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# ASSESSING THE QUALITY OF LIFE OF PATIENTS WITH EPIDERMOLYSIS BULLOSA: APPLICATION OF THE DELPHI METHOD TO DEVELOP A PATIENT-CENTRED QUESTIONNAIRE

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SUMMARY

*Epidermolysis Bullosa is a rare disease that seriously affects the Quality of Life (QoL) of patients and their caregivers and can sometimes constitute an unbearable burden for them. The primary aim of this study was to focus on the patients' experience, capture their point of view and understand their needs in order to develop a QoL questionnaire. The Delphi method was chosen as the most appropriate for this purpose, even if preferring a modified version of the classic procedure, alternating moments of group sharing with private moments of individual compilation covered by anonymity. After four Delphi rounds, the consensus was reached on a questionnaire with 87 items grouped into seven domains suitable for understanding the various aspects of quality of life impacted by the disease. This proposal may be a valid aid for clinicians to understand the patient's needs and identify the areas they are more concerned about; moreover, it may allow them to follow the patients over time and evaluate the impact of any treatments.*

*Keywords: Delphi Method, Quality of Life, Epidermolysis Bullosa, Patient-Centred Questionnaire, Rare Disease.*
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## 1. INTRODUCTION

The concept of health-related quality of life (HRQoL) has evolved since the 1980s to encompass several aspects of overall quality of life. It may be referred to both an individual and a community level. On the individual level, this includes physical and mental health perceptions and their correlates, including health risks and conditions, functional status, social support, and socioeconomic status. On the community

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level, HRQoL includes resources, conditions, policies, and practices that affect health perceptions and functional status of a specific population.

The construct of HRQoL broadens the traditional notion of health to meet the expressed physical and mental health needs of the population, enabling health agencies to legitimately address broader areas of healthy public policy (Centers for Disease Control and Prevention, 2000). Achieving a good HRQoL is recognized as an essential aim of health assistance, regardless of the pathology and the administered therapy (Asadi-Lari, Tamburini and Gray, 2004).

HRQoL is crucial to evaluate how treatments and therapies influence patients' functionality and emotional state to ameliorate interventions and their outcomes. Patient-reported outcomes are generally considered valid indicators of unmet needs and intervention outcomes (Patrick and Deyo, 1989; Rabin and de Charro, 2001; Ware and Sherbourne, 1992). HRQoL instruments are usually designed with the main contribution of clinicians and include items centred on the disease to help determine the best clinical approach. However, they may fail to truly grasp the patient's perspective, needs, perceptions and emotional state, resulting in a significant drawback that sets medical care on clinical parameters alone. The patient's self-assessed health status is a more powerful predictor than many objective health measures. This may be especially true for patients suffering from rare diseases because rarity can hinder research. Improving knowledge of rare diseases is a major public health concern. There are currently around 7,000 rare diseases known around the world. These diseases are often severe and chronic and require careful consideration from a group of physicians of different specialties. Healthcare professionals are not always able to develop specific knowledge for every disease. On the contrary, patients and their caregivers have often acquired specific expertise for a disease thanks to their personal experience. This so-called experiential knowledge can be shared with healthcare professionals to enable them to acquire valuable information on rare diseases.

The present study aims to describe the development of a patient-centred questionnaire to assess the QoL of EB patients. The Delphi methodology was chosen as the most appropriate method for a deeper understanding of the patient's perspective, offering them the opportunity to make their voices heard and to contribute to defining the items of the questionnaire. Indeed, well-defined consensus methodologies are increasingly used to raise the voice of patients and make reliable information available in the context of rare diseases.

### 1.1 *Epidermolysis Bullosa*

Epidermolysis Bullosa (EB) is a group of genetic disorders that are clinically heterogeneous and encompass a broad spectrum of severity. These conditions are characterised by extreme fragility of the skin and mucous membranes, resulting in tissue detachment and the formation of blisters and painful ulcerations. This can result in a range of symptoms, including pain, itch and malodour. The clinical spectrum is

broad and can present with varying degrees of severity, ranging from forms with an early onset and high mortality rate to forms with a longer average life expectancy.

The incidence of these disorders is estimated to be around 500000 cases worldwide, thus being counted among the rare diseases. The prevalence of inherited EB in the US is about 11 cases per 1 million live births, and the incidence is about 20 per 1 million population (Fine, 2016; Tadini, Gualandri, Colombi, *et al.,* 2005).

Despite the improvements in the diagnostic approach and new therapeutic perspectives, there is no cure for this condition. At present, the only available therapeutic options are those that provide symptomatic relief.

The clinical manifestations and severity of the condition are very heterogeneous, and may present acutely or chronically, with symptoms including pain, itchiness, blistering, ulcers, or infection of the skin. Dental problems and blisters inside the mouth and throat, dysphagia, ankyloglossia, microstomia, oesophageal stenosis, and digestive and absorptive problems have an impact on nutrition and food intake (Zidorio, Dutra, Leão and Costa, 2015). Pseudo syndactyly and scarring have an adverse effect on the ability to walk and to grasp objects, which in turn affects the performance of activities of daily living. EB clinical manifestations also include hair loss, muscle, heart, brain, gastrointestinal, bone, or kidney issues. These issues frequently require painful and time-consuming medications and profoundly impact everyday activities because of disease-associated functional limitations. Besides, some symptoms have a disfiguring nature and make it difficult to live an ordinary social life, causing psychological distress and undermining social relationships. The overall EB management may have detrimental financial consequences also because patients and their caregivers may have to face healthcare travel expenses to go to referral centres. Additional problems are related to the lack of awareness and understanding by laypeople and non-specialist healthcare professionals who may take care of EB patients. To address this deficit in knowledge, it is essential to consider the personal experiences of patients and their caregivers, as these can provide invaluable insights from a human, scientific, technical, and relational perspective. The development of translational knowledge, which can be applied to new fields and contexts, can be regarded as a crucial factor in fostering a tangible and evidence-based hope for recognizing the inherent value of life, to the extent that it is deserving of investment to enhance its quality of life and beauty (Barnini, 2022).

All things considered, EB is highly disabling and has substantial emotional and psychological repercussions, which impact expectations and quality of life, self-perception, the development of self-esteem and identity, and the possibility of having satisfying social relationships. EB patients' unmet needs overcome requests for medical support (Dures, Morris, Gleeson and Rumsey, 2011), and their quality of life – as well as that of their families – is seriously affected.

### 1.2 *The Delphi Method*

The Delphi method is a technique aimed at the convergence of opinions to facilitate the achievement of a widely shared view within a group. It unfolds over a pre-specified number of iterations, or rounds, during which the administrator supervising the process, i.e., the Delphi Master, provides participants with an informative summary of the responses given by all panel members and their reasons. The convergence of opinions is a process of structuring communication that channels multiple competent thoughts on the issue under discussion toward conclusions that are as much shared as possible (Pacinelli, 2008). The underlying idea is the assumption that multiple experts can produce a more valid result than an opinion given by a single expert, even when this expert is the best in his or her field (Niederberger and Spranger, 2020). This method is often used in problem areas where knowledge is limited or conflicting or where evidence based on statistical models is not available and subjective judgments on a collective basis may be helpful (Hanafin, 2004). It has also been used to fill in some gaps of knowledge in case of ultra-rare diseases (Scarpa, Barbato, Bisconti, *et al.,* 2023).

Table 1 describes the main distinguishing features of the Delphi methodology (Niederberger and Spranger, 2020; Trevelyan and Robinson, 2015; von der Gracht, 2012).

TABLE 1. - *Characteristics of the Delphi methodology*

| | |
|---|---|
| *Expert input* | Each participant must be knowledgeable about the area of interest. The choice of experts to recruit is a complex and fundamental process. |
| *Anonymity* | The process is coordinated by a moderator who ensures the anonymity of the experts. This aspect leads to some advantages over other group communication methods, such as, for example, ensuring that the opinion of dominant individuals does not influence participants and that there is no socio-psychological pressure. It also avoids leading participants to abandon their views for fear of judgement from others and usually leads to higher response rates. Ensuring the anonymity of experts has always been a fundamental and constant point during the evolution of the method. |
| *Statistical aggregation of the group's response* | This stage allows the results obtained from the round to be analyzed and interpreted. They can be presented either numerically or graphically and usually include measures of central tendency, dispersion and frequency distributions. |

*(follows)*

| | |
|---|---|
| *Iteration with controlled feedback* | Respondents' judgments are summarized and re-stated in aggregated form as feedback for the following round. In particular, after each Delphi round, the survey data is statistically analyzed, and the facilitator decides on the type of feedback and its provision. The described process is usually repeated until stability in responses is achieved, but not always when consensus is reached. There is no single method for determining when to stop the process. The measurement of consensus has been based primarily on descriptive statistics. The fact that group responses are communicated allows participants to share their judgments and reconsider their views, resulting in possible convergence in evaluations. |

At an appropriate juncture during the procedure – ideally at its conclusion – it may be beneficial to convene the participants for an open exchange of views and a resolution of any outstanding uncertainties, particularly when consensus is elusive. It is recommended that the meeting be conducted in a well-structured manner, with the assistance of a moderator to prevent the undue influence of dominant personalities.

The original Delphi method has undergone several modifications over time to reach a consensus, and several methodologies have been developed and have been widely used in healthcare studies. These methodologies can be defined by the term "modified Delphi" (Boulkedid, Abdoul, Loustau, Sibony and Alberti, 2011).

## 2. DEVELOPMENT OF THE QUESTIONNAIRE: CASE STUDY

In this Section, a detailed and complete case study will be presented relating to the application of the Delphi method to develop a HRQoL questionnaire tailored for patients afflicted by a rare disease. The project took several months and part of the project was described along the process (Bartolini, Bertoldi, Benedan, Galeone, Mariani, Sofia and Zenga, 2021; Benedan, El Hachem, Galeone, Mariani, Pilo and Tadini, 2021; Benedan, El Hachem, Galeone, Mariani, Pilo and Tadini, 2022; Benedan, Digrandi, Mariani, Pilo and Zenga, 2023). This study is a final product of the project presenting detailed and complete methods and results in a full manuscript.

The project was proposed and funded by REB ETS Foundation (REB), a non-profit association for patients with Epidermolysis Bullosa (EB). The Foundation is governed by a Scientific Committee comprising not only medical professionals from affiliated clinical centres but also patient representatives. The project engaged participants who were esteemed experts in their respective domains. The patients and the caregivers were required to provide their opinion of experts to contribute to the development of the questionnaire.

In order to describe critical methodologic criteria – as suggested by Diamond, Grant, Feldman, Pencharz, Ling, Moore and Wales (2014) – the study objective, participants selection, consensus definition, how some items were dropped, and the entire Delphi process will be defined.


FIGURE 1. - *Step-by-step description of the Delphi process*

Figure 1 provides a detailed description of the entire questionnaire development process, starting from the initial identification of the unmet need to the achievement of a consensus on each questionnaire item, and on its face and content validity. Figure 2 illustrates the timeline of the Delphi process.

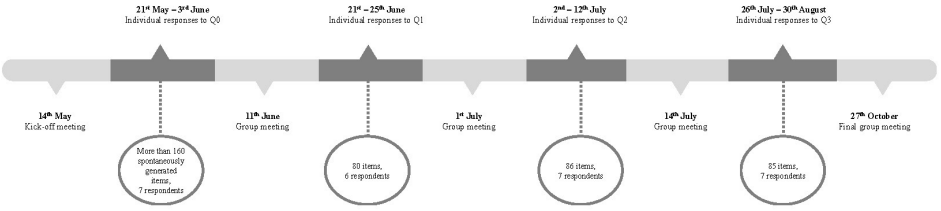



FIGURE 2. - *Timeline of the Delphi process*

## 2.1 *Problem Identification and Research Questions*

EB patients can rely on the non-profit association Debra International that represents the requests and defends the rights of patients with EB globally. In Italy, Debra has created the first Italian Register of people affected by EB, which is maintained and developed by REB ETS Foundation. Considering the complexity and chronicity of EB, the REB ETS Foundation raised the matter to have a tool to evaluate the HRQoL of EB patients as an essential factor for monitoring the disease and addressing the treatment needs, and launched the project to develop a patient-centred questionnaire to assess the HRQoL of patients affected by EB.

## 2.2 *Scientific Literature*

The scientific literature was examined to understand which tools were already available at a national and international level and what were the main strengths and weaknesses of the existing questionnaires. Figure 1 shows the main questionnaires that have been used to assess HRQoL for Epidermolysis Bullosa patients and/or their families from the oldest to the newest, i.e., the Psychological Well – Being Scales (PWB - Ruini, Ottolini, Rafanelli, Ryff and Fava, 2003; Ryff, 1989; Ryff and Keyes, 1995); the Short-Form 36 (SF-36 - Ware, Gandek, Guyer and Deng, 2016); the Dermatology Life Quality Index (DLQI - Finlay and Khan, 1994; Margari, Lecce, Santamato, Ventura, Sportelli, Annicchiarico and Bonifazi, 2010); the Children's Dermatology Life Quality Index (CDLQI,); the Skindex-29 (Abeni, Picardi, Puddu, Pasquini and Chren, 2001; Abeni, Picardi, Pasquini, Melchi and Chren, 2002; Chren, Lasek, Flocke and Zyzanski, 1997; Chren, Lasek, Quinn and Covinsky, 1997; Chren, Lasek, Quinn, Mostow and Zyzanski, 1996); EuroQol-5 Dimension (EQ-5D - Rabin and de Charro, 2001) the Quality of Life Evaluation in Epider-

molysis Bullosa questionnaire (QoLEB - Cestari, Prati, Menegon *et al.,* 2016; Dănescu, Sălăvăstru, Sendrea *et al.*, 2019; Frew, Martin, Nijsten and Murrell, 2009; Frew, Cepeda Valdes, Fortuna, Murrell and Salas Alanis, 2013; Yuen, Frew, Veerman, van den Heuvel, Murrell and Jonkman, 2014); the Epidermolysis Bullosa Burden of Disease (EB-BoD - Dufresne, Hadj-Rabia, Taieb and Bodemer, 2015) and the Infants and Toddlers Dermatology Quality of life (InToDermQoL - Chernyshov, Boffa, Corso *et al.*, 2018; Chernyshov, Suru, Gedeon, Derevyanko, Tiplica and Salavastru, 2019; Chernyshov, Marron, Tomas-Aragones *et al.*, 2020).

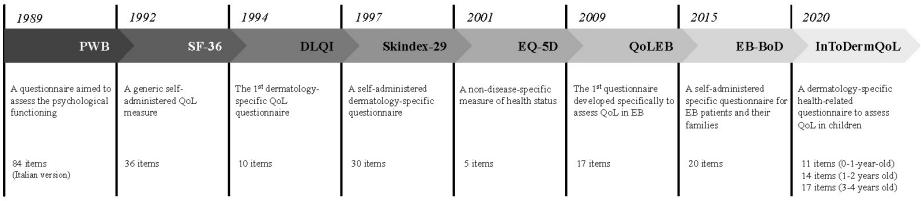



FIGURE 3. - *HRQoL Questionnaires used with EB patients*

## 2.3 *Questionnaire: Settings and Statements*

After having examined the literature to understand what instruments were already available, their main strengths and limitations, it was critical to clearly identify and define the construct to be assessed. Some possible domains were identified: "physical", "emotional", "family and social", "functioning". Some items from the literature were added for each domain. In particular, within the physical domain two items were inserted: "I feel pain because of EB" and "EB causes me itching". The emotional domain contained two items: "I feel frustrated" and "I feel anxious". The family and social domain had three items: "The disease affects relationships with your family members", "I feel embarrassed when I am with other people", and "I am satisfied with the relationship with my friends". The functioning domain included three items: "I find it difficult to write", "I have difficulties in school activities", and "I have difficulty in work activities". For all domains, there were some blanks to fill in and some "Other (specify)" options. This was essential to get into the details of the quality of life. It was also possible to suggest some new domains as deemed appropriate and it was required to provide a brief description of all the domains to include in the questionnaire.

## 2.4 *Panel Definition*

A multidisciplinary expert panel was identified. The success of a Delphi study largely depends on the expertise of the participants who make up the expert panel (Powell, 2003). The choice of experts is critical because the final results will depend

on it, so the panel should be constructed as accurately as possible. Choosing the right people is much more important than choosing how many people to include in the panel. Therefore, pre-specified objective criteria were used to outline the multidisciplinary panel members.

According to the purposes of the present study, and in line with EUPATI (Warner, See, Haerry, Klingmann, Hunter and May 2018), we considered including in the sample the following roles: "Individual Patients", i.e., people with personal experience of living with a disease; "Caregivers", i.e., people supporting family members affected by EB; "Patient Advocates" whose expertise is related to their experience to support a larger population of patients living with EB; in addition, we sought at least two medical doctors with clinical expertise in managing EB patients and recognized as international key opinion leaders on EB; at least two Delphi experts with scientific expertise and specialised in biostatistics and methodological issues; a psychologist to interpret the emerging needs and moderate the group discussions.

Then the sample size was considered. To date, there are no clear guidelines regarding the number of people to be recruited in studies applying the Delphi method. The number of participants may affect the potential for ideas and the amount of data to be analysed: on the one hand, a "small" number might not generate enough ideas to be discussed; on the other hand, a "large" sample might result in cost inefficiencies. Besides, the sample size principles in Delphi studies differ from those of other surveys because participants are not selected randomly, so statistical representativeness is not assured (Powell, 2003).

Hence, the sample consisted of four adult EB patients (three females and one male), two female caregivers of EB child patients, the president of the REB foundation, two EB medical specialists, a biostatistician, a Delphi expert, and a psychologist.

A first group meeting was organised to present the project and its aims.

### 2.5 *First Round: Exploration*

An exploratory phase followed and concerned the construction of the first questionnaire to be submitted to the panel, consisting of a series of open-ended questions designed to bring out the points of view that, once collected, selected and reorganised by the researchers, will flow in a structured manner into the subsequent questionnaires to be submitted again to the same experts.

Hence, the first round involved open-ended questions (Jandhyala, 2020), generating qualitative data that were analysed using content analysis techniques. The patients and clinicians were asked to provide a list of spontaneously generated items to describe different areas of the EB patient's HRQoL. Besides, at this stage the respondents were required to choose the most appropriate measure of the degree of agreement/disagreement to use to describe the issue of interest. The possible choices were Likert scales from 4 to 7 seven points, or other.

All respondents worked separately, and all the answers were collected anony-

mously, allowing every person to freely express their opinions and personal state of mind without any social pressure or external influence.

Seven questionnaires were returned. A total of more than 160 items were created. Data collected from this initial stage were carefully analysed, and similar items were grouped together. Accurate analysis and harmonisation of all the statements were carried out in a first attempt to provide one universal description with a clear value generalizable for the entire reference population. Where several different terms were used for what seemed to be the same issue, the researchers grouped them together. Besides, they were subsequently merged with others related to difficulties in using objects of common use like cutlery, scissors, tubes, hinges, coins, etc. In the following phase, a more generic item was created to sum up all these details ("I have a hard time using everyday objects"). At this stage, no items were added during analysis and the wording used by participants, with minor editing, was used as much as possible in listing items.

The results of the content analysis were presented in the first-round table and a group discussion followed. Great care was taken to ensure a comprehensive and accurate understanding of the experts' points of view.

Firstly, it was necessary to define the dimensions of the questionnaire. As mentioned above, four domains were suggested by researchers in Q0. The respondents had the opportunity to express their opinion about this and proposed the following areas to be investigated: physical, emotional, family, social, functional, affective-sexual, work, independent life, psychological, medical care, medical assistance, economic. Since several new domains were suggested, the group discussion allowed the researchers to make a shortlist and change the original domains: a total of seven domains were identified and inserted in the questionnaire. Consensus was reached about the number and the definition of each domain. The domains and their description are shown in Table 2.

The "functioning and autonomy" domain emerged as a key one because the respondents highlighted that the disease prevents autonomy and independence. Indeed, EB causes difficulty in normal daily activities and personal management: eating, washing, dressing, grabbing objects, dressing, walking, etc.

The "emotional" domain was broadened also to consider the psychological dimension regarding self-esteem, depression, anxiety and discomfort. The "family and social" domain was initially proposed as a single one by the researchers. Still, three respondents independently suggested dividing into two separate domains and successively the group agreed to keep them separate because the daily experiences within the family are very different from those with strangers. On the one hand, family members share everyday experiences and part of the burden of the disease; on the other, prejudices and social stigma often characterise relationships with people outside the family, i.e., friendships, romantic relationships and sexual life, occasional interactions and sporadic encounters with strangers (they stare, make comments, etc.).

Two completely new domains were identified and inserted in the subsequent versions of the questionnaire: "Work and economic", to point out that it is often difficult for EB patients to find a job that suits their needs, and that living with such disease has strong economic repercussions on patients' life; "Medical care and assistance" apart from the EB treatment centre of reference, because local realities may not know

this disease and not be ready to deal with these patients. This section also comprises statements related to the supply shortages of medications and dressings.

TABLE 2. - *Questionnaire domains*

| Domain | Domain description |
|---|---|
| *Physical* | It includes the most relevant aspects in terms of health and physical well-being. |
| *Functioning and autonomy* | It refers to self-sufficiency and includes statements about the ability to perform common routine actions. |
| *Psycho-emotional* | It refers to the psycho-emotional well-being, including emotions, thoughts and feelings. |
| *Family* | It refers to the relationships with parents, siblings, or other family members such as partners and children if it applies. |
| *Relational* | It includes statements about relationships and frequent interactions with people who do not belong to the family (e.g., friends, classmates, colleagues, strangers on the street, etc.). |
| *Work and economic* | It includes statements referring to the work context and the financial implications of the disease. |
| *Medical care and assistance* | It refers to disease-related healthcare, including medical and nursing assistance. |

As regards the most appropriate measure of the degree of agreement/disagreement to use, the 4-point scale ("Not at all", "A little", "Quite a lot", "Very much") appeared to be the best option because of the lack of a neutral intermediate point. According to the participants, a neutral point was not suitable for the purpose, so the answers were meant to be polarised as positive or negative.

### 2.6 *Second Round: Q1 Administration*

The analysis of the responses from this first questionnaire led to the construction of a second questionnaire, which was administered to the experts. A total of 80 items were included and grouped into the seven core domains previously identified. Respondents were required to rank them within each domain according to their importance. Therefore, for every domain the rating may range from a minimum of 0 to a maximum equal to the number of items in that domain (Physical = 14; Functioning and autonomy = 15; Psycho-emotional = 13; Family = 12; Relational = 9; Work and economic = 11, Medical care and assistance = 6). They were also required to comment on the clarity and specificity of each item, to write any potential new

item, and to report any missing information that might have been included. The main aim of this phase was to exclude any irrelevant items to shorten the entire set of questions and have a more manageable questionnaire.

Six questionnaires were returned. All the answers were carefully examined, and a ranking was created for every item within each domain according to the degree of importance indicated by all the respondents. The results were discussed in a group meeting and further refinement of the questionnaire was made by all the participants. At the end of this round, Q1 was carefully reviewed, and several changes were suggested by the panellists and, after an in-depth examination of all the items, many adjustments were made. A new questionnaire (Q2) was defined, considering all suggestions that emerged from the group meeting. The previously identified core domains remained unchanged, but some new items were suggested and inserted. Compared to Q1, 54 (68%) items remained unchanged, 19 (24%) were rephrased, and 7 (9%) were eliminated - including those that were merged. The changes concerned the questionnaire as a whole but also the individual domains. For instance, two items were moved to a different domain (e.g., "I feel I'm self-reliant" was initially in the functioning and autonomy domain and was moved to the psycho-emotional domain). Besides, 13 new statements were inserted.

### 2.7 *Third Round: Q2 Administration*

Q2 was composed of 86 items. The order in which the items were presented changed according to the importance of each statement within the domain so that the more important items were the first, as established in the previous round. Q2 was hence administered to all the participants who were asked to rate both the degree of agreement and the degree of importance of each item on the previously chosen four-point Likert scale. This step allowed the panel to remove some irrelevant statements and evaluate the order in which the items were presented.

In addition, some specific questions were inserted about: the subtype of EB the respondent has been diagnosed with; if needing psychological support because of EB; whether feeling in good hands regarding the care; the region where the treatment centre is located; the age range; the presence of offspring; the presence of a partner; if currently working; the region of residence. Finally, an overall Quality of Life satisfaction question was asked: "On a scale of 1 to 10, how do you rate your quality of life?". An empty space was added at the end of the questionnaire for further comments or suggestions.

Seven questionnaires were returned, and the results were presented to the group. The questionnaire structure was further modified, and a new version of the questionnaire (Q3) was prepared. Forty-six (54%) items remained unchanged, and 39 (45%) were rephrased to be more easily understandable and clear. One was moved from the functioning and autonomy domain to the psycho-emotional domain. Only one statement was removed, and no new items were added.

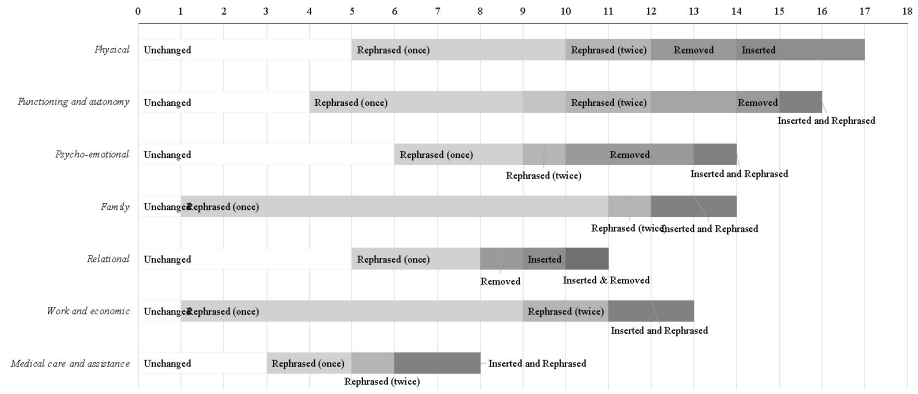
## 2.8 *Fourth Round: Q3 Administration*

The new version of the questionnaire (Q3) comprised 85 items. As in the previous rounds, each participant anonymously filled it in, and the results were subsequently discussed in the group. Seven questionnaires were returned.

Meanwhile, the members of the Steering Committee met some stakeholders of the pharmaceutical industry to understand their perspective and further reflection was made on medications and dressings. This theme was raised with the panellists during the last group meeting, and they pointed out that medications and dressings were an important and time-consuming part of their life. Therefore, the group decided to insert two new items in the final questionnaire to tap this issue "I feel pain during dressing change", "The smell of the ulcers and/or dressings is annoying". Among the other 85 items of Q3, 79 items (93%) remained unchanged, while 6 were slightly rephrased to make the presentation of items homogeneous so that all similar statements started with the same phrase. Hence, the consensus was reached and a final questionnaire with 87 items was developed by the panel.

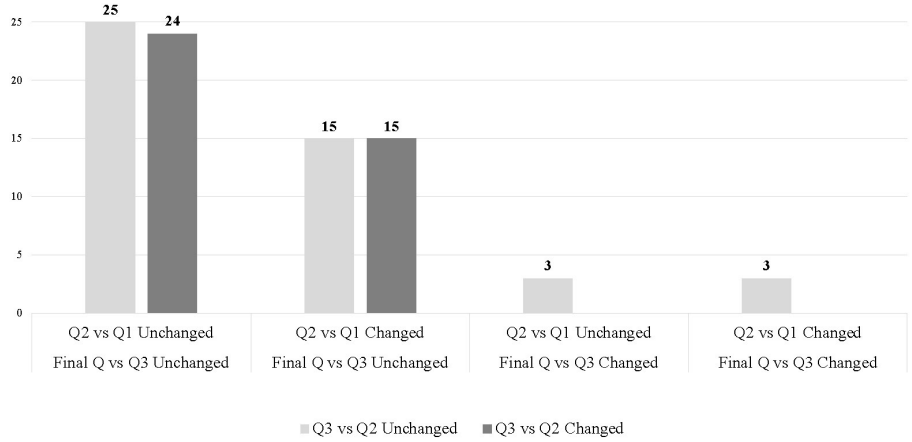
Figure 4 shows how the items within each domain were changed from one round to the subsequent. Figure 5 provides information about overall items changing from the first questionnaire (Q1) to the final one.

Overall, considering the first version of the questionnaire and all the items inserted or removed along the way, the panel created and assessed a total of 93 statements. Only 25 (26.9%) remained utterly unchanged from Q1 to the final version. Fifty-one items (54.8%) were changed at least once, while the remaining 19 (20.4%) were changed twice. No items were changed more than twice. Fifty-four items were rephrased (10 of them were rephrased twice). Eight items were eliminated, while 15 were inserted after Q1 (one of them was inserted and then removed). Three items were originally inserted into one domain and were subsequently relocated into a different one.




Source: elaboration of research data, collected from June to August 2021

FIGURE 4. - Items changing in the different questionnaire domains




Source: elaboration of research data, collected from June to August 2021

FIGURE 5. - *Comparison of items changing from Q1 to the final questionnaire*

## 3. DISCUSSION AND CONCLUSIONS

The present study aimed at developing an easy-to-use and meaningful patient-centred questionnaire for the assessment of HRQoL in patients with EB. The Delphi method was chosen because of its advantages in dealing with broad and complex issues, such as the quality of life of people living with a rare disease. Indeed, it was possible to overcome the methodological limitation of studies with rare diseases patients, namely the small sample size, which makes it difficult to obtain convenient group sizes and undermines the validity of statistical methods. Besides, it was possible to bring together online people with no prior history of communication with one another and living in geographically dispersed locations to effectively discuss a problem as a group. The traditional Delphi method foresees that participants do not meet with each other face to face so that they can freely express unbiased ideas and opinions without feeling the social pressure of the other members (Murphy, Black, Lamping, McKee, Sanderson, Askham and Marteau, 1998). Nevertheless, it was not feasible to guarantee absolute anonymity, as it was chosen to organise (online) face-to-face group meetings to openly discuss the results of each round. Hence, respondents were known by the researchers and even to one another, even though their judgments and opinions when answering the questionnaires remained strictly anonymous making them free to express opinions and positions, filling in the questionnaire at their convenience, having sufficient time to synthesise their ideas and reflect on different sides of the problem. This method proved to be time and cost-effective. The patients proved to be appropriate interlocutors to achieve the aim of the present study and made it possible to create a practical HRQoL questionnaire.

From one iteration to the next, a process of progressive refinement and definition was carried out. Starting from the long list of spontaneously generated statements, a first questionnaire of 80 items was created. The difference between Q1 and Q2 is more pronounced if considering all the items: part of them was modified, others were added or deleted, a couple was moved from one domain to another.

It should be noted that, in some cases, a different view emerged between clinicians and patients, and some information learned by the literature was then rejected or adapted to the language and the experience of the patients (e.g., the terms used to talk about some physical symptoms).

The final patient-centred questionnaire can measure the HRQoL beyond the physical symptoms, encompassing functional autonomy, psycho-emotional state, social relations inside and outside the family context, the working field and several aspects of the medical care and assistance. In line with Pietersma, de Vries and van den Akker-van Marle (2014), mental and social domains were considered crucial when assessing HRQoL. This tool may be a valid aid for clinicians to understand the patient's needs and identify the areas they are more concerned about; moreover, it may allow them to follow the patients over time and evaluate the impact of any treatments. The final version of the questionnaire is to be administered to a sample to assess its qualitative validity and reliability and will be the subject of another study.

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