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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 #2: Appraisal of Existing CPGs and CDSTs for Rare or Low-Prevalence and Complex Diseases**

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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.

Purpose:

To provide guidance for the appraisal of CPGs and CDSTs for rare diseases.



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ABBREVIATIONS

AETSA	Andalusian Health Technology Assessment Department
AGREE II	Appraisal of Guidelines for Research & Evaluation II
AQuAS	Catalan Agency for Health Quality and Evaluation (Agència de Qualitat i Avaluació Sanitàries de Catalunya)
Avalia-t	Scientific Advice Unit of the Galician Agency for Health Knowledge Management (A Unidade de Asesoramento Científico-Técnico)
CATDH	Canadian Agency for Drugs and Technologies in Health
CDSTs	Clinical Decision Support Tool
CPGs	Clinical Practice Guidelines
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
HTA	Health Technology Assessment
IACS	Aragon Health Sciences Institute
ICO	Catalan Institute of Oncology
NICE	National Institute for Health and Care Excellence
OSTEBA	Basque Office for Health Technology Assessment (Osasun Teknologien Ebaluazioko Zerbitzua - Servicio de Evaluación de Tecnologías Sanitarias del País Vasco)
PEMAT	Patient Education Materials Assessment Tool
PREMs	Patient Reported Experience Measures
PROMs	Patient Reported Outcome Measures
QM	Quality Measures
SESCS	Evaluation Service of the Canary Island Health Service (Servicio de Evaluación del Servicio Canario de la Salud)
SIGN	Scottish Intercollegiate Guidelines Network



01.

BACKGROUND

There are a number of challenges surrounding the development of CPGs and CDSTs for rare diseases. One of the most relevant barriers is the lack of high-quality evidence, which cutting-edge methodological frameworks like GRADE¹ 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. The project also aims to provide a common methodology, in order to harmonize the elaboration process of CPGs and CDSTs.



02.

AIM OF THIS DOCUMENT

This document aims to provide methodological guidance on the process of assessing the methodological quality of CPGs and CDSTs for rare diseases, in order to determine whether the existing documents are suitable to cover the needs identified in the prioritisation process.

It consists of a pragmatic assessment of the methodological quality of CPGs and CDSTs for rare diseases. CPGs and CDSTs that meet the minimum requirements will be thoroughly assessed in the Adoption & Adaptation phase, in which a comprehensive assessment of the currency, consistency, acceptability/applicability and clarity of presentation is proposed.

To facilitate this task, an assessment toolkit has been developed based on the set of criteria for assessing the methodological quality of CPGs and CDSTs for rare diseases. It comprises 8 tools specific to each type of product for rare diseases covered by this project (CPGs and CDSTs).

2.1 | Scope

The manual presents specific criteria for appraising the methodological quality of each type of document - CPGs and CDSTs - for rare diseases. The documents have been organised in three different groups:

- ✓ Clinical Practice Guidelines (CPGs)
- ✓ Clinical Decision Support Tools (CDSTs), which comprise:
 - Clinical Consensus Statements
 - Evidence Reports
 - Diagnostic, monitoring and therapeutic pathways
 - Evidence-based Protocols
 - Do's and Don'ts Factsheets for diseases
 - Quality Measures (QM)
- ✓ Informative documents, which comprises:
 - Patient Information Booklets

The appraisal criteria for each type of document are described in each section, together with their specific application.



03.

METHODS

An in-depth analysis of the state of the art on methodologies for the appraisal of CPGs and CDSTs for rare diseases was developed in the WPB-1 of TENDER N°SANTE/2018/B3/030 8 “Report on the Literature Review and Expert Consultation”. The documents identified in the systematic search in databases and the hand search in relevant organisations’ and projects’ websites were taken into account in the definition of the appraisal criteria and the selection of essential (mandatory criteria) and desirable characteristics for the assessment of the quality of CPGs and CDSTs for rare diseases.

This user handbook has been developed based on well-founded methodologies on appraisal of CPGs and CDSTs for common diseases, considering special features of rare diseases (e.g. issues related to the working group).

An expert consultation was conducted on the preliminary appraisal criteria of existing CPGs and CDSTs for rare diseases. ERN members and experts from world-renowned institutions participated in this consultation.

3.1 | Expert Consultation

The preliminary appraisal criteria of existing CPGs and CDSTs for rare diseases were subjected to an expert consultation. Due to the technical complexity of the criteria, it was considered necessary to contact experts from ERNs, institutions and HTA agencies with extensive methodological knowledge, to ensure the relevance and applicability of the appraisal handbook. Twenty-two experts made suggestions and comments, which have enriched and improved the document.

Twelve answers were received from 8 ERNs.

Ten answers were received from the institutions contacted.



04.

USER HANDBOOK

4.1 | Composition of the Appraisal Working Group

The appraisal working group is the group of people who participate in the appraisal process. The number of appraisers who evaluate CPGs and CDSTs will be decided by the ERN. We recommend that each CPGs and CDSTs be assessed by at least 2 appraisers, and preferably 4 (especially in the appraisal of CPGs), as this will enhance the reliability of the assessment ^{2,3}.

Appraisers should be properly trained to assess the documents: they need to be trained in the use of the manual and the toolkit. They should not have been involved in the development of the CPG or CDST that they will review.

Potential conflicts of interests should be carefully identified and duly addressed, following the indications established by our partner FPS. .

4.2 | How to use the handbook

The following instructions are applicable to the evaluation of all the above-mentioned documents for rare diseases:

- ✓ Use the appraisal toolkit to facilitate the assessment. There is a tool for each type of document.
- ✓ Before using the appraisal toolkit, read through the established criteria and the specifications provided in the User Handbook to become familiar with all the items and their application. The User Handbook contains detailed explanations to facilitate the evaluation.
- ✓ Users should first carefully read the document to be appraised in full. In addition to the document to be appraised, users should attempt to identify all information on the development process prior to the appraisal. This information may be contained in the document itself or it may be summarised in a separate technical report or methodological manual.
- ✓ The information that the toolkit contains is concise and straightforward. Keep this user guide handy, as well as other proposed handbooks for the appraisal ^{4,5}, for ready access to the description of each criterion. The handbook contains specifications that should be considered in order to judge the items correctly.
- ✓ When *mandatory* criteria are offered (yes/no questions), all the criteria listed must be met by the CDSTs in order to continue to the next phase (Adoption & Adaptation phase, when a more in-depth assessment will be performed). The aforementioned criteria are considered essential. On the other





hand, characteristics considered *desirable* provide a first indication of the higher quality of a particular CDST, which will be addressed in detail in the next stage (Handbook #3: Adaptation and Adoption of CPGs and CDSTs).

- ✓ Do not skip any criterion. If sub-criteria are provided, all of them must be met to fulfil the criterion, unless they are separated by an “and/or” conjunction.
- ✓ Do not let the rating of one criterion (or sub-criterion) influence the rating of other items. Make sure you rate each criterion separately and distinctly.
- ✓ Focus only on the CPGs or CDST that you are reviewing and do not try to compare it to previous documents.
- ✓ Write down judgements, comments or important information regarding the application of the checklist (e.g. where to locate information, what information is missing, etc.), in order to help the final panel discussion and decision-making.
- ✓ When the term 'patients and/or 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.

4.3 | Overall Assessment

Once the methodological quality of CPGs or CDSTs for rare diseases has been appraised by each evaluator, an overall assessment will be made by the appraisal panel. Individual judgements will be discussed and the final decision will be reached by consensus.

- ✓ If the appraisal panel considers that the document (CPG or CDST) meets the mandatory criteria (minimum requirements) in the assessment, the document will be thoroughly assessed in the Adoption & Adaptation phase, in accordance with the Methodological Handbook.
- ✓ When the document (CPG or CDST) does not meet the minimum requirements of the appraisal (mandatory criteria), it will not be considered suitable for adoption or adaptation.

4.4 | Quality Assessment of Clinical Practice Guidelines and Clinical Decision Support Tools

4.4.1 / Clinical Practice Guidelines

Definition:

Clinical practice guidelines (CPGs) are systematically developed statements that include recommendations, intended to optimise patient care, that are informed by a systematic review of evidence and an assessment of the benefit and harms of alternative care options⁶. The level of evidence needs to be stated.

Appraisal criteria:

Following the identification of guidelines, an assessment of their methodological quality is required. The AGREE II instrument⁵ is one of the most employed and internationally validated grading systems for assessing the methodological quality of Clinical Practice Guidelines (CPGs). The quality standards for evaluating existing guidelines based on the AGREE II instrument have been found to be appropriate for rare diseases⁷⁻⁹. This instrument is proposed for the appraisal of CPGs for rare diseases. Please read the AGREE II instrument manual thoroughly⁵.



The AGREE II Instrument comprises 23 items organised into six domains: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence (Table 1). Each domain captures a unique dimension of guideline quality. The six domain scores are judged as independent factors; they cannot be aggregated into a single quality score. The original rating system of AGREE II uses a 7-point scale for each item (1- strongly disagree to 7-strongly agree). The manual provides a description for each item, with suggestions on where to find the item information and guidance on how to rate ^{5, 10}.

Table 1. Structure and content of AGREE II ⁵

Domain 1. Scope and Purpose is concerned with the overall aim of the guideline, the specific health questions, and the target population (items 1-3).
Domain 2. Stakeholder Involvement focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users (items 4-6).
Domain 3. Rigour of Development relates to the process used to gather and synthesise the evidence, the methods to formulate the recommendations, and to update them (items 7-14).
Domain 4. Clarity of Presentation deals with the language, structure, and format of the guideline (items 15-17).
Domain 5. Applicability pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline (items 18-21).
Domain 6. Editorial Independence is concerned with the formulation of recommendations not being unduly biased with competing interests (items 22-23).

The appraisal of CPGs for rare diseases complies with the same quality standards as those of CPGs for common conditions⁷. Nonetheless, certain peculiarities should be taken into account⁷⁻⁹ (Table 2). The AGREE-II instrument is applicable regardless of the small number of patients, potentially small volume of evidence, and other limitations typically encountered in rare disease guidelines⁹.



Table 2. Additional notes on use of the AGREE II instrument for guideline quality evaluation in rare diseases ^{7-9, 11}

AGREE II Domain	Points to consider
Scope and purpose (Items 1-3)	Rare disease guidelines should be able to address all of the items concerned with scope and purpose.
Stakeholder involvement (Items 4-6)	<p>The working group should be multidisciplinary, and be made up of health professionals involved in one of the stages of management of patients with rare diseases. Although it is likely that one professional group may dominate, comprehensive stakeholder involvement is as important to the development of guidelines for rare diseases as it is for common diseases. The opinion of a general practitioner, and/or a paediatrician in the case of paediatric diseases, should be considered.</p> <p>For diseases revealed at paediatric age, the group should involve specialists in childhood and adulthood management of the disease, to cover the transition from paediatric to adult healthcare services.</p> <p>Patients and/or carers should be included in the group.</p> <p>Consultation/participation of international experts may be useful.</p> <p>Scoring of these items should recognise this principle and reflect the extent to which the guideline addresses each item.</p>
Rigour of development (Items 7-14)	<p>The AGREE II quality rating does not depend on the quantity or type of published evidence but on the rigour of the systematic methods used to identify, select and synthesise evidence and the transparency with which the guideline development group report how they reached recommendations.</p> <p>For item 13 (external review by experts) – the experts should include patients, carers, and/or patient groups.</p> <p>Methodological procedures may be difficult to locate, presented in separate documents (technical reports, methodological manual or guideline developer policy statement), sometimes with no link provided in the guideline document.</p>
Clarity of presentation (Items 15-17)	When scoring item 16 there may not be a range of options for management of the rare condition or health issue. In this case the item would be considered ‘not applicable’ and scored as ‘1’.
Applicability (Items 18-21)	<p>The extent to which a guideline can provide information on potential facilitators to guideline implementation and describe resource implications may be limited for rare disease guidelines where the implementation setting is likely to encompass diverse healthcare contexts.</p> <p>The information provided may be country-specific, healthcare system-specific, or generic.</p>
Editorial independence (Items 22-23)	For many rare diseases there are likely to be only a small number of experts worldwide, which may limit the potential for editorial independence. Scores should reflect how this was addressed .
Overall guideline assessment	<p>Before selecting ‘yes with modifications’, consider whether there are resources available to modify the guideline and any copyright issues.</p> <p>The existence of only a few or only one guideline on a topic should not prevent a judgement of ‘no’ on question 2 (“I would recommend this guideline for use”) as it is worthwhile to indicate that better quality guidelines are needed.</p>
Notes section	<p>Indicate if the guideline is the only (known) guideline available on the topic.</p> <p>Indicate any research recommendations identified in the guideline .</p>



The AGREE II manual also considers the interpretation of domain scores. The appraisal panel should define quality thresholds before beginning the AGREE II appraisals. For example, an approach that can be used to set quality thresholds is prioritising certain domains over others. Thresholds can be created based on scores for the prioritised domains (e.g. high quality guidelines are those with a domain 3 (*Rigour of Development*) and/or domain 6 (*Editorial Independence*) score >85%). Decisions should be guided by the contextual circumstances in which the guideline is to be used and by evaluating the importance of the different domains and items in that context⁵. Scarcity of disease information, recommendation quality, usefulness of specific information for health professionals, etc. may require the adjustment of the criteria that can be used to set quality thresholds⁸ (e.g. prioritisation of one domain). Other examples can be found in the instructions provided in the *AGREE-II User's Manual*⁵. As mentioned above, it is important that guidelines for rare diseases are high quality; therefore, quality standards should not be lowered⁹.

Upon completing the 23 items, an overall guideline assessment is needed. Overall assessment requires the AGREE II user to draw a conclusion on the quality of the guideline, taking into account the criteria considered in the assessment process^{5, 12}. The interpretation of the domain scores can be used to identify strengths and limitations of guidelines or to select high quality guidelines for adaptation, endorsement, or implementation.

In addition to the assessment based on the AGREE-II instrument, it is mandatory to indicate the CPG development, review and/or update date. No more than 3 years should generally have passed since that date to ensure the content is up to date. Otherwise, the guideline should be updated in order to be used¹³.

4.4.2 / Clinical Consensus Statements

Definition:

Clinical consensus statements reflect opinions drafted by subject matter experts for which consensus is sought using explicit methodology to identify areas of agreement and disagreement. In contrast to clinical practice guidelines, which are based primarily on high-level evidence, clinical consensus statements are more applicable to situations where evidence is limited or lacking, yet there are still opportunities to reduce uncertainty and improve quality of care^{14, 15}. They offer specific recommendations on a topic but do not give specific algorithms.

Appraisal criteria:

The evaluation comprises two types of criteria: mandatory criteria that the evidence-based protocols must meet (minimum required), and desirable characteristics (see 4.2. How to use the handbook).

- ✓ Mandatory criteria to be met by clinical consensus statements in order to proceed to the next stage (Adoption & Adaptation Handbook). The evaluated document must fulfil all of these requirements:
 1. The scope, objective and target audience are described.

Clinical consensus statements should be developed for specific topic areas with significant opportunities for quality improvement despite an insufficient evidence base to support a CPG or other types of CDSTs¹⁴. Contextual circumstances are reflected upon and expressed¹⁶.

 - The condition/health problem addressed is reported.
 - The population to whom the document is meant to apply is specifically described.
 - The target audience for which the document is intended is reported (e.g. health professionals, patients and/or carers, etc.).



- .
 - 2. The date of elaboration and/or review or update is indicated ¹⁷.
Since consensus statements provide a “snapshot in time” of the state of knowledge on a specific topic, they must be periodically re-evaluated and re-published, replacing the previous consensus statement. No more than 3 years should generally have passed since that date and the content should be up to date.
 - 3. The expert panel includes individuals from all relevant professional groups affected by the topic area addressed by the Clinical Consensus Statements, integrating the set of activities of all the professionals involved ^{16, 18}. The following information for each expert is included: name, discipline/content expertise, institution, geographical location, a description of the member’s role and contact details.
 - 4. The declaration of conflicts of interest for authors, collaborators and reviewers is provided.
 - 5. The methodology approach (development, adaptation or update) is transparent and explicit, including (all the following subcriteria must be met to fulfil this criterion):
 - It is explicit and well-justified that the scientific evidence is insufficient or limited to formulate evidence-based recommendations ¹⁹.
 - The method used to achieve consensus (e.g. Delphi method, nominal group technique/expert panel, consensus development conferences, informal consensus, etc.) is described ¹⁷.
 - The process used to define the initial question or statement is described.
 - The document has been externally reviewed by relevant stakeholders, including patients, carers, and/or patient representatives.
 - 6. Level of consensus of individual responses or consensus statements is revealed:
 - Clear definition of target “acceptable” level of consensus.
Consensus does not have to be 100%. A lower level of agreement may be used and taken as “consensus” but this should be decided prior to the process and the level of agreement that will be considered “consensus”.
 - 7. Rationale underpinning the clinical consensus statements is clearly detailed in the write-up of the report.
- ✓ Desirable characteristics of clinical consensus statements:
- In the case of a topic deriving from a CPG or CDST, members of the development group have been involved in the development of the clinical consensus statements ¹⁶.
 - Patients and/or carers and/or patient representatives have been included in the development group or their opinions and preferences have been sought in some other way ^{14, 16}.
 - Procedures for reviewing and updating are provided.
Ideally the opinion of a general practitioner, and/or a paediatrician in the case of paediatric diseases, has been considered. For diseases revealed at paediatric age, the group should involve specialists in childhood and adulthood management of the disease, to cover the transition from paediatric to adult healthcare services ¹¹.
 - Representatives from different geographical locations have been incorporated in the expert panel.
 - Peer-review via stakeholder feedback is desirable.



4.4.3 / Evidence Reports

Definition:

Evidence reports are systematic reviews that summarise the best available evidence on a topic. Evidence reports are generally used by clinical professional organisations to support the development of clinical practice guidelines or by policy makers to inform their programme planning and research priorities²⁰.

Appraisal criteria:

The evaluation comprises mandatory criteria that evidence reports must meet (minimum required)^{21, 22} (see section 4.2. How to use the handbook).

- ✓ Mandatory criteria to be met by evidence reports in order to be recommended for adoption or adaptation. The evaluated document must fulfil all of the requirements²¹⁻²⁴:
 1. The condition addressed is well defined.
 2. The objective of the report and the state questions to be answered are clear.
 3. The date of elaboration and/or review or update is indicated. No more than 3 years should generally have passed since that date and the content is up to date.
 4. The declaration of conflicts of interest for authors, collaborators and reviewers is reported.
 5. The methodology approach (development, adaptation or update) is transparent and explicit, including (all the following sub-criteria must be met to fulfil this criterion):
 - Details of the search strategy for collecting the evidence are reported: search terms used, sources consulted, and dates of the literature covered, thus confirming its reproducibility.
 - Patient's preferences are included as an evidence source.
 - Criteria used to include and exclude evidence are reported.
 - Outcomes to evaluate effectiveness are defined.
 - Any subgroup analyses are stated a-priori (and ideally with a rationale).
 - A critical evaluation of the evidence has been performed following a pre-established system (Cochrane evaluation tool for assessing risk of bias^{25, 26}, CASP²⁷, FLC 3.0 Critical Appraisal Tools Application²⁸, GRADE²⁹, etc.) and it is duly reported. If it has been developed from an evidence-based guideline, this must have been evaluated with the AGREE II instrument and rated as recommended or highly recommended.
 - If possible, a meta-analysis has been carried out.
 - It has been externally or peer-reviewed by relevant stakeholders
 6. A narrative data synthesis is included.
 7. Conclusions from the analysis of the literature and an overall conclusion are provided.

4.4.4 / Diagnostic, Monitoring and Therapeutic Pathways

Definition:

Diagnostic, Monitoring and Therapeutic Pathways are multidisciplinary management tools which describe the procedure for the care and treatment of a disease, condition or complex procedure. Their aim is to improve the care and management of patients, while enhancing the coordination of healthcare around the patient. They include the “red flags” that may lead to suspicion on the disease, condition or complex procedure, how to reach a definite diagnosis and the management



and follow-up recommendations, establishing the sequences for each action and defining the responsibilities of the different professionals who will intervene in the diagnostic, monitoring and therapeutic pathway³⁰.

Appraisal criteria:

The evaluation comprises two types of criteria: mandatory criteria that the diagnostic, monitoring and therapeutic pathways must meet (minimum required), and desirable characteristics (see section 4.2. How to use the handbook). Although diagnostic, monitoring and therapeutic pathways are applied in a local context, the following appraisal criteria have been adapted to the European context in which the project is being developed.

- ✓ Mandatory criteria to be met by diagnostic, monitoring and therapeutic pathways, in order to proceed to the next stage (Handbook #3: Adaptation and Adoption of CPGs and CDSTs). The evaluated document must fulfil all of the requirements³⁰.
 1. The diagnostic, monitoring and therapy pathway has been developed with the aim of sequencing and organising clinical work in situations that present a predictable clinical course.
 2. The scope, objective and target audience are described.
 - The condition/health problem addressed is reported.
 - The population to whom the document is meant to apply is specifically described.
 - The target audience for which the document is intended is reported (e.g. health professionals, patients and/or carers, etc.).
 3. The date of elaboration and/or review or update is indicated. No more than 3 years should generally have passed since that date and the content is up to date.
 4. The diagnostic, monitoring and therapeutic pathway development group is multidisciplinary and includes individuals from all relevant professional groups, integrating the set of activities of all the professionals involved.
 5. The following information for each author is included: name, discipline/content expertise, institution, geographical location, a description of the member's role and contact details.
 6. The declaration of conflicts of interest for authors, collaborators and reviewers is reported.
 7. The methodology approach (development, adaptation or update) is transparent and explicit, including (all the following subcriteria must be met to fulfil this criterion):
 - An explicit and structured consensus method has been used for its elaboration.
 - A search strategy has been carried out in the relevant databases, following a pre-established method. The details of the strategy used to search for evidence (search terms used, sources consulted, and dates of the literature covered) must be reported, in order to be reproducible.
 - Patient's preferences are included as an evidence source, and they are preferably included in the development group.
 - The inclusion and exclusion criteria for scientific evidence are reported.
 - If it has been developed from a previous evidence-based document or guideline, the methodology for the procedure is stated.
 - A critical evaluation of the evidence has been performed following a pre-established system (Cochrane evaluation tool for assessing risk of bias^{25, 26}, CASP²⁷, FLC 3.0 Critical Appraisal Tools Application²⁸, GRADE²⁹, etc.) and it is duly reported. If it has been developed from an evidence-based guideline, this must have been evaluated with the AGREE II instrument and rated as recommended or highly recommended.
 - When insufficient information is available to make an evidence-based



- recommendation, and the development working group reaches a consensus on an activity or procedure based on their clinical experience, it is identified and differentiated from those based on scientific evidence.
- The diagnostic, monitoring and therapeutic pathway has been externally reviewed by relevant stakeholders, including patients, carers, and/or patient representatives.
8. It includes pictograms, matrices or diagrams that identify the main components, activities and time-frames of the healthcare process.
 9. The proposed actions are evidence-based, and studies supporting them are identified. In the case of actions that have been reached by group consensus, they are correctly identified and differentiated from those based on scientific evidence.
 10. Process and outcome indicators are established in order to assess compliance and impact.
- ✓ Desirable characteristics of diagnostic, monitoring and therapeutic pathways ³⁰:
- Patients and/or carers and/or patient representatives have been included in the development group or their opinions and preferences have been sought in some other way.
 - Procedures for reviewing and updating are provided.
 - Ideally the opinion of a general practitioner, and/or a paediatrician in the case of paediatric diseases, should be considered. For diseases revealed at paediatric age, the group should involve specialists in childhood and adulthood management of the disease, to cover the transition from paediatric to adult healthcare services ¹¹.
 - Representatives from different geographical locations should be included in the development group.

4.4.5 / Evidence-based Protocols

Definition:

Evidence-based protocols are agreed detailed frameworks outlining in chronological order the care procedures that will be performed in a designated area of practice. Evidence-based protocols state what should be done, and how it should be done. They are adapted to the healthcare environment and available resources ³¹. In order to facilitate their use, evidence-based protocols usually include a flowchart clearly depicting the steps to be taken and the agents involved in the workflow of each evidence-based protocol.

Appraisal criteria:

The evaluation comprises two types of criteria: mandatory criteria that the evidence-based protocols must meet (minimum required), and desirable characteristics (see section 4.2. How to use the handbook). Although evidence-based protocols are applied in a local context, the following appraisal criteria have been adapted to the European context in which the project is being developed.

- ✓ Mandatory criteria to be met by evidence-based protocols, in order to proceed to the next stage (Handbook #3: Adaptation and Adoption of CPGs and CDSTs). The evaluated document must fulfil all of the requirements ³¹.
1. The evidence-based protocol has been developed with the aim of facilitating clinical work when dealing with specific health problems.
 2. The scope, objective and target audience are described.
 - The condition/health problem addressed is reported.
 - The population to whom the document is meant to apply is specifically described.



- The target audience for which the document is intended is reported (e.g. health professionals, patients and/or carers, etc.).
- 3. The date of their elaboration and/or review or update is indicated. No more than 3 years should generally have passed since that date and the content is up to date.
- 4. The evidence-based protocol development group is multidisciplinary and includes individuals from all relevant professional groups, integrating the set of activities of all the professionals involved.
The following data for each author is included: name, discipline/content expertise, institution, geographical location, a description of the member's role and contact details.
- 5. The declaration of conflicts of interest for authors, collaborators and reviewers is reported.
- 6. The methodology approach (development, adaptation or update) is transparent and explicit, including (all the following subcriteria must be met to fulfil this criterion):
 - An explicit and structured consensus method has been used for its development.
 - A search strategy has been carried out in the relevant databases, following a pre-established method. The details of the strategy used to search for evidence (search terms used, sources consulted, and dates of the literature covered) are reported, in order to be reproducible.
 - Patient's preferences are included as an evidence source, and preferably they are included in the development group.
 - The inclusion and exclusion criteria for scientific evidence are reported.
 - If it has been developed from a previous evidence-based document or guideline, the methodology for the procedure is stated.
 - A critical evaluation of the evidence has been performed following a pre-established system (Cochrane evaluation tool for assessing risk of bias ^{25, 26}, CASP²⁷, FLC 3.0 Critical Appraisal Tools Application ²⁸, GRADE ²⁹, etc.) and it is duly reported. If it has been developed from an evidence-based guideline, this must have been evaluated with the AGREE II instrument and rated as recommended or highly recommended.
 - When insufficient information is available to make an evidence-based recommendation, and the development working group reaches a consensus on an activity or procedure based on their clinical experience, it is identified and differentiated from those based on scientific evidence.
 - The evidence-based protocol has been externally reviewed by relevant stakeholders, including patients, carers, and/or patient representatives.
- 7. It includes diagrams, algorithms or other supporting tools.
- 8. Diagnostic or treatment procedures are listed in chronological order and linked to consensus statements or evidence-based recommendations.
- 9. Indicators are established in order to assess compliance and impact.
- ✓ Desirable characteristics of evidence-based protocols ³¹:
 - Patients and/or carers and/or patient representatives have been included in the development group or their opinions and preferences have been sought in some other way.
 - Procedures for reviewing and updating are provided.
 - Ideally the opinion of a general practitioner, and/or a paediatrician in the case of a paediatric diseases, has been considered. For diseases revealed at paediatric age, the group should involve specialists in childhood and adulthood management of the disease, to cover the transition from paediatric to adult healthcare services ¹¹.

- Representatives from different geographical locations have been included in the development group.

4.4.6 / Do's and Don'ts Factsheets for Diseases

Definition:

Do's and Don'ts Factsheets are tools that provide advice that needs to be considered when assisting patients with specific rare diseases, conditions or in need of complex procedures. These documents aim to assist patients, carers and the medical community in knowing the basic do's and don'ts of common and emergency situations (e.g. delivery, physical activity, anaesthesia, stroke, surgery) ³². Do's and don'ts factsheets can be based on existing CPGs or CDSTs recommendations (i.e. one or more documents), or they may consist of a stand-alone product developed from scratch by experts making recommendations by consensus (e.g. specialists on rare diseases who collect established and well-known clinical practice information about patient management, as a guide to other specialists involved in the treatment of people living with a rare disease).

Appraisal criteria:

The evaluation comprises two types of criteria: mandatory criteria that the do's and don'ts factsheets must meet (minimum required), and desirable characteristics (see section 4.2. How to use the handbook).

- ✓ Mandatory criteria to be met by do's and don'ts factsheets in order to be recommended for adoption or adaptation. The evaluated document must fulfil all of the requirements ³².
 1. The scope, objective and target audience are described.
 - The condition/health problem addressed is reported.
 - The population to whom the document is meant to apply is specifically described.
 - The target audience for which the document is intended is reported (e.g. health professionals, patients and/or carers, etc.).
 2. The date of elaboration and/or review or update is indicated. No more than 3 years should generally have passed since that date and the content is up to date.
 3. The development group is multidisciplinary and includes individuals from all relevant professional groups, integrating the set of activities of all the professionals involved. The following data for each author is included: name, discipline/content expertise, institution, geographical location, a description of the member's role and contact details.
 4. The declaration of conflicts of interest for authors, collaborators and reviewers is reported.
 5. The methodological approach (development, adaptation or update) is transparent and explicit (consult appraisal criteria for CPG and the rest of CDST):
 - It is derived from either an evidence-based document or clinical consensus statements and it is explained.
 - If it is based on a CPG or a CDST, the original document is valid .
 - To assess the quality of the documents on which a do's and don'ts factsheet is based, please consult the appraisal criteria described previously (see the Appraisal criteria for each type of document).
 6. It has been externally or peer reviewed by relevant stakeholders.
- ✓ Desirable characteristics of do's and don'ts factsheets:
 - Patients and/or carers and/or patient representatives have been included in the

development group or their opinions and preferences have been sought in some other way.

- Procedures for reviewing and updating are provided.
- Ideally the opinion of a general practitioner, and/or a paediatrician in the case of a paediatric diseases, has been considered. For diseases revealed at paediatric age, the group should involve specialists in childhood and adulthood management of the disease, to cover the transition from paediatric to adult healthcare services ¹¹.
- Ideally representatives from different geographical locations should be included in the development group.

4.4.7 / Quality Measures

Definition:

Quality measures (QM) are tools that quantify healthcare processes, outcomes, patient perceptions, and organisational structure and/or systems. These instruments provide clinicians and policy makers with information on healthcare performance and the extent to which high quality health care is being provided. There are three types of quality measures/indicators (structure, process, and outcome), as framed in the Donabedian model ^{33, 34}.

There are different frameworks for classifying quality measures. The main models structure measurements based on six aims for healthcare systems ³⁵, which are effective, safe, efficient, patient-centered, equitable, and timely care according to the Institute of Medicine ³⁶ approach.

Appraisal criteria:

The evaluation comprises two types of criteria: mandatory criteria that quality measures must meet (minimum required), and desirable characteristics (see section 4.2. How to use the handbook).

- ✓ Mandatory criteria to be met by QM in order to proceed to the next stage (Adoption & Adaptation Handbook). The evaluated document must fulfil all of the requirements ³⁷.
 1. The need for the quality measure/indicator is justified and the general and specific objectives are described.
 2. The date of their elaboration is indicated.
 3. Specific measure focus is:
 - evidence-based. This information may be contained in the same document or it may be summarised in a separate technical report. The methodology approach is transparent and explicit (study identification and selection, data collection, study appraisal, synthesis and findings, appraisal of bias risk) ²².
 - and/or
 - developed with consensus methods when evidence is scarce, whereby the measure/indicator might be accepted as a valid marker for quality (e.g. a review by an expert panel). Dynamics of the panel are transparent and the decision is well-founded ³⁸.
 4. Evidence or the rationale used for specific timeframes or thresholds included in a measure should be presented. If evidence is limited, then literature regarding standard norms would be considered.
 5. The document is reliable, and the measure is internally consistent and reproducible:
 - It is well defined and precisely specified so it can be implemented consistently within and across organisations and allows for comparability. Specifications are precise, unambiguous, and complete.

- The method is described and appropriate for assessing the proportion of variability due to real differences.
- 6. The document produces credible results, meaning the scores from a measure represent the variable they are intended to:
 - The potential threats to validity that are relevant to the measure were assessed:
 - exclusions
 - need for risk adjustment
 - capacity to identify statistically-significant and clinically-meaningful differences, missing data/non response
 - As regards PROMs/PREMs, the document is internally valid and respondents' answers are consistent across the items on a multiple-item measure. The items reflect the same underlying construct; hence, people's scores on those items should be correlated with each other.
- 7. The instrument is easy to administer and process.
The required data elements are readily available in a format that can be used for performance measurement and can be collected without undue burden to the healthcare organisation or clinical practice.
 - It should be available in electronic health records or other electronic sources.
 - If the required data are available in a format other than electronic health records or existing electronic sources, it should be feasible to input the data into a database for its analysis.
- 8. It has been externally reviewed by relevant stakeholders, including patients, carers, and/or patient representatives.
- ✓ Desirable characteristics of QM ³⁷:
 - The measure has been assessed by checking the consistency of results:
 - across time (test-retest)
 - across different observers (interrater)
 - across parts of the test itself (internal consistency)
 - There is a balance between being specific, but also generalizable enough for use in multiple healthcare systems and/or healthcare services.
 - Format is adapted to the target audience (e.g. response scales, questions, visual analogue scales, etc.).
 - Data are displayed in the most complete and understandable way. The use of self-explanatory graphs or the introduction of interpretation legends for data, calculations or statistical concepts, etc. is recommended.

4.5 | Quality Assessment of Informative Documents

4.5.1 / Patient Information Booklets

Definition:

Document that provides condition-specific information in lay language, to inform patients on best medical practice in an informative and accessible way ^{39, 40}. Patient information booklets can be based on a CPG, a CDST or consist of a stand-alone product providing general information for the patient.

Appraisal criteria:

Patient Information Booklets evaluated must fulfil all of the requirements in order to be recommended for adoption or adaptation:

1. The scope, objective and target audience are described.
2. It must be explicit if the patient information booklet is based on a CPG, a CDST, or it consists of a stand-alone product.
 - If it is based on a CPG or a CDST, the original document must be in force and of good quality (see the Appraisal criteria for each type of document). Patient Information Booklets should be based on the latest evidence-based practice.
 - If the patient information booklet is a stand-alone product, the methodology of the evidence review is described. The methodology approach is transparent and explicit (identification and selection of studies, data collection, study appraisal, synthesis and findings, judging risk of bias)²².
3. The date of elaboration is indicated.
 - Ideally the information is reviewed and updated regularly.
4. The development group is multidisciplinary, and includes individuals from all relevant professional groups, integrating the set of activities of all the professionals involved. Patients and/or carers and/or patient representatives have been included in the development group or their opinions and preferences have been sought in some other way. The following data for each author is included: name, discipline/content expertise, institution, geographical location, a description of the member's role and contact details.
5. The declaration of conflicts of interest for authors, collaborators and reviewers is reported.
6. In addition to their participation in development of the Patient Information Booklet, it has been externally reviewed by patients, carers, and/or patient representatives.
7. The Patient Education Materials Assessment Tool (PEMAT) 4 is proposed to determine whether patients will be able to understand and act on information in a patient information booklet. Please read the *PEMAT User Guide* carefully⁴.

PEMAT is a systematic method to evaluate and compare the understandability and actionability of patient education materials. It is designed as a guide. All items have the response options "Agree" or "Disagree"; and only some items also have a "Not Applicable" response option.

It is important to consider each item from a patient perspective. For example, for "Item 1: The material makes its purpose completely evident," ask yourself, "If I were a patient unfamiliar with the subject, would I readily know what the purpose of the material was?"⁴

The tool includes a guidance for rating the material on each item (Table 3).



Table 3. Additional guidance for rating the material on each item ⁴.

1	Rate an item "Agree" when a characteristic occurs throughout a material, that is, nearly all of the time (80% to 100%). Your guiding principle is that if there are obvious examples or times when a characteristic could have been met or could have been better met, then the item should be rated "disagree." PEMAT User Guide provides additional guidance for rating each item.
2	Do not skip any items. If there is no "Not Applicable" option, you must score the item 0 (Disagree) or 1 (Agree).
3	Do not use any knowledge you have about the subject before you read or view the patient education material. Base your ratings ONLY on what is in the material that you are rating.
4	Do not let your rating of one item influence your rating of other items. Be careful to rate each item separately and distinctly from how you rated other items.
5	If you are rating more than one material, focus only on the material that you are reviewing and do not try to compare it to the previous material that you looked at.

The PEMAT provides two scores for each material, one for understandability and a separate score for actionability, depending on the previous answers. The higher the score, the more understandable or actionable the material.

The overall assessment requires evaluators to make a judgement as to the quality of the patient information booklet, taking into account the appraisal items considered in the assessment process (see PEMAT manual and tool) ⁴. The evaluators should judge which score indicates exceptionally good or exceptionally poor materials; and reach a consensus on its recommendation for adoption or adaptation.



05.

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06.

ANNEXES

ANNEX 6.1 | List of Institutions for Expert Consultation

	Institution
1	Agency for Health Quality and Assessment of Catalonia (AQuAS)
2	Andalusian Health Technology Assessment Department (AETSA)
3	Basque Office for Health Technology Assessment (OSTEBA)
4	Canadian Agency for Drugs and Technologies in Health (CATDH)
5	Catalan Institute of Oncology (ICO)
6	Cochrane Iberoamérica
7	Evaluation Service of the Canary Islands Health Service (SESCS)
8	National Institute for Health and Care Excellence (NICE)
9	Navarre Health Service, Cochrane Associate Centre in Spain
10	Scientific Advice Unit (Avalia-t) of the Galician Agency for Health Knowledge Management (ACIS)
11	Scottish Intercollegiate Guidelines Network (SIGN)
12	University of Laval, Canada



ANNEX 6.2 | Expert consultation - ERNs

See annexed file:

- ✓ 2_D-B2_Appraisal_Annex2.pdf





ANNEX 6.3 | Expert consultation - Institutions

See annexed file:

- ✓ 2_D-B2_Appraisal_Annex3.pdf





European
Reference
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