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

September 28th 2020

Methodological Handbooks &
Toolkit for Clinical Practice Guidelines
and Clinical Decision Support Tools for Rare
or Low-Prevalence and Complex Diseases
**Handbook #1: Prioritisation of Rare
or Low-Prevalence and Complex
Rare Diseases that Require CPGs or CDSTs**

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EUROPEAN COMMISSION

Directorate-General for Health and Food Safety

Directorate B — Health systems, medical products and innovation

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This handbook includes a detailed explanation of the process for developing Diagnostic, Monitoring and Therapeutic 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 are 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, resulting from an 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 CPGs or CDSTs.

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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 CPGs and CDSTs for rare diseases. One of the most relevant barriers is the lack of high-quality evidence, 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 (CDSTs) 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 CDSTs and CPGs in ERNs.

02.

AIM OF THIS DOCUMENT

This document aims to provide guidelines on the prioritisation of topics that require CPGs or CDSTs. It covers the use of the prioritisation tool and the prioritisation process and also explains, the development of the prioritisation criteria.

2.1 | Scope

The guidelines provided in this document do not replace the judgements of the prioritisation panel as a whole but is rather enriched with their practical knowledge and perspectives on the conditions to be prioritised. These guidelines should be regarded as a reference and a method for obtaining a list of prioritised topics according to a set of objectified prioritisation criteria, and have certain limitations, such as the lack of patient representativeness or existence of a strong community behind certain conditions.

Within the scope of this handbook and tool, a "topic" is deemed to refer to both a condition and a specific care area of a condition.

03.

METHOD

For the purpose of developing the prioritisation criteria that would be the basis for the prioritisation tool, the results from the in-depth 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 the websites of relevant organisations and projects were taken into account in the definition of the prioritisation criteria.

Other rigorous and commonly-accepted prioritisation tools – although not specific for rare diseases – were also 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 Programme 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, keeping in mind that the prioritisation was aimed at the adoption, adaptation or development for CPGs and CDSTs.

After this review, 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 for expert review by the ERNs and WP-B partner, in this case 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 of expert consultation

The expert consultation consisted of an online consultation in the EU Survey platform.

In the survey, the information on the consultation and other practical data were provided, together with the preliminary prioritisation criteria, as well as the consultation methodology. 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 of these domains for rare diseases in order to translate the mean of the aforementioned weights to the prioritisation tool, thus ensuring the relative importance of the domains reflected the needs and particularities of rare diseases.
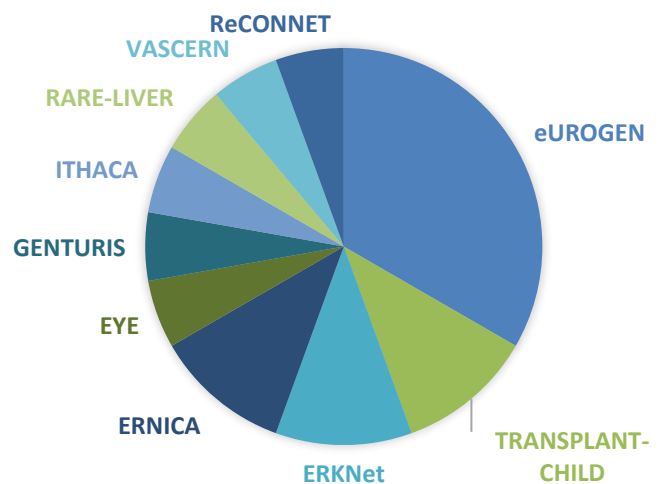
A link to a beta version of the prioritisation tool was also provided to help the reviewers understand how these criteria will be used in the prioritisation process.

3.1.2 / Expert consultation turnout

The consultation with the ERNs was open from April 27th to May 20th.

Sixteen answers were received from 10 ERNs:). See Figure 1. ERN Turnout.

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.

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 of each domain for rare diseases in order to better adapt the prioritisation tool to the needs and particularities of rare or low-prevalence and complex diseases, in such a way that, for instance, the topics that obtained a higher score in the most important domains for rare diseases would obtain a higher final score.

Overall, the mean and median weights obtained for each domain were very similar to each other but were also highly dispersed. To address this, a default weight was assigned for each domain (25%), enabling the prioritisation panel to, if necessary, modify the weights to adapt them to the ERN in which the prioritisation is being made.

It is worth noting that due to 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 individual ERNs by means of a consensus process, in order to tailor them to the specific context and needs of each ERN.

04.

PRIORITISATION CRITERIA

The prioritisation criteria are the basis for the prioritisation tool. It is structured into domains and items. The domains are the broader ideas of the criteria. They represent the underlying concepts into which the prioritisation items are grouped. 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:
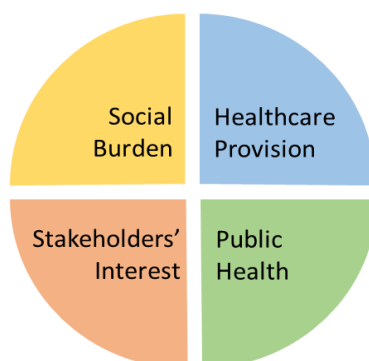

Figure 2. Prioritisation domains

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, their families or society, such as productivity loss (deriving from absences or loss of work),

drugs (out-of-pocket), private care needs, education or travel, 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 is therefore are less resilient or have fewer 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 (patients, carers, users), health professional (healthcare professionals) and European (decision makers, policy makers) level.

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 on 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 programmes 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.

05.

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 carried out 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 document.

5.2 | Prioritisation panel

The prioritisation panel is the group of people who participate in the prioritisation process. The group should comprise 5-10 individuals, with expertise and in-depth knowledge of the conditions under the umbrella of the ERN, together with a complete understanding of the prioritisation criteria. It is recommended that the views of ERN stakeholders are represented in their respective panel, including healthcare professionals, patients and carers and managers. International expertise can be included in the panel.

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
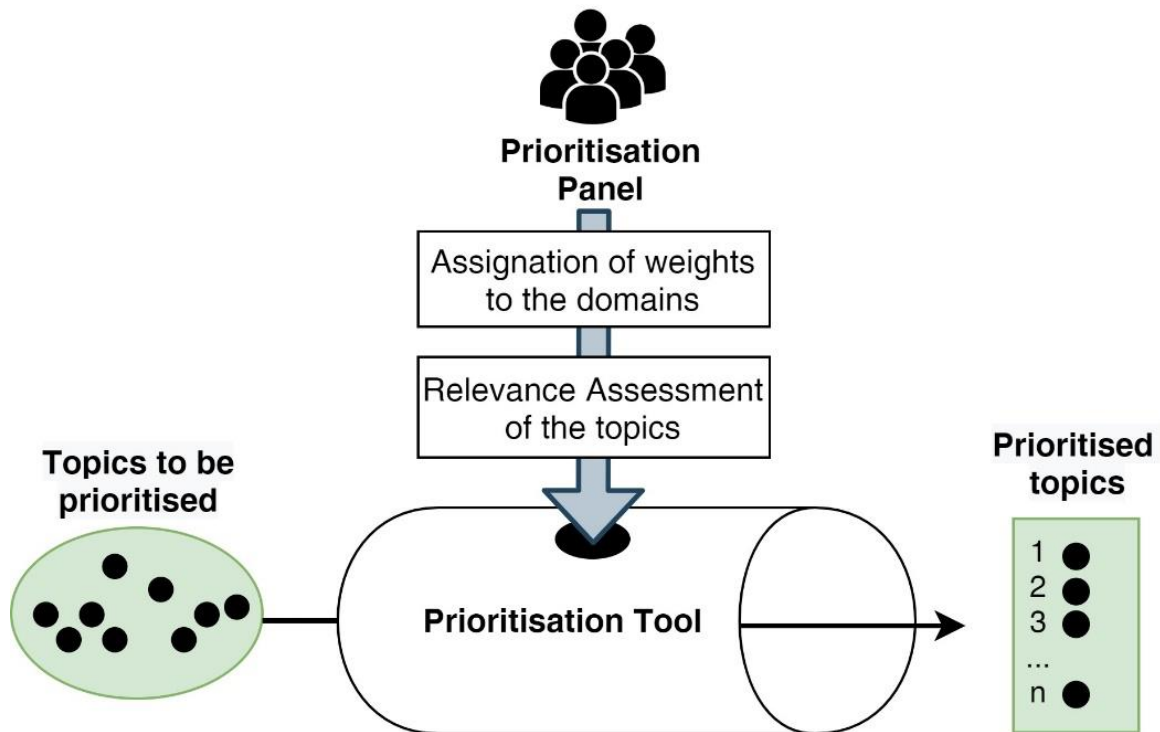
5.3.1 / Step 1 – Assignation of weights

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 presence (existence). If the user answers 'yes' to the existence of an item/factor, then it will assess its relevance according to a five-level classification scale (very relevant, relevant, moderately relevant, slightly relevant, not relevant) for each topic requiring a CPG or CDST. The grading of 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 introduced. 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 complete an individual relevance assessment and share it with the rest of the group. This option could be more effective 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 there are likely to be many 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 performed

according to the default weights or to those initially assigned by the panel at the beginning of the prioritisation process. The data and references supporting the relevance grading should be included in the tool, and will be useful if, after having reached an initial agreement, the panel decides to further discuss the relevance of some or all the itemsan 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
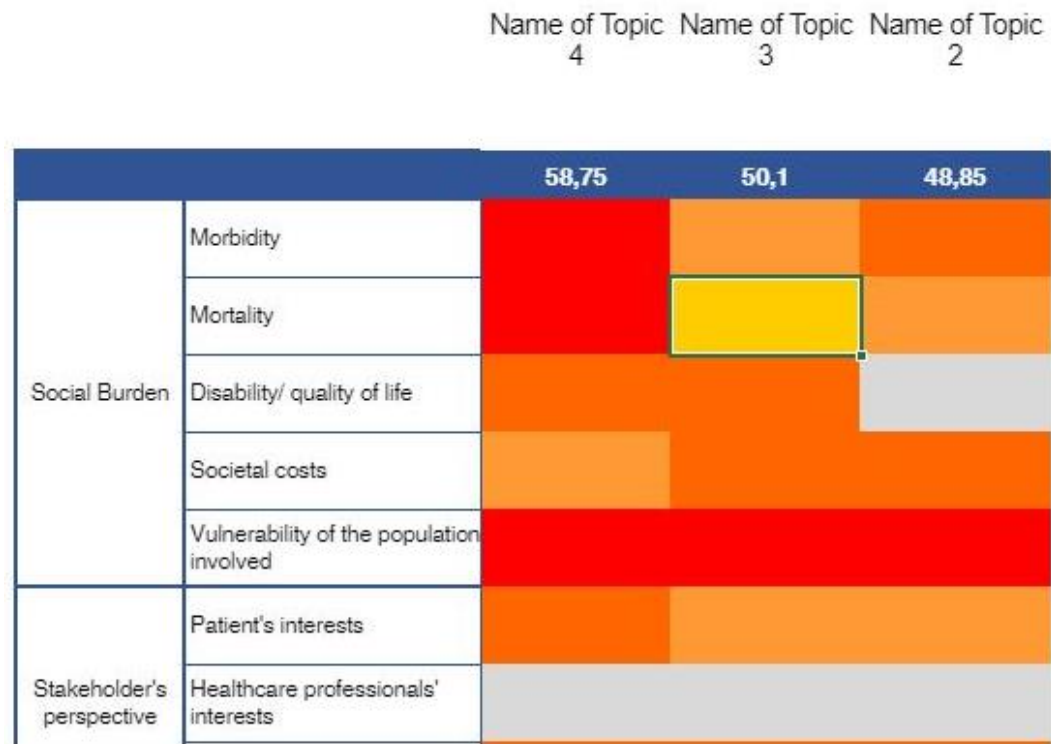

5.3.3 / Step 3 – Presentation of results: Prioritised list of topics

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 the presentation 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 the presentation of a heat map for different topics

		Name of Topic 4	Name of Topic 3	Name of Topic 2
		58,75	50,1	48,85
Social Burden	Morbidity			
	Mortality			
	Disability/ quality of life			
	Societal costs			
	Vulnerability of the population involved			
Stakeholder's perspective	Patient's interests			
	Healthcare professionals' interests			

06.

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3. National Institute for Health and Clinical Excellence (NICE). Topic selection process manual. Manchester: NICE; 2008.

07.

ANNEXES

ANNEX 7.1 ǀ 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	Data
				Very relevant/ Relevant/ Moderately relevant/ Slightly relevant/ Not relevant	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. is interest 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 programmes 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?			