen for the presence of anxiety or depressive disorders. However, HADS items are not eligible for momentary symptom assessment due to the retrospective nature. Verhagen et al recently described psychometric validation properties of ESM in patients with mental disorders. Thirteen mood items were included in their ESM questionnaire which could be divided into positive affect (four items) and negative affect (nine items) based on factorial analysis. The authors demonstrated excellent reliability, and significant correlations were found between mean scores for positive and negative affect, and the HADS scores, demonstrating concurrent validity.²⁴ However, inclusion of thirteen psychological items in an outcome measure for FD was considered too much of a burden, and we therefore reduced the psychological ESM items from 13 to seven, in line with the previously developed ESM-IBS PROM.¹⁸ Additional research is necessary to validate these psychological ESM items in patients with functional gastrointestinal disorders.

Somatization is also considered a factor contributing to symptom generation in functional gastrointestinal disorders.³⁶⁻³⁸ The Patient Health Questionnaire 12 (PHQ-12) is frequently used in clinical trials to assess somatic complaints.³⁹ In the final ESM-FD PROM, five of the 12 items of the PHQ-12 were included because participants mentioned these complaints in focus group interviews (ie, chest pain, dizziness, palpitations, dyspnea, and fatigue). The remaining seven items were not included, because they were not mentioned by focus group participants (back pain and pain in extremities or joints), they were mentioned by only one participant (headache and fainting), or the items were not eligible for assessment in a momentary questionnaire (sleeping problems).

Currently available outcome measures use several types of response options including visual analogue scales (VAS), Likert scales, pictorial scales, and binary endpoints (adequate relief of symptoms: yes/no).²⁵ Recently, our research group performed focus groups in IBS patients for the development of an ESM-based PROM and discussed several endpoints including a seven-point NRS (formerly used in ESM) and 11-point NRS.¹⁸ Finally, the 11-point NRS scale was incorporated, as the use of an end-of-day 11-point NRS is recommended by the FDA as primary endpoint in clinical trials of IBS patients.²¹ In contrast to IBS, a recommended response scale for FD is currently lacking. The 11-point NRS, which has been incorporated into the ESM-based IBS-PROM, was discussed during the focus group meetings and was considered appropriate by FD patients. Therefore, the 11-point NRS was chosen, in order to have a uniform response option for ESM-based PROMs in functional gastrointestinal disorders.

TABLE 3 Definitive set of items for the morning questionnaire for assessment once a day

	Morning questionnaire	Answer scale
1	How long did it take you to fall asleep last night?	0-5 min.; 5-15 min.; 15-30 min.; 30-45 min.; 45 min.-1 hour; 1-2 hours; 2-4 hours; more than 4 hours
2	Last night, how many times did you wake up during the night?	0, 1, 2, 3, 4, 5, more than 5 times
3	I slept well	0 (none) - 10 (very much)
4	I feel rested	0 (none) - 10 (very much)
5	I had abdominal problems during the night	0 (none) - 10 (very much)
5a	During the night I suffered from:	a full feeling, a heavy feeling, bloating, pain in my upper abdomen, a burning feeling in my upper abdomen, pain in my lower abdomen, nausea, vomiting, a burning feeling behind the breastbone, nocturnal defecation

Strengths of this study include the fact that the ESM-based PROM was developed according to steps recommended by the FDA, with development of a conceptual framework after an extensive literature search, organization of patient focus groups interviews and an international expert meeting, and arrangement of cognitive interviews.⁸ Due to the extensive literature search, a broad spectrum of items was identified and only a few additional symptoms (eg, headache and fainting) were mentioned by individual patients during the focus group interviews.

Several limitations should be noted. Firstly, we intended to invite five to 10 participants per focus group in order to ensure active participation of patients and gain a variety of perspectives. Although the final sample of 14 participants could be considered relatively small, focus group interviews were continued until saturation of input was achieved. Moreover, comparable sample sizes have been described in previous studies.^{25,26} Secondly, there may be a risk of limited representativeness, as only 32% of the initially invited patients eventually participated, and all patients were secondary and tertiary care patients. One could hypothesize that more confident patients and/or patients with more severe symptoms may be more willing to participate in focus group meetings. However, we assume that the risk of altered representativeness is limited, due to the inclusion of patients with a variety of symptoms matching different FD subtypes, the extensive item selection, and the limited additional input of symptoms by patients during focus group interviews. Another limitation may reside in the distribution of FD subtypes among participants as only one patient with the FD-PDS subtype participated in patient focus group sessions, whereas during cognitive grasp interviews only one patient with the EPS subtype was included. Nevertheless, in total four patients with PDS (20%), seven patients with EPS (35%), and nine patients with PDS-EPS (45%) were included. Therefore, we assume that the entire spectrum of dyspeptic symptoms was captured.⁴⁰⁻⁴² Participants did have to have sufficient command of the Dutch language, which means minority groups were underrepresented. Due to the inclusion of dyspeptic patients according to the Rome IV criteria, it not possible to extrapolate this PROM to patients with a selected number of dyspeptic symptoms

not fulfilling Rome criteria. Another potential limitation was the fact that during the cognitive interviews the draft of the PROM was presented on paper, as the digital application was not yet available.

Next step in the development of this novel ESM-based PROM is a validation study in patients with FD according to Rome IV criteria. In this study, psychometric validation properties (eg, reliability, validity, and responsiveness) will be assessed, and the final goal is to define a minimum clinically important difference for use in clinical trials. Another point of interest during this validation study is the compliance rate, as a subgroup of patients during the focus group interviews thought that ten assessments per day would be quite burdensome. However, an adequate compliance rate of 76.8% was found in a small pilot study in IBS patients using a 60-item ESM questionnaire.¹⁷

In conclusion, we report on the development of a digital disease-specific PROM for real-time assessment of symptoms in patients with FD using the ESM. Although future studies with this novel PROM are necessary to assess construct validity, reliability, and responsiveness, we suggest that the newly developed ESM-based PROM might be able to assess FD, identify specific triggers for symptoms, optimize (individualized) treatment strategies, and could potentially be used as an instrument to quantify therapeutic efficacy.

DISCLOSURE

No competing interests declared.

AUTHOR CONTRIBUTIONS

FGMS conceived and designed the study; acquired, analyzed, and interpreted the data; and drafted the manuscript; DK conceived and designed the study; acquired, analyzed, and interpreted the data; and critically revised the manuscript for important intellectual content; LV conceived and designed the study, acquired the data, and critically revised the manuscript for important intellectual content; JT, NJT, ACF, MS, JMC, JWK, and JVO analyzed and interpreted the data, and critically revised the manuscript for important intellectual

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