**Patient participation in the development of a clinical guideline for inherited retinal dystrophies**

P. Serrano-Aguilar, M. M. Trujillo-Martín, T. del Pino-Sedeño, A. Pérez de la Rosa, A. M. de Pascual y Medina, L. Perestelo-Pérez, A. Toledo-Chávarri, M. Posada de la Paz, and A. Sarría Santamera, and the Spanish Inherited Retinal Dystrophies CPG Development Group*

*Evaluation Service of the Canary Islands Health Service (SESCS), Santa Cruz de Tenerife, Spain; Spanish Network of Health Services Research for Chronic Diseases (REDISSEC), Madrid, Spain; Centre for Biomedical Research of the Canary Islands (CIBICAN), University of La Laguna, Canary Islands, Spain; Canary Foundation for Health Care Research (FUNCANIS), Canary Islands, Spain; Canaryian Foundation for Advances in Biomedicine and Biotechnology (BIOAVANCE), Canary Islands, Spain; The Institute of Rare Diseases Research, The Institute of Health Carlos III. Ministry of Economy and Competitiveness, Madrid, Spain; Health Technology Assessment Agency, The Institute of Health Carlos III. Ministry of Economy and Competitiveness, Madrid, Spain.*

**ABSTRACT**

**Objective:** To identify the most relevant self-perceived health problems and unmet needs among adults with inherited retinal dystrophies (IRDs) in order to incorporate patients' perspective from the initial design of a clinical practice guideline (CPG) for IRDs in Spain.

**Research design and methods:** A systematic review (SR) and a survey according to the Delphi method were carried out.

**Main Outcome Measures:** Self-perceived health problems, unmet needs of care and treatment expectations related to IRDs.

**Results:** From the SR, no information was found regarding unmet health care needs or dissatisfaction with health care services. In the survey, the most significant self-reported health problems were progressive decrease in visual acuity, visual field loss, abnormal sensitivity to light or glare, and night blindness. The main unmet needs were scarcity of disease information, lack of protocols for effective disease management and limited professional empathy. Treatment expectations were focused on the availability of protective and aids devices, easier access to rehabilitative services and psychological support.

**Conclusion:** Patient involvement in CPG development helps to reduce the gap between the drawbacks of the routine clinical management and real-life needs of patients, especially in the context of rare diseases as IRDs where evidence-based therapies are scarce.

---

1. **Introduction**

Inherited retinal dystrophies (IRDs) are a group of clinically and genetically diverse rare diseases that constitute a relevant cause of vision loss [1] due to a gradual damage of photoreceptor cells, affecting about 1 in 4000 for a total of more than 1 million affected individuals.[2]

Despite similarities among different IRDs, more than 200 genes associated with various IRDs have been identified and partially characterized at the genetic and molecular level.[3] Therefore, accurate and comprehensive molecular diagnosis is critical to confirm the clinical diagnosis and setting a disease prognosis.[4]

Despite increasing attempts to prevent, arrest, slow, or reverse IRDs, no treatment has proven clear effectiveness to date. The low frequency of IRDs, the complexity of its clinical management, the lack of effective treatment...
alternatives, the increasing role of patient advocacy, and the growing worldwide role of health policies for rare diseases justify the resolution of the Spanish Ministry of Health (MoH) to fund the development of a Clinical Practice Guideline (CPG) to improve the clinical management of IRD patients. This CPG was commissioned to the Evaluation Service of the Canary Islands Health Service (SESCS) as part of the Spanish Network of Agencies for Health Technology Assessment. Besides, SESCS is partner of the project RARE-Bestpractices funded by the European Union Seventh Framework to set methods and improve the availability of high-quality best practice guidance for rare diseases such as IRDs.\[5\]

Several authors suggest patient involvement in CPG development to make them more patient-centered as opposed to disease-centered.\[6–11\] Patients can recognize additional relevant subjects, less valued by health professionals, and emphasize topics where the patient’s perspective varies from the visions of health professionals, ensuring that key issues for affected people are considered. The Program ‘GuiaSalud’ for CPG development, funded by the Spanish MoH (http://portal.guiasalud.es/web/guest/informacion-pacientes), endorses patient participation as a primary stage for patient empowerment, but no specific methodological procedure is recommended to achieve real patient participation in CPG development.

This article describes both the methods used and the results obtained to make sure that the most relevant self-perceived health problems, unmet needs of care, and treatment expectations related to IRDs were early recognized and considered for its inclusion in the planning of CPG development.

2. Patients and methods

Two main activities were implemented to achieve that CPG contents were really patient-focused:

1. Systematic review of the international literature on health problems of IRD patients and their perceived health-care needs and
2. Opinion survey involving people affected by IRDs also scheduling the presence of some representatives of the Spanish Federation of patients with IRDs (FARPE) in the Steering Committee coordinating the CPG design and development.

The focus of these actions has been the identification of the most important health problems and needs of care related to IRDs perceived by the affected patients.

This study was approved by the Ethics Committee of the University Hospital Nuestra Señora de la Candelaria (Tenerife, Canary Islands, Spain).

2.1. Literature review

Initially, an electronic search strategy was developed for Medline (Table 1) including the search filter for patient issues developed by SIGN [12] to identify both qualitative and quantitative studies exploring patient experiences, needs, and preferences related to IRDs. Electronic searches were conducted in Medline and PreMedline via OVID (1966 to January 2014), EMBASE via Elsevier (1974 to January 2014), PsycINFO via EbscoHost (1806 to January 2014), in CINAHL via (1982 to January 2014), and Social Sciences Citation Index via Web of Science (1956 to January 2014). No restrictions in study design were applied. The full search strategy is available from the study authors.

In addition, manual review into all reference lists of included studies was performed. We included studies published in English or Spanish that informed about the perspective of IRD patients and/or their caregivers about their self-perceived main health problems and needs related with the care processes, including diagnosis, treatment, follow-up care, and health-related quality of life; the unmet health needs; the information needs; participation on treatment decision making; and overall satisfaction with the care received. We conducted a peer review process, where two reviewers evaluated in parallel and independently, titles, keywords, and abstracts.

The electronic searches were updated in July 2015. However, no new studies that fulfilled eligibility criteria were identified.

2.2. Opinion survey among IRD patients

We conducted a three-round consensus-building survey to IRD patients by means of the Delphi method supported by electronic mail. Participants were recruited with the support of FARPE to maximize patient enrolment by means of an

| Table 1. Medline/PreMedline search strategy. |
|-----------------------------------------------|
| 1. "Retinal Dystrophies/or "Retinitis Pigmentosa/" |
| 2. (Pigmentary retinopathy or Rod-cone dystroph* or Rod cone dystroph* or Retinal Dystrophy* or Retinitis pigmentosa or pigmentary retinosi* or retinosis pigmentary or retinosis pigmentosa or North Carolina Macular Dystrophy or Stargardt-Fundus flavimaculatus or stargardt’s fundus flavimaculatus or Stargardt’s disease or Stargardt Macular Degeneration or Stargardt disease or fundus flavimaculatus or Sorsby dystrophy or Gyrate Atrophy or Atrophia Gyrala or Enhanced S-cone Syndrome or Goldman- Fave or Wagner-Stickler or vitreoretinal dystroph* or X-linked Juvenile Retinoschisis or Occult Macular Dystrophy or Macular dystrophy* or Choroideremia or Congenital Stationary Night Blindness or central areolar choroidal dystrophy or Bestrophinopathy or Bestrophinopathies or Best Vitelliform Macular Dystrophy or Vitelliform Macular Dystrophy or Familial Exudative Vitreoretinopathy or adult-onset foveomacular Dystrophy or Butterfly-shaped pattern dystrophy or Pattern dystrophies in Retinal Pigment Epithelium or Autosomal dominant Stargardt-like macular dystrophy or Stargardt Macular Degeneration or Stargardt disease).ab.ti. |
| 3. (Preferences or priorities or needs or quality of life or satisfaction or health behavi* or attitudes or demands or perspective or perception or narrative or psicolog* or patient information or ethics or life style or health knowledge or decision making or acceptability).tw. |
| 4. (Recruit* or participat* or ‘focus group’ or instrument* or scale* or questionnaire* or survey* or interview* or ‘nominal group’ or delphi*).mp. |
| 5. 1 or 2 |
| 6. 3 or 4 |
| 7. ‘Patient Education as Topic’ |
| 8. Retinal Diseases/px [Psychology] |
| 9. 5 or 8 |
| 10. 6 or 7 |
| 11. 9 and 10 |
| 12. limit 11 to (English or Spanish) |
Supplemental data

vision days, possibly depending upon the type of RP, 17 and 90th percentile range state higher 13

affected by retinitis pigmentosa (RP) and other types of IRDs, the same median, the 10–90th percentile range states higher 13

including a cover letter signed by the presidency of FARPE and the principal investigator. This letter contained information about the study aims and the proposed methodology (Supplemental data). Consent was requested according to the Declaration of Helsinki. To warrant anonymity, an alphanumeric code was allocated to every participant.

The three consecutive questionnaire templates were built on the SurveyMonkey® Data Analysis tool and distributed by e-mail (Supplemental data). The survey started in May 2014 and ended in July 2014. All patients who responded to the previous survey received the questionnaire of the subsequent round. According to Serrano-Aguilar et al.[13] for the first stage, three open-ended questions concerning (1) the most important self-reported health problems associated to IRDs, (2) unmet needs and unsatisfactory aspects of health care for IRD patients in the Spanish National Health Service (NHS), and 3) therapies of interest for IRD patients were e-mailed to each participant consenting to participate.[13] First round answers were analyzed in detail and grouped into categories, for every question. The second Delphi stage was designed to prioritize previously identified categories for every question. The importance of each category was assessed by each participant on a scale from 1 to 10, giving the top scores to the main topics and the bottom scores to the less important. Responses were ordered along with its importance level by estimating the median value due to its highest validity to manage extreme scores when figures do not follow a normal distribution. To set ranking differences for topics with the same median, the 10–90th percentile range was used, given that topics with lowest 10–90th percentile range state higher agreement levels among participants.[13]

The last survey was aimed to reach final agreement. After ordered, results achieved along the second stage were sent back to participants with added information about every participant’s prior assessment. With this supportive information, patients were asked to review their previous responses. We used majority voting to analyze definitive answers due to its value to provide reliable outcomes and to resolve contentious issues in large Delphi panels.[14]

3. Results

3.1. Literature review

The literature review provided very scarce results on health problems self-perceived by IRD patients. From 97 initially identified studies of potential interest, specific findings on IRDs-related health problems were limited to two quantitative studies based in surveys [15,16] and three qualitative studies using in-depth interviews [17,18] or focus groups.[19] No information was found regarding unmet health-care needs or dissatisfaction with health-care services. The main characteristics of included studies are shown in Table 2.

Heckenlively et al.[16] in a prospective study with patients affected by retinitis pigmentosa (RP) and other types of IRDs, reported on the main clinical symptoms and signs self-perceived by patients. Though all patients showed contracted visual fields at examination, 23.2% claimed no visual field changes, 13.8% reported no symptoms of night blindness, and 18.0% stated that they saw better at dusk. The most common reported problem was headache (53.3%) with a weekly or even lower frequency. The second most common problem affecting 34.6% of patients was light flashes associated to advances stages of IRDs. Numbness or tingling, mainly in extremities, was reported by 20% patients. Choroideremia and Usher syndrome patients had early nyctea-lopia. Episodes of acute visual loss were identified by 40.1% patients, 16.8% claiming stress as main potential factor. Deafness (partial or full) was reported by 20.6% patients, arthritis by 8.4%, neurologic deficits by 7.2%, vascular problems by 6.2%, polydactyly by 2.2%, and seizures by 3.2%. Overall, no improvement was reported by medication use, and of 83 smokers, only 2 stated that cigarettes affected their vision. Some myths or misstatements were incorrectly managed by ophthalmologists related to the predicted dates for blindness, the need of learning Braille and white cane. Mobility training is seldom wanted by patients unless their visual field is less than 3 degrees. Genetic counseling was frequently erroneous or misleading.

Bittner et al. [19] provided self-reported patients’ experiences with disease by means of focus groups limited to legally blinded patients affected by RP. In spite of the limited sample used, their outcomes seems valid for qualitative studies, highlighting several types of day-to-day visual fluctuations: intermittent diplopia; difficulty for focusing and using the two eyes; photopsias, flashes or moving patterns of light; Charles Bonnet syndrome; and transient white vision due to high glare and characterized by a circadian changeability. The subjects with the smallest visual fields described worst vision early in the morning, requiring several minutes to hours to reach their usual function levels. Participants described that stress caused by fast paced work might explain their visual fluctuations. Stress was also reported to increasing flashes and floaters frequency and intensity. There was no clear consensus among participants as to whether cloudy or sunny weather affected ‘good’ and ‘bad’ vision days, possibly depending upon the type of RP, specific genetic mutation in the retina, and degree of vision loss. On the other hand, the level of brightness does affect vision in RP, likely due to a loss of contrast sensitivity. According to Bittner et al. [15] in a previous survey to RP patients, besides stress, other factors associated with increasing photopsias were bright light, fatigue, exercise, and absence of light. The use of coping strategies to manage the stress of vision loss was common. Social support and communicating with other RP patients are part of the coping process that has been helpful. Patients found helpful to keep hope for advances in therapeutic research. Access to assistive technology and devices for low vision are considered very helpful to maintain independence and ability to carry out daily activities.[19] Similar findings were reported by Combs et al. in two publications focused on exploring self-perceived needs and access to genetic ophthalmological services by IRD patients in interviews.[17,18]
3.2. Opinion survey among IRD patients

Ninety-six complete answers were obtained in the first round of consultation after inviting approximately 300 associated patients from FARPE. The participation dropped to 58 and 49 in the second and third rounds of consultation, respectively, reaching a participation rate for all Delphi rounds of 60.46% in respect to the initial number of participants. The main demographic and clinical characteristics are presented in Table 3. Participants’ distribution of residency was spread through 15 of the 17 Spanish autonomous regions.

Prioritized self-reported IRD-associated symptoms provided by patients are shown in Table 4, ranked according to the median and percentile range. Consensus was obtained by majority voting with a 93% of agreement. The most frequently reported health problems, in decreasing order of importance, were progressive loss of visual acuity, visual field reduction, abnormal sensitivity to light or glare, loss of autonomy and depending on others for daily life activities, and night blindness. Besides, acute visual loss was occasionally identified related to stressful situations.

Though satisfied with the general care offered by the NHS in Spain, participants showed frustration with the small amount of funding devoted to research in new treatments and with the information available on these diseases. Patients claimed for more and valid information regarding diagnosis, expected clinical progression and prognosis, therapeutic options and protective measures available. Other sources of dissatisfaction were the lack of specific clinical units or qualified services; barriers to genetic studies; difficulties to get professional, technical, and economic support to the disease adaptation process; waiting lists for diagnosis confirmation and follow-up; reduced professional empathy; barriers to access to psychological treatment; and lack of protocols for effective and homogeneous clinical management. The degree of importance of main IRD-related unmet needs and reasons for dissatisfaction with the Spanish NHS are shown in Table 5.

Information on therapeutic and/or rehabilitative approaches of interest was obtained from the 96 participants in the first round of consultation (Table 6). This information is categorized in three groups, i.e. rehabilitative support, psychological support, and pharmacological/supplement products. Something less than a third of participants (30.21%, 29/96) had access to some type of visual/hearing rehabilitative

### Table 2. Main characteristics of selected studies.

| Study | Country | Design          | Sample size | Type of IRDs                                                                 | % Women | Objective                                                                 | Sample Characteristics                                                                 |
|-------|---------|-----------------|-------------|-----------------------------------------------------------------------------|---------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Bittner, 2010 [15] | USA | Survey          | 127         | RP, CHD, and other IRDs                                                      | 55      | To explore photopsias in self-reported retinitis pigmentosa               |                                                                                         |
| Heckenlively, 1988 [16] | USA | Survey          | 500         | RP, USH, CHD, and other IRDs                                                 | 45      | To review symptoms and associated health problems                        |                                                                                         |
| Combs, Hall, Payne, and Lowndes, 2013 [17] | UK | In-depth interview | 20         | RP, USH, CHD, and other IRDs                                                  | 12      | To explore the views and perception of patients with IRDs and their relatives |                                                                                         |
| Combs, McAllister, Payne, Lowndes, 2013 [18] | UK | In-depth interview | 20         | RP, USH, CHD, and other IRDs                                                  | 12      | To explore the views and perception of patients with IRDs and their relatives |                                                                                         |
| Bittner, 2010 [19] | USA | Focus group     | 8           | RP, USH, CHD, and other IRDs                                                  | 75      | To understand RP patient perceptions of stress and management of IRDs    |                                                                                         |

### Table 3. Demographic and clinical characteristics of the patients (N = 49).

| Variable                        | Value        |
|---------------------------------|--------------|
| Age, years [mean, (SD)]         | 44.29 ± 5.1  |
| Sex (%)                         |              |
| Women                           | 38.50        |
| Men                             | 62.50        |
| Diagnostic (%)                  |              |
| Retinitis pigmentosa            | 65.30        |
| Stargardt’s disease             | 18.38        |
| Familial drusen                 | 6.12         |
| Cone-rod dystrophy              | 6.12         |
| Usher syndrome                  | 2.04         |
| Bietti’s crystalline dystrophy   | 2.04         |
| Mean duration of illness, years [mean, (SD)] | 19.15 ± 12.3 |
| Support for daily life activities (%) | 41.63       |
Table 4. Self-reported IRD-related health problems ordered by the median and 10–90th percentile range*.

| Visual symptom patterns in IDRs                      | All   | RP     | STGD   | FD     | CRD    |
|-----------------------------------------------------|-------|--------|--------|--------|--------|
|                                                    | Median| PR     | Median | Median | Median | Median | Median |
| Progressive loss of visual acuity                   | 10    | 8–10   | 10     | 7.5–10 | 10     | 9–10   | 10     | 10–10  | 6      | 4.4–7.6|
| Reduced visual field                                | 10    | 6.7–10 | 9      | 8–10   | 9      | 6.5–10 | 7      | 4.6–9.4| 9      | 8.2–9.8|
| Abnormal sensitivity to light or glare              | 9     | 8–10   | 8.5    | 6.5–10 | 9.5    | 5.5–10 | 8.5    | 8.1–8.9| 9      | 8.2–9.8|
| Night blindness                                     | 9     | 5–10   | 9      | 6.5–10 | 8      | 5.5–10 | 5.5    | 3.5–7.5| 7      | 4.6–9.4|
| Reduction of visual contrasts and color recognition | 8     | 4–9    | 7      | 3–9    | 7.5    | 6–9    | 8      | 8–8    | 5.5    | 4.3–6.7|
| Eye strain                                          | 7     | 3–9    | 6      | 3–8    | 7      | 4–8.5  | 7      | 7–7    | 5.5    | 4.3–6.7|
| Loss of relief vision                               | 7     | 3–8.3  | 7      | 2–9    | 7.5    | 6.5–9  | 7      | 6.2–7.8| 6      | 5.2–6.8|
| Blurred vision that patient perceived as cataract-related | 6   | 3–9    | 6      | 3.5–9  | 5.5    | 4–6.5  | 7      | 5.4–8.6| 3.5    | 2.3–4.7|
| Other health problems                               |       |        |        |        |        |        |        |        |        |        |
| Lack of autonomy for daily life activities          | 9     | 5.5–10 | 10    | 6–10   | 9.5    | 8.5–10 | 3      | 2.2–3.8| 5.5    | 4.3–6.7|
| Headache and/or neck contracture to compensate for visual impairment | 5     | 1–8    | 6      | 1–8.5  | 6      | 3–7.5  | 3.5    | 1.5–5.5| 5.5    | 5.1–5.9|

CRD, cone-rod dystrophy; FD, familial drusen; PR, 10–90th percentile range; RP, retinitis pigmentosa; STGD, Stargardt’s disease.

*Usher syndrome and Bietti’s crystalline dystrophy were omitted because n = 1.

Table 5. Self-reported IRD-related unmet needs and reasons for dissatisfaction with the Spanish NHS ordered by the median and 10–90th percentile range.

| SERC'i needs                                         | Median | 10–90th percentile range |
|-----------------------------------------------------|--------|--------------------------|
| Scarcity of research on therapeutic options          | 10     | 10–10                    |
| Lack of information about the disease                | 10     | 8–10                     |
| Lack of specialized care units                       | 9      | 7–10                     |
| Access difficulties to genetic studies               | 9      | 6–10                     |
| Lack of support in the adaptation process (professional, technical, and economic) | 9      | 5–10                     |
| Waiting lists for diagnostic tests and monitoring    | 8.5    | 5–10                     |
| Lack of professionals empathy                        | 8      | 4–10                     |
| Access difficulties to treatment or counseling       | 8      | 3.7–10                   |
| Lack of valid and homogeneous protocols for diagnosis and clinical management | 8      | 4.1–10                   |

Table 6. Self-perceived IRD-related therapeutic alternatives of interest for patients ordered by the median and 10–90th percentile range.

| Adequate protective and aids devices                | 10     | 8–10                     |
| Comprehensive rehabilitation (visual and /auditory) | 9      | 5.7–10                   |
| Recommendations to prevent worsening                | 9      | 8–10                     |
| Healthy behaviors: diet, physical activity, adequate rest, and activities to avoid Psychological support | 9      | 7–10                     |
| Vitamins and other supplements                      | 8      | 5.7–10                   |
|                                                    | 7      | 4.7–9                    |

services; 23.96% (23/96) received some form of psychological support; 33.33% (32/96) underwent some type of pharmacological or supplement treatment. While 14.58% (14/96) of participants underwent psychological support and visual rehabilitation, only 4.16% (4/96) received pharmacological treatment combined with visual rehabilitation. In all cases where patients reported using visual rehabilitation and/or psychological support services, these were provided by the Spanish National Organization for the Blind (ONCE), a nongovernmental national organization.

Finally, the most valued treatment expectations were, in decreasing order of importance, protective and aids devices such as special glasses for ultraviolet sun radiation protection, filters and magnifying glasses to work with computers and phones; better access to integral rehabilitative services (visual and auditory); psychological support; and vitamins and diet supplements. In addition, more accessible and evidence-based information about healthy lifestyles to improve self-management and to avoid disease worsening was requested by patients.

Finally, all subjects addressable by the CPG were identified and used to feed the list of possible clinical questions to be included in the CPG and to improve the search strategy for the systematic review on patients’ values and preferences. Table 7 shows the preliminary list of topics for the CPG developed after joining the three sets of prioritized subjects provided by patients with the questions prioritized by expert clinicians and researchers. The following four questions suggested exclusively by IRD patients finally included after consideration by the Steering Committee, were as follows: Are vitamin and nutritional supplementation effective?; Are there effective measures to avoid or reduce disease worsening?; Which is the effectiveness of psychosocial interventions to improve quality of life of patients and caregivers?; and Are lifestyle changes (diet, physical exercise, and tobacco consumption) effective to improve health status in IRD patient? Other four included topics were coincidently suggested both by clinical experts and by patients (Table 7).

4. Discussion and conclusion
This study describes both the process used to identify the main IRD-related health problems and needs of care from the patients’ perspective, as well as the outcomes obtained to guide the design and development of a CPG.

We only found five previous studies providing information about self-reported health problems related to IRDs by means of surveys,[15–18] or focus groups,[19] three of them from the USA [15,16,19] and two from the UK.[17,18] Despite the differences in the methods used to get the information in these studies, we obtained comparable results in Spain by using a Delphi-based approach. As we could not find published information related with unmet health-care needs and/or patient dissatisfaction with health care services for IRD patients neither in Spain nor in any other country we took advantage of the properties of the Delphi technique to gather this information in the Spanish context.
Table 7. Selected topics for the CPG provided by clinical experts and/or patients.

| Selected clinical topics                                             | Experts | Patients |
|----------------------------------------------------------------------|---------|----------|
| Early clinical awareness of IRDs for children in primary care        |         | x        |
| Early clinical awareness of IRDs for adults in primary care          |         | x        |
| Appropriate tests and indications for diagnosis confirmation         | x       |          |
| Indications for genetic tests                                       | x       | x        |
| Early clinical awareness of syndromic IRDs                          |         | x        |
| Criteria for referring IRD patients to ORL specialists                |         | x        |
| Criteria for referring IRD patients to pediatric specialists          |         | x        |
| Appropriate electrophysiological tests and indications               |         | x        |
| Established diagnostic criteria of IRDs                             |         | x        |
| Appropriate indications of genetic counseling                        | x       | x        |
| Family physicians’ role in management of IRD patients                |         | x        |
| Frequency of follow-up ophthalmological visits                       |         | x        |
| Effective treatments and outcome measures                            |         | x        |
| Effectiveness and safety of vitamin and nutritional supplementation   |         |          |
| Effective measures to avoid worsening of IRDs                        |         | x        |
| Effectiveness of psychosocial interventions on patients’ and caregivers’ quality of life | x | x |
| Appropriate structured education to patients and families            |         | x        |
| Effectiveness and benefits of low vision rehabilitation and vision aids devices | x | x |
| Effectiveness of lifestyle recommendations for IRD patients          |         | x        |
| Pregnancy in women with IRDs                                       |         | x        |
| Appropriate indications of associate cataract surgery in IRD patients|         | x        |
| Prevention of retinal detachment in IRD patients                    |         | x        |
| Appropriate retinal detachment treatment in IRD patients            |         | x        |
| Appropriate treatment of associated macular edema in IRD patients    |         | x        |
| Appropriate treatment of associate vascular membranes according to age of IRD patients | x |          |

IRDs, inherited retinal dystrophies.

Most participants highlighted the importance of visual rehabilitation and psychological support, regardless of accepting that neither of them are curative. The fact that no participant received these particular supportive services from their respective public regional health services in Spain gives us an argument not just to include these topics in the CPG but also to draw the attention of health authorities, at national and regional levels, to improve the availability of these supportive services for IRD patients. Expectations on low vision rehabilitation (assistive technology and devices) are focused on improving the ability to perform daily-life activities in order to maintain independence. Patient expectations about psychological support seek to improve disease acceptance, mental well-being, self-esteem, and social relationships.

Despite that recognized institutions in the development of CPGs promotes patient participation, documented experiences of collaboration between CPG developers, clinicians, researchers, and affected people are infrequent.[13,20] Several authors state that this type of participation increase the need of additional resources and time.[21,22] Nevertheless, with the aid of communication technologies, this study achieved a satisfactory level of recruitment, rapidly and inexpensively regardless of that IRDs are rare diseases. According to Jones and Hunter, the Delphi method is an operative qualitative methodology to elucidate unclear subjects and it provides quantitative estimates that should be broadly interpreted and tested against observed data before conceding them full confidence.[23] For that reason, we use to combine a review of the published literature with a following context-specific Delphi consultation.

This study provides additional evidence on the achievability and value of patient participation in the design of CPG, suggesting the use of the Delphi technique supported by e-mail distributed in cooperation with patient organizations as a valid and efficient method. Consideration of patient experiences with their diseases warrants that CPG responds to the patients’ main needs.[24,25] We had observed similar results using the same methodology for a CPG on systemic lupus erythematosus.[20]

According to other researchers, this study illustrates that patients are willing and capable to efficiently provide information to guide the contents of CPG, complementing the contents suggested by clinicians and researchers,[13,20] preventing difficulties experienced by patients caused by face-to-face interactions with professionals. Besides, this method also prevents contamination effects among patients.[26,27] Similarly to this reported case, several authors claim that patients’ input should be incorporated in CPG development by means of a multicomponent approach including inviting them into the guideline coordinating team, a literature review focused on patient needs and expectations, and a patients’ survey in the specific setting where the CPG is intended to use.[11,13,20,28]

We acknowledge several limitations in this study. Firstly, the lack of probabilistic selection of participants. Patients were asked to join the study by means of electronic mails from FARPE at national and regional levels, blinding the possibility of assessing the representativeness of IRD participants. Despite that not all types of IRDs were represented in the study, the sample distribution of the included IRDs is similar to the prevalence distribution published by Orphanet.[29] Besides, the sample was similarly distributed in relation to the need of a caregiver (41.65% need the support of a companion). This finding, together with those from the literature review, contributes to the internal validity of our results.[15,16,19] Though according to Serrano-Aguilar et al.[13,20] data collection by means of electronic mail using the Delphi technique has shown effectiveness, the accessibility to electronic equipment and physical restrictions, especially among visually impaired patients, might be considered as another potential limitation and source of bias. Nevertheless, other authors have also successfully completed broad surveys to IRD patients by means of Internet.[15] Finally, as the three-round Delphi consultations were supported by means of electronic templates attached to e-mails messages requiring considerable effort and the use of screen readers’ devices and/or magnification tools to be used by IRD patients, the visual limitation itself might also have impeded the participation of those more affected patients.[13,20]

We conclude that the early patients’ involvement in the CPG development by a combination of valid and efficient methods improves its patient-centeredness, particularly in the context of rare diseases where limited availability and validity of scientific information on clinical issues open the opportunity to include relevant issues for patients.
Acknowledgments

We gratefully acknowledge the cooperation of Mr. Germán López Fuentes, President of the Spanish Federation of Association of Retinitis Pigmentosa (FARPE).

Declaration of interest

This work was supported by the Ministry of Health, Social Affairs and Equality of Spain in cooperation with the Institute of Health Carlos III, the Canary Foundation for Health Care Research (FUNCANIS) in the framework of the Spanish Network of Health Technology Assessment, the Spanish Network of Health Services Research for Chronic Diseases (REDISSEC), and the IMBRAIN project (FP7-REGPOT-2012-CT2012-31637-IMBRAIN) funded under the 7th Framework Programme (Capacities). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as:

- of considerable interest
  1. Inglehearn C. Molecular genetics of human retinal dystrophies. Eye. 1998;12:571–579.
  2. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet. 2006;368:1795–1809.
  3. Daiger SP, Sullivan LS, Bowne SJ. RetNet: genes and mapped loci causing retinal diseases, RetNet - retina. Inf Netw. 2016 [cited 2016 April 12]. Available from: https://sph.uth.edu/RetNet/sum-dis.htm#A-Genes
  4. Jin X, Qu LH, Meng XH, et al. Detecting genetic variations in hereditary retinal dystrophies with next-generation sequencing technology. Mol Vis. 2014;20:553–560.
  5. Serrano-Aguilar P, Linertová R, Posada-de-la-Paz M, et al. Recruitment procedures for descriptive socio-economic studies in rare diseases. The BURQOL-RD project. Expert Opin Orphan Drugs. 2015;3:759–765.
  6. Tong A, Lopez-Vargas P, Howell M, et al. Consumer involvement in topic and outcome selection in the development of clinical practice guidelines. Heal Expect. 2012;15:410–423.
  7. Rankin N, Newell S, Sanson-Fisher R, et al. Consumer participation in the development of psychosocial clinical practice guidelines: opinions of women with breast cancer. Eur J Cancer Care (Engl). 2000;9:97–104.
  8. Schümemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 10. Integrating values and consumer involvement. Health Res Policy Syst. 2006;4:1–8.
  9. Van Wersch A, Eccles M. Involvement of consumers in the development of evidence based clinical guidelines: practical experiences from the North of England evidence based guideline development programme. Qual Heal Care. 2001;10:10–16.
  10. Graham ID, Beardall S, Carter AO, et al. The state of the science and art of practice guidelines development, dissemination and evaluation in Canada. J Eval Clin Pract. 2003;9:195–202.

**This is the first publication that explores self-reported IRDs-related symptoms and health problems.**

11. Health Council of the Netherlands: From implementing to learning: The importance of a dialogue between practice and science in health care. The Hague: Health Council of the Netherlands, 2000; publication no. 2000/18E.

12. Scottish Intercollegiate Guidelines Network. Scotland: Scottish Intercollegiate Guidelines Network, Patient Issues, Search Filters; 2014 [cited 2014 January 13]. Available from: http://www.sign.ac.uk/methodology/filters.html#pat

13. Serrano-Aguilar P, Trujillo-Martin MM, Ramos-Goñi JM, et al. Patient involvement in health research: A contribution to a systematic review on the effectiveness of treatments for degenerative ataxias. Soc Sci Med. 2009;69:920–925.

14. Ali AK. Using the Delphi technique to search for empirical measures of local planning agency power. Qual Rep. 2005;10:718–744.

15. Bittner AK, Diener-West M, Dagnelie G. A survey of photopsias in self-reported retinitis pigmentosa: location of photopsias is related to disease severity. Retina. 2010;29:1513–1521.

16. Heckenlively JR, Yoser SL, Friedman LH, et al. Clinical findings and common symptoms in retinitis pigmentosa. Am J Ophthalmol. 1998;105:504–11.

**This is the first publication in Spain that describes this methodology to incorporate patients’ perspective in the design of a clinical practice guideline.**

17. Combs R, Hall G, Payne K, et al. Understanding the expectations of patients with inherited retinal dystrophies. Br J Ophthalmol. 2013;97:1057–1061.

18. Combs R, McAllister M, Payne K, et al. Understanding the impact of genetic testing for inherited retinal dystrophy. Eur J Hum Genet. 2013;21:1–5.

19. Bittner AK, Edwards L, George M. Coping strategies to manage stress related to vision loss and fluctuations in retinitis pigmentosa. Ophthalmometry. 2010;81:461–468.

20. Serrano-Aguilar P, Trujillo-Martin M, Pérez De La Rosa A, et al. Patient participation in a clinical guideline development for systemic lupus erythematosus. Patient Educ Couns. 2015;98:1156–63.

**This is the first publication in Spain that describes this methodology to incorporate patients’ perspective in the design of a clinical practice guideline.**

21. Boote J, Telford R, Cooper C. Consumer involvement in health research: a review and research agenda. Health Policy (New York). 2002;61:213–236.

22. Whitstock MT. Seeking evidence from medical research consumers as part of the medical research process could improve the uptake of research evidence. J Eval Clin Prac. 2003;9:213224.

23. Jones J, Hunter D. Consensus methods for medical and health services research. Br Med J. 1995;311:376–380.

24. Buckley B. Identifying uncertainties to prioritise research. Nurs Times. 2008;104:38–39.

25. Partridge N, Scadding J. The James Lind Alliance: patients and clinicians should jointly identify their priorities for clinical trials. Lancet. 2004;364:1923–1924.

26. Amstein SR. A ladder of participation. Young. 1969;35:216–224.

27. Oliver S, Rees R, Milne R, et al. Involving consumers in research and development agenda setting for the NHS, health technol. Assess (Rocky). 2004;8:1–148.

28. Bastian H. Raising the standard: practice guidelines and consumer participation. Int J Qual Heal Care. 1996;8:485–490.

29. Rath A. Prevalence and incidence of rare diseases: bibliographic data. Orphanet Rep Ser Rare Dis Collect. 2013;1:1–55.