European Reference Networks | ERN GUIDELINES

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

December 20th 2023

Methodological Handbooks & Toolkit for Clinical Practice Guidelines and Clinical Decision Support Tools for Rare or Low-Prevalence and Complex Diseases

Quick Guide

Prepared by the coordination team:
Health and Progress Andalusian Public Foundation (FPS)

Legal notice

European Commission:

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ABBREVIATIONS

CDSTs	Clinical Decision Support Tools
CPGs	Clinical Practice Guidelines
EBP	Evidence-Based Protocol
ERNs	European Reference Networks
EU	European Union
FPS-AETSA	Health Technology Assessment Area of Fundación Progreso y Salud

01.

BACKGROUND

European Reference Networks (ERN) are virtual networks bringing together healthcare providers across Europe to tackle complex or rare medical conditions that require highly specialized treatment and a concentration of knowledge and resources. Most of the ERNs are actively working in the domain of development or implementation of Clinical Practice Guidelines (CPGs) with different levels of maturity or organisational approaches. While some of the networks are already in the phase of implementation or adaptation, other ERNs are starting to set-up their plans and priorities. There are also important differences between networks on the number of existing CPGs or Clinical Decision Support Tools (CDSTs) in the different domains of expertise and in the methodological knowledge and capacity to elaborate, appraise or evaluate such tools. Taking into account this background, the tender European Reference Networks: Clinical Practice Guidelines & Clinical Decision Support Tools (Contract Nº SANTE/2018/B3/030) was developed.

The overall purpose of this programme is to provide assistance to the ERNs and their healthcare providers in the process of development, appraisal and implementation of CPGs and CDSTs taking in account the objectives and criteria set under the framework of Article 12 of Directive 2011/24/EU on patients' rights in cross-border healthcare and relevant implementing measures and procedures. The programme started in January 2020 and had a duration of 48 months.

On 15 September 2023, at the request of the European Commission, a scientific review by independent experts was performed on the content developed within the ERN Guideline programme. The results of this review were good with satisfactory opinions regarding the developed deliverables. However, some modifications were recommended, especially concerning Work Package B: Preparation of the methodologies for the development, appraisal and implementation of clinical practice guidelines and Clinical Decision Support Tools. The reviewers found partially difficult to understand and apply the Handbooks by the clinicians. Therefore, the reviewers asked for some improvements in order to obtain a better understanding of their daily use by clinicians.

In this document, the Coordination Team in charge of the ERN Guideline programme summarizes the 13 Methodological Handbooks. It also incorporates relevant links for training materials, links to the open access articles and different examples from the area of rare diseases. The main objective of this document is to enhance the usefulness of the Methodological Handbooks and the training materials for relevant stakeholders.

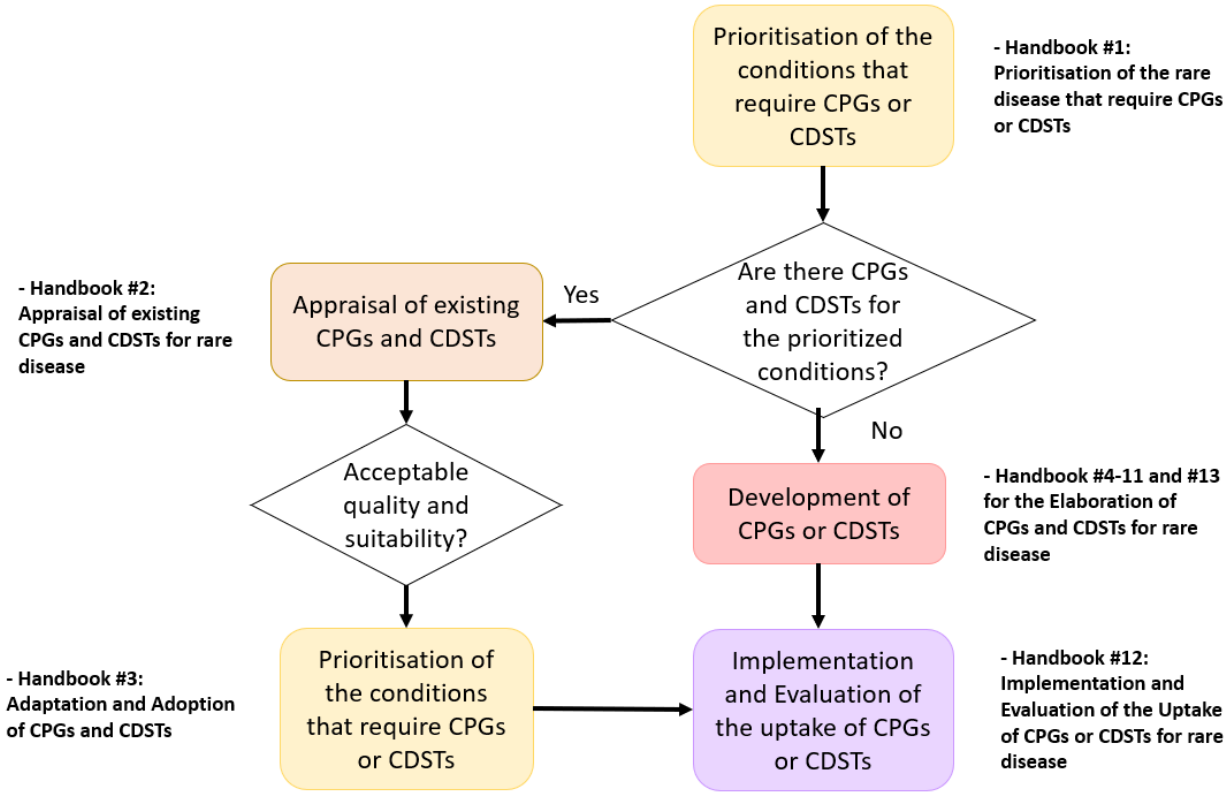
1.1 | Scope and Structure of the Summary Document

This document offers a brief overview of the thirteen Methodological Handbooks and toolkit for Clinical Practice Guidelines and Clinical Decision Support Tools for Rare or Low-Prevalence and Complex Diseases. The purpose of this document is to provide quick guidelines to facilitate the use of the handbooks. The information presented for each handbook consists of a summary and a table

with the following data: aims, key points, tools, annexes, training material links, and download links. Examples of articles based on the methodology and figures representing the process described in the handbooks have been provided when available.

The whole process of using and undertaking clinical guidelines (CPGs) and Clinical Decision Support Tools (CDSTs) includes the following steps: prioritization of rare diseases, development and implementation of CPGs and CDSTs, and the appraisal, adoption, and adaptation of existing guidelines and tools. The handbooks involved in each step are specified in the Figure 1

Figure 1. Milestones for the use of CPGs and CDSTs



02.

PRIORITISATION (HANDBOOK #1)

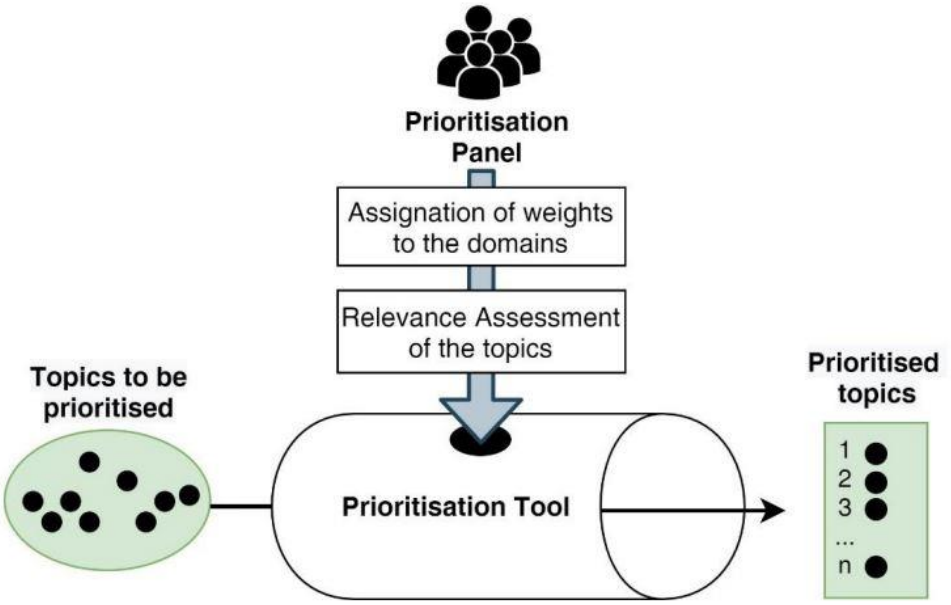
2.1 | Handbook #1: Prioritisation of Rare Diseases that Require CPGS or CDSTS

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

Aims	To provide guidance for the prioritisation of topics that require CPGs or CDSTs.
Key Points	✓ Prioritisation method ✓ Prioritisation criteria ✓ Prioritisation process
Process Tools	**Tool #1: Prioritisation Tool for Conditions that Require CPGs or CDSTs** This tool provides a prioritised list of conditions and a heat map resulting from the assessment of the relevance of a pre-defined list of conditions for the development of CPGs or CDSTs. This tool is available in the training material in the Module: **Topic 2.**
Annexes	✓ Surveys for expert consultation ✓ Relevance assessment chart structure
Training Material Links	The training materials related to this handbook can be accessed in the Module: **Topic 2.** Instructions on how to access the course are available in Annex 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/document/download/aabb1990-8291-4a90-9b5f-6c361ec92683_en?filename=ern_cpg-cdst_hb1_en.pdf

The prioritisation process for rare diseases that require CPGs or CDSTs and the prioritisation tool are available in Handbook #1. Figure 2 shows the whole process.

Figure 2. Prioritisation process



03.

APPRAISAL (HANDBOOK #2)

3.1 | Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases

The handbook presents specific criteria for appraising the methodological quality of each type of document – CPGs and CDSTs- for rare diseases. This handbook includes:

- ✓ Detailed explanation of the process for appraising CPGs and CDSTs
- ✓ The development and rationale of the appraisal criteria, which is the basis for the appraisal process.
- ✓ The use of this handbook and the appraisal tools. AGREE II is proposed for the appraisal of CPGs and specific tools are provided for the appraisal of CDSTs

Aims	To provide guidance for the appraisal of CPGs or CDSTs for rare diseases.
Key points	✓ Expert Consultation of the preliminary appraisal criteria of existing CPGs and CDSTs. ✓ Composition of the Appraisal Working Group ✓ How to use the handbook ✓ Overall Assessment by the appraisal panel ✓ Quality Assessment of CPGs and CDSTs ✓ Quality Assessment of Informative Documents
Tools	**Tool #1: AGREE II instrument** https://www.agreetrust.org/ This tool is one of the most employed and internationally validated grading systems for assessing the methodological quality of CPGs and the quality standards have been found to be appropriate for rare diseases. **Tool #2: Cochrane evaluation tool for assessing risk of bias** https://methods.cochrane.org/risk-bias-2

	This tool is used to systematically and objectively evaluate the methodological quality of individual studies in a systematic review, ensuring a comprehensive a rigorous assessment of potential biases that could impact the reliability of the evidence. **Tool #3: Critical Appraisal Skills Programme (CASP)** http://www.casp-uk.net/casp-tools-checklists This tool provides a structured framework to critically assess and appraise the quality, relevance, and validity of research evidence. **Tool #4: Grading of Recommendations Assessment, Development and Evaluation (GRADE)** https://www.gradeworkinggroup.org/ This system is employed to systematically evaluate the quality of evidence and strength of recommendations in clinical guidelines. **Tool #5: FLC 3.0 Critical Appraisal Tools Application** http://www.lecturacritica.com/en/index.php This application enables the analysis of the quality and reliability of scientific studies. **Tool #6: The Patient Education Material Assessment Tool (PEMAT) 4.** https://www.ahrq.gov/health-literacy/patient-education/pemat.html This tool is a systematic method to evaluate and compare the understandability and actionability of patient education material.
Annexes	✓ List of Institutions for Expert Consultation ✓ Expert consultation-ERNs ✓ Expert consultation- Institutions
Training material link	The training materials related to this handbook can be accessed in the Module: **Topic 3** Instructions on how to access the course are available in the Annex 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/system/files/2023-03/ern_cpg-cdst_hb2_en.pdf

04.

ADOPTION AND ADAPTATION (HANDBOOK #3)

4.1 | Handbook #3: Adaptation and Adoption of CPGs and CDSTs

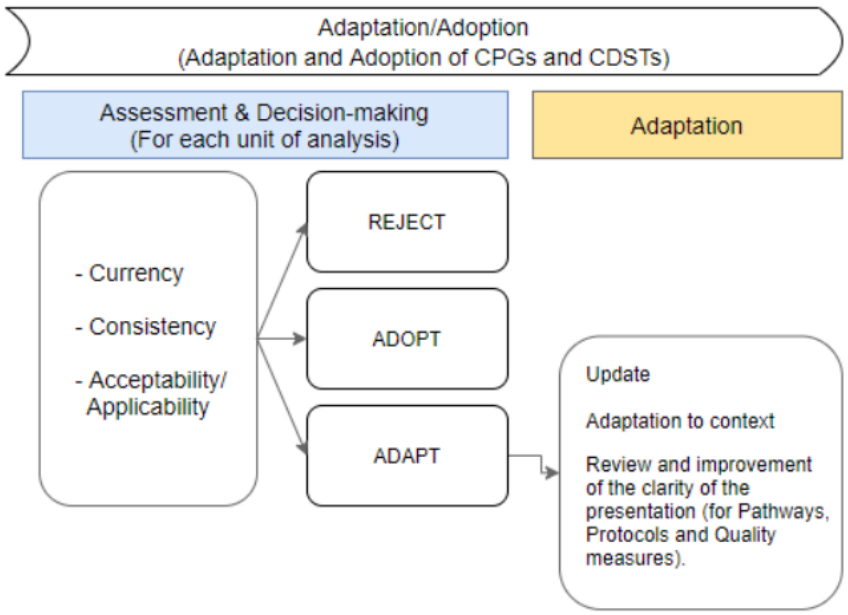
This handbook describes the elements that should be addressed in order to decide on whether a CPG or a CDST for rare diseases can be adopted or adapted and describes the actions that must be followed to adopt and adapt a CPG and a CDST for rare diseases.

Aims	To provide guidance for assessing and making decisions on the adoption or adaptation of existing CPGs and CDSTs.
Key Points	✓ Method for the adaptation and adoption of CPGs and CDSTs ✓ Assessment & decision-making ✓ Adaptation, based on ADAPTE methodology
Quality Assessment Tools	**Tool #1: Cochrane RoB 2.0 Tool** https://methods.cochrane.org/risk-bias-2 This tool is proposed for assessing the risk of bias in randomised controlled trials. **Tool #2: Critical Appraisal Skills Programme (CASP)** http://www.casp-uk.net/casp-tools-checklists This tool provides a structured framework to critically assess and appraise the quality, relevance, and validity of research evidence. **Tool #3: FLC 3.0 Critical Appraisal Tools Application** http://www.lecturacritica.com/en/index.php This application can be used to analyse the quality and reliability of scientific studies. **Tool #4: GRADEpro Guideline Development Tool (GDT)** http://www.gradeworkinggroup.org/ This tool guides the user through the process of guideline development. It is recommended that GDGs use this tool in the ERN context to foster homogeneity between the rare disease guidelines produced by different ERNs.

Annexes	✓ Assessment and Decision-Making Phase Checklist ✓ Checklist of Adapted Documents Content
Training Material Links	The training materials related to this handbook can be accessed in Module: **Topic 4.** Instructions on how to access the course are available in Annex 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/document/download/42b34408-bc86-4e82-8e86-8fa2c57bf734_en?filename=ern_cpg-cdst_hb3_en.pdf

The process of adaptation and adoption of existing CPGs and CDSTs for rare diseases, including the critical assessment tools, are included in Handbook #3. Figure 3 shows the process.

Figure 3. Overview of the adaptation/adoption process.



05.

DEVELOPMENT (HANDBOOK #4–#11)

These handbooks explain the steps for developing CPGs or CDSTs for rare diseases, including the definition of their scope and purpose, the formulation of clinical questions and the search, selection, appraisal and synthesis of scientific evidence, among other aspects. There is a development handbook for CPGs and each CDSTs covered in this toolkit.

5.1 | Handbook #4: Methodology for the Development of CPGs for Rare Diseases

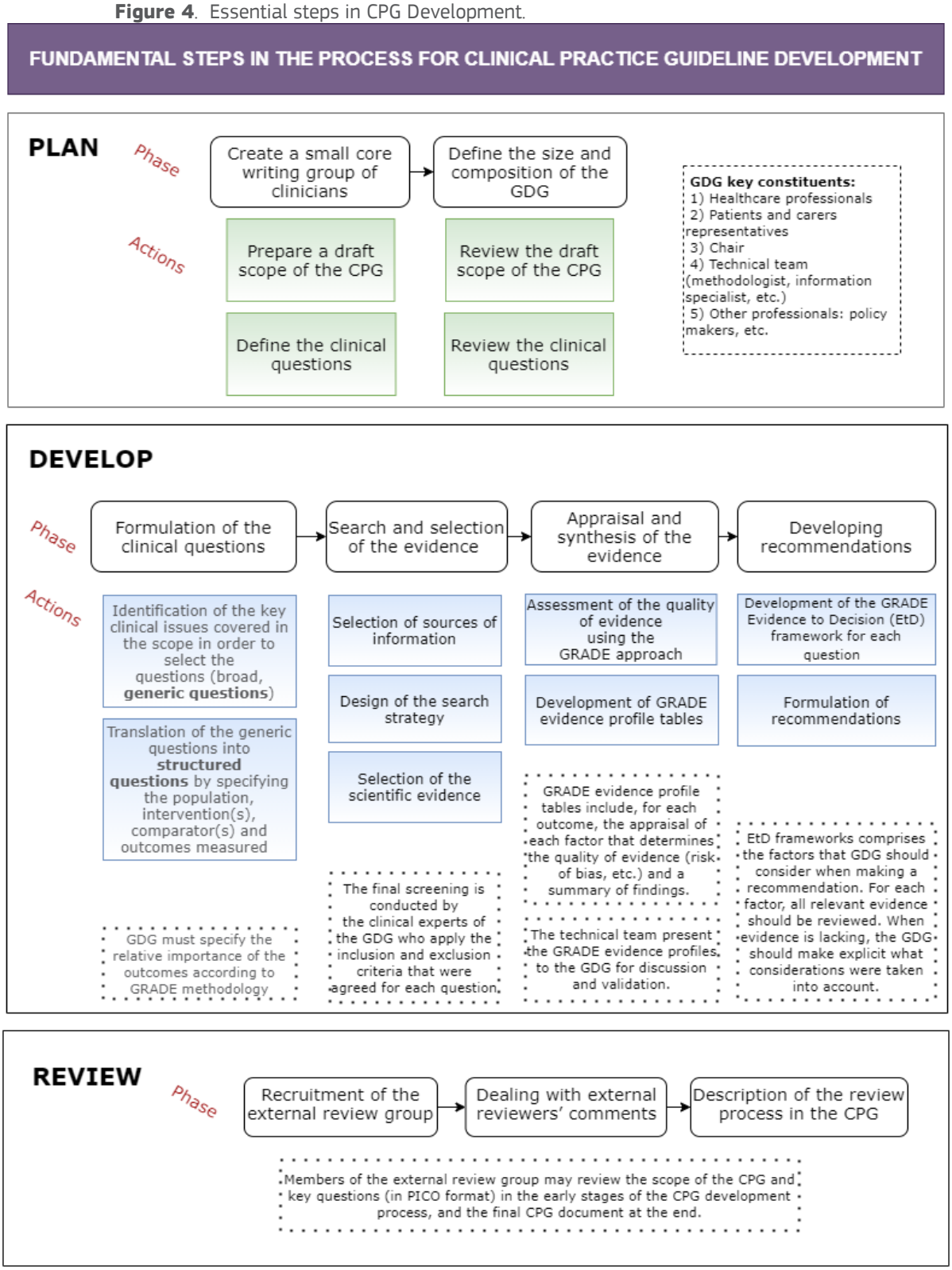
This handbook seeks to support the development of CPGs for rare diseases by covering all the steps of guideline development and has been designed to meet the reporting standards for trustworthy guidelines. It therefore includes a detailed explanation of the process for developing Clinical Practice Guidelines for rare diseases.

Aims	To provide guidance for the development of CPGs for rare diseases.
Key points	✓ Scope and purpose of the CPG ✓ Guideline Development Group (GDG) ✓ Formulation of the clinical questions ✓ Search and selection of scientific evidence ✓ Appraisal and synthesis of scientific evidence ✓ Considering resource use and rating the quality of Economic Evidence ✓ Developing recommendations from evidence ✓ External review process in the CPG ✓ Guideline reporting format ✓ Updating the CPG

Tools	**Tool #1: GRADEpro Guideline Development Tool (GDT)** https://www.gradeworkinggroup.org/ This tool guides the user through the process of guideline development. It is recommended that GDGs use this tool in the ERN context to foster homogeneity between rare disease guidelines produced by different ERNs. **Tool #2: Cochrane RoB 2.0 Tool** https://methods.cochrane.org/risk-bias-2 This tool is proposed for assessing the risk of bias in randomised controlled trials. **Tool #3: Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I)** https://methods.cochrane.org/robins-i This tool is proposed for assessing the risk of bias in observational studies. **Tool #4: Newcastle-Ottawa Scale** https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp This tool is proposed for assessing the risk of bias in observational studies. **Tool #5: Quality Appraisal Checklist for Case Series of the Institute of Health Economics (IHE)** https://www.ihe.ca/publications/ihe-quality-appraisal-checklist-for-case-series-studies This tool is suggested for the quality appraisal of case series. **Tool #6: Quality Assessment of Diagnostic Accuracy Studies (QUADAS)** https://www.bristol.ac.uk/population-health-sciences/projects/quadas/ This tool aims to assess the risk of bias in studies of diagnostic accuracy.
Annexes	✓ Template for the definition of the scope and purpose of the CPG ✓ Template for presenting the results of the initial screening of the evidence for a clinical question ✓ Template for external reviewers Barriers ✓ Template for the methodological material of a clinical question ✓ Questionnaire for gathering evidence from experts and members of the GDG
Training material link	The training materials related to this handbook can be accessed in Module: **Topic 5.** Instructions on how to access to the course are available in the Annex 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/system/files/2023-03/ern_cpg-cdst_hb4_en.pdf

The Methodology to undertake CPGs for rare diseases and the different tools are described in Handbook #4. An overview is illustrated in Figure 4.

Figure 4. Essential steps in CPG Development.



Example of article published based on the methodology described in HB #4:

Nou-Fontanet L, Martín-Gómez C, Isabel-Gómez R, Bachoud-Lévi AC, Zorzi G, Capuano A; NKX2-1-Related Disorders Guideline Working Group; Blasco-Amaro JA, Ortigoza-Escobar JD. Systematic review of drug therapy for chorea in NXK2-1-related disorders: Efficacy and safety evidence from case studies and series. Eur J Neurol. 2023. Dec;30(12):3928-3948. doi: 10.1111/ene.16038. Epub 2023 Sep 11. PMID: 37694681.

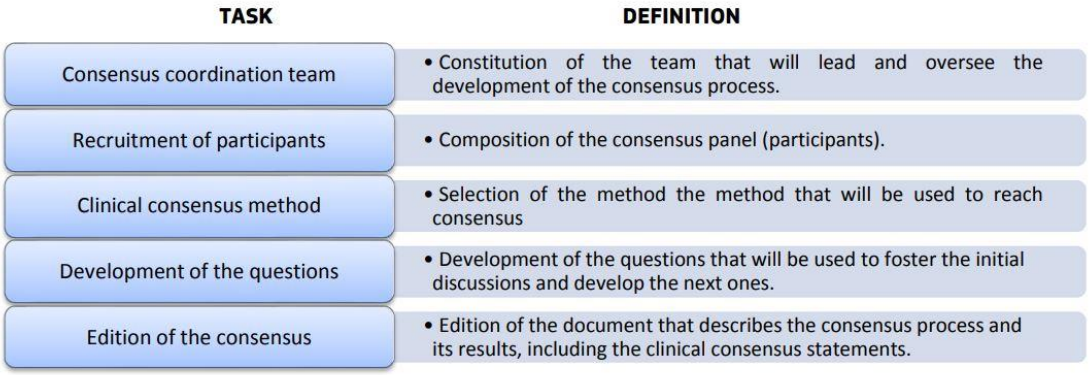
5.2 | Handbook #5 Methodology for the Development of Clinical Consensus Statements for Rare Diseases

This handbook explains the methodology for the Development of Clinical Consensus Statements for Rare Diseases.

Aims	To provide guidance for the development of Clinical Consensus Statements for rare diseases
Key Points	✓ Consensus coordination team ✓ Recruitment of participants (consensus panel) ✓ Clinical Consensus Methods ✓ Development of the questions ✓ Edition of the Clinical Consensus Statement
Tools	✓ None
Annexes	✓ None
Training Material Links	The training materials related to this handbook can be accessed in Module: **Topic 5.** Instructions on how to access the course are available in Annex 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/document/download/92d12de1-aae6-4dd5-b9d9-9afce9042ba3_en?filename=ern_cpg-cdst_hb5_en.pdf

Handbook #5 describes the main steps for the clinical consensus statement development process. An overview of this process and a definition of each step are shown in Figure 5.

Figure 5. The Clinical Consensus Statement development process: main steps.



5.3 | Handbook #6: Methodology for the Development of Evidence Reports for Rare Diseases

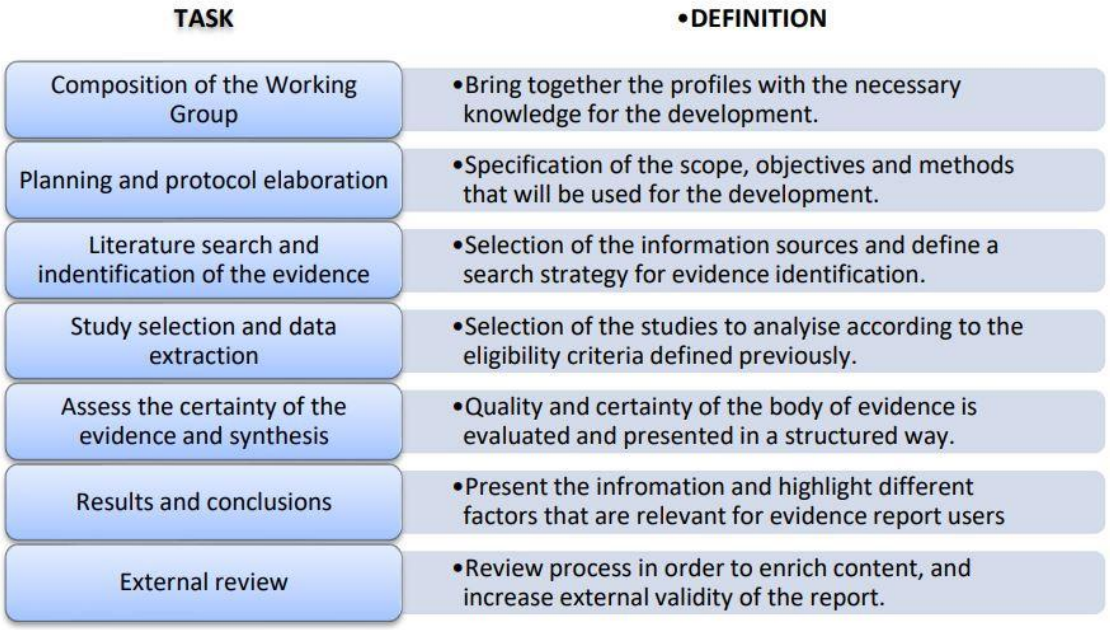
This handbook explains the methodology for the Development of Evidence Reports for Rare Diseases.

Aims	To provide guidance for the development of Evidence reports for rare diseases
Key Points	✓ Composition of the Working Group ✓ Planning and protocol preparation ✓ Literature search and identification of the evidence ✓ Study selection and data extraction ✓ Assess the certainty of the evidence and synthesis ✓ Results and conclusions ✓ External review
Quality Assessment Tools	**Tool #1: Assessment of Multiple Systematic Reviews (AMSTAR-2)** https://amstar.ca/Amstar_Checklist.php This tool is suggested for the quality appraisal of systematic reviews. **Tool #2: Cochrane RoB 2.0 Tool** https://methods.cochrane.org/risk-bias-2 This tool is proposed for assessing the risk of bias in randomised controlled trials. **Tool #3: Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)** https://methods.cochrane.org/robins-i This tool is proposed for assessing the risk of bias in observational studies. **Tool #4: Newcastle-Ottawa Scale** https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp This tool is proposed for assessing the risk of bias in observational studies.

	Tool #5: Quality Assessment of Diagnostic Accuracy Studies (QUADAS) https://www.bristol.ac.uk/population-health-sciences/projects/quadas/ This tool aims to assess the risk of bias in diagnostic accuracy studies. **Tool #6: British Medical Journal Checklist for authors and peer reviewers of economic submissions.** https://handbook-5-1.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm This tool is suggested for the quality appraisal of economic studies. **Tool #7: Consensus on Health Economic Criteria (CHEC)** https://handbook-5-1.cochrane.org/chapter_15/figure_15_5_b_evers_checklist_evers_2005.htm This tool is suggested for the quality appraisal of economic studies. **Tool #8: Confidence in the Evidence from Reviews of Qualitative research (CERQual)** https://www.cerqual.org/ This tool is proposed to assess how much confidence to place in findings from qualitative evidence. **Tool #9: The Quality Appraisal Checklist for Case Series of the Institute of Health Economics** https://www.ihe.ca/publications/ihe-quality-appraisal-checklist-for-case-series-studies This tool is suggested for the quality appraisal of case series.
Training Material Links	The training materials related to this handbook can be accessed in Module: **Topic 5.** Instructions about how to access the course are available in Annexe 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/document/download/61664b27-4b30-4264-aaa9-9fa691a7476d_en?filename=ern_cpg-cdst_hb6_en.pdf

The handbook #6 explains the main steps to develop evidence report for rare diseases and includes several critical appraisal tools for the quality assessment. The figure 6 shows an overview of this process and a definition for each step.

Figure 6. The development process of Evidence Reports: Main Steps.



5.4 | Handbook #7: Methodology for the Development of Diagnostic, Monitoring and Therapeutic Pathways for Rare Diseases

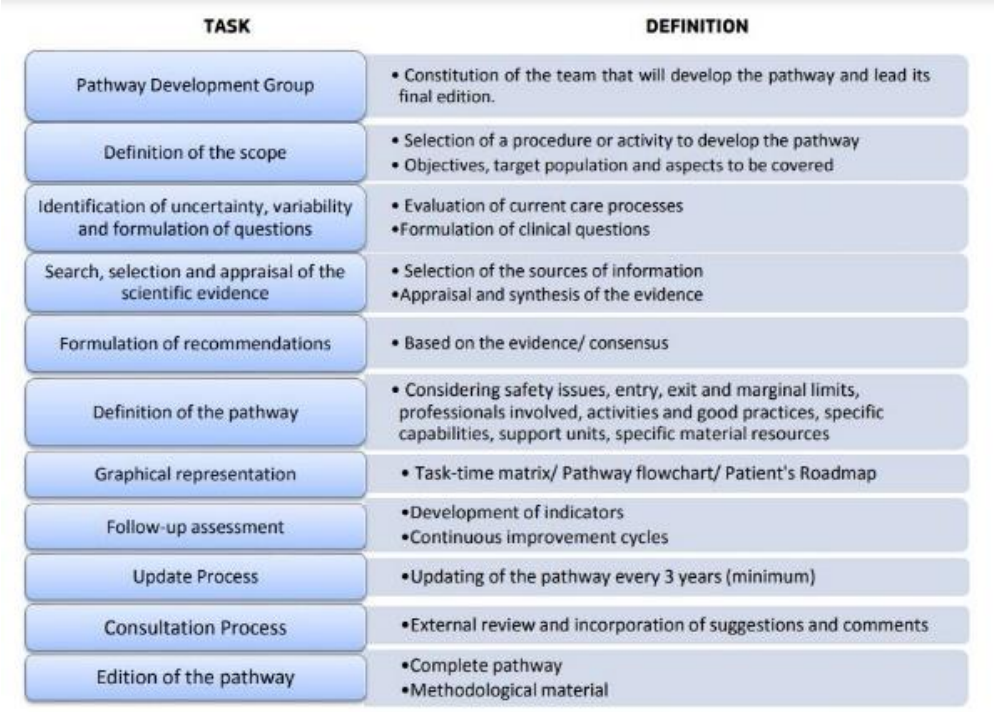
This handbook explains the methodology for the Development of Diagnostic, Monitoring and Therapeutic Pathways for Rare Diseases.

Aims	To provide guidance for the development of Diagnostic, Monitoring and Therapeutic Pathways for rare diseases
Key Points	✓ Pathway Development Group ✓ Definition of the scope ✓ Identification of uncertainty, variability and formulation of questions ✓ Search, selection and appraisal of the scientific evidence ✓ Formulation of recommendations ✓ Definition of the pathway ✓ Graphical representation ✓ Follow-up assessment ✓ Update process ✓ Consultation process ✓ Edition of the pathway

Tools	**Tool #1: AGREE II** https://www.agreetrust.org/ This tool is used to assess the methodological quality of CPGs. **Tool #2: Assessment of Multiple Systematic Reviews (AMSTAR-2)** https://amstar.ca/Amstar_Checklist.php This tool is suggested for the quality appraisal of systematic reviews. **Tool #3: A Toolkit for Developing a Clinical Pathway** https://citeseerx.ist.psu.edu/viewdoc/download?rep=rep1&type=pdf&doi=10.1.1.204.1097 This tool is suggested for the development for clinical pathways.
Annexes	✓ Template 1. Task-time matrix
Training Material Links	The training materials related to this handbook can be accessed in Module: **Topic 5.** Instructions on how to access the course are available in Annex 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/document/download/552cd1cf-f8e2-404e-9bb9-bec43ef18e68_en?filename=ern_cpg-cdst_hb7_en.pdf

Handbook #7 describes the methodology for the development of pathways for diagnosis, monitoring and therapy of rare diseases. This handbook also includes a toolkit for developing clinical pathways and critical assessment tools. An overview of this process and definitions for each step are shown in Figure 7.

Figure 7. The Diagnostic, Monitoring and Therapeutic Pathway development process: main steps.



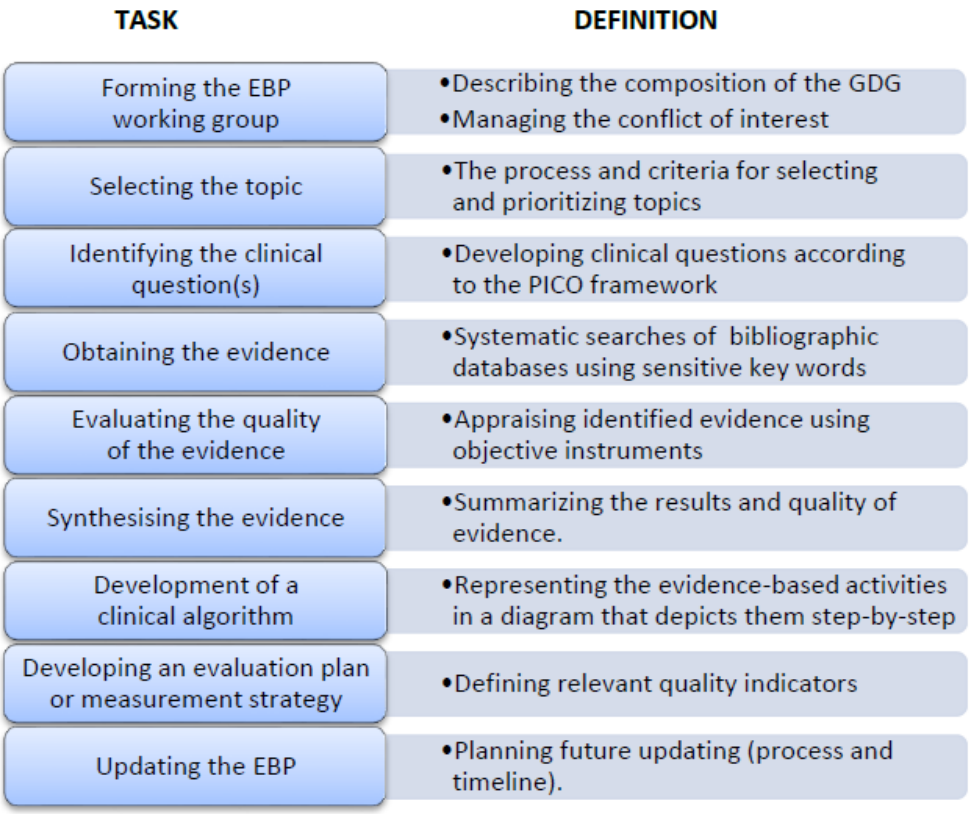
5.5 | Handbook #8: Methodology for the Development of Evidence-Based Protocols for Rare Diseases

This handbook provides information on keys issues related to the development of an Evidence-Based Protocol (EBP), including the composition of the EBP working group, the selection of the topic, search and critical appraisal of the evidence, and development of the clinical algorithm.

Aims	To provide guidance for the development of an EBP
Key points	✓ Evidence-Based Protocol Development Group ✓ Selection of the topic for the EBP ✓ Justification, scope and purpose of the Evidence-Based Protocol ✓ Identification of the clinical questions ✓ Gathering of evidence ✓ Evaluating the quality of the evidence ✓ Step-by-step activities to be followed ✓ Development of a clinical algorithm ✓ Development of an evaluation plan or measurement strategy ✓ Consultation process and dealing with stakeholders ´ comments ✓ Edition of the final document
Tools	**Tool #1: AGREE II** https://www.agreetrust.org/ This tool is used to assess the methodological quality of CPGs. **Tool #2: GRADEpro Guideline Development Tool (GDT)** https://www.gradeworkinggroup.org/ This tool guides the user through the process of guideline development. It is recommended that GDGs use this tool in the ERN context to foster homogeneity between rare disease guideline produced by different ERNs.
Annexes	✓ None
Training material link	The training materials related to this handbook can be accessed in Module: Topic 5. Instructions on how to access the course are available in Annex 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/system/files/2023-03/ern_cpg-cdst_hb8_en.pdf

The main steps in the process for developing Evidence-Based Protocols for rare diseases and their available tools are described in Handbook #8. Figure 8 shows the different steps and their definitions.

Figure 8. The development process of Evidence-Based Protocols for Rare Diseases: Main Steps



5.6 | Handbook #9: Methodology for the Development of Do's and Don'ts Factsheets for Rare Diseases

This handbook explains the methodology for the Development of Do's and Don'ts 2 Factsheets for Rare Diseases.

Aims	To provide guidance for the development of Do's and Don'ts factsheets for rare diseases
Key Points	✓ Composition of the Development Group ✓ Define the scope and purpose ✓ Developing a Do's and Don'ts Factsheet for Rare Diseases ✓ Edition of the final document ✓ External review

Tools	**Tool #1: GRADEpro Guideline Development Tool (GDT)** http://www.gradeworkinggroup.org/ This tool guides the user through the process of guideline development. It is recommended that GDGs use this tool in the ERN context to foster homogeneity between rare disease guidelines produced by different ERNs. **Tool #2: AGREE II** https://www.agreetrust.org/ This tool is used to assess the methodological quality of CPGs.
Training Material Links	The training materials related to this handbook can be accessed in Module: **Topic 5.** Instructions on how to access the course are available in Annex 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/document/download/ffcab20c-ee07-49d1-b33a-90104e3bb5ab_en?filename=ern_cpg-cdst_hb9_en.pdf

The methodology for the process of developing Do´s and Don´ts Factsheets for rare diseases and the tools are available in Handbook #9. Figure 9 shows the different tasks to be followed and their definitions.

Figure 9. The process for developing Do´s and Don´ts.

TASK	DEFINITION
Composition of the Development Group	• The develoment group shall be multisiciplinary, consisting of patients and carers, health professionals and a technical team
Define the scope and purpose	•The objective of the document, the target audience and the condition/health problem addressed are described
Developing a Do's and Don'ts Facsheet for Rare Diseases	• Structure of the document • Selection of the conten, key recommendations from CPGs, CDSTs and good-practice points • The documents retrieves must be assessed •Key ideas must be selected
Edition of the final document	•Do's and Don'ts Facsheets for rare diseases should be easily accesible to end-users.
External review	• The draft should undergow an external review by experts, to ensure its relevance and appropriateness

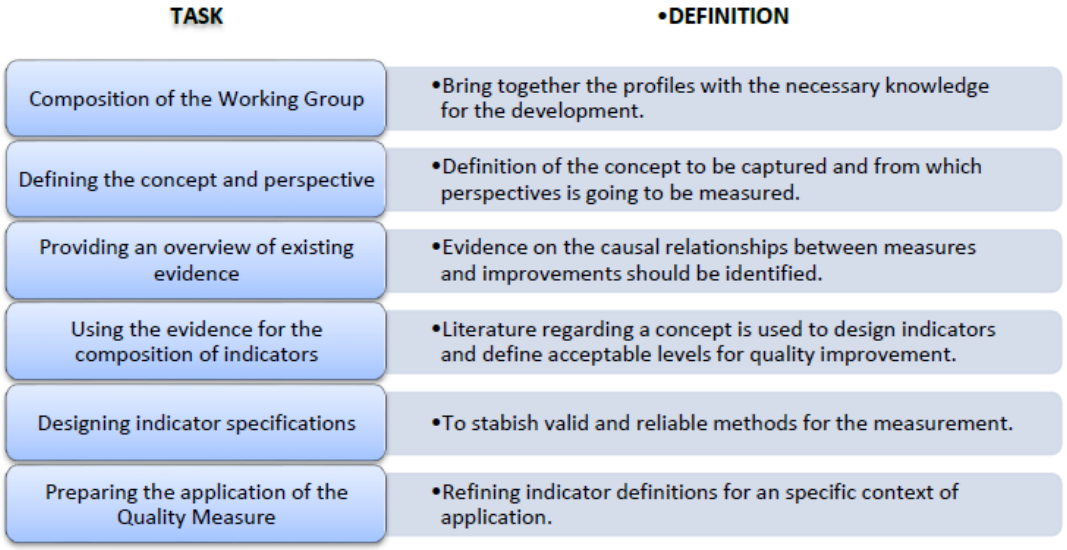
5.7 | Handbook #10: Methodology for the Development of Quality Measures for Rare Diseases

This handbook includes a detailed explanation of the process for developing Quality Measures for rare diseases, including guidelines on the following: the composition of the working group, defining the concept and perspective, providing an overview of existing evidence, using the evidence for the composition for indicators, designing indicators specifications and the preparation of the application of the Quality Measure.

Aims	To provide guidelines for the development of Quality Measures for rare diseases.
Key points	✓ Composition of the Working Group ✓ Quality Measures development model ✓ Steps in the development of Quality Measures ✓ Best practices for developing a Quality Measure
Tools	**Tool #1: Quality Measures development checklist** (Found in the annexes of HB #10) This tool is a checklist presented to describe the steps to follow and the information detailed during the indicator development process.
Annexes	✓ Quality Measures development checklist
Training material link	The training materials related to this handbook can be accessed in Module: **Topic 5.** Instructions on how to access the course are available in Annex 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/system/files/2023-03/ern_cpg-cdst_hb10_en.pdf

The main steps for the development of quality measures for rare diseases and the available tool are described in Handbook #10. The different tasks for the quality measures development process and their definition are shown in Figure 10.

Figure 10: The quality Measures Development Process: Main Steps.



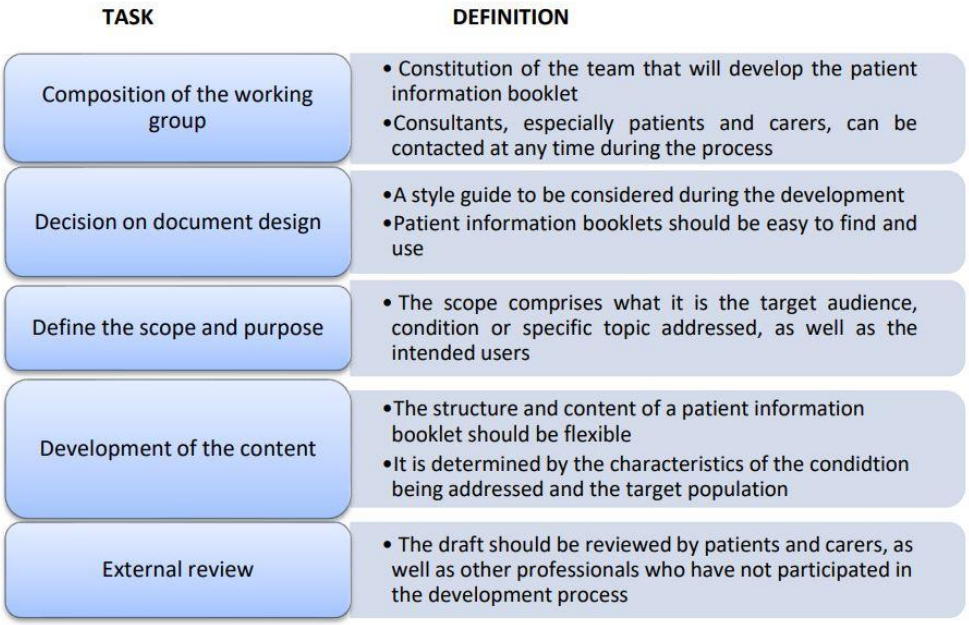
5.8 | Handbook #11: Methodology for the Development of Patient Information Booklets for Rare Diseases

This handbook explains the methodology for the Development of Patient Information Booklets for Rare Diseases.

Aims	To provide guidance on the development of Patient Information Booklets for rare diseases
Key Points	✓ Composition of the working group ✓ Decision on document design ✓ Definition of the scope and purpose ✓ Development of the content ✓ External review
Tools	**Tool #1: GRADEpro Guideline Development Tool (GDT)** http://www.gradeworkinggroup.org/ This tool guides the user through the process of guideline development. It is recommended that GDGs use this tool in the ERN context to foster homogeneity between rare disease guidelines produced by different ERNs.
Training Material Links	The training materials related to this handbook can be accessed in Module: **Topic 5.** Instructions on how to access the course are available in Annex 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/document/download/de5e2d19-3a08-4954-8057-c851d5617f1e_en?filename=ern_cpg-cdst_hb11_en.pdf

The process for the development of patient information booklets for rare disease and the tool used are described in Handbook #11. The main steps for the development of patient information booklets are defined in Figure 11.

Figure 11: The process for developing Patient Information Booklets: main steps.



Example of an article published based on the methodology described in HB #11:

Martín-Gómez C, Ortigoza-Escobar JD, Nou-Fontanet L, Molina-Linde JM, Bachoud-Lévi AC, Léger J, Blasco-Amaro JA; NKX2-1-Related Disorders Guideline Working Group. Exploring the values, preferences, and information needs of patients with NKX2-1-related disorders: A qualitative study protocol. PLoS One. 2023 Feb 9;18(2):e0281573. doi: 10.1371/journal.pone.0281573. PMID: 36758103; PMCID: PMC9910649.

06.

IMPLEMENTATION (HANDBOOK #12)

6.1 | Handbook #12: Implementation and Evaluation of the Uptake of CPGs and CDSTs for Rare Diseases

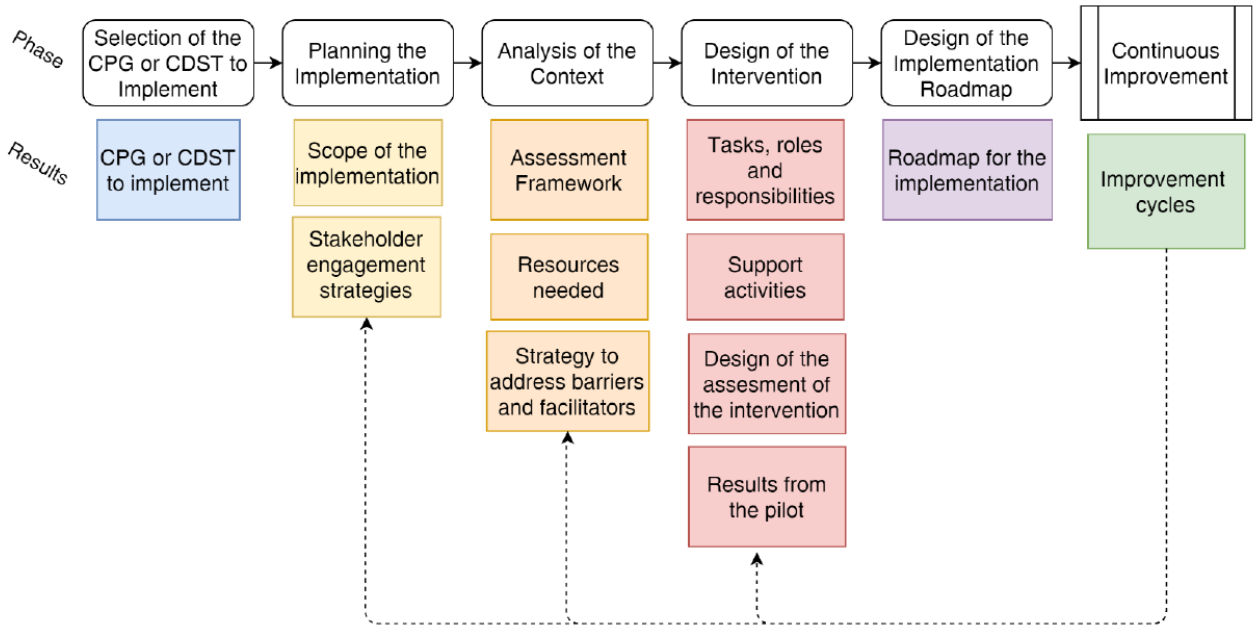
This handbook provides the steps necessary to implement CPGs or CDSTs for rare diseases, including the selection of the specific CPG or CDST to be implemented, implementation planning, context analysis, design of the interventions and methods to carry out the evaluation of the implementation and uptake of the CPG or CDST, development of the implementation roadmap and design of the continuous improvement mechanism.

Aims	To provide guidance to systematically plan, perform and evaluate the implementation of CPGs or CDSTs
Key points	✓ Scope ✓ Composition of the implementation working group ✓ Implementation process ✓ Development of the implementation Roadmap ✓ Design of the continuous improvement mechanism
Tools	**Tool #1: The Donabedian model of Structure, Process and Outcome (SPO)** https://pubmed.ncbi.nlm.nih.gov/26151519/ This model provides an evaluation framework that supports systematic enquiry into health services. It is traditionally used to evaluate quality of care, and is consistent with the implementation in the sense that the improvement of health care quality is the expected result of evidence-based practice. **Tool #2: The Plan-Study-Act (PDSA)** https://www.england.nhs.uk/wp-content/uploads/2022/01/qsir-pdsa-cycles-model-for-improvement.pdf A model that consists of a logical sequence of four repetitive steps for continuous improvement, specific activities and recommendations regarding every step.

Annexes	✓ Definitions of Implementation outcome ✓ Research techniques to explore the context ✓ Potential Strategies to Maximise Facilitators and Minimise Barriers
Training material link	The training materials related to this handbook can be accessed in Module: **Topic 6.** Instructions on how to access the course are available in Annex 1. It can be accessed through the following link: https://academy.europa.eu/
Download	https://health.ec.europa.eu/system/files/2023-03/ern_cpg-cdst_hb12_en.pdf

The steps to implement CPGs and CDSTs for rare diseases and the necessary tool are available in Handbook #12. The implementation process has different phases and results as shown in Figure 12.

Figure 12. Implementation process.



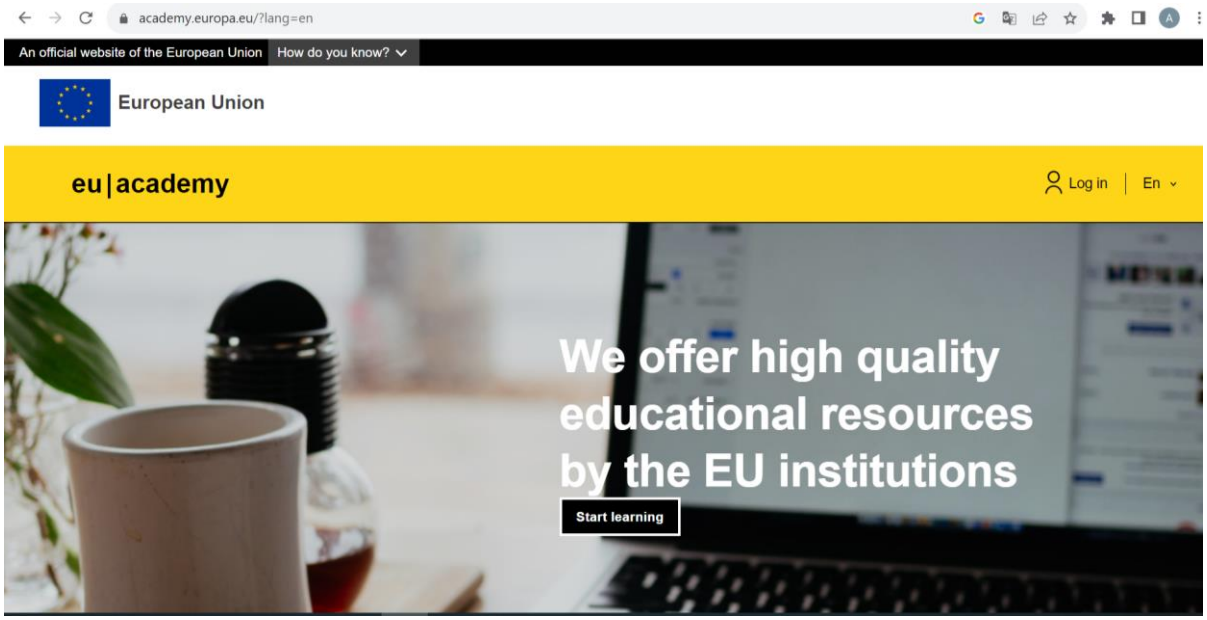
07.

ANNEXES

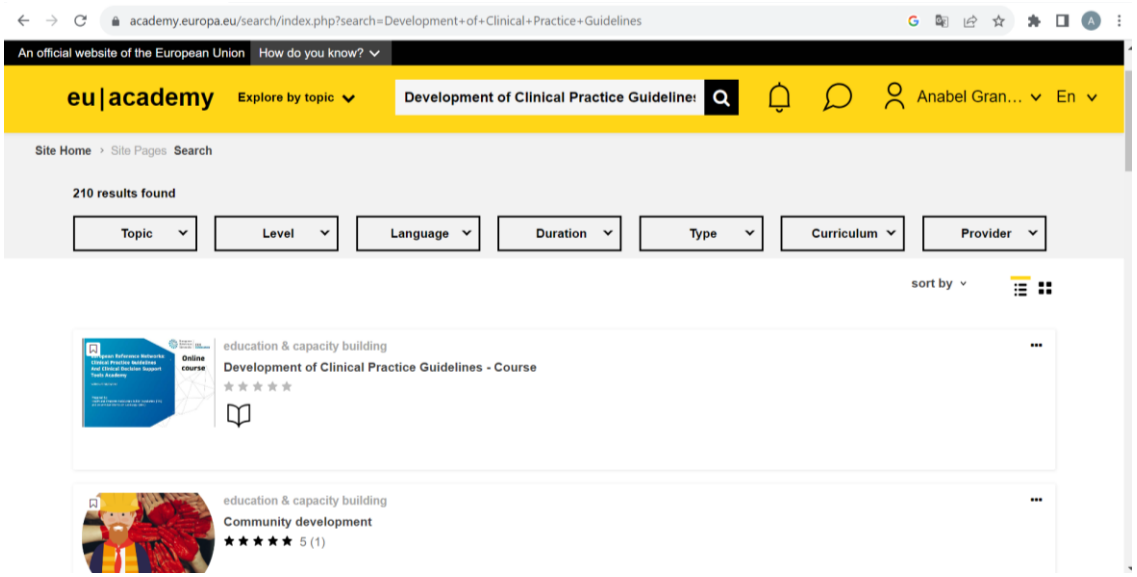
ANNEX 7.1 I How to access the "Development of Clinical Practice Guidelines" course

First step: Access the following link: https://academy.europa.eu/

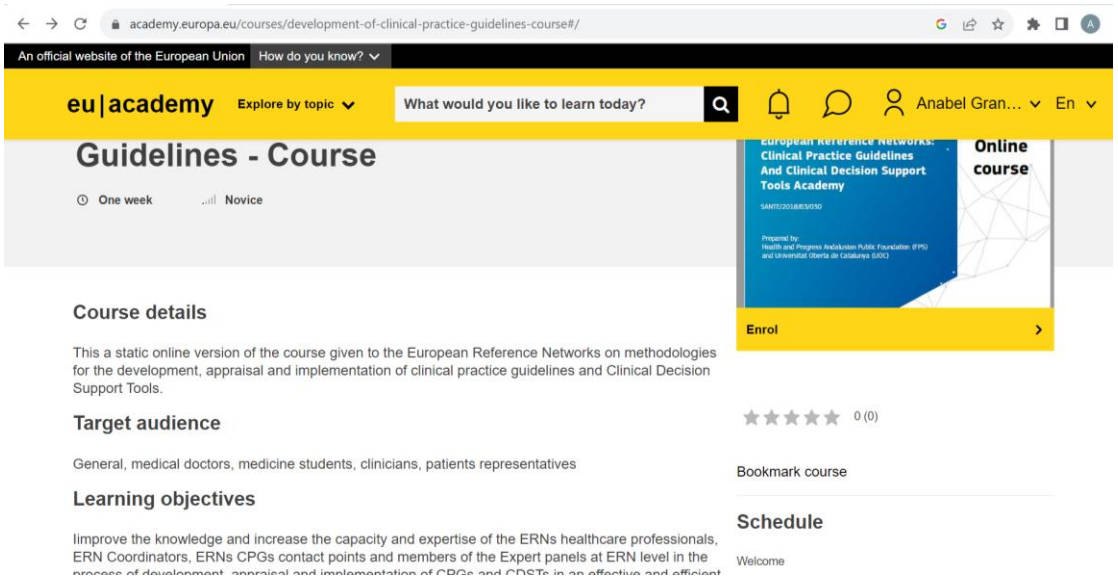
Second step: Register with your personal data. After completing registration, access the website through LOG IN (upper right corner).



Third Step: To access the different courses, click on “Explore by topic” and type: “Development of clinical practice guidelines” (Click on the first option)



Last step: Click on Enrol, and then it´s possible to access the course.



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