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

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Methodological Handbooks &
Toolkit for Clinical Practice Guidelines
and Clinical Decision Support Tools for Rare
or Low prevalence and Complex Diseases
**Handbook #1: Prioritisation of the rare
or low prevalence and complex
rare diseases that require CPGs or CDSTs**

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LEGAL NOTICE

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This handbook includes a detailed explanation of the process for developing Diagnostic, monitoring and therapy pathways for rare diseases, including:

✓ Detailed explanation of the process for prioritising topics for the development of CPGs or CDSTs

✓ The development and rationale of the prioritisation criteria, which is the basis for the prioritisation process.

✓ The use of the prioritisation tool, within the prioritisation process. This tool provides a prioritised list of conditions and a heat map, as a result of the assessment of the relevance of a pre-defined list of conditions for the development of CPGs or CDSTs.

Purpose:
To provide guidance for the prioritisation of topics that require CPG or CDST.

TABLE OF CONTENTS

ABBREVIATIONS

AETSA	Andalusian Health Technology Assessment Department
AQuAS	Catalan Agency for Health Quality and Evaluation
CDSTs	Clinical Decision Support Tools
CPGs	Clinical Practice Guidelines
DG	Development Group
EC	European Commission
ERN	European Reference Network
EU	European Union
FPS	Fundación Pública Andaluza Progreso y Salud
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IACS	Aragon Health Sciences Institute
ICO	Catalan Institute of Oncology
RD	Rare Disease
SR	Systematic Reviews

01.

BACKGROUND

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 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.

02.

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.

03.

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 NºSANTE/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, our partner the 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.

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 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.

Sixteen answers were received from 10 ERNs:). See Figure 1. ERN Turnout.
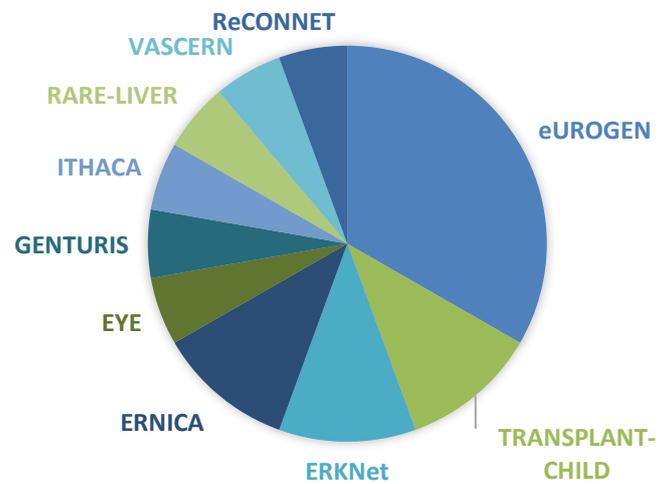
3.1.3 / Modifications to the criteria from the Expert Consultation

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.

Figure 1. ERN Turnout

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

The experts were 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 to make the prioritisation tool more adjusted to the needs and particularities of rare or low prevalence and complex 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.

Overall, the mean and median weights obtained of each domain were very similar to each other, yet have high dispersion. To address this, a default weight was assigned 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 time constrains for the development of these criteria, a general approach, applicable for all ERNs, was considered 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.

04.

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:
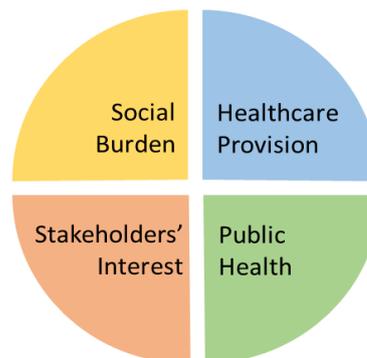
Figure 2. Prioritisation domains

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.

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.

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.

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. The meetings of the prioritisation panel can be held online, by means of web conferencing tools. If possible or feasible, the prioritisation panel may meet face-to-face. If face-to-face meetings are possible or feasible but limited, the prioritisation panel should prioritise meeting 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
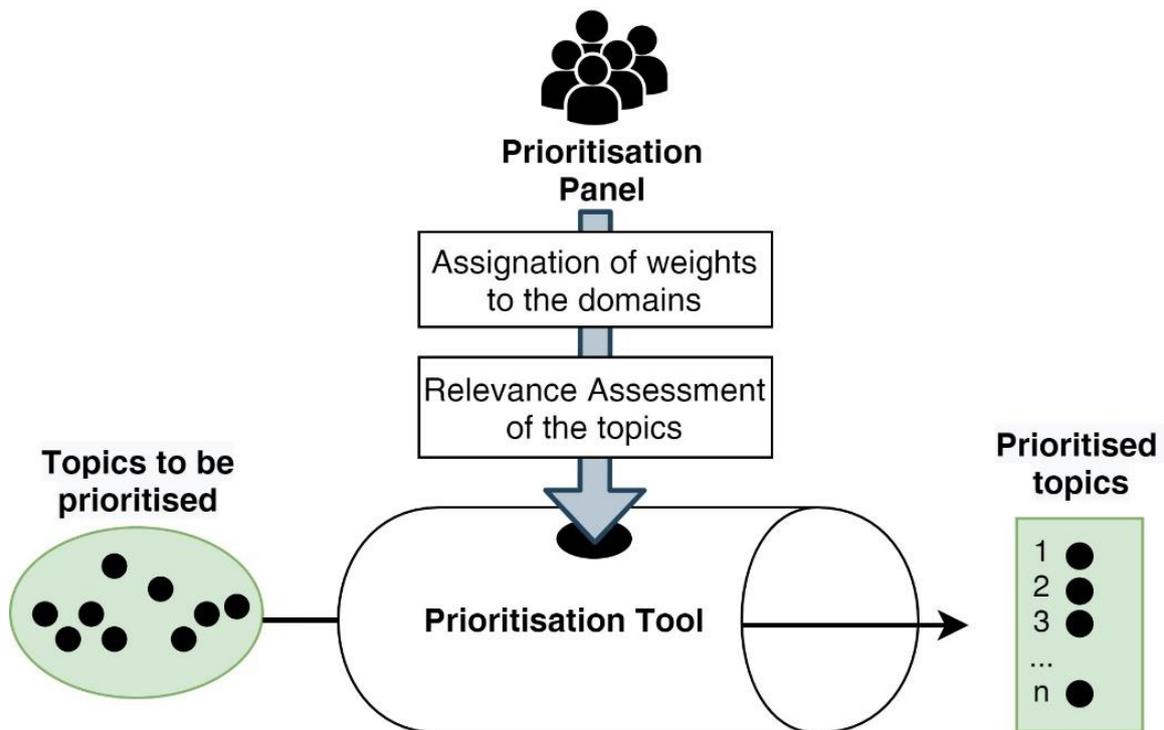
5.3.1 / Step 1 – Assignation of weights

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.

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

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, incapabilities 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 of 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.

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.

Figure 5. Example of relevance assessment in the prioritisation tool

| 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	Very relevant
	Mortality		Does the proposed topic cause premature death?		Relevant
	Disability		Does the proposed topic cause impairments, incapabilities and handicaps, including the impact of physical and mental development during childhood?		Moderately relevant
	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.)?		Slightly relevant
	Vulnerability of the population involved		Does the proposed topic affect vulnerable population?		
	Patient's interest		Is the proposed topic directly related to initiatives, proposals or requests from patients, patients' representatives, carers or users?		

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.

Figure 6. Example of visualisation of prioritised topics

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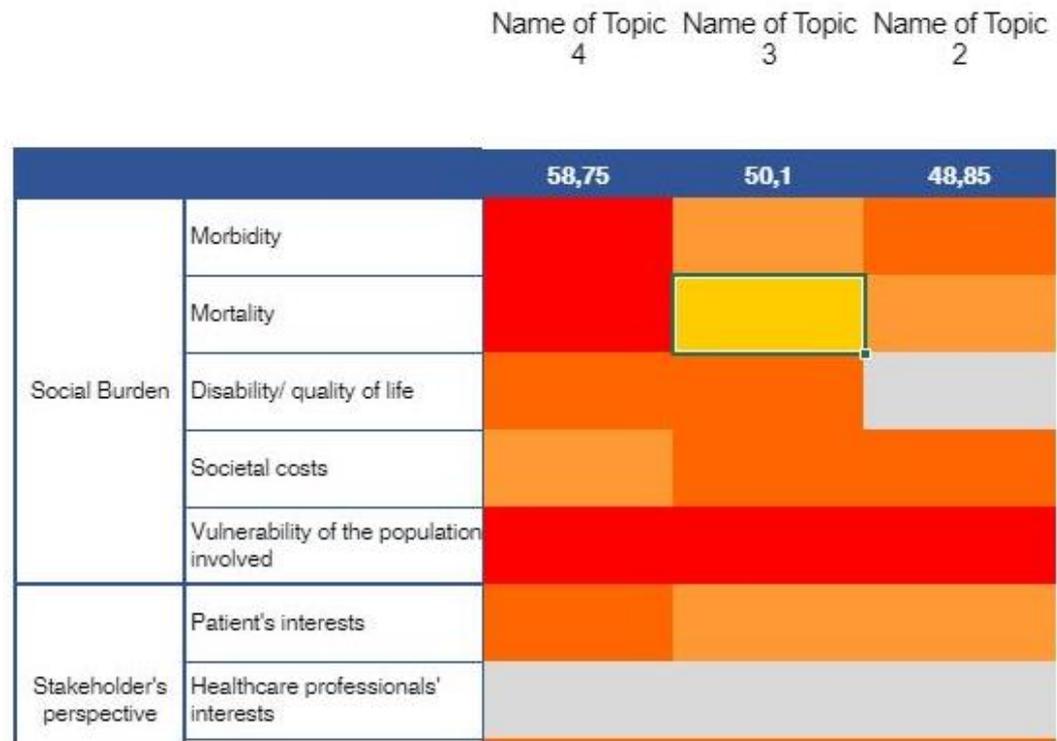
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ANNEXES

ANNEX 7.1 | Surveys for Expert Consultation

See annex file:

- ✓ 1_D-B2_Prioritisation_Annex1_ERNs.pdf
- ✓ 1_D-B2_Prioritisation_Annex1_Institutions.pdf

ANNEX 7.2 | Relevance Assessment Chart Structure

Domain	Item	Questions	Y/N	Relevance *Very relevant/ Relevant/ Moderately relevant/ Slightly relevant/ Not relevant*	Data *Provide references (if possible, from systematic reviews) that sustain the existence and relevance of each item*
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?			
Healthcare Provision	New knowledge	Has there been a recent breakthrough development in relation to the proposed condition that has contributed to the appearance of knew 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?			