

D-B.2

Methodological Handbooks & Toolkit for Clinical Practice Guidelines and Clinical Decision Support Tools for Rare Diseases

TENDER N° SANTE/2018/B3/030 EUROPEAN REFERENCE NETWORK: CLINICAL PRACTICE
GUIDELINES AND CLINICAL DECISION SUPPORT TOOLS

Aragon Health Sciences Institute (IACS), June 2020

Handbook #1: Prioritisation of the rare diseases that require
CPGs or CDSTs



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Handbook #1: Prioritisation of the rare diseases that require CPGs or CDSTs

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Short Description:

This handbook includes a detailed explanation of the prioritisation criteria and of the prioritisation process, including the use of the prioritisation tool.

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1. Background

With the launching of the first European Reference Network (ERN) in 2017, a care model based on the concentration of knowledge and resources in highly specialised care units for rare diseases became effective in Europe. As of today, 24 European Reference Network work co-ordinately and demand reliable and practical tools, like Clinical Practice Guidelines (CPG) and Clinical Decision Support Tools (CDST) to ensure the safest and most efficient care is provided to patients with rare diseases and carers through the EU.

Nonetheless, there are a number of challenges surrounding the development of CPG and CDST for rare diseases. One of the most relevant barrier is the lack of high-quality evidence, in which the foremost methodological frameworks like GRADE ¹ [cita] rely on.

Therefore, there is a need for specific methodological approaches that can provide reliable and useful Clinical Practice Guidelines (CPGs) and Clinical Decision Support Tools (CDST) for rare diseases to be used by ERNs. The project also aims to provide a common methodology, in order to harmonise the elaboration process of CDST and CPGs in the ERNs.

1.1 Work Package B: Methodologies for CPGs and CDSTs for Rare Diseases

Work Package B of TENDER N^oSANTE/2018/B3/030 pursues the development of methodologies for the prioritisation, appraisal, adaptation, development and implementation of CPGs and CDSTs for rare diseases.

The objective of WP-B of TENDER N^oSANTE/2018/B3/030 entails two main steps: Firstly, an analysis of the state of the art on methodologies for CPGs and CDSTs for rare diseases, and secondly, the elaboration of methodological handbook and toolkit for the prioritisation, appraisal, adaptation, development and implementation of CPGs and CDSTs for rare diseases.

It is worth noting that within the scope of WP-B, “rare diseases” is the term used to refer to rare diseases as well as low prevalence complex diseases.

2. Aim of this document

The aim of this document is to provide guidance for the prioritisation of topics that require CPG or CDST. This guidance covers the use of the prioritisation tool and the prioritisation process. In addition to this, the development of the prioritisation criteria is explained.

2.1 Scope

The guidance provided in this document does not replace the judgement of the prioritisation panel as a whole, which is enriched with their practical knowledge and perspective on the conditions subject to prioritisation. This guidance should be regarded as a reference and a method for obtaining a list of prioritised topics according to a set of objectified prioritisation criteria.

Within the scope of this handbook and tool, topic is understood both as a condition and as a specific care area of a condition.

3. Method

With the purpose of developing the prioritisation criteria that would be the basis for the prioritisation tool, the results from the exhaustive analysis of the state of the art on methodologies for the prioritisation of CPGs and CDSTs for rare

diseases conducted in WP-B.1 of TENDER N°SANTE/2018/B3/030 “Report on the Literature Review and Expert Consultation” were considered. The documents located in the systematic search in databases and the manual search in relevant organisations’ and projects’ websites were taken into account in the definition of the prioritisation criteria.

In addition to this, other rigorous and commonly accepted prioritisation tools –although not specific for rare diseases– were taken into account^{2,3}, including a list of criteria currently being collaboratively developed by professionals involved at different levels of care provision for the prioritisation of conditions within the Spanish National Program for Clinical Practice Guidelines (GuiaSalud).

These resources and tools were reviewed considering the relevance and applicability of their criteria in relation to the specific needs and particularities of rare diseases and taking into account that the prioritisation was aimed at the adoption, adaptation or development for CPGs and CDSTs.

After this review, a preliminary prioritisation criteria were developed and structured in domains and items. The domains are the broader ideas of the criteria. They represent the underlying concepts on which the prioritisation items are grouped into. The items are the specific issues on which the relevance assessment will be made during the prioritisation process.

3.1 Expert Consultation

The preliminary prioritisation criteria were submitted to expert review by the ERNs and WP-B partner, Catalan Agency for Health Quality and Evaluation (AQuAS). The aim of this consultation was to ensure that the criteria were adjusted as much as possible to the needs and context of rare diseases.

3.1.1 Method for the Expert Consultation

The expert consultation was made through an online consultation in the EU Survey platform.

The contact points of ERNs were those provided for the expert consultation performed in Deliverable B.1 Report on the literature review and expert consultation (D-B.1). The criteria were also reviewed by WP-1 partner, AQuAS, which was contacted by IACS.

The consultation was created and made available online via EU Survey. As per the European Commission’s request, two surveys were created, one for the ERNs and the other for WP-B partner AQuAS. These surveys differed in the questions regarding the personal information of the respondent but coincided in those referred to the consultation.

WP-B team at IACS contacted the previously identified contact points from the ERNs and AQuAS via a standard email.

In this email, information on the consultation was provided, including the background of the TENDER, WP-B, the purpose of the consultation, the deadline and a contact point at IACS, as well as a link to the survey of the consultation.

In the survey, the information on the consultation and other practical information was provided, together with the preliminary prioritisation criteria, as well as the methodology followed for developing it. The participants were asked to review the preliminary criteria and indicate whether relevant information was missing or modifications were needed. Participants were also invited to upload any relevant document to support their suggestions. See Annex 1. Surveys for Expert Consultation.

The ERNs were also asked to assign weights to the four domains of the criteria (see chapter 4), i.e., they were asked to distribute 100 points among the four domains according to the relative importance these domains have for rare

Recruitment of participants from ERNs for D-B.1

Following the indications provided by the European Commission (EC) to the project coordination team at Fundación Progreso y Salud (FPS), the ERNs were previously contacted by FPS and asked to provide contact points to which the consultation would be sent. A total of 75 contact points were provided by 22 ERNs.

diseases. The purpose of this was to translate the mean of those weights to the prioritisation tool, thus ensuring the relative importance of the domains reflected the needs and particularities of rare diseases.

In addition to this, a link to a beta version of the prioritisation tool was provided, in order to facilitate the reviewers to understand how these criteria will be used in the prioritisation process.

3.1.2 Expert consultation turnout

The consultation with the ERNs was opened from April 27th - May 20th. AQuAS reviewed the criteria from May 19th – May 29th.

Sixteen answers were received from 10 ERNs: eUROGEN (6), TRANSPLANT-CHILD (2), ERKNet (2), ERNICA (2), EYE (1), GENTURIS (1), ITHACA (1), RARE-LIVER (1), VASCERN (1), ReCONNET (1). See Figure 1. ERN Turnout. One expert was representing both ERKNet and TRANSPLANT-CHILD and another one was representing ERNICA and eUROGEN.

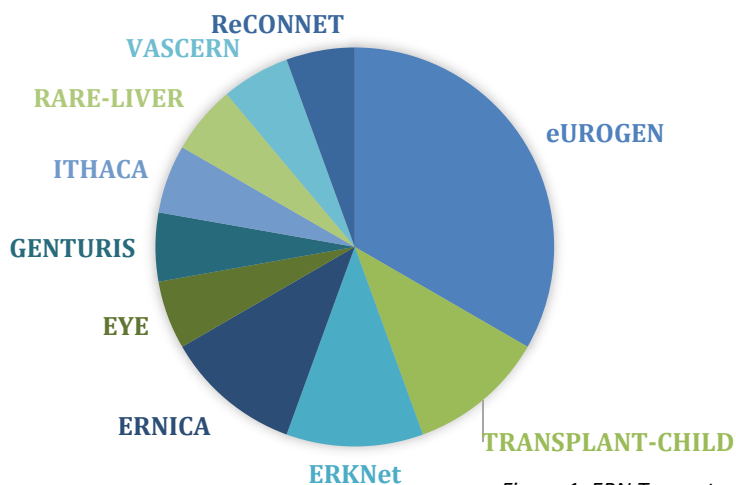


Figure 1. ERN Turnout

Most of the ERN experts that participated in the consultation were healthcare professionals (13). Also one manager and one methodologist participated.

3.1.3 Modifications to the criteria from the Expert Consultation

From the sixteen participants, twelve from 7 ERNs made suggestions and comments to the prioritisation criteria. Numerous comments and suggestions were made to all domains and items of the preliminary criteria. The suggestions implemented helped refine the domains and items, by making them more specific for rare diseases and including a clearer language and examples.

The remaining suggestions were not implemented because they were not within the scope of the prioritisation process (e.g. criteria to select a healthcare intervention), or were not applicable to all ERNs or were already covered by the criteria (e.g. suggestions of including items already present in other domains).

3.1.4 Results of the weights of the domains from the Expert consultation

As explained previously, during the consultation the experts were also asked to assign weights to the four domains of the criteria in order to reflect the relative importance that each domain has for rare diseases. The aim of this request was to make the prioritisation tool more adjusted to the needs and particularities of rare diseases, in such a way that, for instance, the topics that obtain a higher score in the most important domains for rare diseases would obtain a higher final score.

For this, the experts were asked to distribute 100 points among the four domains. These weights were to be used to calculate a mean weight for each domain. These mean weights would be included in the prioritisation tool and used to weight the scores of the topics and compose the list of prioritised topics. The weights assigned by the experts are detailed in Table 1.

#	ERN	WEIGHTS				TOTAL
		DOMAIN 1. SOCIAL BURDEN	DOMAIN 2. STAKEHOLDERS' INTEREST	DOMAIN 3. HEALTHCARE PROVISION	DOMAIN 4. PUBLIC HEALTH	
1	eUROGEN	10	40	40	10	100
2	VASCERN	10	25	40	25	100

3	ERKNet & TRANSPLANT-CHILD	30	20	20	30	100
4	ERNICA & eUROGEN	30	30	30	10	100
5	ERKNet	70	10	10	10	100
6	RARE-LIVER	45	15	15	25	100
7	eUROGEN	60	20	15	5	100
8	eUROGEN	20	50	20	10	100
9	eUROGEN	10	40	40	10	100
10	eUROGEN	20	20	50	10	100
11	ITHACA	0	75	20	5	100
12	EYE	10	10	10	70	100
13	GENTURIS	25	25	25	25	100
14	ERNICA	40	10	20	30	100
15	TRANSPLANT-CHILD	35	30	15	20	100
16	ReCONNET	20	30	40	10	100
	MEAN	27,19	28,13	25,63	19,06	
	MEDIAN	22,50	25,00	20,00	10,00	
	STANDARD DEVIATION	19,23	17,02	12,63	16,15	

Table 1. Weights assigned to the domains by the experts

Overall, the mean and median weights of each domain are very similar to each other, yet have high dispersion. To address this, it is decided to assign a default weight for each domain (25%), enabling the prioritisation panel to, if deemed necessary, modify the weights to adapt them to the ERN in which the prioritisation is being made.

It is worth noting that due to the limited time available for the development of these criteria, it was considered that a general approach, applicable for all ERNs, was a more feasible option. Nonetheless, these criteria could be further reviewed and discussed within each ERNs by means of a consensus process, in order to tailor them to the specific context and needs of the ERNs.

4. Prioritisation criteria

The prioritisation criteria are the basis for the prioritisation tool. It is structured in domains and items. The domains are the broader ideas of the criteria. They represent the underlying concepts on which the prioritisation items are grouped into. The items are the specific issues on which the relevance assessment will be made during the prioritisation process (see chapter 5).

4.1 Domains and items

The prioritisation criteria comprise four domains: Social Burden, Stakeholders' Interest, Healthcare provision and Public Health (See Figure 2. Prioritisation domains), and fourteen items. The prioritisation criteria are listed and described herein:

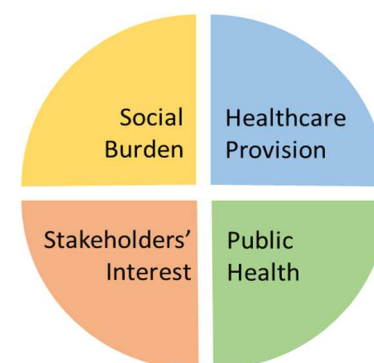


Figure 2. Prioritisation domains

Domain 1 | Social Burden

This domain covers the issues that have a direct impact on the well-being of society, including patients and caregivers.

Items

1.1 **Morbidity**: Loss of health (disease) caused by the condition, including psychosocial morbidity.

1.2 **Mortality**: Loss of life (deaths) caused by the condition.

1.3 **Disability**: Impairments, incapability and handicaps caused by the condition, including impact on physical and mental development during childhood.

1.4 **Societal costs:** Direct and indirect costs derived from the condition that are covered by the patients, by their families or by society, such as productivity loss (derived from absences or loss of work), drugs (out-of-pocket), private care needs, education or travels, amongst others.

1.5 **Vulnerability of the population involved:** The degree to which the population affected by the condition is more susceptible to negative impacts, either physical or emotional, and therefore are less resilient or have less resources to cope with the consequences of the condition.

Domain 2 | Stakeholders' Interest

This domain refers to the existence of initiatives, proposals or requests related to the condition that the stakeholders involved in or affected by the condition may have. The stakeholders are considered at public level (patients, carers, users), health professional level (healthcare professionals) and European level (decision makers, policy makers).

Items

2.1 **Patients' interest:** Existence of initiatives, proposals or requests related to the condition from patients, patients' representatives, carers or users.

2.2 **Healthcare professionals' interest:** Existence of initiatives, proposals or requests related to the condition from healthcare professionals.

2.3 **Policy makers' interest:** Existence of initiatives, proposals or requests related to the condition from policy makers at European level, i.e., the interest is expressed formally for the whole European territory.

Domain 3 | Healthcare Provision

This domain covers the issues that influence the provision of healthcare on which evidence-based practice can have a greater impact.

Items

3.1 **New knowledge:** Existence of new relevant knowledge that can have a considerable impact in clinical practice, such as a breakthrough innovation in treatment or diagnosis, amongst others.

3.2 **Uncertainty:** Lack of robust and clear guidance on the condition.

3.3 **Unwarranted clinical variability:** Variation in clinical practice that cannot be explained by illness, medical need, or evidence-based guidance in relation to the condition.

3.4 **Inefficiency:** Inadequate use of resources, i.e. overuse or misuse, related to the condition.

Domain 4 | Public health

This domain refers to the issues related to the protection and promotion of health of the population on which addressing the condition could have a positive impact.

Items

4.1 **Promotion of health:** Potential impact of addressing the condition on healthcare education programs or other activities aimed at promoting healthy habits.

4.2 **Prevention:** Potential impact of addressing the condition on prevention activities, such as early diagnosis, screening interventions or timely intervention.

5. Prioritisation process

The prioritisation process is the sequence of actions that lead to a prioritised list of topics for the development of CPGs or CDSTs. It starts with a list of topics to be prioritised and is done by the prioritisation panel.

5.1 Definition of topics to be prioritised

The definition of topics is a preliminary step in the prioritisation process. Note that more than one CPG or CDST can be developed for a single condition, according to the scope and objectives of each of the documents. The definition of the list of topic to be prioritised will be done in WP-D, as well as the definition of the scope and objectives of the CPGs and CDSTs that will be adopted, adapted or developed, they fall beyond the scope of the prioritisation process.

5.2 Prioritisation panel

The prioritisation panel is the group of people who participate in the prioritisation process. The group should be 5-10 individuals, with expertise and deep knowledge of the conditions under the umbrella of the ERN, together with a completed understanding of the prioritisation criteria. It is recommended that the views of the stakeholders of the ERN are represented in their respective panel, including healthcare professionals, patients and carers and managers. Nonetheless, the specific composition of the prioritisation panel will be established in WP-A.

When the term 'patients and carers' is used in this handbook, it is intended to include people with specific rare disease conditions and disabilities and their family members and carers. It also includes members of organisations representing the interests of patients and carers.

Potential conflict of interests within the members of the prioritisation panel should be carefully identified and duly addressed, following the indications established in WP-A of the TENDER.

It is recommended that the prioritisation panel meets face-to-face at least once, at the end of the prioritisation process, where agreement must be reached to produce a single relevance assessment (see subsection 5.3.2).

5.3 Prioritisation Tool

The prioritisation tool enables the prioritisation panel to obtain a list of prioritised topics, according to the relevance assessment of the prioritisation items for each topic that is being considered for prioritisation. For this to happen, the prioritisation panel must first assign weights to the domains of the prioritisation criteria (or use the default weights (25%)) and second, assess the relevance of the topic according to the criteria.

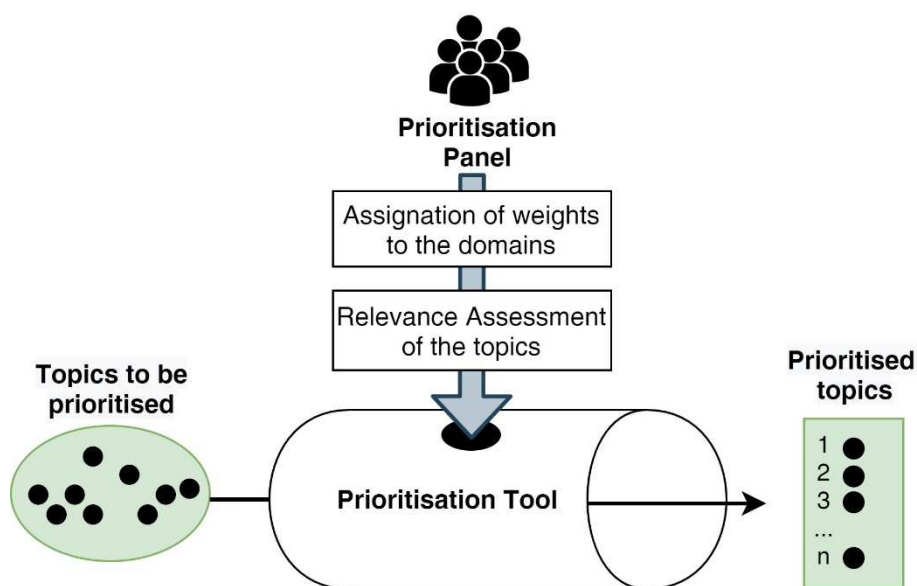


Figure 3. Prioritisation process

5.3.1 Step 1 - Assignment of weights

The first step of the prioritisation process is to choose between using the default weights of the four domains (25% each) or assigning new weights, as shown in Figure 4.

Please, insert the weight below

Domain 1 Social Burden	25%
This domain covers the issues that have a direct impact on the well-being of society, including patients and caregivers.	
Items	
1.1 Morbidity: Loss of health (disease) caused by the condition, including psychosocial morbidity.	
1.2 Mortality: Loss of life (deaths) caused by the condition.	
1.3 Disability: Impairments, incapacities and handicaps caused by the condition, including impact on physical and mental development during childhood.	
1.4 Societal costs: Direct and indirect costs derived from the condition that are covered by the patients, by their families or by society, such as productivity loss (derived from absences or loss of work), drugs (out-of-pocket), private care needs, education or travels.	
1.5 Vulnerability of the population involved: The degree to which the population affected by the condition is more susceptible to negative impacts, either physically or emotionally and therefore being less resilient or with less resources to cope with the consequences of the condition.	

Figure 4. Example of assignment of weights in the prioritisation tool

5.3.2 Step 2 - Relevance assessment

The second step of the prioritisation process is the assessment of the relevance of each topic.

In this process, the prioritisation panel is asked to assess the presence (existence). If the user answers yes to the existence of an item/factor, then it will assess its relevance according to a four-level classification scale (very relevant, relevant, moderately relevant, slightly relevant, not relevant) for each of the topics that require CPG or CDST. The grading of the relevance must be based on data and references, in order to ensure reliability and impartiality. See Annex 2. Relevance Assessment Chart Structure.

In order for the tool to provide a prioritised list of topics, a single relevance assessment for each item has to be input. Therefore, the panel has to be able to agree on a single relevance assessment for each item. For instance, the panel could choose to have each member do an individual relevance assessment and share it with the rest of the group. This option could be more efficient if there are not many discrepancies, since it could help focus the discussion on the few existing discrepancies. Another possibility could be for the panel to go through each item together and do the relevance assessment together from the beginning. This option may be more time consuming but optimal if it is likely that there are a lot of discrepancies within the panel. Nonetheless, the panel should decide on the most suitable way to reach an agreement.

Once the prioritisation panel has agreed on the relevance of each item for all the topics, this information can be introduced, as a single input, in the prioritisation tool, which automatically transforms the grades of relevance into numerical scores.

The tool sums all the scores and calculates a final score for each topic. This calculation is done according to the default weights or to those initially assigned by the panel at the beginning of the prioritisation process. The data and references that sustain the relevance grading should be included in the tool, and will be useful in case, after having reached an initial agreement, the panel decides to further discuss the relevance of some or all the items.

Please insert topic name below

Topic 1		Topic name	Name of Topic 1	Y/N	Relevance
Domains	Items	Questions			
Social Burden	Morbidity	Does the proposed topic cause avoidable morbidity, including psychosocial morbidity?		Yes	
	Mortality	Does the proposed topic cause premature death?			Very relevant
	Disability	Does the proposed topic cause impairments, incapacities and handicaps, including the impact of physical and mental development during childhood?			Relevant
	Societal costs	Is the proposed topic linked to societal costs (e.g., productivity loss (derived from absences or loss of work), drugs (out-of-pocket), private care needs, education or travels.)?			Moderately relevant
	Vulnerability of the population involved	Does the proposed topic affect vulnerable population?			Slightly relevant
	Patient's interest	Is the proposed topic directly related to initiatives, proposals or requests from patients, patients' representatives, carers or users?			

Figure 5. Example of relevance assessment in the prioritisation tool

5.3.3 Step 3 - Visualisation of results: Prioritised list of topics

The prioritisation results are presented in two different ways in the prioritisation tool: A list of prioritised topics (greatest to least priority) according to their respective total relevance score (see Figure 6) and a heat map of the relevance assigned to each item of the prioritisation criteria for each topic (see Figure 7), which can help the panel to better understand how the relevance of each topic is distributed in relation to the criteria.

Ranking	Condition	Points
1	Name of Topic 4	58,75
2	Name of Topic 3	50,1
3	Name of Topic 2	48,85
4	Name of Topic 1	

Figure 6. Example of visualisation of prioritised topics

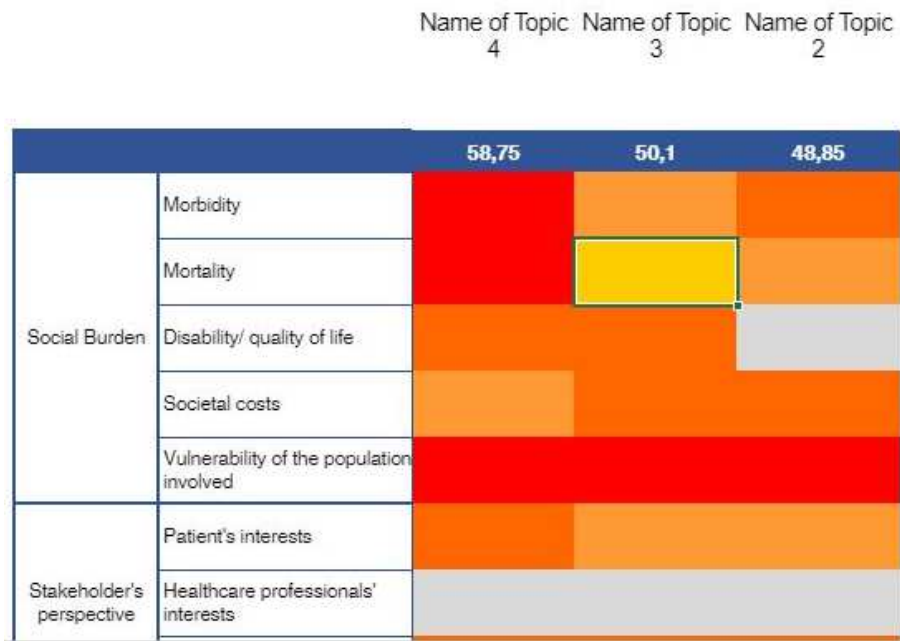


Figure 7. Example of visualisation of heat map for different topics

Abbreviations

CDST	Clinical Decision Support Tool
CPG	Clinical Practice Guideline
DG	Development Group
EC	European Comission
ERN	European Reference Networks
EU	European Union
FPS	Fundación Progreso y Salud
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IACS	Aragon Health Sciences Institute (Instituto Aragonés de Ciencias de la Salud)
ICO	Catalan Institute of Oncology
RD	Rare Disease
SR	Systematic Reviews
WP	Work Package

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Annexes

Annex 1. Surveys for Expert Consultation

(pdfs EU Survey)

Annex 2. Relevance Assessment Chart Structure

Domain	Item	Questions	Y/N	Relevance	Data
				<i>Very relevant/ Relevant/ Moderately relevant/ Slightly relevant/ Not relevant</i>	<i>Provide references (if possible, from systematic reviews) that sustain the existence and relevance of each item</i>
Social Burden	Morbidity	Does the proposed topic cause avoidable morbidity, including psychosocial morbidity?			
	Mortality	Does the proposed topic cause premature death?			
	Disability	Does the proposed topic cause impairments, incapability and handicaps, including the impact of physical and mental development during childhood?			
	Societal costs	Is the proposed topic linked to societal costs (e.g., productivity loss (derived from absences of loss of work), drugs (out-of-pocket), private care needs, education or travels.)?			
	Vulnerability of the population involved	Does the proposed topic affect vulnerable population?			
Stakeholders' Interest	Patient's interests	Is the proposed topic directly related to initiatives, proposals or requests from patients, patients' representatives, carers or users?			
	Healthcare professionals' interests	Is the proposed topic directly related to initiatives, proposals or requests from healthcare professionals?			
	Policy makers' interests	Is the proposed topic directly related to initiatives, proposals or requests from policy makers at European level, i.e., the interest is expressed formally for the whole European territory?			

European Reference Network: Clinical Practice Guidelines and Clinical Decision Support Tools

Healthcare Provision	New knowledge	Has there been a recent breakthrough development in relation to the proposed condition that has contributed to the appearance of new relevant knowledge that would entail a major advance or change in healthcare provision?			
	Uncertainty	Is there significant uncertainty regarding the management of the proposed condition?			
	Unwarranted clinical practice variability	Is there significant unwarranted variability in clinical practice related to the proposed condition?			
	Inefficiency	Is the proposed condition related to significant inefficiency, i.e., the necessary resources (human, financial or other) are being overused or misused, thus not achieving the expected or potential results?			
Public health	Promotion of health	Could addressing the proposed topic contribute to health promotion activities, such as healthcare education programs or other activities aimed at promoting healthy habits?			
	Prevention	Could addressing the proposed topic contribute to prevention activities, such as early diagnosis, screening interventions or timely intervention?			