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Handbook #13: Patients' involvement in the development of CPGs and CDSTs on rare, low-prevalence and complex diseases: a guide for the chair and members of GDGs

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LEGAL NOTICE

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(DG Health and Food Safety).

Purpose:

This handbook provides the main steps and relevant considerations for including the patient community when developing a clinical practice guideline or a clinical decision support tool on rare diseases. It also sets out approaches to involve and engage them throughout the process and methods to gather feedback from them.

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ABBREVIATIONS

CDSTs	Clinical Decision Support Tools
CPGs	Clinical Practice Guidelines
CWG	Core Writing Group
ERN	European Reference Networks
ETD	Evidence to Decision
EU	European Union
FPS	Fundación Progreso y Salud
GDG	Guideline Development Group
GIN	Guideline International Network
GRADE	Grading of Recommendation Assessment, Development and Evaluation
PAG	Patient Advisory Group
PICO	Population, Intervention, Comparison and Outcome
PROM	Patient-Reported Outcome Measure
RKMMF	Rare Knowledge Mining Methodology Framework
SPIDER	Sample size, Phenomenon of Interest, study Design, Evaluation, Research

01.

BACKGROUND

There are a number of challenges surrounding the development of CPGs and CDSTs for rare diseases. One of the most relevant barriers is the lack of high-quality evidence, which cutting-edge methodological frameworks like GRADE[1] rely on.

Therefore, there is a need for specific methodological approaches that can provide reliable and useful CPGs and CDSTs for rare diseases. The project also aims to provide a common methodology to harmonise the development of CDSTs and CPGs.

It is worth noting that within the scope of this document, "rare diseases" is the term used to refer to rare diseases, as well as low prevalence complex diseases. In addition, the term "patient community" includes patients themselves, as well as their representatives, relatives and carers.

1.1 | Context for the involvement of patients with rare diseases in the development of CPGs and CDSTs

Patient involvement in guideline development is recognised by all international methodologies (GRADE, AGREE, ADAPT, GIN) as an essential foundation stone for a high-quality guideline[1, 2, 3,4]

The importance of meaningful involvement of patients and patient representatives in further underlined rare disease guidelines is due to the low prevalence of each condition, the medical expertise, knowledge, and care being scarce, and future research opportunities being limited[4].

Thus, including them at earlier stages of CPG development helps to identify, prioritize, and take in several topics relevant for patients with rare diseases, as questions to be answered in the CPG that would otherwise be missed by clinical experts and researchers[5].

Consensus deriving from the international best practice methodology requires that active involvement of patient and patient representatives in the guideline development group is essential. Furthermore, a broader cohort of patients and patient representatives should be engaged at critical stages throughout the guideline development process[23].

This document aims to provide guidance on the process of enabling active **participation** and **engagement** of the patient community with rare diseases in the development of CPGs and CDSTs.

1.2 | Profiles within the patient community and their participation in the development of CPGs

Participants with different profiles can make the voice of the patient community heard in the

development of CPGs. Each profile can give a different perspective on the condition. Thus, it is important to involve individual patients, carers, expert patients and representatives of the patient groups that can provide several complementary perspectives. The characteristics of each participant and the potential contributions they could make to the CPG development process are described below.

Individual patients and carers affected by a rare disease have expertise gained from the lived experience of living with their health issue and understanding the holistic needs and impact on daily life. They can provide valuable insight that could be important for the development of CPGs and compensate for the lack of information on rare diseases[4].

Expert patients demonstrate profound understanding of pertinent facts, possess experience within a specific field, give a perspective and have strong communication skills. Beyond having knowledge of the disease, they have relevant engagement experience with academic and other stakeholders. These patients can assume diverse roles. For example, they can be responsible for patient education and self-management with the condition, as well as for educating healthcare professionals, particularly physicians and nurses, who may sometimes overlook the significance of the experimental knowledge of the patient with the disease by focusing only on disease[6].

Representatives of the patient groups play an important role in ensuring that the perspective of the patient community, patient organisations and real-life experiences are integrated in GDG deliberations. They also play an important role in identifying potential topics that may require or would benefit from additional patient consultation, ensuring that patient inputs are adequately considered. The representatives encourage the GDG to reflect on the real-life implications of regulatory decisions, promoting a patient-centred approach[7]. Among the patient representatives, there are those called "**patient advocates**" who have a potential advantage because they are specialised in representing patients, survivors and carers. Patients advocates have the resources and capacity to prepare responses that are based on a wide range of patient experiences, which is why they represent a very good option for giving a voice to the patient community[8]. Patient advocacy groups may be a useful resource for recruiting patients to participate in CPG development[9]. Therefore, before beginning to develop a CPG, it is advisable to contact relevant patient advocacy groups or patient organisations involved in rare disease research to ask about opportunities for their patients to participate in CPG development and recruitment strategies[9].

An important aspect to highlight for the representatives of the patient groups is the need to be totally transparent with respect to their activities and funding sources[10]. This aspect is something that they will have to declare before becoming involved in the development of a CPG, like the other members of the GDG.

As mentioned, the importance of considering all the profiles described when preparing a CPG lies in the different inputs that each one can contribute. While individual patients and carers provide first-hand experiences, expert patients contribute specialised knowledge, and representatives of the patient groups ensure the inclusion of diverse patient perspectives. Their involvement in the guideline development process ensures guidelines that truly prioritizes patient-centred care[4,6,7].

For the purpose of this document, the term "patients" is used as a generic term that encompasses individual patients, carers and representatives of the patient groups.

Key issues

- ✓ Rare diseases patients and cares can bring first-hand experiences and interesting aspects that can compensate for the lack of information in rare disease.
- ✓ Expert patients possess experience and give a profound understanding, perspective, while representatives of the patient groups ensure a patient-centred approach in CPG.

02.

REPRESENTATIVES OF THE PATIENT COMMUNITY: THE ROLE IN THE GUIDELINE DEVELOPMENT GROUP(GDG) AND THE PATIENT ADVISORY GROUP (PAG)

2.1 | Composition of the GDG, and its relationship with the PAG

As stated in Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare or Low-Prevalence and Complex Diseases[11], Handbook #3: Adaptation and Adoption of Clinical Practice Guidelines and Clinical Decision Support Tools for Rare or Low-Prevalence and Complex Diseases[12] and Handbook #4: Methodology for the Development of CPGs for Rare Diseases, the GDG must be multidisciplinary and represent the expertise and views relevant to the particular needs of the guideline[13]. The GDG has four key constituents:

- ✓ Healthcare professionals who are involved at any stage of care for patients with rare diseases.
- ✓ International experts in the guideline topic.
- ✓ **Representatives of the patient community**
- ✓ Technical team (methodologist, information specialist, health economics expert).

In this document (Handbook #13), the focus is on one of these four constituents: Representatives of the patient community (referred to in the previous 12 handbooks as patient and carer representatives), who, for the purpose of this document, cover: Individual patients and carers, expert patients and representative of the patient group.

The GDG is made up between 7 and 15 members, as mentioned in Handbook #4: Methodology for the Development of CPGs for Rare Diseases. A large group exceeding 15 members is deemed excessive and unmanageable, while a group with less than 7 members lacks the necessary

representativeness[13]. While no consensus exists regarding the optimal number of representatives from the patient community that should be involved, it is essential to include at least one or two[14]. The involvement of at least two patients has been reported to offer different advantages, such as[2, 4]:

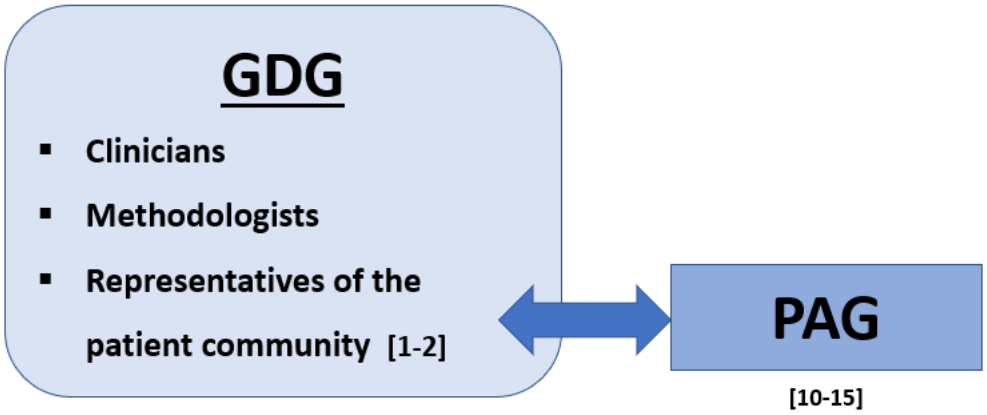
- Providing partners to work with other patients and members.
- Reducing the feeling of isolation, which is a known barrier to patient participation.
- Building confidence, providing social support and empowering meaningful patients to contribute.
- Expanding the groups ´ experiences and ensuring different aspects of the CPG are covered from the patients' or members ´ perspective.
- Compensating for the lack of information on rare diseases.

A good example of this practice can be seen in the study conducted by Bruce et al., (2022). This study specifically focused on the inclusion of three patient advocates as active participants in the CPG development process[15]. However, it is recommended to recruit people who represent the different profiles within the patient community[2] so that they can make contributions on the complex conditions addressed and to deal with different roles or tasks.

In addition to the individuals representing the patient community who will participate as core members of the GDG, it is advisable to create a Patient Advisory Group (PAG). The PAG is made up of between 10-15 patients or representatives of the patient group to provide advice on the CPG development. In this way, the GDG will have direct access to a broader range of patient perspective, allowing for a structured way of participating in key stages of the guideline development process. The communication flow between the PAG and the GDG is carried out bidirectionally through the members of the patient community that are part of the GDG. This dynamic has been postulated by the European Respiratory Society as a best practice[16].

Figure 1 shows a graph of the relationship between GDG and PAG across representatives of the patient community.

Figure 1. Communication flow between the GDG (through representatives of the patient community) and the PAG.



2.2 | Roles and functions of patients in the Core Writing Group, GDG and PAG

In the development of a CPG, representatives of the patient community are best able to weigh up the benefits and harms of clinical decisions, and express their preferences based on the balance between desirable and undesirable effect[17]. They can help in reducing uncertainties around clinical benefit, affordability, and adoption/diffusion[26]. In addition, they can have a role as partners in the process of producing knowledge and in addressing evidence gaps for the management of rare diseases[16]. Then, it is critical that representatives of the patient groups become involved in the Core Writing Group (CWP) because the CWP selects members/experts for the GDG, as representatives of the patient community. The representative of the patient community in CWP can help to select and recommend experts[18]. As indicated in Handbook #4: Methodology for the Development of CPGs for Rare Diseases, the first meeting of the GDG is the moment to establish the roles and functions of each member. As for the representatives of the patient community, this handbook adapts the National Institute for Clinical Excellence (NICE) proposal, and states that the roles and functions will be as follows:

- ✓ Advise on the guideline scope and clinical questions.
- ✓ Provide comments on the evidence review and ensure that recommendations address patients´ and/or carers´ issues and concerns.
- ✓ Consider the extent to which published evidence reflects outcome measures that patients and carers consider important.
- ✓ Highlight areas where patient preferences and patient choice may need to be acknowledged in the guideline.
- ✓ Participate in formal consensus-building procedures where there are gaps in evidence.
- ✓ Ensure that the guidelines are worded appropriately, and in particular the recommendations.
- ✓ Identify grey literature expertise in areas where there is a gap in the evidence.

To fulfil this role and these functions, representatives of the patient community who are members of the GDG can also be the chairs of the PAG, as mentioned above. These representatives must act as consultants to the patients to summarize their perspectives and transmit them to the GDG[17].

The following sections will provide more details on the specific tasks that representatives of the patient community have in assuming the roles discussed above.

2.3 | Selection and recruitment of patients

According to the Guideline International Network (GIN), there are two key types of recruitment for including patients in the development of CPGs[2] and both can be used to recruit patients as core members of the GDG or to engage them in the process[2] through the PAG:

- ✓ Open recruitment: guidelines developers recruit for this role using the person specification, thus enabling a wider range of people to become involved. This is a transparent procedure.
- ✓ Nomination: used when developers approach a patient organisation which designates someone to be their representative, who understands and reflects on the patient issues that are relevant to the CPG.

The methods to address open recruitment can first be secured through the European Reference Networks members and through online and annual meetings[19]. They can also be identified at conference presentations, public engagement events, patient charities, research activities organised by organisations for rare diseases and different scientific events where there may be an opportunity to recruit patients with rare diseases[20–22]. At these events, it is possible to contact medical societies that have access to different patients, patient organisations and networks that could facilitate access to patients with rare diseases[23]. Ultimately, in recent years there has been an increase in the use of web-based technologies. For example, government and scientific and academic platforms, such as Orphanet, and others channels, including social media such as Facebook, Instagram and Twitter. These resources provide a potentially powerful approach to population recruitment that is otherwise hard to reach for the engagement of patients over a wide geographical area. These approaches have demonstrated to be successful compared to more traditional ones, such as pamphlets for example[22,24,25].

The methods for nominated recruitment include resources such as patient advocacy groups. It is recommended to first contact existing patient advocacy groups (ePAGs) or relevant organisations that are active with the ERN or involved in rare disease research in order to inquire about opportunities for patient involvement in guideline development and recruitment strategies[16,18,20,23]. Additionally, it is important to involve healthcare professionals specialised in the rare disease in question, which can be an effective method to identify potential participants[9,25].

Furthermore, rare disease umbrella federations and genetic alliances can provide access to more than 30 million people with a wide variety of rare and undiagnosed diseases. These entities are non-profit health advocacy organisations with extended networks that connect different disease-specific advocacy organisations and have the possibility to recruit patient with rare disease via email[23]. Moreover, healthcare providers specialised in treating rare disease may also be helpful in identifying potential participants[9,25]. Finally, the patient organising committee can identify individuals in their networks who, in their opinion, would be interested in participating in the development of different scientific tools[26] such as CPGs and CDSTs.

Some of the methods used for each of the above-mentioned types of recruitment are presented in Table 1:

Table 1. Recruitment methods.

Recruitment	
Open	**Nominated**
○ ERN Annual Meeting[20]	○ Patient representatives active in the ERN[19]
○ Medical and Professional Societies[23]	○ Patient advocacy groups/ organisation/ representatives[25]
○ Government and academic websites[25]	○ Healthcare providers[9,25]
○ Patient charities[21]	○ Contacted by email[23,26,27]
○ Public engagement events[21]	○ Patient organising committee [26]
○ Patients advocacy groups[9,25]	○ Non-profit health advocacy such as Genetic Allianze[23]
○ Web-based approach: Instagram, Twitter (now called X), Facebook and Google advertising[22,24,25]	
○ Contact with organisations through multiple communications platforms and social media channels[28]	
○ Conference presentations[21]	
○ Research activities organised by rare diseases organisations[22]	

2.4 | Approaches for involving and engaging patients throughout the CPG development process

It is first important to clarify the differences between patient `involvement´ and patient `engagement'. The concept of patient involvement refers specifically to the rights and benefits of patients to have a central position in the healthcare process, it goes beyond the sharing of information: it is about the interaction between the patient and the healthcare provider and encompasses a wide range of different aspects[5]. Then, when it is said that representatives of the patient community are `involved´, it implies that they belong to a GDG and are working throughout the different steps of the guideline development process as core members of the GDG. Patient involvement is recognised as a core standard and quality indicator in guideline development in all international methodologies (GRADE, AGREE, ADAPT, GIN)[1, 2, 3,4, 29]. Furthermore, international best practice methodologies recognise that if patients are involved from the beginning and through all stages of the process, the results will be more succesful[30].

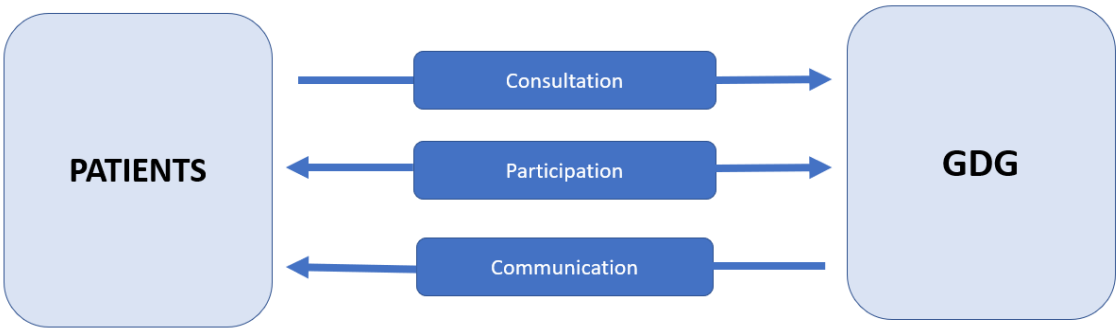
In contrast, patient `engagement', refers to patient/representatives of the patient groups as external stakeholders who operate outside the GDG, so that patients are committed at specific points in the CPG development process. In these cases, patients can be best engaged through the establishment of a time-limited Patient Advisory Group with which the GDG can engage at specific points in the process. To achieve this engagement, the chair of the GDG and the representatives of the patient community in the core team should determine and agree on the optimal approach to engage patients and their representatives throughout the different stages of the guideline development process[18].

Although the processes of involvement and engagement are different, the strategies to achieve this are similar and can be organised through three mains approaches: consultation, participation and communication. The set of strategies proposed below is based on the GIN toolkit (https://g-i-n.net/toolkit), which is a guideline on how to involve patients in CPGs, and on other scientific publications. These strategies are defined by the flow of information between the GDG which will develop the CPG and the patient(s):

- ✓ Consultation: this is a process in which patients are asked about issues that are of greatest importance to them[26]. This process entails the collection of information from patient[2], based on a one-way flow of information from the patient to GDG[29].
- ✓ Participation: there are two types of participation. Firstly, active participation, which entails the exchange of information between the GDG and the patients[2]. This type of participation involves a two-way flow of information. These strategies can be used from the beginning to the end of the development of the CPGs. Secondly, passive participation, which usually occurs when patients take part in a research study as subjects/or participants or where representatives of the patient group support recruitment[31].
- ✓ Communication: this implies a one-way information flow from the GDG to patients. Communication refers to different strategies to inform patients by accompanying them in the management of the disease, or assisting them in individual health decisions and choices. The language used depends on the target audience, using scientific language when addressing expert patients, or lay language for non-expert patients[2]. Examples of such strategies are patient information booklets or educational materials.

Figure 2 shows the type of participation according to the direction of the information flow.

Figure 2. Proposal of the GIN toolkit classification of involvement and engagement strategies.



According to the above classification, consultation is the process that fits best to engage patients[29] and participation is the approach used to include representatives of the patient community in the GDG. Both processes share methods for incorporating patient views such as surveys, focus groups, interviews[18] and GDG meetings[2,32]. Moreover, methods for communication are available because the information flow is targeted at the patients, so there are events where this process occurs such as in conference presentations[21] or annual meetings[20]. Furthermore, it is important to maintain transparency and keep patients up to date with the developments of the CPGs through newsletters[9] or scientific publications[33]. Additionally, platforms, social media channels and campaigns are methods that can be used to reach large geographically-dispersed groups[34]. Section 2.5 describes and provides a more in-depth insight into all the available methods for collecting information from the patient community in the different stages of the CPG. Table 2 shows some of the above-mentioned methods with which to approach the proposed strategies.

Table 2. Examples of available methods on how to recruit, involve and engage patients.

		Consultation	Participation	Communication
Recruitment	**Open**	• Web-based approach: Facebook and Google advertising[22,24,25] • Government and academic websites[25]	• Public engagement events[21] • ERN Annual Meeting[20]	NA
	Nominated	• Contacted by email[23,26,27] • Patient Representatives active in the ERN[19]	• Patient advocacy groups[25] • Healthcare providers[25]	NA
Involvement/Engagement		• Focus group [18] • Surveys [18] • Public comment [2,32] • Workshop [2,32] • GDG meetings[13]		• Conference presentations[21] • Annual meeting[20] • Platforms and social media channels or /and campaigns[34] • Newsletters[9] • Scientific publications[33]

*NA: not applicable

2.5 | Available methods to collect information from the patient community on the different stages of the CPG

As mentioned previously, recognising the importance of the different methods available to collect information from patients with rare diseases within the CPG development is of paramount importance. By encompassing a range of perspectives, these CPGs achieve a broader, patient-centred scope, and ensure the aspects of care that will be covered in the CPG. To do so, a strategy is needed that captures the expectations, views, and needs of patients with rare disease [14]. The first strategy often employed is consultation, which can be addressed using the different methods presented in Table 3 below.

Among the available methods, workshop processes allow patients with rare diseases to share information about their disease and its individual and social impact and highlight the importance of uncertainties regarding clinical benefits, harms, and affordability, among other aspects. In the

workshop discussions, the thematic analysis can be conducted according to the goal, and in order to avoid losing information the workshops could be audiotaped and transcribed[21,35, 17,36] and thus recover all needs, expectations and views shared. An innovative method for conducting workshops is the "World Café". This is a consensus-building-community participatory tool designed to allow several small group conversations to take place at separate tables, with participants systematically rotating to different tables approximately every 20 minutes. This method provides a setting in which community participants can discuss diverse perspectives. There is also an online option that allows geographically-dispersed participants with rare diseases engaging in discussions to convene as a single large group and in smaller concurrent and separate group discussions as there are online platforms that allow for random distribution in separate discussions group, thus maintaining the same methodology as in the face-to-face modality[28].

Another one of the most commonly used methods to obtain information about needs, expectations, perspectives and preferences are focus groups, discussions groups, interviews or surveys[2]. The benefit of interviews conducted via telephone or face to face is to provide additional data on the experience of the patient, including the diagnosis process, symptoms and specific impacts[37]. It is very important in the context of rare diseases because it offers the flexibility of being held at the participants' preferred time and location (e.g. University Department, workplace, home), contributing to a more accommodating and participant-friendly approach[33]. Focus groups and discussions groups allow for a thematic analysis of the information collected, making it possible to determine whether the clinical question encompasses the needs, expectations, benefits and harms of patients with rare diseases[21,38,39]. Moreover, surveys allow feedback to be obtained from patients on the relative importance of a range of health outcomes[2].

On the other hand, if the preference is to find a major group view, there are patient organising committees which have functions such as consultations and focus on those issues which are of greatest importance to patients (these committees are usually formed for patient advocates)[26].

Nowadays, CPG developers can use online methods such as social media threads, chat room discussions and virtual meetings to post key questions to a public forum for feedback, which may include an open space for discussion, ensuring a dynamic exchange of information. These kinds of approaches may be useful for topics where a range of patient and public views are needed[2,26,40].

Table 3. Available methods for collecting information from patients on CPG development.

Available methods for collecting information from patients within the scope of CPGs	

• Workshop[21,3517,28,36]
• Online surveys[21,33,35]
• Patient organising committee[26]
• One-to-one interviews[37]
• Focus groups [21,38,39]
	• Virtual meeting[26]
	• Targeted consultation with stakeholders [2]
	• Social Media [42]:
	  ○ Social media threads
	  ○ Chat rooms discussions
	  ○ Public comments with the patient advocacy group online

03.

PATIENT TRAINING AND SUPPORT DURING THE GUIDELINE DEVELOPMENT PROCESS

3.1 | Type and target of training

One of the objectives of the first GDG meeting is to identify the training needs of the group members. As stated in Handbook 4#: Methodology for the Development of CPGs for Rare Diseases, the members of the GDG may need to be familiar with aspects related to the development of CPGs from the formulation of the clinical question in PICO format to the making decision on recommendations based on the evaluation of the evidence with GRADE[13].

Providing training before starting work on the CPG is particularly relevant for representatives of the patient community who belong to the GDG, as they have been shown to be reluctant to contribute if they do not feel adequately trained[41]. This barrier can be easily mitigated through good capacity building training, which includes the principles of evidence-based medicine, research methodology, and effective communication[34]. Supplying them with the necessary skills and knowledge about the CPG development process would ensure that they contribute effectively along with the rest of the GDG[33].

When designing training for representatives of the patient community include the adapting the content and format to their specific needs and roles during the development of the CPG. For this reason, it is important to involve patients in the design and development of training to ensure that it is relevant and effective for their needs [13,33,34]. It should also be noted that if the CPG work is to be conducted in English, the language level of representatives of the patient community should be considered in case they need support in this area as well[33,34].

One innovative approach that can be applied to this training is to integrate experiential learning methodologies. This may include interactive workshops, case-based discussions, and simulated exercises that mimic real-world scenarios in CPG development[42].

3.2 | Training opportunities

The expansion of patient-centred approaches and e-research tools has underlined the need to effectively educate patients in order to provide them with a set of skills to support their active and meaningful participation in research (which includes the development of CPGs). Hence, several training opportunities (many with a heavy Internet-based component) have been created specifically for patients with rare diseases, representatives of the patient group, and caregivers[33, 38]. Among the training courses available, special mention should be made of those designed and implemented by EURORDIS through the EURORDIS Open Academy (https://openacademy.eurordis.org/). This initiative offers a blended learning approach that includes e-learning courses, webinars and face-to-face training, as well as research visits and networking opportunities. Among the webinars available, there are some specific ones on GPC development (https://www.eurordis.org/clinical-practice-guidelines-webinars/).

Other options available are offered by the European Lung Foundation (ELF, https://europeanlung.org/en/about-us/our-patient-input-process/) and the European Patients Academy on Therapeutic Innovation (EUPATI, https://eupati.eu/). They can help develop patients' skills and enable them to understand the scientific landscape, to discuss with researchers and other stakeholders on an equal footing, or to develop those personal skills that are essential for the interactions with the GDG or the development of CPGs[33].

Finally, a specific training for the development of CPG is designed and carried out within the framework of the ERN Guidelines Programme, called "Development of Clinical Practice Guidelines"[43], which is aimed at clinicians, methodologists and members of the patient community. It is designed to be flexible and to address the needs, expectations and preferences of the target population. It includes content on methodologies for the development, appraisal and implementation of CPGs and CDSTs, and also offers strategies for involving patients in the process. Synchronously, it ran from March to June 2021, with the participation of members of the ERNs. Currently, this training is available to do on a self-managed basis in the EU Academy[39] and is intended for anyone who is involved in a CPG development process, specifically clinicians and representatives of the patient community. This training is an interesting tool for patients before the start of the development of CPGs and CDSTs[43]. It can be accessed through the following link: https://academy.europa.eu/ (see easy access in Annex I).

In addition to the formal training programmes such as those discussed above for providing valuable knowledge, the inclusion of ongoing mentorship and peer support mechanisms is equally crucial. These support structures can offer a continuous learning environment, where experienced mentors guide representatives of the patient community in navigating challenges and sharing insights gained through practical experiences. In this respect, initiatives like mentorship programmes can significantly contribute to the sustained development of skills and confidence among representatives of the patient community involved in CPG and CDST development[44].

04.

FACILITATING PATIENT INVOLVEMENT AND ENGAGEMENT IN THE DEVELOPMENT OF CPGS AND CDSTS

Due to the unique characteristics of rare diseases, which are characterised by low prevalence and small and dispersed patient populations, participation in the development of a CPG can be challenging[34]. The heterogeneous nature of rare conditions can also magnify the practical challenges for patients involved in the development of a CPG, such as the efficient organisation of meetings, focus groups or face-to-face interviews[34]. Therefore, a number of considerations need to be taking into account to facilitate both the involvement of representatives of the patient community as members of the GDG and patients' engagement in the PAG.

4.1 | Considerations to enhance the involvement of rare disease patients in the development of CPGs and CDSTs

There is a number a of general considerations that can contribute to successful patient involvement and engagement in the development of CPG. Among these, the following have been suggested[33,34,45–47]

- ✓ To begin with, it is recommended that the GDG chair organise a pre-meeting or introductory call with representatives of the patient community to discuss the process and their role in the GDG.
- ✓ Implement a patient-centred communication strategy. This requires taking into account the preferences of patients. Individualizing approaches to disseminating information, such as through targeted emails, newsletters, or social media updates, can effectively enhance consciousness, strengthen dedication, and cultivate an atmosphere of inclusiveness among patients.
- ✓ Make the meeting accessible. Match the meeting to their schedule and consider the preferences regarding location and transport. In this respect, the incorporation of virtual meeting platforms, online forums, and teleconferencing resolves the logistical challenges that arise when attempting to coordinate in-person exchanges. By leveraging technology,

inclusivity is ensured by allowing patients from different geographic locations to actively participate.

- ✓ After each meeting, provide patient community representatives the opportunity to follow up on the meeting. In this way, they can secure their input and discuss any areas of concern separately from the main GDG.
- ✓ Promote a collaborative and supportive context. It is imperative that GDGs and PAGs place emphasis on the establishment of environments that foster transparency, adaptability, and a readiness to incorporate a wide range of viewpoints. By adopting this approach, not only does it optimise the overall patient experience, but it also fosters a more vibrant and efficient collaborative effort during the CPG and CDST development process.

In general, the most important things are to be flexible and to adapt to their needs, limitations and aspects imposed by the disease[34].

05.

CPG SCOPE

5.1 | The role of patients in setting the scope of the CPG

The initial setting up of the scope of a CPG is a step prior to the creation of the GDG and would be determined based on a combination of factors, including the available evidence, the perspective of patients and other stakeholders, and clinical experience[18]. Acknowledging the critical significance of patient perspective, specifically regarding rare diseases, is essential for developing a comprehensive and patient-centred CPG scope[18]. Based on this `outline´ scope, the CWG identifies a range of experts that can be invited to join the GDG.

As outlined in Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare or Low-Prevalence and Complex Diseases[11] and Handbook #4: Methodology for the Development of CPGs for rare disease, and also defined by other key organisations such as NICE, GIN toolkit, SIGN and GuíaSalud, there are central steps that have to be followed when establishing the final scope of the CPG:

A small CWG of clinicians and representative of the patient group with appropriate expertise in the area of the CPG is set up based on the agreed guideline topic area that has been prioritised. The CWG conducts a preliminary literature search or scoping review of the disease of interest to identify the key clinical questions. It is essential to include the representatives of the patient groups from the start in the CWG. The scope of the CPG is then drafted and review questions covering all specified areas are defined. A process of external consultation with wider relevant patient community should then be undertaken to ensure their preferences and perspectives are taken into account. At this time a PAG is set up to provide patient´s perspective that can inform the development of the guideline scope, specifically identifying any key challenges and concerns that are relevant to them. This ensures that the guideline addresses real-world challenges and provides practical recommendations that resonate with the patient community.

The final scope will require input from the GDG. At this point it is necessary to establish the size and composition of the GDG.

The scope should be reviewed periodically to ensure that it remains up-to-date and relevant, and the representatives of the patient community and the PAG have to participate to ensure that their needs continue to be met. These steps in the definition of the scope must involve patients and are presented in Table 4.

There are examples of umbrella patient organisations which can be found on Orphanet, such as European Patients´ Forum (EPF)EURORDIS (Rare Diseases Europe), Alliance Maldies Rares (France), ACHSE (Germany Allianz Chronischer Seltener Erkrankungen) and FEDER (Spanish Federation of Rare Diseases), among others, which are experienced in supporting patient involvement in CPG

development and have been active in drafting new CPGs in the ERNs. These organisations can be invited to participate in the step of setting the scope of the CPG.

Table 4. Steps to defining the scope and the patient involvement.

Steps to defining the Scope	Patient Involvement
Creation of a small CWG	Involve 1-2 representatives of the patient groups in the CWG
Preparation of the CPG topic within a scope by developing the PICO questions	Representatives of the patient groups can help shape the PICO questions to ensure the guideline meets the needs
Process of external consultation	Involve patients and the PAG to ensure their preferences and perspectives are taken into account
Consideration of the size and composition of the GDG	Involve representatives of the patient group in the election of the representative of the patient community to the GDG
Finalise the CPG scope	Revise the outline scope based on the external consultation into a final scope
Periodic review of the scope	Involve representative of the patient group and the PAG to ensure their needs continue to be met

06.

FORMULATION OF THE CLINICAL QUESTION

6.1 | Setting the formulation of a clinical question

Once the CWG has established the overall scope of the CPG, the chair of the GDG prepares a preliminary list of clinical questions. These clinical questions should cover all key areas specified in the scope without introducing new areas[47]. The chair will then send it to all GDG members (including the representatives of the patient community) before the first meeting.

The representatives of the patient community will share and discuss the proposal with the PAG, which should provide feedback[13,47]. The methods used to collect information from patients in this step will ensure that the topics and outcomes addressed are relevant to them, the questions asked include their issues of interest, as well as the credibility and meaningfulness of the CPG to those who will be using it[14,34]. With this aim in mind, the methods shown in Table 3, among others, can be used.

Furthermore, the GDG chair will coordinate an external review of this draft with experts, such as clinicians and patients, who can explain their needs, preferences, and experiences[13,47].

The next step is to turn a specific clinical question into a structured question with the aim of identifying the relevant scientific evidence. The structure will depend on the type of question to be addressed, but usually the PICO format is used. The PICO format refers to Population, Intervention, Comparison, and Outcome[14]. In the case of the rare diseases in question, it is essential that specific questions be formulated about patients' views and experiences. For this type of outcome, which will be qualitative, the recommended format for establishing the clinical question is the SPIDER (Sample size, Phenomenon of Interest, study Design, Evaluation, Research type) tool[46].

07.

SYSTEMATIC SEARCH FOR AND SELECTION, APPRAISAL AND SYNTHESIS OF THE SCIENTIFIC EVIDENCE

Both, the representatives of the patient community and the members of the PAG can provide experiences and perspectives during the different steps of the CPG development process and contribute by participating in different tasks. For optimal patients ´ participation, it is important to share with them clear, concise and understandable summaries of the evidence and emerging of the systematic review, to give them the opportunity to provide their feedback.[34] Likewise, it is essential that all members of the GDG, inclusive of the representatives of the patient community are educated to understand how to conduct a systematic review, so that they can play an active role in this process [34].

7.1 | Systematic search for and selection of the literature

Specifically, the representatives of the patient's community belonging to the GDG can play a role in determining the key words for the bibliographic search and in reviewing the retrieved literature to fill the gap[14,15]. The PAG can also participate in these tasks through different methods of consultation, such as workshops and public comment, among others (see Table 3). Workshops allow patients to help define research objectives, shape search strategies, and determine data extraction criteria[33]. Through public comment, feedback for the research protocol for systematic reviews could also be obtained[2].

Another strategy for gathering patient insights during these stages of the CPG development process is through patient-centred systematic reviews. These searches for patient views in published literature can be challenging, but standard search strategies tailored to specific topics or study types can streamline the process. The GDG should consider the time and resources available when selecting a search strategy, with narrower searches being appropriate where resources are limited[2]. To gather this type of evidence, information specialists can explore traditional databases such as Medline, Embase, PsycInfo, Orphanet, CINAHL and the Cochrane Library. Other subject-specific databases focus on rare disease resources, such as EURORDIS, NORD, or RARE-Bestpractice, and Gene Reviews should also be explored. Additionally, valuable understandings can be found in grey literature, rare disease organisation websites and research sites such as the International Rare Diseases Research Consortium (IRDiRC, https://irdirc.org/)[2,33].

An example of how to proceed in this sense can be found in the algorithm developed by the Spanish Network of Agencies for the Evaluation of Health Technologies and Services of the SNS (RedETS), for Patient Involvement in Health Technology Evaluations. This could also be useful in the development of CPGs. In this process, patients have three minimum phases of participation: i. review of the protocol, ii. assessment of the appropriateness of including additional patient-based evidence, and iii. review of the draft report[48].

7.2 | Appraisal and synthesis of the evidence

After identifying the evidence needed to address the clinical question, the next step involves assessing its quality and summarising the finding. This is accomplished by employing the methodology established by GRADE (Grading of Recommendations, Assessment, Development, and Evaluation[1]). It assesses aspects such as evidence quality, consistency, effect size, outcome importance and contextual factors. By using this methodology, the strength of the recommendations deriving from the selected evidence is presented in a transparent way [1].

As stated in Handbook #4: Methodology for the Development of CPGs for Rare Diseases, the technical team will present the GRADE evidence profiles to the GDG for discussion and validation. Although members of the patient's community within the GDG may not have a specific role in evidence appraisal, their active participation in discussions and validation of GRADE evidence profiles enriches the process and ensures the patient's voice is considered[14].

08.

WRITING RECOMMENDATIONS AND THE GUIDELINES

The formulation of recommendations is an iterative process because they need to be revised and discussed several times before achieving the final guidelines[13] and patient participation is also essential at this step.

8.1 | Developing recommendations from the evidence

The GRADE Working Group has developed the Evidence-to-Decision (ETD) framework that establishes explicit criteria that are used to assess interventions or options, the judgments made by the panel for each criterion, the research evidence and additional considerations used to inform each judgment[48]. In addition, it is important to document how the available evidence was translated into each recommendation and the issues that influenced decision-making [13,47].

Furthermore, in the case of rare diseases, other factors deriving from their characteristics must be considered. In particular, it is very common that evidence on efficacy or effectiveness is lacking, uncertain, insufficient or of low methodological quality. To deal with this situation, NICE suggested[47] **making recommendations by consensus** or **making research recommendations**. It is also possible to **make no recommendations**, although this should be done with caution, as the scoping will have shown that guidance was needed.

The choice among these options depends on the specific circumstances, the quality of available evidence, and the potential consequences of the recommendation for patient care. Always consider the best interest of patients in the discussion on formulating recommendations, therefore including the preferences and insight of patients, from the affect individuals are best place to balance the risk and benefits related to any clinical recommendations on treatment options. The goal must be to provide patient-centred, safe and effective healthcare.

A further consideration would be the integration of patient-reported outcomes (PROMs) into the recommendation development process, ensuring that the impact of interventions on patients' daily lives and well-being is comprehensively addressed.

8.2 | Patient involvement in making recommendations

The representatives of the patient community who belong to the GDG should actively participate in the recommendation formulation stage. To perform this task, they will review and discuss the GRADE evidence profiles presented by the technical team (methodologist and expert on health economics). After that, the GDG, including the representative of the patient community, will consider the relevant criteria included in ETD frameworks[13].

After this, the draft recommendations will be shared with the PAG, because their feedback will help to ensure that their values and preferences have been integrated into the recommendations[2]. Patients can be engaged by offering insights into intervention value, reflecting on varied preferences, promoting equity, and reviewing recommendation wording. This approach ensures comprehensive and patient-centred CPG development, enhancing real-world utility[2,13,47]. To gather their perspective on the recommendations, the consultation methods listed in Table 3 could be used (e.g. surveys, interviews, workshops and virtual meetings, among others[2]). At this point, it could be useful to explore the incorporation of patient-generated data, such as patient-reported experiences and preferences, in the development of recommendations [2].

09.

FINAL STAKEHOLDER CONSULTATION

9.1 | How to identify stakeholders and the advantages of their inclusion

The main objective of the final consultation with stakeholders is to know if the CPGs effectively reflect the different needs of those for whom they are intended, ensuring that all perspectives are taken into account. Likewise, it aims to consider a broader vision of healthcare, and not only that of the people who have participated in the GDG.

When reference is made to stakeholders, this refers to people from organisations who use health and social care services, including their families and carers, as well as the general public[47]. To address this step, the final draft of the CPG is usually sent to the organisations for the specific disease or, where appropriate, to umbrella associations, to receive their feedback[2,47]. Engaging the general public is possible through a public exposure process in which a public presentation of the draft CPG is made. This presentation aims to allow potential individuals interested in the topic to contribute any considerations that were not taken into account during the development of the CPG or during the external review process, and that are encompassed within the scope and objectives of the CPG[49].

To ensure stakeholder participation, it is recommendable to leverage virtual technology to facilitate meetings, forums, and collaborative platforms, since this can improve accessibility and encourage diverse input, ensuring a comprehensive final review process[2,47]. Furthermore, it is recommended to provide alternative formats, accommodate diverse communication preferences, and ensure that participation avenues are inclusive, considering different accessibility needs [2,47].

Other aspects to consider would be, on the one hand, maintaining clear and timely communication with stakeholders, as well as transparency in decision-making and the ability to respond to their queries, in order to foster trust, thus ensuring an open and collaborative approach[2,47]. On the other hand, consideration should also be given to ensuring cultural competence, adapting engagement strategies, promoting inclusion and sensitivity to different cultural needs and expectations[2,47]. Finally, stakeholders should be encouraged not only to share feedback but also to actively contribute to the refinement of the guidelines. Their active involvement can enrich the final document by incorporating diverse insights and real-world experiences [2,47].

This entire process of stakeholder inclusion has numerous advantages, such as those listed below[2,47]:

- ✓ Stakeholders can describe both positive and negative attributes of the CPG that affect its overall usefulness.
- ✓ They can uncover gaps in coverage within the CPG, revealing areas within the scope that have not been addressed.
- ✓ They can reveal inconsistencies in the interpretation of the evidence, or disagreements with it, thus allowing this to be adjusted to reality.
- ✓ They can highlight concerns relating to equality, diversity and discrimination, something that requires vigilance to ensure equitable representation.
- ✓ They can help clarify recommendations and definitions, something that is essential for understanding.

10.

DISSEMINATION

Dissemination is a relevant stage when the general development of a CPG has been completed, but it is of greater importance when that CPG is about a rare disease, due to scarce in the limited information that is normally available. For this reason, a great effort must be made to reach the CPG target population and the clinical staff who care for them.

As described previously, involving members of the patient community during the CPG development process has multiple advantages, and this also occurs at this stage, since they can inform the public and clinical experts about the specific condition addressed[50,51]. They can also increase the awareness about the clinical possibilities available to them[2]. In this process, the organisations belonging to the ERNs that deal with the condition addressed also play an important role in dissemination[51].

10.1 | CPGs and CDSTs dissemination strategies

Several strategies have been proposed for disseminating CPG and CDSTs among professionals and members of the patient community. These strategies take different forms depending on the target audience. One such strategy that is often used is co-creation of information based on the CPG, between members of the patient community and members of the GDG[31]. Members of the patient community will also be involved in dissemination through participation in science promotion events[33] or public meetings[33]. In addition, the findings could be disseminated to a broad audience through journal publications[33], academic conferences[33], and project website[33]. In the last few years, there has been an increase in the use of web-based approaches, and social media are an effective resource for dissemination tasks due to their greater reach. Furthermore, some web pages on rare diseases and organisations have provided access to digital repositories of CPGs and CDSTs.

Another innovative strategy frequently used is the visual storytelling. This strategy enhances accessibility, captures attention, and conveys key messages effectively. This approach makes the CPG content more engaging for a diverse audience, including those with varying levels of health literacy. By blending visual elements with textual information, the dissemination materials become more inclusive and user-friendly[52].

A methodological strategy is the one called Rare Knowledge Mining Methodological Framework (RKMMF). It aims to improve the development of knowledge translation products and their dissemination in rare diseases. This methodological framework highlights the patients´ experiences and can be adapted to the specific context required. Moreover, this framework includes other sources of evidence including registry information and qualitative studies and the involvement of expert patients. The RKMMF consist of four phases: 1) Knowledge mining; 2) Group sharing phases; 3) External Validation; 4) Knowledge translation where the products (e.g. CPG) reach end users[53].

Regarding interactive patient-professional workshops, we can find a platform for direct engagement, fostering dialogue between healthcare professionals and patients. This approach promotes a collaborative and interactive dissemination strategy, ensuring that the CPGS are well-received by both healthcare providers and those directly impacted by the rare disease[21,35]. Furthermore, partnering with patient advocacy organisation ensures targeted outreach to affected communities, maximizing the impact of CPG dissemination efforts. These platforms can play a pivotal role in reaching diverse patient groups and fostering a sense of community engagement in the dissemination process[25].Other strategies focused on healthcare professionals, researchers, students and policy makers are those related with peer-reviewed scientific publications and participation in academic conferences [33].

Table 5 presents the aforementioned examples of strategies for disseminating CPG.

Table 5. Strategies for disseminating CPG.

Strategies for disseminating CPG	
• Public meetings[33]	• Science promotion events[33]
• Academic conferences[33]	• Scientific publications[33]
• Social media campaigns[33, 54]	• Project website[33, 54]
• Digital repositories[33, 54]	• Journal publications[33]
• Rare Knowledge Mining Methodological Framework (RKMMF)[53]	• Interactive Patient-Professional Workshops[33]
• Visual Storytelling[52]	• Patient Advocacy platforms[25]

11.

CPG IMPLEMENTATION

11.1 | Participation of patients with rare diseases in the CPG implementation process

As indicated in Handbook #12: Implementation and evaluation of the adoption of CPGs and CDSTs for rare or low-prevalence and complex diseases, a structured implementation is essential as it can improve the adherence to CPG recommendations[2,32]. To achieve this, it is first necessary to form the implementation work group, which must be multidisciplinary and include[45]: an implementation leader, a methodological coordinator, some specialists (e.g. data analyst manager, health professionals or social workers), methodologists, users and/or patient group representatives and other stakeholders [43].

When members of the patient community are already involved in the working group, they can participate throughout the different stages of the process: **planning the implementation** (scope of the implementation and stakeholder engagement strategies), considering the **analysis of the content** (assessment framework, resources needed, and strategy to address barriers and facilitators), **design of the intervention** (tasks, roles and responsibilities, support activities, design of the assessment of the intervention, and results from the pilot), **pursuing the implementation roadmap** and its **continuous improvement**[32].

Involving patients can help to break down barriers that healthcare professionals may face in this step, such as lack of awareness and knowledge or familiarity with the CPG and their recommendations [2].

To ensure that the patients' voice is consistently integrated in decision-making processes, the PAG can act as a channel between members of the patient community and the implementation work group. They play a vital role in sustaining long-term engagement and fostering a collaborative environment for effective implementation[25].

11.2 | CPG and CDST implementation strategies

Disseminating information to patients and healthcare professionals with personalised communication strategies is considered as a strategy to implement CPGs[2]. This approach not only improves awareness but also addresses potential barriers that healthcare professionals may face when implementing the CPGs, fostering a sense of shared responsibility for successful adoption[33]. Communication resources include podcasts, presentations in video and poster format. Other widely used resources are virtual platforms, such as online forums, or applications where patients can share their experiences, challenges and successes relating to the adoption of CPG

recommendations. Such platforms facilitate real-time communication and enhance the iterative nature of the implementation process[26,47].

Furthermore, the co-design workshops for implementing strategies bring together patients, healthcare professionals, and other stakeholders, offering them the opportunity to work together in the implementation process. Patients can contribute unique insights into potential barriers, facilitators, and practical considerations that might impact the successful adoption of CPG recommendations[33].

Finally, capturing patients' perspectives on the impact of CPG adherence on their health and well-being through PROMs allows continuous improvement cycles that align with patients' changing needs and experiences[55].

Some implementation strategies that can contribute to a successful CPG implementation process are shown in Table 6.

Table 6. Strategies for enhancing patient participation in the implementation process.

Available methods for the implementation strategies

• Co-Design Workshops[33]
• Patient-Led Information sessions[33]
• Patient-Reported Outcome Measures (PROMs)[55]
• Web-based resources [26,47]
  ○ Virtual patient feedback platforms
  ○ Podcasts
  ○ Video presentations
  ○ Posters

12.

UPDATING THE CPG

As stated in Handbook #4: Methodology for the Development of CPG for Rare or Low-Prevalence and Complex Diseases, scientific knowledge is continually developed and improved. In addition, the emergence of new studies requires the ongoing review of clinical practice. For this reason, updating the CPGs is essential in order to ensure the validity and quality of CPG recommendations.

12.1 | Participation of patients with rare diseases in the CPG update process

Members of the original GDG must be invited to participate in the update process. So, representatives of the patient community who participated in the development of the CPGs should participate in the updating of recommendations[13], and can be involved throughout the whole process,[13] which involves the following steps:

- ✓ Convening of the CPG updating working group
- ✓ Identification of new relevant evidence
- ✓ Assessment of the need for an update
- ✓ Updating process
- ✓ External review
- ✓ Publication

The steps of the external review, where it is necessary to engage external patients, can be carried out using consultation methods, for example, a systematic criteria-based rating or survey[2].

Likewise, in this updating process consideration could be given to the following aspect[2,13]:

- ✓ Ensure that the update of the CPG includes the perspectives of patients from different demographics and of different age, gender, ethnicity, and socio-economic background. This inclusivity can help to make the CPG more comprehensive and representative.
- ✓ Considering the incorporation of a section on long-term follow-up strategies ensures optimised outcomes, early complication detection, treatment improvement, patient-centred care, and research facilitation, among other aspects.
- ✓ Encourage patient group representatives to advocate for dissemination of updated CPGs within their communities.

13.

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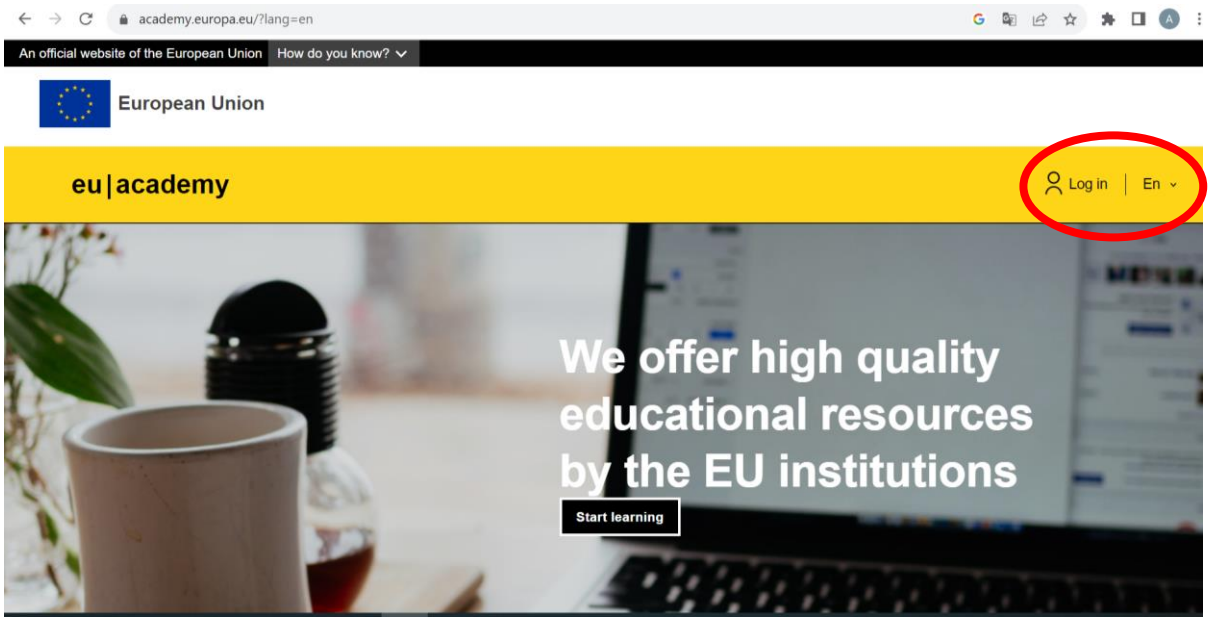
14.

ANNEXES

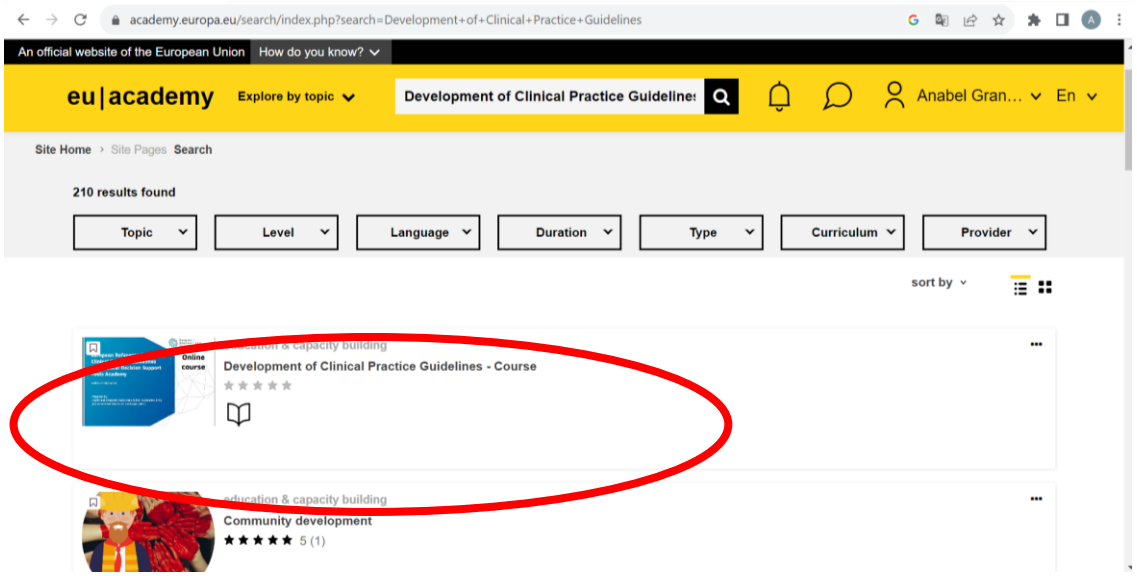
ANNEX 14.1 | How to access the "Development of Clinical Practice Guidelines" course

Step 1: Access the course using the following link: https://academy.europa.eu/

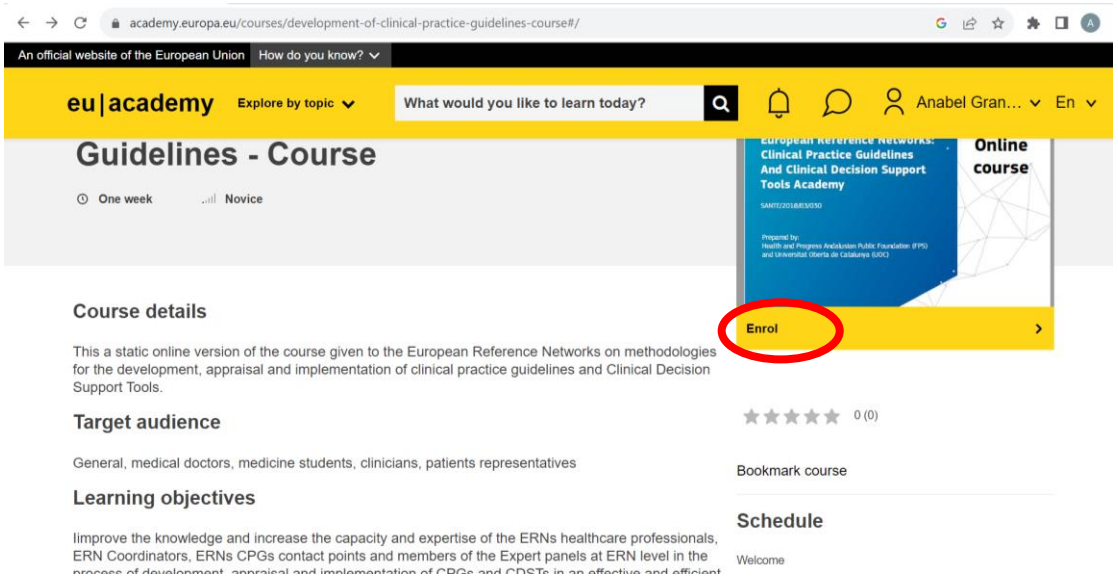
Step 2: Register with your personal data; once registration has been completed, you can access through LOG IN (top right corner).



Step 3: Access the different courses by clicking on search by different topics and type: development of clinical practice guidelines. This will provide access to the course (this is the first option)



Final step: Click on Enrol. You can now access the course.



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