



Content validity of the Leicester Cough Questionnaire in adults with refractory or unexplained chronic cough: a qualitative interview study

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Abstract

Background: Chronic cough, a cough lasting >8 weeks, includes refractory chronic cough (RCC) and unexplained chronic cough (UCC). Patient-reported outcome (PRO) measures are needed to better understand chronic cough impacts that matter most to patients. The 19-item Leicester Cough Questionnaire (LCQ), an existing PRO measure of chronic cough, assesses impacts of cough across physical, psychological, and social domains. However, the content validity of the LCQ evaluating these concepts in patients with RCC/UCC had not been established.

Objectives: To evaluate the content validity of the LCQ in patients with RCC/UCC.

Design: A cross-sectional, qualitative interview study.

Methods: First, previously completed qualitative interview results in adults with RCC/UCC ($N=30$) were evaluated and mapped to LCQ concepts. Next, a clinical cough expert reviewed each LCQ item and assessed the salience of its concepts for patients with RCC/UCC. Finally, semistructured interviews—including both concept elicitation and cognitive debriefing—were conducted in adults with RCC/UCC ($N=20$) to elicit a comprehensive set of participant experiences and to assess the appropriateness of using the LCQ in this population.

Results: Concepts reported in the past and present qualitative interviews were included across all LCQ items, and most impacts reported to be the “most bothersome” were assessed in the LCQ. In the current study, all participants indicated that reduced cough frequency would be an important treatment target. During cognitive debriefing, each LCQ item was endorsed by $\geq 70\%$ of participants. Additionally, participants were generally able to understand, recall, and select a response for each LCQ item. All participants and the clinical expert indicated that the LCQ was appropriate and assessed the impacts most relevant to patients with RCC/UCC.

Conclusion: Our findings support the content validity of the LCQ and demonstrate that this measure is fit-for-purpose and includes important cough impacts in adults with RCC/UCC.

Keywords: chronic cough, content validity, cough-specific health-related quality of life, Leicester Cough Questionnaire, patient-reported outcome, refractory chronic cough, qualitative interviews, unexplained chronic cough

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Introduction

Chronic cough, a cough lasting more than 8 weeks, affects up to 10% of adults worldwide.^{1,2} This challenging condition has been reported in

regions across the globe.¹ Types of chronic cough include refractory chronic cough (RCC) or unexplained chronic cough (UCC).³ RCC persists in patients with comorbid conditions (e.g., asthma,

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gastroesophageal reflux disease, rhinitis) despite receiving treatment, whereas in UCC, no underlying causes of cough are identified through guideline-based clinical evaluation.^{4,5}

Chronic cough can last for years or decades, leading to significant morbidity.^{6,7} While symptoms and impacts of chronic cough vary between patients, physical impacts can include cough syncope, chest pain, hoarse voice, urinary incontinence, sleep disturbances, and exhaustion.^{3,8,9} In addition to considerable physical impacts, chronic cough is associated with underrecognized yet significant psychosocial impacts.^{6,9,10} Depressive symptoms, frustration, anxiety, uncomfortable public attention, negative impacts on daily life, hindered social relationships, and reduced health-related quality of life (HRQOL) have all been linked to chronic cough.^{9,11–14} As there are currently no approved treatments for chronic cough, patients need new treatment options that have been developed and evaluated in light of patients' individual lived experiences.^{8,15,16} Patient-reported outcome (PRO) measures can be used to obtain important patient experience data, including data evaluating outcomes that are most meaningful to patients and ultimately support assessment of novel treatments for RCC/UCC.¹⁶

One such measure, the Leicester Cough Questionnaire (LCQ), is a valid and reliable cough-specific PRO, with 19 items addressing the physical, psychological, and social impacts of cough.^{6,17} The LCQ was developed according to accepted standards for PRO measures; it included input from 15 patients with chronic cough and was cognitively debriefed among a separate sample of 104 patients with chronic cough.⁶ This measure has been widely used by researchers to assess treatments for chronic cough,¹⁸ has been shown to be responsive to changes in chronic cough impacts,^{17,19} and has acceptable psychometric properties supporting its use among patients with RCC/UCC.¹⁷ However, subsequent to the development of the LCQ, new regulatory guidance documents were released, most recently by the United States (US) Food and Drug Administration (FDA), that place greater focus on the evaluation and documentation of content validity for PRO measures.^{20,21} Content validity demonstrates how well a measure evaluates its

intended construct, ensuring the accuracy, relevance, and representativeness of PRO measures. While the initial development of the LCQ included patients with chronic cough,⁶ which by definition includes RCC/UCC,³ the content validity of the LCQ specifically in patients with RCC/UCC had not been established. In this study, we evaluated the content validity of and the appropriateness of using the LCQ in patients with RCC/UCC through concept mapping and qualitative interviews, in accordance with 2009²⁰ and 2022²¹ FDA regulatory guidance.

Methods

Study design

A cross-sectional, qualitative interview study design was employed. This research included concept mapping to compare the content of the LCQ with data from a previously conducted qualitative study (concept elicitation in RCC/UCC),¹⁴ a clinical expert interview to gauge the appropriateness of the LCQ in an RCC/UCC patient population, and in-depth, novel qualitative interviews with adults who had a clinical diagnosis of RCC/UCC. This study followed the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines.²²

The LCQ measure

The LCQ is a self-completed PRO measure with 19 cough-specific items addressing the impacts of chronic cough across 3 domains (Physical (items 1–3, 9–11, 14, 15), Psychological (items 4–6, 12, 13, 16, 17), and Social (items 7, 8, 18, 19)).⁶ LCQ items are assessed using seven-point Likert response scales with a recall period of 2 weeks. Response scales include 1 = “all of the time” to 7 = “none of the time” for items 1, 3, 5–10, 12–14, 16, and 17; 1 = “every time” to 7 = “never” for item 2; 1 = “none of the time” to 7 = “all of the time” for items 4 and 15; 1 = “all of the time (continuously)” to 7 = “none” for item 11; 1 = “every time” to 7 = “none of the time” for item 18; and 1 = “every time I cough” to 7 = “never” for item 19. Higher domain scores (average score across individual domain items; range, 1–7) and higher total scores (sum of the domain scores; range, 3–21) indicate better health status or less impact of cough.

Concept mapping in a chronic cough study by Bali et al.¹⁴

We examined the results of past concept elicitation qualitative interviews ($N=30$) conducted via telephone in adults with a clinical diagnosis of RCC or UCC.¹⁴ Deidentified data from Bali et al.,¹⁴ including ethics approval and participant consent details, were on file at the time of this study and have since been published. Concept saturation was reached in the study by Bali et al.,¹⁴ and the concepts (i.e., symptoms, impacts, and experiences) reported by the interview participants were extracted. Existing clinical outcome assessments were not evaluated by Bali et al.¹⁴ Therefore, we mapped these qualitative findings to the concepts included in the LCQ.

Clinical expert review

On 16 November 2022, a 60-min telephone interview was conducted with a leading clinical cough expert on the appropriateness of using the LCQ to assess the impact of chronic cough on patients with RCC/UCC. This semistructured interview was facilitated by a detailed agenda; during the interview, the clinical expert reviewed each item of the LCQ, provided feedback on the salience of the concepts included in the LCQ, and noted whether any important impacts of RCC/UCC were missing from the LCQ. Concepts reported or endorsed by the clinical expert were also mapped to concepts included in the LCQ.

Qualitative interviews

In-depth interviews were conducted with a targeted sample of 20 adults²³ living with RCC/UCC (evenly divided across RCC/UCC subgroups) to evaluate the content validity of the LCQ and to determine whether the LCQ could be used as a fit-for-purpose PRO measure for assessing the impact of chronic cough in adults with RCC/UCC. Interviews used a hybrid approach where the first half of the interview focused on concept elicitation and the second half included cognitive debriefing of the LCQ.

Participant recruitment. Participants were recruited through two clinical sites using a convenience sampling method in which adult patients with RCC/UCC who met study criteria were identified prospectively. To be eligible for inclusion, individuals must have been adults (aged ≥ 18 years)

from the US who had chronic cough for ≥ 1 year and a clinical diagnosis of RCC/UCC and must have scored ≥ 4 on a numerical rating scale assessing cough severity (ranging from 0 = “no cough” to 10 = “extremely bad cough”) over the past 7 days. Participants also needed to read, speak, and understand English, agree to be audio recorded during the interview, and be able to complete the interview via telephone. Individuals were excluded if they had been diagnosed with an illness that could exacerbate symptoms of chronic cough or had other circumstances that could confound interview results (e.g., chronic obstructive pulmonary disease, chronic bronchitis, current smoker, use of an angiotensin-converting enzyme inhibitor, positive for coronavirus disease 2019 (COVID-19) in the past 4 weeks, participation in clinical trials). Individuals were also excluded if they had an impairment that may have impacted their ability to provide informed consent or participate in an interview. Complete details of participant inclusion and exclusion criteria are outlined in Table S-1, Supplemental Material. Clinical site personnel contacted patients meeting the screening criteria via telephone or screened patients in person to determine whether they would like to participate in an interview. Potential participants were then given the researcher’s contact information and were asked to call to complete the screening process.

Interview methods. During January–February 2023, each approximately 60-min interview was conducted via telephone. There was no pilot testing, but to ensure that the interviews were conducted in a consistent manner and that the research objectives were met, each interview was conducted by two of three highly experienced qualitative researchers (one who led and one who took field notes during the interview) according to a standardized, semistructured guide; interviewers were females with 5–18 years’ experience in qualitative research (Research Health Outcomes Scientist Margaret Mayorga, MS, MPH; Research Health Outcomes Scientist Mirlene Milien, MS; and Executive Director of Patient-Centered Outcomes Assessment Claire Ervin, MPH). Each interview began with an introduction to the interviewers, review of the study purpose and interview format, and collection of verbal informed consent before continuing to the concept elicitation and subsequent cognitive debriefing phases. Outside of names and affiliations, personal details about the researchers were not disclosed, but participants

were encouraged to ask any questions throughout the interviews; only the research participants and interviewers were present. During concept elicitation, participants were asked open-ended questions designed to elicit a comprehensive set of participant experiences (i.e., impacts) associated with RCC/UCC. Concept saturation, defined as the point at which no new information is reported by participants, was evaluated between the first 10 and the second 10 interviews.

The next phase, cognitive debriefing, was intended to assess the appropriateness of the US English version of the LCQ for assessing the impact of chronic cough in adults with RCC/UCC. During cognitive debriefing, participants were asked to think aloud and describe their thought process as they responded to each item of the LCQ. The interviewers posed follow-up questions to evaluate how participants interpreted each item, response options, and the ease with which they understood each item. Upon completion of the debriefing, participants were asked if any important RCC/UCC impacts were missing from the LCQ. Each participant completed one single interview; no follow-up or additional interviews occurred.

Data analysis. Descriptive analyses were used to summarize the demographic and clinical data provided by participants at screening for categorical variables (e.g., sex, education level) and continuous variables (e.g., patient's current age). Standard qualitative analysis methods were applied to the interview data, including interviewer field notes and transcripts, and data were managed via Microsoft Word and Excel. Transcripts from the interview audio recordings were prepared and deidentified by a qualified medical transcriptionist to facilitate data analysis. In addition, each transcript underwent multiple levels of review to ensure accuracy. Interview data were analyzed using applied thematic analysis—the initial qualitative coding framework was based on the content in the interview guide and was adapted to incorporate any new concepts or themes identified during transcript review. To ensure consistency, all coding and analyses were conducted by the same three researchers (Margaret Mayorga, MS, MPH; Mirline Milien, MS; and Claire Ervin, MPH). Themes and concepts identified during the concept elicitation phase of each interview were compared to identify and confirm the RCC/UCC impacts of greatest importance to

participants. Similarly, for analysis of the cognitive debriefing phase, LCQ concepts of importance and potential problems with content or comprehension were identified in each interview; these findings were compared with the results of other interviews to document the frequency with which patients reported these concepts and issues. In addition to overall experiences with RCC/UCC, concepts reported or endorsed by participants across both the concept elicitation and cognitive debriefing phases were mapped to concepts included in the LCQ. Deidentified transcripts were used for data analysis and provided only to the study sponsor; interview participants did not provide feedback on the study findings.

Results

Concept mapping in a chronic cough study by Bali et al.

After extracting concepts reported by the Bali et al.¹⁴ concept elicitation study, which comprised 30 participant interviews, we identified that each of the 19 items included in the LCQ was reported as an important concept across patients with RCC/UCC (Table 1). In addition, 13 of the concepts assessed in the 19-item LCQ were reported as among the most bothersome impacts by interview participants in Bali et al.¹⁴ Participants reported a few concepts that were not specifically included in the LCQ (i.e., vomiting or gagging, postnasal drip, fainting or feeling faint, incontinence). However, some of these concepts were commonly described as overlapping/not entirely distinct from concepts included in the LCQ or were concepts that were not salient to the broader (i.e., both male and female) population. Upon further discussion/probing, we found that study participants described vomiting and gagging as associated with mucus or postnasal drip. While the LCQ does not specifically include those items, it does include an item asking about phlegm (mucus), which limits the need for the more distal (vomiting/gagging) or potentially redundant (postnasal drip) items. Likewise, only 10% of the qualitative study participants reported fainting (or feeling faint), and incontinence primarily impacts women.²⁴ Overall, interview participants in the prior study by Bali et al.¹⁴ consistently described the salience of RCC/UCC concepts that are assessed in the LCQ and the significance of these impacts on their lives.

Table 1. LCQ concept mapping across all study inputs.

LCQ Concept	Past RCC/UCC concept elicitation (Bali <i>et al.</i> ¹⁴) (N=30)	Clinical expert	Current qualitative interviews (N=20)
Stigma (others think something is wrong)	✓, MB	✓, MB	20 (S=18), MB
Job/daily task interference	✓, MB	✓, MB	20 (S=16) MB
Lack of control	✓, MB	✓, MB	20 (S=15), MB
Frustrated/fed up	✓	✓	20 (S=13), MB
Interrupt conversations/phone calls	✓	✓	20 (S=11), MB
Coughing bout frequency	✓, MB	✓	20 (S=8), MB
Anxious	✓, MB	✓	19 (S=9), MB
Annoyed partner, family, or friends	✓, MB	✓, MB	19 (S=15), MB
Interfered with life enjoyment	✓, MB	✓, MB	19 (S=8), MB
Embarrassed	✓, MB	✓	19 (S=12) MB
Tired/lack of energy	✓	✓	18 (S=13)
Chest, stomach, rib pain	✓, MB	-	18 (S=8)
Pain or fumes	✓	✓	18 (S=6)
Phlegm	✓, MB	-	17 (S=12), MB
May indicate serious illness	✓	✓	17 (S=5)
Hoarse voice	✓	✓	16 (S=4), MB
Sleep disruption	✓, MB	✓, MB	14 (S=6)

During the current qualitative interviews, the following coughing impacts were spontaneously reported by one participant each: nosebleed, fainting, broken blood vessels in face, straining of back muscles, interruption of intimacy, headaches, eye pain, and physical activity. Also, the clinical expert indicated that chest discomfort was among the most bothersome aspects of cough. They distinguished chest pain from discomfort.

All 19 LCQ items are represented here, but the following concepts have been grouped: frustrated/fed up (LCQ items 12 and 13) and tired/lack of energy (LCQ items 3 and 15). Check mark (✓)=reported symptom/impact.

LCQ, Leicester Cough Questionnaire; MB, most bothersome; RCC, refractory chronic cough; S, spontaneous report; UCC, unexplained chronic cough.

Clinical expert review

The clinical expert reported that 17 of the 19 concepts included in the LCQ were relevant to patients with RCC/UCC (Table 1). The two concepts not regarded to be quite as salient were chest pain (LCQ item 1) and phlegm (LCQ item 2). When describing why these concepts were potentially less important to the RCC/UCC patient population, the clinical expert noted that patients more commonly described chest “discomfort” instead of pain and that the coughs associated with RCC/UCC tended to be dry,

unproductive coughs. The expert further noted that although the cough itself was dry, some patients do describe a feeling *as if* phlegm were involved in or a contributing factor to their cough.

The clinical expert described all other concepts assessed in the LCQ as relevant to the RCC/UCC patient population. Furthermore, the expert indicated that the LCQ was the most comprehensive instrument available to assess the impact of cough for patients with RCC/UCC. When asked if any important concepts were missing, the expert

Table 2. Interview participant characteristics reported at screening.

Characteristic	Total (N=20)
Sex, <i>n</i>	
Male	1
Female	19
Age, mean (range), years	65.9 (44–76)
Duration of symptoms, mean (range), years	13.6 (2–40)
Time since diagnosis, mean (range)	3.3 years (1 < month–30 years)
Cough severity (1–10), mean (range) ^a	7.4 (5–10)
RCC	
UCC	10
Race/ethnicity, <i>n</i>	
White	20
Education, <i>n</i>	
High school	3
College degree	13
Advanced degree	4

^aIn the past 7 days, participants rated how bad their cough was on a scale from 0 to 10, where 0=No cough and 10=Extremely bad cough.
RCC, refractory chronic cough; UCC, unexplained chronic cough.

noted urinary incontinence as an important concept missing from the LCQ; the expert described urinary incontinence as primarily impacting female patients.

Qualitative interviews

Participant characteristics. A total of 20 interviews (evenly divided across RCC (*n*=10) and UCC (*n*=10) subgroups) were conducted. The sample was primarily female (*n*=19), with one male participant. Participants’ average duration of symptoms was 13.6 years (range, 2–40 years). Table 2 summarizes participant demographics and clinical characteristics provided via self-report at screening. No patients refused to participate after enrollment and interview scheduling.

Experiences with cough. When asked to describe their experiences with chronic cough, participants

generally described a lengthy journey to seek treatment for and understanding of their unremitting cough (Figure 1 and Table S-2, Supplemental Material). Factors contributing to this lengthy and often distressing journey centered on the participants’ inability to find healthcare providers who understood their diagnosis and how to potentially treat their cough, as well as the toll their cough took on their (and their families’) lives:

Yeah, I’ve been on such a long journey and it’s almost like everyone just wants to kind of give you a Band-Aid and move on. But when it keeps coming back it’s just frustrating because it’s not like you have a certain condition and they know exactly how to treat it and then therefore it all gets better. It just keeps coming back repeatedly and they just keep throwing the kitchen sink at it every time. [Participant 3, RCC]

When asked to describe their cough, participants generally described a frequently occurring (i.e., daily) cough commonly associated with a tickly sensation that could occur in short or prolonged bouts. Participants generally noted that the duration and force of their cough made one coughing experience/bout more intense or severe than another. As such, prolonged bouts of coughing were reported to be more severe and were often associated with physical, social, and emotional impacts.

Well, it never stops, but during the day or some days are worse than other days, but no, it doesn’t stop. There isn’t . . . I cannot remember a day that I have not coughed. [Participant 10, RCC]

With a bad and lengthy coughing fit, I feel exhausted. The ones that they’re just very tiring. And there’s the pain and then the exertion and the lack of even breathing. It just takes a toll on my body and mentally as well. [Participant 14, RCC]

Despite trying multiple mitigation strategies (such as sucking on lozenges and sipping water), most participants described a complete lack of control over at least some of their coughing experiences.

Again, I think for me it impacts you emotionally because you feel like I do . . . I try to do everything right. You feel, why? How is this not getting better? How am I not finding a way to control it? [Participant asked rhetorically] [Participant 11, UCC]



Experiences of Cough

“It has had an impact on my life. And it’s just concerning, and I’ve tried everything. There was never really a lot of doctors that diagnose or even know about...they just say, oh get allergies tested, or do you have some sort of upper respiratory thing? Which I knew it never was. So, anyway it wasn’t...it was not great when I started coughing.”

[Participant 11, UCC]

“It is a dry cough, and like a tickly cough in the back of the throat.”

[Participant 3, RCC]

“When it’s at its worst, it’s very severe. I mean, **it’s debilitating.**”

[Participant 19, UCC]

“If it’s one of those times when I feel like I’m trying to get something up, I’ve thrown up from it so it’s pretty severe. I’ve coughed so hard; I’ve broken blood vessels in my face. **It’s pretty bad.**”

[Participant 3, RCC]

“Sometimes, I’ll have a long cough where I’m trying to, I guess, cough stuff up and that can go on for a good 5, 10 minutes. Then I just have the regular little, tiny couple of seconds’ coughs.”

[Participant 2, UCC]

“That’s right. And I used to take a cough drop when it started, and it seemed to help a little bit. [...] The cough drops or cough syrup, nothing helps now. **Nothing helps at all.** Sip of water. People always say, here, have some water. You want a cough drop? And it just doesn’t make any difference.”

[Participant 15, UCC]

Figure 1. Experiences of Cough Reported During Concept Elicitation, Representative Quotes. RCC, refractory chronic cough; UCC, unexplained chronic cough.

Impacts of cough. Participants spontaneously reported many ways in which their lives had been negatively impacted by their often-uncontrollable cough (Table 3 and Table S-2, Supplemental Material). Specifically, 21 impacts were spontaneously reported by ≥ 2 participants. The most frequently reported impacts were those that had a psychological or social component to them, such as stigma (i.e., other people thinking something is wrong; $n=18$); interference with job and daily tasks ($n=16$); lack of control over the cough ($n=15$); and annoying their partner, family, or friends ($n=15$):

Well, if I’m coughing at the grocery store or something, I go to the . . . an aisle where no one is or something. Or I’ve been known to leave a store and go back out to my car, just so I don’t worry people. My gosh, this person is either very ill or having some sort of attack. You just want to get away at that point in time. [Participant 1, UCC]

My husband has a home office. I can’t be in the same room when he’s doing business because my incessant cough drives him crazy. Yes. My son was living with us, and it was irritating to him as well. He

moved out. I don’t know if that was the reason or not. [Participant 20, RCC]

Of the spontaneously reported impacts of chronic cough, 11 had physical components, including feeling tired/lack energy ($n=13$), phlegm ($n=12$), and coughing bouts ($n=8$):

It’s constant. It doesn’t stop. As far as for more than like maybe 20 minutes, I don’t have a cough. It’s just all day long. [Participant 2, UCC]

When asked to identify the most bothersome aspect of their cough, participants most often described impacts that influenced their desire to participate in social or public events, reporting aspects like embarrassment ($n=10$) or stigma ($n=10$; Figure 2). Other impacts reported by ≥ 2 participants included interrupted daily tasks/work ($n=5$), annoyed partner/family/friends ($n=4$), anxiety or worry ($n=3$), lack of cough control ($n=2$), interrupted conversations/phone calls ($n=2$), and being frustrated/fed up ($n=2$):

When I’m with other people it bothers me most. I can be at a meeting and start coughing, sitting down

Table 3. Summary of RCC/UCC Impacts Spontaneously Reported (≥ 2) During Current Concept Elicitation Interviews.

Impact/concept	Total spontaneous report (N=20)
Stigma (others think something is wrong)	18
Job/daily task interference	16
Lack of control	15
Annoyed partner, family, or friends	15
Frustrated/fed up	13
Tired/lack energy	13
Embarrassed	12
Phlegm	12
Interrupt conversations/phone calls	11
Vomit/reflux	10
Anxiety/worry	9
Nasal drip, sneezing, throat clearing	9
Coughing bout frequency	8
Chest, stomach, rib pain	8
Dyspnea	8
Throat pain/irritation	8
Interfered with life enjoyment	8
Sleep disruption	6
Urinary incontinence	5
May indicate serious illness	5
Hoarse voice	4

The following coughing impacts were spontaneously reported by one participant each: nosebleed, fainting, broken blood vessels in face, straining of back muscles, interruption of intimacy, headaches, eye pain, and physical activity.
RCC, refractory chronic cough; UCC, unexplained chronic cough.

to dinner, and wanting to have a conversation and I start coughing . . . it's a bother but I'm used to it, but when I'm with other people it bothers me most. I often have to get up and leave the meeting, if I don't have water, it interrupts the meeting, and my ability to follow what's going on in the meeting. It bothers my husband. He will stop talking. 'I can hear even if I'm coughing.' He looks at me like 'ok.' [Participant 4, RCC]

After describing the impacts associated with their cough, participants were asked what aspects of their chronic cough they would most want to see change with an effective treatment. The responses were highly consistent in that all participants wanted their cough to stop completely (Figure 3). Furthermore, all participants indicated that any reduction in the frequency and/or intensity of cough would constitute a meaningful improvement and limit the significant impacts associated with frequent, uncontrollable coughing (i.e., physical, psychological, and social impacts):

Well, ideally you would like it to stop completely, but to just have much less of a cough and the severity of it would be helpful. Just not to be coughing all the time and worry about going somewhere and coughing. [Participant 9, RCC]

Well, that I didn't cough anymore. I would appreciate or be very happy with that. Hopefully, I would be maybe more verbal. That I would feel comfortable speaking at church, in front of a group . . . to be able to just talk and enjoy being with other people. And just not, always wondering when and if I'm going to start coughing. [Participant 4, RCC]

Concept saturation. A total of 21 potential impacts associated with chronic cough were reported spontaneously (by ≥ 2 interview participants) across the 20 interviews (Table S-3, Supplemental Material). A total of 20 concepts were spontaneously reported during the first set of 10 interviews, while only 1 impact (worried cough may indicate serious illness) was spontaneously reported in the second set of 10 interviews. Of note, 8 impacts of cough not covered by the LCQ were reported only once each across the 20 interviews, but these were commonly described as being distal to severe coughing bouts. Coughing bout frequency is covered by the LCQ and was captured as a separate concept. Overall, data from the concept elicitation component of the interviews were highly consistent, and concept saturation was achieved with respect to the impacts associated with chronic cough.

Cognitive debriefing

LCQ instructions, response options, and recall period. All 20 interview participants described the LCQ instructions as clear and easy to understand. When asked to describe in their own words



Figure 2. Most Bothersome Impacts of Cough Reported by ≥ 2 Participants During Concept Elicitation Participants commonly reported more than 1 most bothersome aspect. Most bothersome aspects, each reported by a single participant ($n = 1$), included phlegm, coughing bout frequency, unspecified physical pain, interfered with life enjoyment, hoarse voice, urinary incontinence, coughing severity, and physical activity. RCC, refractory chronic cough; UCC, unexplained chronic cough.

what the instructions were asking them to do, participants generally indicated that they were able to think about their cough and select a response

option that reflected their experience (Figure 4). No changes to the instructions were suggested or recommended by the participants.



Treatment Benefit

"I think **any decrease in my coughing would be wonderful** as far as I'm concerned. Well, because basically I wouldn't cough as much. You know you're watching television and all of the sudden you start coughing, you can't hear what's being said. You know you're at the dinner table and you start coughing, and so, you know it's disruptive to the meal. So, any change would be welcome."

[Participant 7, UCC]

"I'd like to see the frequency go down and the intensity of the cough diminished. If it's a chronic cough, it's not going to go away completely, but **if there's a way to control the symptoms or diminish them somewhat, that would be really good.**"

[Participant 14, UCC]

"I just think that **it would feel like life was more normal again** like most people that don't cough."

[Participant 11, UCC]

"Well, I would feel like I have a lot more control. And I think **I would take something as soon as I could.** I don't have much warning."

[Participant 15, UCC]

"I don't know what I'd like to see change. The drip, the incontinence, and just the cough itself. I mean, we all cough with irritants and whatever else, but the frequency, **I would like to see the frequency of the coughing diminished drastically.**"

[Participant 5, UCC]

Figure 3. Treatment Benefits Reported During Concept Elicitation, Representative Quotes RCC, refractory chronic cough; UCC, unexplained chronic cough.

They're clear. Easy to understand. [Participant 14, RCC]

harder. But 2 weeks is pretty easy to remember back on. [Participant 2, UCC]

All participants were able to select a response to each of the LCQ items, using the 7-point Likert response scales, and participants generally indicated that selecting a response was relatively easy. Participants also indicated that the response options across all scales were relatively distinct and that they could describe the difference between response choices:

It was not hard. No, it was not hard, because I do get tired. I was just kind of going between 'a lot of the time' or 'some of the time,' but really it is 'a lot of the time' I end up tired. [Item 3, Participant 15, UCC]

All interview participants reported that it was relatively easy to recall the past 2 weeks when responding to the items and noted that the 2-week recall period was appropriate:

Oh, it's easy. Two weeks is super easy . . . if you ask me 3 months ago or 3 . . . that would have been a lot

LCQ Item-specific responses. For each LCQ item, the number of participants spontaneously reporting a concept and those who endorsed the concept when probed are presented in Figure 5. LCQ item-specific responses from participants with RCC/UCC are summarized in Figure 6 and Table S-4 (Supplemental Material).

Seven LCQ concepts were endorsed by all 20 participants. These concepts included lack of control, job/daily task interference, coughing bout frequency, frustrated, fed up, stigma, and interrupted conversations (corresponding to LCQ items 4, 7, 11, 12, 13, 17, and 18, respectively) and covered each of the 3 LCQ domains (Physical, Psychological, and Social/Emotional; Figure 6):

It [coughing bout] just means another episode of embarrassment, discomfort. Fear, a little bit of fear. Just episodes of coughing that are serious. I hardly ever just cough to clear my throat. That happens rarely. [Participant 15, UCC, Item 11]

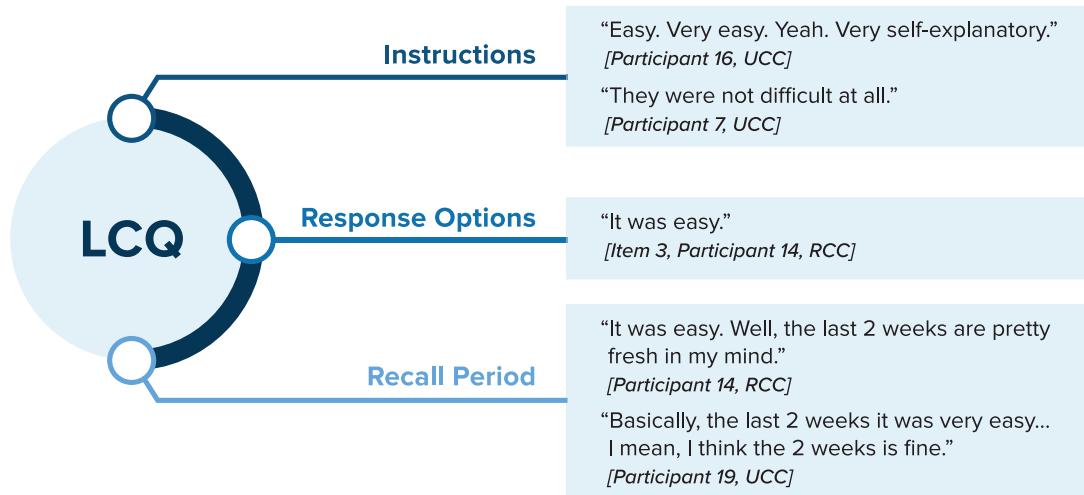


Figure 4. Representative Quotes Reported During Cognitive Debriefing of the LCQ Instructions, Response Options, and Recall Period LCQ, Leicester Cough Questionnaire; RCC, refractory chronic cough; UCC, unexplained chronic cough.

A little of the time. For instance, when I’m in church and I’m coughing or I’m clearing my throat, I’m afraid that somebody else thinks that I’ve got COVID or something like that. [Participant 20, RCC, Item 17]

Interfere with your job, like maybe you have to pause if you’re in a meeting and you were talking and you start coughing. Or even if you go to the grocery store and you’re about to go into the checkout, you don’t want to go up there coughing. So, you wait, go down another aisle, try to hide yourself then go back. [Participant 11, UCC, Item 7]

Most participants reported they could easily understand and answer each item of the LCQ. Although a few participants indicated that some questions were more difficult to respond to than others, all participants were able to select a response they felt was accurate to describe their chronic cough for each of the LCQ items. Eighteen of the 19 concepts included in the LCQ were endorsed by at least 80% of participants ($n \geq 16$). The remaining concept, “sleep disruption,” was endorsed by 70% of participants ($n = 14$). When probed, those participants who did not experience a specific impact generally indicated that the concept was indeed relevant to assess in a questionnaire that evaluates the impact of chronic cough.

Overall, participants described the LCQ as easy to understand and as a comprehensive assessment of the relevant impacts of chronic cough (Figure

7(a)). When asked whether any important chronic cough impacts were missing from the LCQ, 17 participants indicated that the measure was completely comprehensive (all important impacts were included) (Figure 7(b)). When probed, three participants reported an impact as potentially missing from the LCQ: urinary incontinence ($n = 1$), sneezing ($n = 1$), or other bodily impact ($n = 1$):

It was good. It was easy. It definitely covered all the things that constant coughing is, basically. It covers everything that . . . I can’t even think of anything else that you could add because it just covers everything. [Participant 2, UCC]

Discussion

The LCQ is a rigorously developed HRQOL measure designed to assess the physical, psychological, and social impacts of chronic cough via self-report in adults with clinically diagnosed chronic cough. This robust evaluation of the content validity of the LCQ in adult patients with RCC/UCC was consistent with 2009²⁰ and 2022²¹ FDA guidance for patient-focused drug development. Concepts reported across the concept mapping, clinical expert review, and qualitative interview study components were represented in the 19 concepts included in the LCQ. Also, interview responses during concept elicitation and cognitive debriefing were consistent across RCC/UCC patient populations. Overall, these results support that the LCQ assesses the chronic

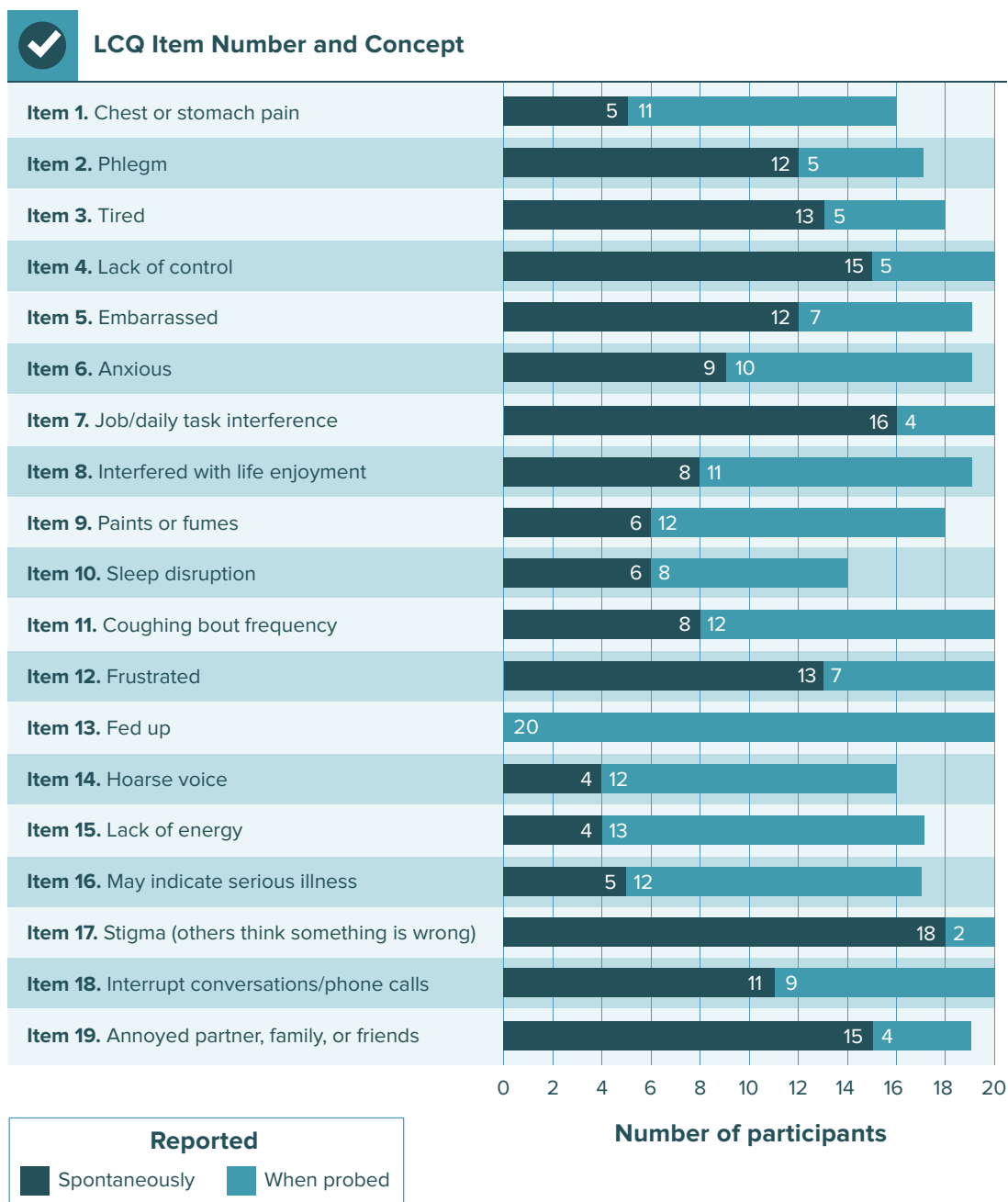


Figure 5. Number of Participants That Reported Experiencing Each LCQ Concept During Cognitive Debriefing. For each item, the number of participants spontaneously reporting the concept, as well as the number of participants who endorsed the concept (either in the past 2 weeks or ever) when probed/shown the LCQ item, is reported. LCQ, Leicester Cough Questionnaire.

cough impacts that are most often experienced by patients with RCC/UCC. Furthermore, the evidence presented here supports the content validity of the LCQ and its appropriateness for use in patients with RCC/UCC.

During concept elicitation, participants spontaneously reported 21 impacts associated with chronic cough that included impacts with a social or public component (e.g., stigma; interference with job and daily tasks; lack of control over the

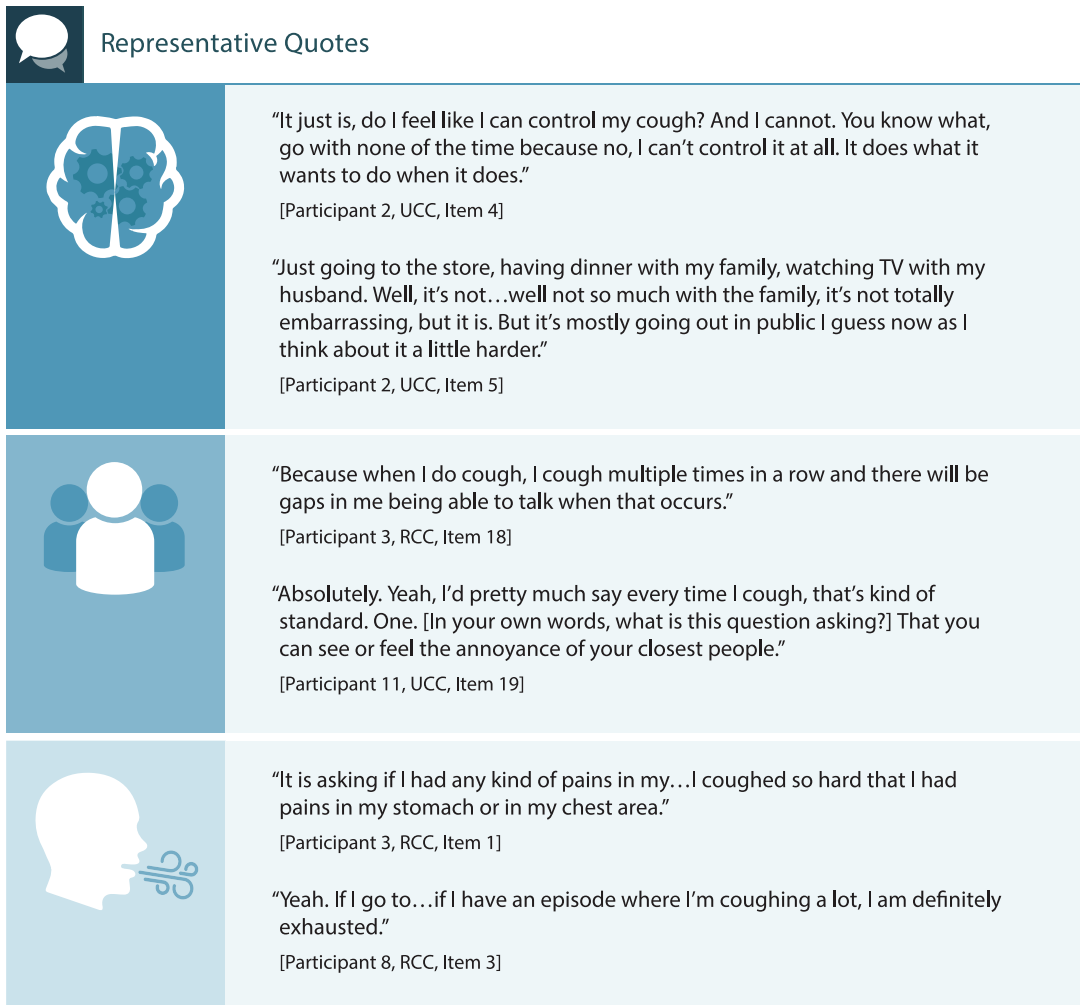


Figure 6. Representative Quotes Reported During Item-Specific Cognitive Debriefing of the LCQ LCQ, Leicester Cough Questionnaire; RCC, refractory chronic cough; UCC, unexplained chronic cough.

cough; annoying their partner, family, or friends). Similar impacts of chronic cough have been reported in other studies, highlighting the emerging importance of assessing these psychological/social impacts in PRO measures like the LCQ.^{10,11} The psychological and social impacts of cough often occur alongside the physical impacts of chronic cough.^{3,10} During the concept elicitation phase, over half of spontaneously reported concepts (11 of 21 concepts) had physical components (e.g., feeling tired/lack energy; coughing bouts). Most of the reported physical concepts are included in the LCQ, are widely relevant to the experiences of chronic cough, and are important to consider in the development of new therapies for patients with RCC/UCC.^{10,11}

Because many participants in this study described a lengthy and often distressing journey when seeking clinical treatment for their chronic cough, and because patients with RCC/UCC often experience delays in diagnosis and limited effectiveness of medications,¹¹ a better understanding of patients' lived experiences with chronic cough may help guide the development of relevant therapeutic strategies for these patients. While most interview participants in the current study and in Bali *et al.*¹⁴ prioritized improvements in physical impacts (e.g., reduced cough frequency) over psychological and social impacts, the aspects of cough reported to be the "most bothersome" often included psychological and social impacts (e.g., embarrassment or stigma, interrupts daily

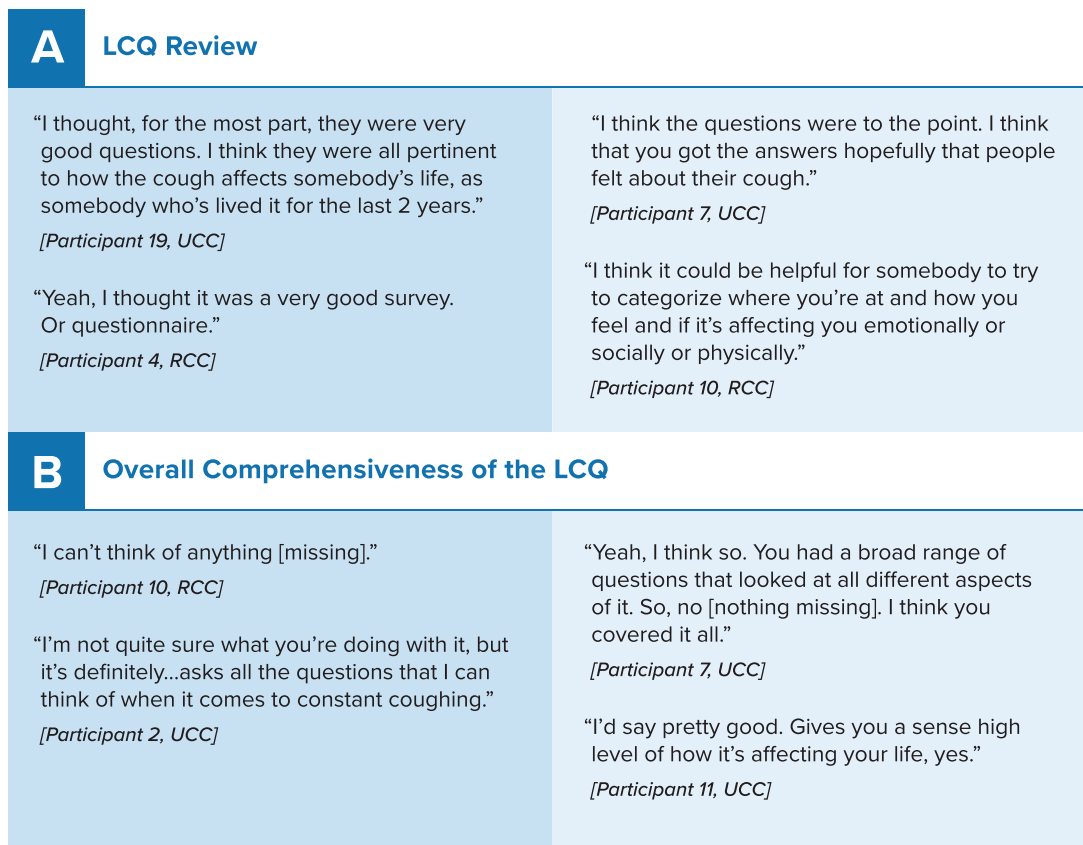


Figure 7. Representative Quotes Reported (A) During Cognitive Debriefing of the LCQ or (B) When Asked About the Overall Comprehensiveness of the LCQ. LCQ, Leicester Cough Questionnaire; RCC, refractory chronic cough; UCC, unexplained chronic cough.

tasks/work). Also, all participants reported that a reduction in cough frequency would subsequently reduce the impacts of frequent, uncontrollable coughing, including psychological and social impacts. Overall, these data support the notion that, to evaluate the impacts of RCC/UCC in a meaningful way, measures should assess physical, psychological, and social impacts (all of which are included in the LCQ).

While most chronic cough impacts reported by participants during concept elicitation were included in the LCQ, five spontaneously reported impacts were not directly assessed in the LCQ (i.e., vomit/reflux, nasal drip/sneezing/throat clearing, dyspnea, throat pain/irritation, and urinary incontinence). However, only two of these five concepts (sneezing ($n = 1$) and urinary incontinence ($n = 1$)) were reported as potentially missing from the LCQ. Also, most of these impacts (vomit/reflux, nasal drip/sneezing/throat clearing, dyspnea, and throat pain/irritation) were described

as conceptually redundant or distal to concepts assessed in the LCQ (phlegm (mucus), coughing bouts, or hoarse voice). Lastly, although most chronic cough patients are female²⁵ and urinary incontinence is an important impact of cough in women,^{24,25} the addition of an item specific to the impact of cough on urinary incontinence would not be appropriate for a measure intended for use in a broader population that includes both male and female participants. Overall, findings from the concept elicitation component of the interviews were highly consistent across the sample, and concept saturation was reached.

Participants confirmed during cognitive debriefing that the LCQ was generally easy to understand, and all participants were able to select a response they felt was accurate to describe their chronic cough. Similarly, all participants reported that the 2-week recall was reasonable and appropriate. During LCQ item-specific responses, participants endorsed each of the 19 LCQ items.

Participants who did not experience a specific impact, when probed, generally indicated that the concept was relevant to assess in a questionnaire that evaluates the impacts of chronic cough. When asked to provide their overall thoughts regarding the LCQ, all participants indicated that the measure was appropriate and that it assessed the impacts most salient to their experiences with chronic cough. Nearly all ($n=17$) interview participants reported that the LCQ was a comprehensive assessment of their chronic cough impacts, with only three participants each identifying a single symptom as potentially missing from the LCQ.

Several valid and reliable PRO instruments are available to assess the impact of cough on HRQOL,^{18,26} including measures for children (the Parent Cough-Specific Quality of Life questionnaire (PC-QLQ)²⁷) and adolescents/adults (the LCQ^{6,26} and Cough-Specific Quality of Life Questionnaire (CQLQ)²⁸). The LCQ is a 19-item questionnaire with 3 health domains (Psychological, Social, and Physical) scored on 7-point response scales, while the CQLQ is a 28-item questionnaire with 6 domains (Social Psychology, Emotional State, Personal Safety Fears, Somatic Symptoms, Extreme Somatic Symptoms, and Functional Ability) scored on 4-point response scales.²⁹ The LCQ and CQLQ are both widely used in research and clinical trials to assess the outcomes of chronic cough.^{6,18,26,28} The LCQ has been available for more than 20 years, and our findings now support its direct use for patients with RCC/UCC, adding to its relevance as a cough-specific PRO.^{6,17}

One limitation of this study is that participant recruitment occurred across two clinical sites and was limited to patients in the US who had chronic cough for ≥ 1 year. While participants included only those with a clinical diagnosis of RCC/UCC, the results of this study may not be generalizable to all patients with chronic cough. Additionally, our study only included one male participant; however, several studies report chronic cough affects mostly females.^{2,25} The results of qualitative interviews are based on self-reported data, which may be subject to recollection bias or the participants' temptation to provide socially fulfilling responses. However, concept saturation was reached,^{30,31} which indicates the findings reported here on impacts are representative of patients

with RCC/UCC and support the comprehensive nature of the LCQ.

Conclusion

The LCQ is a rigorously developed measure designed to assess the impact of chronic cough on patients with a clinical diagnosis of chronic cough, including patients with RCC/UCC. An extensive evaluation of the content validity of the LCQ in adults with RCC/UCC supports that it is fit for the purpose of assessing the impact of cough. Furthermore, these findings support the LCQ's ability to (1) assess the chronic cough impacts most commonly experienced by participants with RCC/UCC and (2) represent impacts participants most commonly want to see improved.

Declarations

Ethics approval and consent to participate

The RTI International Institutional Review Board (IRB) (Federal-Wide Assurance #3331) reviewed the study procedures prior to participant recruitment and determined them to be exempt. To reduce participant and recruitment site burden (and due to the very low risk involved with this study, as determined by IRB review), verbal consent was obtained prior to each interview being conducted. Specifically, each potential interview began with a detailed informed consent discussion, and at the end of the discussion, the potential interview participant was asked if they had any questions and then to confirm their desire to participate (including their permission to have the interview audio recorded and transcribed); consent was documented by study staff via audio recording.

Consent for publication

Not applicable.

Author contributions

Allison Martin Nguyen: Conceptualization; Formal analysis; Methodology; Writing – review & editing.

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Alexandra Cornell: Conceptualization; Writing – review & editing.

Mandel Sher: Investigation; Writing – review & editing.

Jonathan Bernstein: Conceptualization; Writing – review & editing.

Surinder S. Birring: Conceptualization; Methodology; Writing – review & editing.

Carla (DeMuro) Romano: Funding acquisition; Investigation; Methodology; Supervision; Writing – review & editing.

Margaret Mayorga: Data curation; Formal analysis; Project administration; Writing – review & editing.

Mirline Milien: Data curation; Formal analysis; Project administration; Writing – review & editing.

Claire Ervin: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Writing – review & editing.

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Competing interests

A.M. Nguyen, C. La Rosa, and A.G. Cornell are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and hold shares and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. M.R. Sher is a Clinical

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Availability of data and materials

Data are primarily in the form of transcripts and cannot be made available in order to protect participant privacy in accordance with the principles of the Belmont Report.

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Supplemental material

Supplemental material for this article is available online.

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