Applied Health Economics and Health Policy (2023) 21:119–130
https://doi.org/10.1007/s40258-022-00770-9

ORIGINAL RESEARCH ARTICLE

Determining What Represents Value in the Treatment of Refractory or Unexplained Chronic Cough from the Perspective of Key Stakeholders in Spain Using Multi-Criteria Decision Analysis

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Accepted: 9 October 2022 / Published online: 2 November 2022

Abstract

Background and Objective Chronic cough is defined as cough lasting for more than 8 weeks. It can be described as refractory when persisting despite thorough clinical assessment and treatment of any cough-related underlying condition, or unexplained when no underlying cough-related condition can be identified. Refractory or unexplained chronic cough (RCC|UCC) greatly affects patient health-related quality of life (HRQoL). Although around 10% of the population suffer from chronic cough (with 40–60% of these patients suffering from RCC|UCC), there is limited information available in the literature about the condition and the assessment of treatment success. This study aimed to determine what represents value in the treatment of RCC|UCC from the perspective of key stakeholders in Spain using Multi-Criteria Decision Analysis (MCDA) methodology.

Methods A literature review was conducted to adapt the MCDA framework to the specific context of RCC|UCC. A total of 24 participants were involved, representing three key stakeholder groups (7 patients, 9 physicians and 8 hospital pharmacists). The study was structured in two phases. In Phase 1, participants validated the adapted MCDA framework and assigned relative weights (100-point allocation) to the framework's value criteria/sub-criteria during three individual stakeholder meetings, one per each stakeholder group. In Phase 2, participants were brought together in a multi-stakeholder meeting to review findings of each stakeholder group, after which stakeholders repeated the weighting exercise as a collective group. All meetings included reflective discussion by participants of each value criteria/sub-criteria included within the adapted MCDA framework, where stakeholders shared their perspectives and opinions on what represents value in RCC|UCC.

Results Refractory or unexplained chronic cough is regarded as a chronic medical condition, with variable severity across patients and the potential to heavily impact their HRQoL (including physical, psychological and social/work productivity domains). Current treatments used by healthcare professionals, which have not been specifically developed and are not approved for RCC|UCC, show limited clinical effectiveness and associated safety and tolerability issues, which result in frequent treatment discontinuations. The reduction of the average cough frequency over a 24-h period is regarded as the primary goal of treatment by stakeholders, with the aim of improving HRQoL. Improvement of other cough symptoms, such as intensity, is also considered important. Minor adverse events and a slower onset of treatment effect would be acceptable to stakeholders if accompanied by strong efficacy and improvement in HRQoL. Given the inability to measure cough frequency in clinical practice, Patient-Reported Outcomes (PROs) could be considered a proxy of treatment effectiveness. A multidisciplinary approach to the condition is regarded as key for treatment success.

Conclusions Refractory or unexplained chronic cough is a medical condition that seriously impacts patients' HRQoL. The primary goal of treatment is to improve patients' HRQoL by reducing the frequency and intensity of cough.

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Key Points for Decision Makers

Refractory or unexplained chronic cough is a frequent, yet not well known, medical condition that can have serious impact in patients' HRQoL.

Any reduction in the symptoms of cough needs to be strongly correlated with improvements in HRQoL to be considered clinically meaningful and patient-relevant.

Minor adverse events and a slower onset of treatment effect would be acceptable if accompanied by strong efficacy and improvement in HRQoL.

1 Background

Excessive and protracted cough is a common and disabling complaint, with recent guidelines defining a cough that persists longer than 8 weeks as chronic cough [1–3]. Chronic cough has the potential to significantly affect patient's health-related quality of life (HRQoL), including physical symptoms such as incontinence, cough syncope and dysphonia, leading to social isolation, depression, difficulties in personal relationships and negative impact on work productivity [1, 4].

Chronic cough can affect up to 10% of the general population [5]. In approximately 40%–60% of these patients, cough could remain unresolved despite thorough investigation and treatment [6–9]. Refractory Chronic Cough (RCC) persists despite optimal treatment of any underlying cough-related condition (e.g., Asthma, Gastroesophageal Reflux Disease [GERD], or Upper Airway Cough Syndrome [UACS]) [1, 2, 10, 11]. Unexplained Chronic Cough (UCC) is a cough without an identifiable, underlying cough-related condition [2, 10]. Together, RCC|UCC is described as a clinical entity in itself, whose pathological features and accompanying symptomatology deviate beyond the protective physiological role of cough [6, 8, 10].

The aetiology of RCC|UCC is not yet clear, although most recent research and expert opinion point to a hypersensitivity of airway sensory nerves as the common feature behind different chronic cough phenotypes [12–15]. Refractory or Unexplained Chronic Cough can be heterogeneous clinically, possibly requiring clinical investigation by different medical specialties including allergy, otolaryngology, gastroenterology and pulmonology [3, 16].

Current RCC|UCC management is described in the latest guidelines and recommendations from international bodies [1, 2]. In Spain, there is a protocol for chronic cough management available, including a section with recommendations for RCC|UCC [3]. Currently, there is no treatment approved for RCC|UCC. The latest recommendations include the trial of agents targeting cough hypersensitivity, such as low-dose morphine, pregabalin or gabapentin. However, these treatments are used off-label, since they have not been specifically developed and are not approved for chronic cough [1]. Innovative treatment alternatives, which target the nociceptors responsible for the irritant sensation that precedes cough, are currently under development [1, 16]. Among these treatments, the most promising results to date have been shown by the P2X3 antagonists [6].

Multi-Criteria decision analysis (MCDA) methodology allows the determination of what represents value in a given medical condition, considering criteria that are relevant to inform healthcare decision making in a transparent and systematic manner [17–19]. Multi-Criteria decision analysis enables collaboration through a reflective dialogue among stakeholders to better understand individual perspectives and thereby further guide decision making [17, 20, 21]. With innovative treatment options for patients with RCC|UCC currently under development, it becomes important to determine, understand and reflect on the perceptions and expectations of treatment effect by patients, physicians and hospital pharmacists. The aim of this study was to determine what represents value in RCC|UCC from the perspective of these three stakeholder groups in Spain using MCDA methodology.

2 Methods

2.1 Study Design

The study was designed following good practice recommendations for MCDA methodology [22, 23], namely, literature review, MCDA framework adaptation (including definition of criteria and sub-criteria), criteria/sub-criteria weighting (100-point allocation) and discussion of results. The Evidence and Value: Impact on Decision Making (EVIDEM) MCDA framework validated for the Spanish healthcare context was used as the starting point for this study [20, 24, 25].

2.2 Literature Review

A literature review was performed to obtain relevant information about RCC|UCC and its current management in Spain. Search terms were based on the EVIDEM MCDA framework, and no time span limit was applied. The search strategy can be reviewed in Supplementary Material 1. Original articles focused on clinical practice and research containing relevant information to describe value in RCC|CC were included. Articles were excluded if they were duplicated, written in a language other than Spanish or English or related to animal studies. The search was performed in July 2020 using the following three biomedical databases: MEDLINE [26], Cochrane [27] and MEDES [28]. Grey literature sources, such

as Google Scholar or the websites of relevant scientific societies and patient organisations were used to complement the search. The search resulted in 26 publications, after screening a total of 252 publications by title and abstract.

2.3 MCDA Framework Adapted for RCC|UCC

The EVIDEM MCDA framework was specifically adapted to RCC|UCC based on literature review results [29]. Criteria definitions were adapted to reflect the specific characteristics of RCC|UCC, while sub-criteria relevant for the condition were included in each criterion. The framework adaptation was then complemented with data and information obtained through nine initial individual telephone interviews with key stakeholders (2 patients, 4 physicians and 3 hospital pharmacists). Through these interviews, criteria definitions were completed and additional sub-criteria relevant for RCC|UCC from the perspective of stakeholders were identified. The resulting MCDA framework specifically adapted for RCC|UCC included 12 quantitative and 4 contextual criteria as shown in Fig. 1A. Value sub-criteria were defined for each of the criteria in the "comparative outcomes of the treatment" domain (comparative efficacy/effectiveness, safety/tolerability and Patient-Reported Outcomes [PROs]) as shown in Fig. 1B. Criteria/sub-criteria definitions can be reviewed in Supplementary Material 2.

2.4 Panel Participants and Development of the Study

Study participants were identified through the literature review and contacted via email. Participants were selected to represent all the relevant stakeholder profiles in RCC|UCC, including physicians, hospital pharmacists and patient representatives. Physicians represented the different medical specialties involved with the management of the condition (Allergy, Otolaryngology, Gastroenterology and Pulmonology), including key opinion leaders in Spain with published articles on RCC|UCC. Hospital pharmacists had significant experience in evaluating treatment options for respiratory diseases, including members of the working group for respiratory diseases of the Spanish Society of Hospital Pharmacy (SEFH). The Spanish Federation for patients with Allergic or Respiratory diseases (FENAER) helped identify and contact patients who experienced RCC|UCC for their inclusion in this study. The study was carried out remotely due to the COVID-19 pandemic and structured in two phases. All the meetings were performed online using the Zoom platform.

2.4.1 Phase 1: Single Profile Stakeholder Meetings

In the first phase, three separate meetings were held in October 2020 with each of the following stakeholder groups: patients ($n = 7$), physicians ($n = 9$) and hospital pharmacists ($n = 8$). Each of the homogeneous-profile stakeholder groups validated the MCDA framework adapted for RCC|UCC and performed a weighting of the criteria and sub-criteria included in the framework reflecting each group's interpretation of the relative importance of the included criteria. Patients, physicians and hospital pharmacists shared their perspectives and opinions regarding what represents value in RCC|UCC during the reflective discussion held during each of the single profile stakeholder meetings.

The weighting was performed using the 100-points allocation weighting method [30], where patients, physicians and hospital pharmacists had to distribute a total of 100 points among the criteria of the framework first, and then perform the same exercise among the sub-criteria in each of the criteria of comparative efficacy/effectiveness, safety/tolerability and PROs. The weighting exercise was completed individually by each participant.

2.4.2 Phase 2: Multi-Stakeholder Meeting

In a second phase, a selection of 15 participants from Phase 1 (5 participants from each of the stakeholder groups) participated in a multi-stakeholder meeting (held in November 2020). Participants for the Phase 2 were selected based on their degree of involvement and participation during the single profile stakeholder meetings. The total number of participants was smaller in Phase 2 to facilitate participation in group discussions and sharing of perspectives for each profile. The results obtained in the individual stakeholder meetings were presented and reflectively discussed as a group. Patients, physicians and hospital pharmacists were able to listen to what the other stakeholder profiles considered as representative of value in RCC|UCC and then discussed whether any of their initial perspectives had changed from those they had previously considered during the single profile stakeholder meetings. After the multi-stakeholder meeting, stakeholders were requested to repeat the weighting exercise to assess the consistency of results. The exercise was sent by email and participants completed it remotely.

2.5 Data Collection and Analysis

Participants completed the weighting exercise in each of the two phases of the project using an Excel spreadsheet specifically designed for this study, available in Supplementary Material 3. The spreadsheet allowed participants to distribute 100 points across each of the criteria and then subsequently across each of the sub-criteria. All respondents returned their completed weights via email, and these were then aggregated and analysed by two independent researchers (quantitative data results).

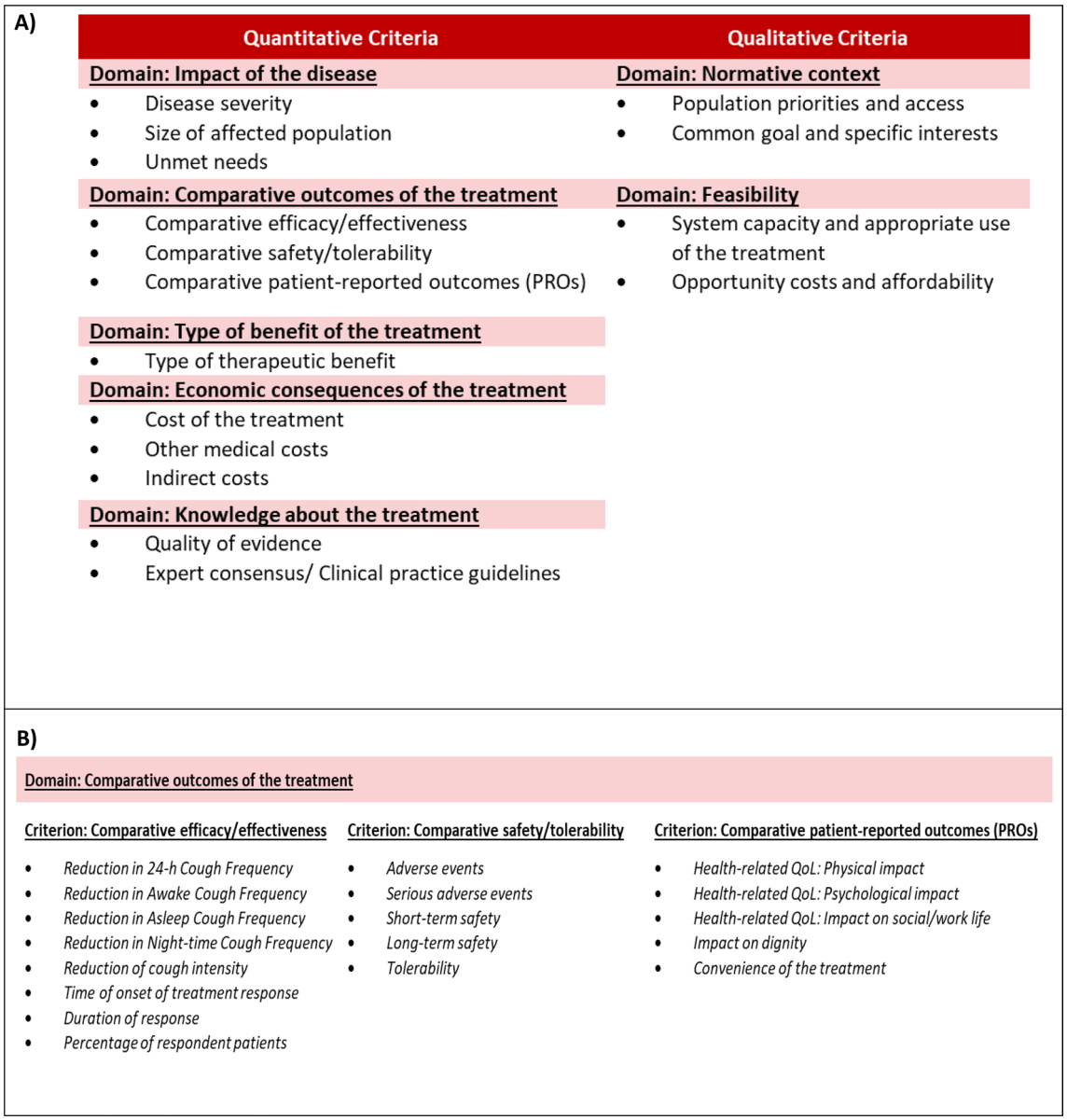

Fig. 1 Multi-Criteria decision analysis (MCDA) framework adapted for refractory or unexplained chronic cough (RCC|UCC). **A** Criteria in the MCDA framework adapted for RCC|UCC; **B** Sub-criteria included in each of the criteria of the Comparative outcomes of the treatment domain. *QoL* quality of life

Weighting results were calculated as the mean and standard deviation (SD) of the scores assigned by stakeholders and were then presented in the meetings of the two phases of the project. Stakeholders reflected and discussed the prioritisation of criteria and sub-criteria in the MCDA framework. Researchers compiled the deliberation from each stakeholders' perspectives on what represents value in RCC|UCC (qualitative data results) following published MCDA good methodological practices [17, 22, 23, 29].

To assess potential differences in the weighting results from stakeholders participating in Phases 1 and 2, a *t* test for paired samples was completed. The statistical analysis was performed using Microsoft Excel 2016 software.

3 Results

3.1 Single Profile Stakeholder Meetings

3.1.1 Patients

Results from the criteria weighting by patients based on points allocated are presented in Fig. 2A. The top three

most important criteria for patients were disease severity (mean ± SD: 14.7 ± 7.0 points), type of therapeutic benefit (12.9 ± 7.5) and unmet needs (10.0 ± 3.9), while criteria related to costs, including indirect costs (5.3 ± 2.8), other medical costs (5.1 ± 3.1) and cost of the treatment (4.4 ± 3.0) were considered the three least important. Patients stated that the severity of RCC|UCC sustained without resolution through the years greatly impacted on HRQoL. In their view, the benefit provided by a treatment is understood mainly as an improvement in HRQoL. Patients felt that if HRQoL was improved, treatment-related adverse events could be tolerated to a degree. Costs were considered secondary to the potential health benefit of treatment.

Patient sub-criteria weighting results based on points allocated are presented in Fig. 2B–D. The three most important sub-criteria were the reduction in 24-h cough frequency (18.7 ± 4.3 points), serious adverse events (25.0 ± 5.0) and HRQoL: Physical impact (26.4 ± 7.5), while the three least important sub-criteria were the percentage of respondent patients (8.6 ± 3.8), short-term safety (15.7 ± 4.5) and HRQoL: Impact on social/work life (16.4 ± 3.8). Patients agreed that a reduction in 24-h cough frequency (including cough during day- and sleep-time) represents the most desirable efficacy outcome, given some patients suffer more from cough-derived sleep disruption (e.g., GERD patients) while others are more affected in their daily activities (e.g., at work). All HRQoL domains (physical, psychological and social/work productivity) can be negatively impacted by RCC|UCC. Some patients may experience a stronger physical impact, with intense cough leading to, for example, urinary incontinence, rib fractures and cough syncope. However, other patients are more impacted at the psychological level: exhausted, depressed and frustrated for not achieving cough resolution after many years of failed treatment approaches. These aspects, in turn, can negatively affect the social domain of a patient's HRQoL as well as the patient's work productivity, with some patients needing even to stop working with negative financial implications for the patient and the family. The safety profile of a new treatment, including any potential tolerability issues, was perceived as secondary to reducing the frequency and intensity of cough and improving HRQoL.

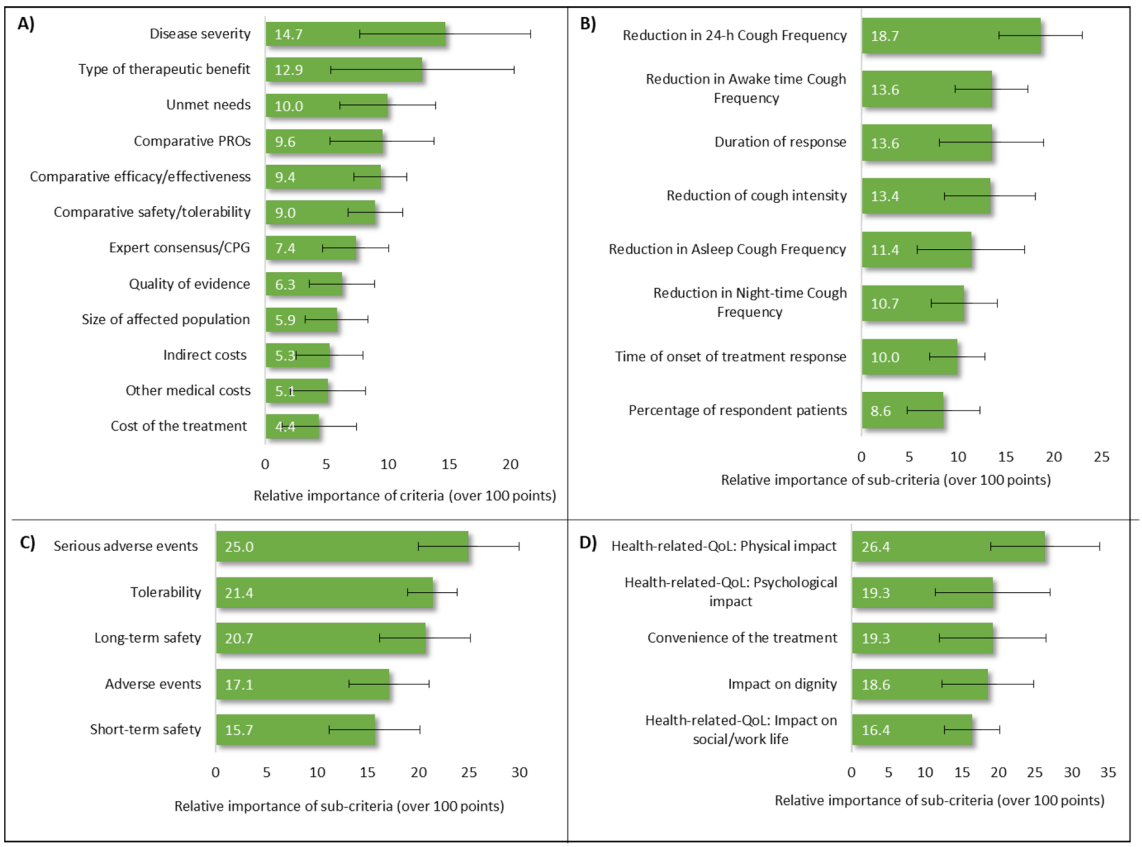

Fig. 2 Weighting results obtained by patients in the single profile stakeholder meeting. **A** Quantitative criteria weighting results; **B** Comparative efficacy/effectiveness sub-criteria weighting results; **C** Comparative safety/tolerability sub-criteria weighting results; **D** Comparative Patient-Reported Outcomes (PROs) sub-criteria weighting results. *CPG* clinical practice guidelines, *QoL* quality of life

3.1.2 Physicians

Results from the criteria weighting by physicians based on points allocated are presented in Fig. 3A. The top 3 most important criteria for physicians were disease severity (14.7 ± 5.0 points), comparative efficacy/effectiveness (13.3 ± 3.9) and safety/tolerability (11.0 ± 4.1). The 3 least important criteria were cost-related criteria, including cost of the treatment (4.6 ± 1.6), other medical costs (3.9 ± 1.2) and indirect costs (2.7 ± 2.1). Physicians discussed that RCC|UCC is a frequent clinical problem in their daily practice, which can severely impact patients' HRQoL. There is a need for an effective and safe treatment, since there are no treatments currently approved for RCC|UCC. Neuromodulators can temporarily improve cough symptoms in some cases but are known to lose effectiveness over a short period of time and can be associated with safety and tolerability issues resulting in frequent treatment discontinuations. Physicians consider the cost of the treatment relevant but secondary to other criteria when deciding to prescribe an available treatment.

Physician sub-criteria weighting results based on points allocated are presented in Fig. 3B–D. The three most important sub-criteria were the reduction in 24-h cough frequency (20.1 ± 5.5 points), serious adverse events (31.7 ± 10.6) and HRQoL: Psychological impact (27.2 ± 7.1), while the 3 least important sub-criteria were the time of onset of treatment response (5.7 ± 3.8), short-term safety (12.8 ± 5.1) and impact on dignity (13.6 ± 4.5). Physicians discussed that an effective treatment should reduce 24-h cough frequency, improving the disruption caused by cough on both the patient's sleep quality and their daily activities. Health-related quality of life of patients is affected almost equally physically and psychologically and any improvement of these aspects would be related with an improvement of patients' dignity. Physicians do not perform HRQoL questionnaires on RCC|UCC patients regularly in clinical practice. An improved safety profile compared to currently used neuromodulators would be considered valuable. The time to onset of treatment effect is not that relevant given the chronicity of the condition. Also, the occurrence of some adverse events and tolerability issues could be acceptable

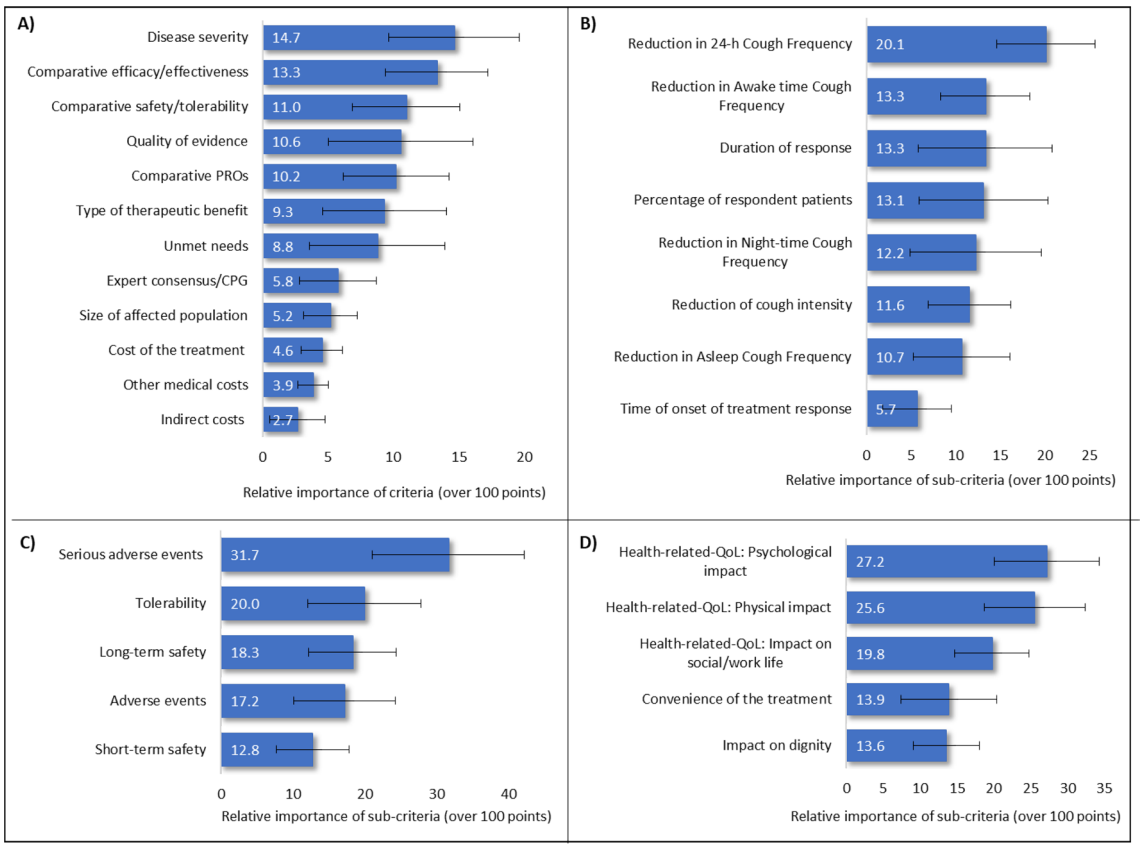

Fig. 3 Weighting results obtained by physicians in the single profile stakeholder meeting. **A** Quantitative criteria weighting results; **B** Comparative efficacy/effectiveness sub-criteria weighting results; **C** Comparative safety/tolerability sub-criteria weighting results; **D** Comparative Patient-Reported Outcomes (PROs) sub-criteria weighting results. *CPG* clinical practice guidelines, *QoL* quality of life

if treatment effectiveness, and the consequent perception of clinical improvement by the patient, is demonstrated.

3.1.3 Hospital Pharmacists

Results from the criteria weighting by hospital pharmacists based on points allocated are presented in Fig. 4A. The top three most important criteria for hospital pharmacists were comparative efficacy/effectiveness (13.3 ± 3.5 points), safety/tolerability (11.8 ± 2.3) and quality of evidence (10.4 ± 3.5). The 3 least important criteria were other medical costs (5.7 ± 2.3), expert consensus/clinical practice guidelines (5.6 ± 2.8) and indirect costs (5.1 ± 1.7). Hospital pharmacists initially mentioned a low level of awareness about the severity and impact of RCC|UCC, mainly explained by the lack of available therapeutic options. According to hospital pharmacists, the primary focus when performing the assessment of a treatment is efficacy and safety. Patient-reported outcomes could also be important, but they are frequently not available. The robustness of the clinical studies is a key aspect when performing an assessment of treatment effect. Conversely, other medical and indirect costs were considered relatively less important due to the lack of direct impact on the pharmaceutical budget.

Hospital pharmacist sub-criteria weighting results based on points allocated are presented in Fig. 4B–D. The 3 most important sub-criteria were the reduction in 24-h cough frequency (17.2 ± 3.1), serious adverse events (28.1 ± 7.5) and HRQoL: Physical impact (25.0 ± 6.0). The 3 least important sub-criteria were the time of onset of treatment response (8.8 ± 3.3), short-term safety (15.0 ± 3.8) and the impact on dignity (15.0 ± 5.3). Hospital pharmacists recognised that a reduction in cough frequency could be the only objective endpoint to assess treatment effect. Any improvement in the safety profile would be considered a benefit when compared with the issues associated with neuromodulators currently prescribed for treatment. The time until treatment response, as well as short-term safety, were perceived as less important sub-criteria, considering the chronicity of the condition. Hospital pharmacists agreed that the negative impact of RCC|UCC on patient dignity would be reduced by any improvement in patients' HRQoL.

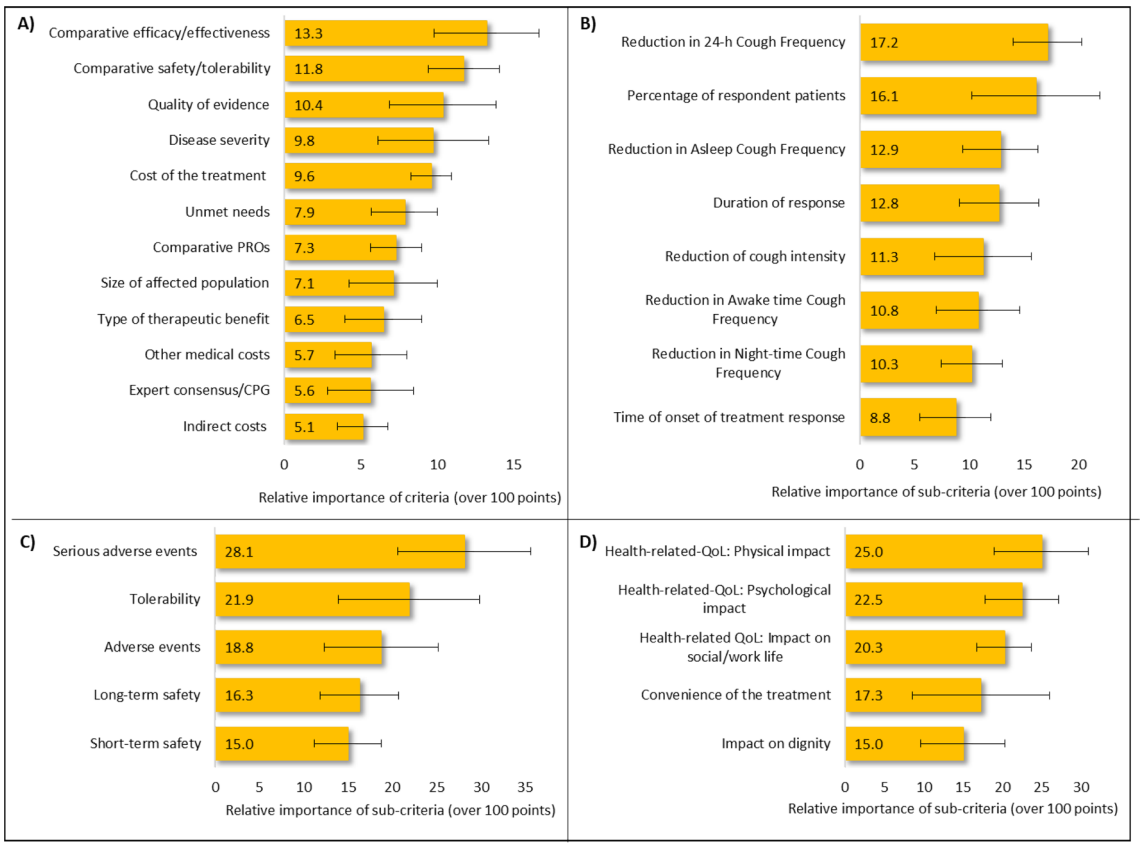

Fig. 4 Weighting results obtained by hospital pharmacists in the single profile stakeholder meeting. **A** Quantitative criteria weighting results; **B** Comparative efficacy/effectiveness sub-criteria weighting results; **C** Comparative safety/tolerability sub-criteria weighting results; **D** Comparative Patient-Reported Outcomes (PROs) sub-criteria weighting results. *CPG* clinical practice guidelines, *QoL* quality of life

3.2 Multi-Stakeholder Meeting

The results of the weighting scores of criteria/sub-criteria assigned by stakeholders as one group after the multi-stakeholder group meeting, based on points allocated are presented in Fig. 5. The 3 most important criteria in RCC|UCC from the perspective of key stakeholders in Spain were disease severity (13.5 ± 5.6 points), comparative efficacy/effectiveness (11.0 ± 2.9) and safety/tolerability (10.9 ± 3.5). The 3 least important criteria were those related to costs, including cost of the treatment (5.1 ± 2.8), other medical costs (4.0 ± 2.5) and indirect costs (3.9 ± 2.2). The 3 most important sub-criteria were the reduction in 24-h cough frequency (16.8 ± 3.3), serious adverse events (31.2 ± 9.2), and HRQoL: Physical impact (28.5 ± 4.8), and the 3 least important were the time of onset of treatment response (8.9 ± 3.8), adverse events (15.2 ± 6.0) and convenience of treatment (12.9 ± 4.7). The results of the statistical analysis of the weighting scores between Phase 1 and 2 confirmed the consistency of scoring by the stakeholders, as none of the differences in the criteria/sub-criteria were statistically significant ($p > 0.05$ in all the criteria/sub-criteria). Weighting score changes between Phase 1 and 2 can be reviewed in the Supplementary Material 4.

Physicians and hospital pharmacists acknowledged that the primary goal of treatment from the patients' perspective was to achieve an improvement in their HRQoL, namely through a reduction of cough symptoms such as frequency and intensity. Additionally, stakeholders agreed on the importance of assessing the impact on the patients' HRQoL during clinical visits. While physicians and hospital pharmacists rely on objective variables (i.e., cough frequency in the case of RCC|UCC) for the assessment of treatment effect, stakeholders agreed on the importance of correlating improvement in objective measure(s) with those of subjective measures including HRQoL in the assessment of RCC|UCC treatment effect. The lack of tools in the clinical setting that can assess cough frequency and the burden of RCC|UCC on the patient's HRQoL suggests that PROs could be used as a proxy to assess treatment effect in clinical practice. The use of a visual analogue scale (VAS) was proposed as a simple, easy to use tool that could help evaluate the burden and improvement of cough in RCC|UCC patients in clinical practice. All stakeholders agreed on the benefit of a

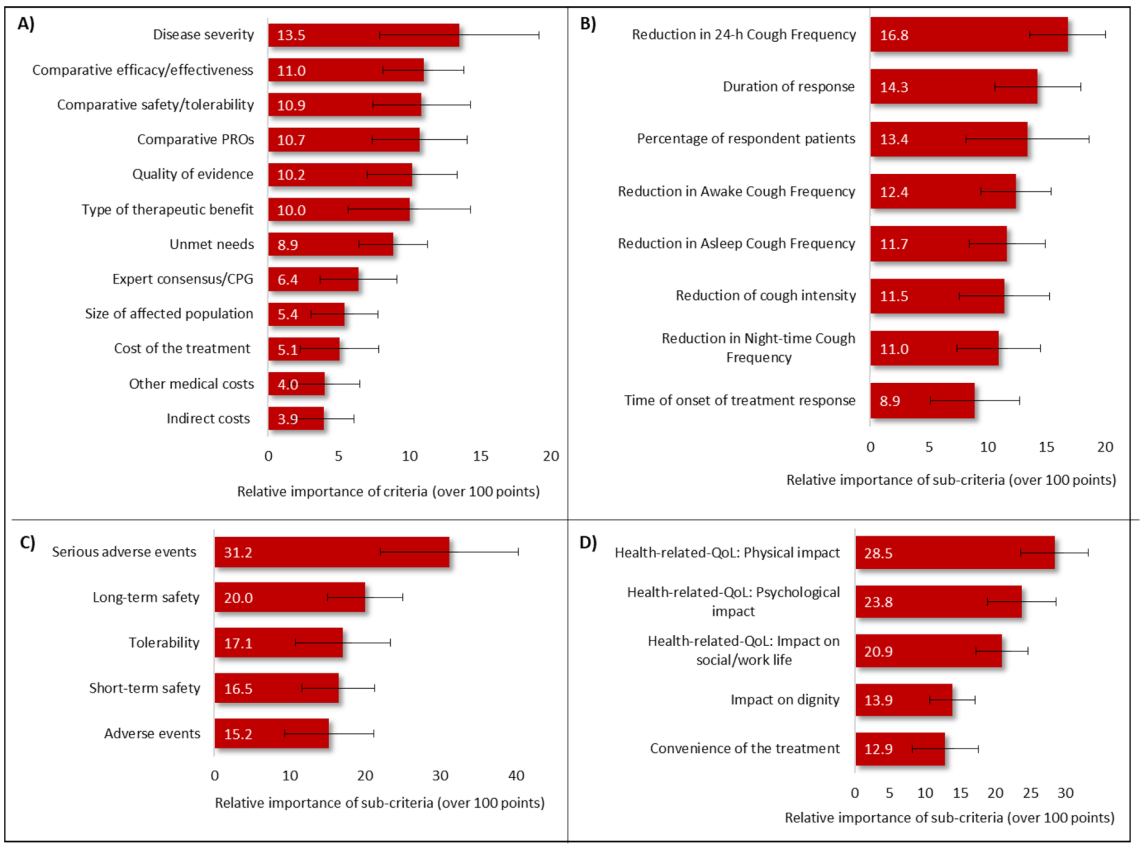

Fig. 5 Weighting results obtained by stakeholders as a group in the multi-stakeholder meeting. **A** Quantitative criteria weighting results; **B** Comparative efficacy/effectiveness sub-criteria weighting results; **C** Comparative safety/tolerability sub-criteria weighting results; **D** Comparative Patient-Reported Outcomes (PROs) sub-criteria weighting results. *CPG* clinical practice guidelines, *QoL* quality of life

multidisciplinary approach to help optimise care of difficult to treat patients with RCC|UCC.

Stakeholders agreed that any reduction in cough frequency should preferably be maintained throughout the 24-h period, rather than only during the day or only at night, considering the inter-patient variability of time of day when cough impacts on patients. Despite not being one of the top-rated criteria, determining the improvement of cough intensity in the assessment of treatment success was discussed as a relevant aspect for all stakeholders. There was agreement that some treatment-related adverse events and tolerability issues might be acceptable if the reduction in cough frequency and subsequent improvement in HRQoL is clinically relevant. Finally, participants agreed that key unmet needs include the awareness about the condition, its impact on HRQoL, and the availability of effective treatment options.

4 Discussion

Cough that persists despite adequate investigation and management remains an unsolved clinical problem. Many challenges are associated with the appropriate diagnosis and management of RCC|UCC, starting by a general lack of awareness among patients with persistent cough and their treating health care providers. The heterogeneity of the patient population that requires the collaboration of several medical specialties, the lack of an effective treatment, and the lack of agreement on the optimal approach to assessing treatment success are some of the barriers that physicians and hospital pharmacists will continue to face in the near term. Further understanding of RCC|UCC and its impact on HRQoL could help optimise patient access to upcoming therapeutic options expected to become available in the next few years [31–33].

Throughout the study, participants helped determine the general level of awareness about RCC|UCC in Spain and define what represents value in RCC|UCC from their own perspective, facilitated through the adaptation of an MCDA framework specific to RCC|UCC. All criteria and sub-criteria considered relevant for healthcare decision making in RCC|UCC were identified and integrated into the adapted MCDA framework, which was subsequently validated through the input of study participants.

Patients, physicians and hospital pharmacists agreed that RCC|UCC is a condition with a high degree of unmet need. Refractory or unexplained chronic cough affects patients to varying degrees of severity, yet frequently, its impact is not appropriately assessed by the medical community. In certain patients, RCC|UCC can be severe and produce significant burden on all aspects of the patient's HRQoL, including physical, psychological and social impact as well as impairment of the ability to work. This is in line with that reported in recent publications [4, 6, 8, 15, 34, 35]. Since impact on HRQoL represents the main burden associated with RCC|UCC, any reduction in the symptoms of cough needs to be strongly correlated with improvements in HRQoL to be considered clinically meaningful and patient-relevant. Reduction in cough frequency throughout a 24-h period is perceived as valuable since some patients are more affected during waking hours while others suffer from sleep disruption. Although the reduction in 24-h cough frequency was the top-rated sub-criterion, the improvement of cough intensity was also consistently mentioned by stakeholders as a relevant aspect to be assessed when treating to reduce the burden of cough. Improvements in the physical, psychological and social/work productivity domains of HRQoL are interrelated and are considered equally important. Stakeholders agreed that potential adverse events of any new therapeutic option could be acceptable to patients and their treating physicians if the reduction in 24-h cough frequency and subsequent improvement on HRQoL was clinically meaningful and patient-relevant. Involving the different relevant medical specialties for RCC|UCC in a multidisciplinary approach to the condition would be a key aspect to optimising patient management and treatment, as confirmed by recently published literature [36, 37].

Stakeholders first worked within their own homogeneous peer group and afterwards came together as a multi-stakeholder group. The weighting results obtained in the two phases were consistent, showing that the perception of what represents value for a given attribute is inherent to each stakeholder profile. Patients placed emphasis on the severity of the disease and the goal of treatment to improve HRQoL, while trusting physicians and hospital pharmacists to assess the efficacy and safety of the new treatments that are expected to become available in the upcoming years. Physicians emphasised the relevance of following a patient-focused treatment approach and agreed on the importance of adopting a standardised HRQoL assessment tool in clinical practice to help assess impact of the condition and improvement attributable to treatment. Physicians discussed that a VAS could assess HRQoL of RCC|UCC patients quickly and easily in clinical practice. Hospital pharmacists primarily considered objective variables, such as efficacy and safety, when evaluating a new treatment but recognised that impact on HRQoL could be used as a proxy of clinical relevance in RCC|UCC patients. Bringing different stakeholder perspectives together was key to help study participants gain a better understanding of the condition. Study participants were able to discuss, reflect and agree on key aspects, such as the potential severity of RCC|UCC, its associated burden on HRQoL and health care resources as well as that improvement in objective variables (such as cough frequency) should correlate with improvements in HRQoL in order to be considered clinically meaningful and patient relevant. Given

the lack of clinical practice tools that can record objective cough measures (frequency), stakeholders recognised that PRO measures could be used as a proxy for assessing treatment effectiveness in clinical practice.

Recent studies in Spain have used the EVIDEM MCDA framework to help assess value across different medical conditions and therapeutic areas [21, 24, 25, 38–41]. One of the limitations typically highlighted in these studies is the relatively small number of participants. In an attempt to overcome this limitation, this study included a larger number of participants across a diverse set of stakeholders' profiles. However, the present study is not exempt from some other limitations. First, a risk of bias in the selection of participants cannot be totally excluded, since experts were identified through a literature review specific for RCC|UCC, and hence their experience and knowledge of the condition is above that of the general population. This study could benefit from further investigation with physicians and payers with lesser experience with RCC|UCC, where displacements from their initial perspectives could be higher and which could be more representative of their respective stakeholder group. The information used to adapt the MCDA framework to RCC|UCC was limited by the information and data publicly available at the time of the study. The current value framework could, therefore, benefit from further work once more information about the condition and the upcoming treatments becomes available. The number of stakeholders that participated in Phase 1 was reduced in Phase 2 to allow for a higher level of participation and more in-depth analysis of the value criteria. This selection could have also introduced some potential bias. To overcome this limitation and increase result robustness, a statistical analysis of the stakeholders' weighting results from Phase 1 and 2 was performed and confirmed that weighting results did not significantly change between the two phases.

Adapting the EVIDEM MCDA framework to RCC|UCC has proven to be useful for value determination in this specific medical condition. This study represents the first attempt to assess value in RCC|UCC from the perspective of key stakeholders in Spain. The MCDA framework adapted for RCC|UCC developed during this study may be used as the starting point for discussions of value contribution during the assessment of upcoming treatments and for future studies in the field of RCC|UCC.

5 Conclusions

Refractory or unexplained chronic cough is not a well understood medical condition. Key unmet needs include the level of awareness across medical specialties and hospital pharmacists, lack of multidisciplinary patient management, lack of availability of efficacious treatment options and the inconsistency of how treatment success is assessed and recognised in clinical practice. This study brings to light the serious impact RCC|UCC can have on patients and health care resources and the importance of assessing the improvement in HRQoL when treating to reduce the frequency and intensity of cough.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40258-022-00770-9.

Acknowledgements The authors would like to thank the participants that constituted the RCC|UCC MCDA study group for their contribution during the study.

Declarations

Funding This study was funded by Shionogi Inc.

Conflict of interest CD, MF, NG, JMP, AP and CT received fees for their participation in the study. IMF is a member of the patient organisation FENAER. IM is a member of the patient organisation ASMABI. FENAER and ASMABI received a donation from Shionogi for the participation of its member in the study. RB is an employee of Shionogi Inc. RS and AG are employees of Omakase Consulting S.L. Omakase Consulting S.L. received funding from Shionogi Inc. to develop and conduct this study.

Ethics approval The study was developed following all the legal and ethical requirements for Market Research studies established by National and International Authorities and is compliant with the 2021 Codes of Conduct by Farmaindustria (Spain) and EPHMRA (Europe).

Consent to participate All participants agreed to participate in the study, formalised through the signature of a contract which included a detailed description of the activities to be performed. Patients were contracted through the Spanish Federation for patients with Allergic or Respiratory diseases (FENAER), in accordance with the requirements set in the 2021 Farmaindustria Code of Conduct.

Consent for publication All participants yielded the right to use and publish the data obtained in the study to the sponsor of the study.

Availability of data and material No additional data available.

Code availability Not applicable.

Author contributions CD, MF, NG, JMP, AP, CT, IMF, IM, RB, RS and AG contributed to the design of the study, data acquisition, analysis, and interpretation, drafting of the work, revising the work critically for important intellectual content, approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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