D-B.2

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

TENDER Nº SANTE/2018/B3/030 EUROPEAN REFERENCE NETWORK: CLINICAL PRACTICE GUIDELINES AND CLINICAL DECISION SUPPORT TOOLS

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Handbook #2: Appraisal of Existing Clinical Practice Guidelines and Clinical Decision Support Tools for rare diseases

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Document Information

D-B.2. Methodological manual and toolkit for the development, appraisal, adaptation and implementation of CPGs and CDSTs.

This document contains the methodological manual and toolkit for the appraisal of CPGs and CDSTs for rare diseases.

Short Description

This document comprises the methodological basis and procedure for the appraisal process of existing CPGs and CDSTs for the rare diseases.

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1. Background

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

Nonetheless, 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, in which the foremost methodological frameworks like GRADE [1] rely on.

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

1.1. Work Package B: Methodologies for CPGs and CDSTs for rare diseases

For this reason, Work Package B of TENDER NºSANTE/2018/B3/030 pursues the development of methodologies for the prioritisation, appraisal, adaptation, development and implementation of CPGs and CDSTs for rare diseases.

The objective of WPB of TENDER NºSANTE/2018/B3/030 entails two main steps: Firstly, an analysis of the state of the art on methodologies for CPGs and CDSTs for rare diseases, and secondly, the elaboration of methodological manual and toolkit for the prioritisation, appraisal, adaptation, development and implementation of CPGs and CDSTs for rare diseases.

This report provides the European Reference Networks with a guide to evaluate the methodological quality of CPGs and CDSTs for rare diseases on the second phase of WPB of TENDER NºSANTE/2018/B3/030.

2. Aim of this document

The aim of this document is to provide a methodological guidance in 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. Those CPGs and CDSTs that meet the minimum requirements will be thoroughly assessed in the Adoption & Adaptation phase, where a comprehensive assessment on the currency, consistency, acceptability/applicability and clarity of presentation is proposed.

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

2.1. Scope

The manual consists of specific criteria for the appraisal of the methodological quality of each type of document, CPGs and CDSTs, for rare diseases. Documents have been organised in three different groups:

- Clinical Practice Guidelines (CPGs)
- Clinical decision support tools (CDSTs), which comprises:
    - 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, as well as their particular application.

3. Method

An exhaustive analysis of the state of the art on methodologies for appraisal of CPGs and CDSTs for rare diseases was developed in the WPB-1 of TENDER NºSANTE/2018/B3/030 8 Report on the Literature Review and Expert Consultation. The documents located in the systematic search in databases and the manual search in relevant organizations' 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 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.

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 the ERNs, institutions and HTA agencies with extensive methodological knowledge, to ensure the relevance and applicability of the appraisal handbook.

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

Recruitment of participants

The ERNs were contacted by WP-B team at IACS. The contact points were those provided by ERNs for the previous expert consultation (Deliverable B.1 Report on the literature review and expert consultation, WP D-B.1).

As for the institutions, 12 institutions were contacted by WP-B team at IACS by email (see Annex 1). In addition to Catalan Institute of oncology (ICO), which had previously participated in the consultation of the preliminary report on the Literature Review (WP D-B.1), the others institutions and HTA agencies were contacted as a result of previous IACS collaborations and networking.

Expert consultation methods

The consultation was created and made available online with EU Survey platform. Two surveys were created, one for the ERNs (Annex 2) and the other for the institutions (Annex 3). These surveys differed in the questions regarding personal information of the respondent but coincided in those relating to the consultation.

WP-B team at IACS sent a generic email to the ERNs and institutions contact points. In these emails, information on the consultation was provided, including the background of the TENDER NºSANTE/2018/B3/030, WP-B, the purpose of the consultation, the deadline and a contact point at IACS, as well as a link to the survey of the consultation.

In the survey, the information on the consultation and practical information was provided together with the preliminary appraisal criteria. In order to facilitate the review, the preliminary appraisal handbook was divided into nine parts:

- An introduction with general information about the aim of the appraisal handbook, methodology followed for its development, how to use the manual and the composition of the appraisal working group, and
- One file for each type of document covered by this project: CPGs; clinical consensus statements; evidence reports; diagnostic, monitoring and therapeutic pathways; evidence-based protocols; do's and don'ts factsheets; quality measures, and patient information booklets

Participants were asked to review the preliminary appraisal criteria for each type of document and answer whether they agreed with the proposal or whether they had any further comment. Participants were also invited to upload any relevant document.

Expert consultation turnout

The consultation was opened from the 27th of April to the 20th of May 2020. One institution requested an extension of the deadline, and an additional week was accorded.

Twelve answers were received from 8 ERNs: ERKNet, ERNICA, eUROGEN, EYE, GENTURIS, ITHACA, ReCONNET, and TRANSPLANT-CHILD. Most of the ERN experts that participated in the consultation were healthcare professionals (9), also 1 researcher, 1 methodologist, and 1 manager participated. One expert was representing both ERKNet and TRANSPLANT-CHILD, another one was representing ERNICA and eUROGEN.

As for the institutions contacted, ten answers were received from: Agency for Health Quality and Assessment of Catalonia (AQuAS) (1); Andalusian Health Technology Assessment Department AETSA) (1); Basque Office for Health Technology Assessment (OSTEBA) (1); Canadian Agency for Drugs and Technologies in Health (CATDH) (1); Catalan Institute of Oncology (ICO) (1); Evaluation Service of the Canarian Health Service (SESCS) (1); National Institute for Health and Care Excellence (NICE) (2); Navarre Health Service, which is Navarre Cochrane Associate Centre in Spain; Scientific Advice Unit (Avalia-t) of The Galician Agency for Health Knowledge Management (ACIS) (1); and University of Laval (1).

Results from the Expert Consultation

Twenty-two experts made suggestions and comments, which have enriched and improved the document.

The suggestions regarding wording, synonyms and clarifications were included in the final version of the handbook (e.g., patient representatives have also been considered along the handbook, since it may be a challenge to recruit patients with a rare disease or family members to be part of the groups, and incorporate patient representatives is more feasible). The inclusion of some criteria or subcriteria derived from the review has helped to enhance the handbook. For example, in the case of patient information booklets, mandatory criteria were added, in order to align informative documents with the rest of the CDSTs.

On the other hand, other comments and suggestions have not been implemented, but they will be considered in the Adoption & Adaptation Handbook, and the Elaboration Handbook. Similarly, it was suggested to include additional details on the adaptation of documents; however, adaptation is addressed in detail in the Adoption & Adaptation Handbook.

Furthermore, three experts agreed on their concern about how to capture the need to address and/or avoid conflicts of interest of authors, collaborators or reviewers, which is being considered in the Methodological Handbook, and also addressed by the WP-A team.

Some institutions proposed to bring together all the criteria, not making differences for each particular product. Even though all documents covered by the TENDER NºSANTE/2018/B3/030 share common criteria (how bias has been

minimised in the evidence collection, and how systematic review used to inform recommendations/activities/indicators), all of them have special characteristics (e.g., evidence-based protocols must include an algorithm, diagram or other support tool, while a clinical consensus statement should not). Due to the idiosyncrasy of each document, maintaining the criteria separate according to the type of product simplifies the application of the handbook.

Experts from the institutions and HTA agencies suggested that criteria considered as mandatory should be reinforced. However, as mentioned at the beginning of this chapter (*Aim of this document*), the Appraisal Handbook proposes criteria to pragmatically assess the methodological quality of CDSTs for rare diseases. The mandatory criteria are essential requirements that CDSTs should meet, and therefore set a threshold. This methodology has been proposed to facilitate the work to the ERN members and to avoid unnecessary loss of time by assessing extensively documents that can be quickly discarded at this stage. The CPGs and CDSTs that successfully pass the threshold will be assessed thoroughly in the next phase (Adoption & Adaptation Handbook) (e.g., consistency of the evidence will be assessed).

As explained in the following section, the method proposed to assess whether a CDST meets a criterion (or a subcriterion) is an exclusive response (yes/no questions). One of experts mentions the usefulness of graduated answers (e.g., Likert scale) and propose rating scores. It is worth noting that the use of scales does not avoid subjective judgements. Furthermore, it would entail the development of a validated mathematical model in which each criterion would have a weight, in order to be useful and to reflect the needs of each type of document for rare diseases. This involves the application of qualitative techniques. Hence, it is a complex process which, due to the limited timeframe envisaged for the development of this handbook, has not been feasible to perform.

4. 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 increase 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.

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

4.2. How to use the handbook

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

1. Use the appraisal toolkit to facilitate the assessment. There is a tool for each type of document.
2. Before using the appraisal toolkit, read through the stablished criteria and the specifications provided in the User Handbook, in order to be familiarised with all the items and their application. The User Handbook contains detailed explanations to facilitate the evaluation.
3. 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 about the development process prior to the appraisal. This information may be contained in the same document or it may be summarised in a separate technical report or methodological manual.

4. 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 the description of each criterion. The handbook contains specifications that should be considered in order to judge the items correctly.
5. When *mandatory* criteria are offered (yes/no questions), all the criteria listed must be met by CDSTs in order to continue to the next phase (Adoption & Adaptation phase, when a more in-depth assessment will be performed). Those criteria are considered essential. On the other hand, characteristics considered *desirable* provide a first indication of a 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).
6. Do not skip any criterion. If subcriteria are provided, all of them must be met to fulfil the criterion, unless an "and/or" conjunction separate them.
7. Do not let the rating of one criterion (or subcriterion) influence the rating of other items. Be careful to rate each criterion separately and distinctly.
8. Focus only on the CPGs or CDST that you are reviewing and do not try to compare it to previous documents.
9. 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.
10. 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 appraisal of the methodological quality of CPGs or CDSTs for rare diseases is completed 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, according to 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 options [6]. The level of evidence needs to be stated.

Appraisal criteria:

Following identification of guidelines, an assessment of their methodological quality is required. The AGREE II instrument [5] 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 appropriate for rare diseases [7-9]. This instrument is proposed for the appraisal of CPGs for rare diseases. Please read the AGREE II instrument manual thoroughly [5].

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 domains 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 for where to find the item information and guidance on how to rate [5, 10].

Table 1. Structure and content of the 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 role of high-quality guidelines as tools for healthcare improvement is as relevant to rare diseases as it is to common conditions, therefore standards should not be lowered for rare diseases [7], although some additional guidance has been proposed [7-9] (table 2). The AGREE-II instrument is applicable regardless of the small patient numbers, potentially small volume of evidence, and other limitations typically encountered in rare disease guidelines [9].

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)	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 a 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. Patients and/or carers should be included in the group. Consultation/participation of international experts may be useful. Scoring of these items should recognise this principle and reflect the extent to which the guideline addresses each item.
Rigour of development (Items 7-14)	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. For item 13 (external review by experts) – the experts should include patients, carers, and/or patient groups. 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.
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)	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. The information provided may be country-specific, healthcare system-specific, or generic.
Editorial independence (Items 22-23)	For many rare diseases there are likely to be only a small number of experts worldwide. This may limit the potential for editorial independence. Scores should reflect how this was addressed.
Overall guideline assessment	Before selecting 'yes with modifications', consider whether there are resources available to modify the guideline and any copyright issues. 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.

Notes section	Indicate if the guideline is the only (known) guideline on available on the topic. Indicate any research recommendations which the guideline identifies.

AGREE II manual also considers the interpretation of domain scores. A panel of all relevant stakeholders should define quality thresholds before beginning the AGREE II appraisals. For example, an approach that can be used to set quality thresholds is prioritising some domains over others. Thresholds can be created based on scores for the prioritised domains (e.g., high quality guidelines are those with a domain score 3 (*Rigour of Development*) and/or domain 6 (*Editorial Independence*) >85%). Decisions should be guided by the context circumstances in which the guideline is to be used and by evaluating the importance of the different domains and items in that context [5]. Scarcity of disease information, recommendation quality, usefulness of specific information for health professionals, etc. may provoke the adjustment of the criteria that can be used to set quality thresholds [8] (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 lowered [9].

Upon completing the 23 items, an overall guideline assessment is needed. Overall assessment requires the AGREE II user to make a conclusion as to 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 AGREE-II instrument, it is mandatory that the date of elaboration, review and/or update of the CPG is indicated. No more than 3 years should generally have passed since that date in order for the content is up to date. Otherwise, the guide should be updated in order to be used [13].

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]. It offers specific recommendations on a topic. It does 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 document evaluated 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 CDSTs [14]. Contextual circumstances are reflected upon and expressed [16].
     - 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 in a particular topic, they must periodically be re-evaluated and published again, replacing the previous consensus statement. No more than 3 years should generally have passed since that date and the content is 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 data 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 conflict of interest of authors, collaborators and reviewers is reported.
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 case of a topic derived from CPG or CDST, members from 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 summarises 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 priorities [20].

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 document evaluated must fulfil all of the requirements [21-24]:
  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 conflict of interest of authors, collaborators and reviewers is reported.
  5. The methodology approach (development, adaptation or update) is transparent and explicit, including (all the following subcriteria must be met to pass this criterion):
     - The details of the search strategy to collect the evidence is reported: search terms used, sources consulted, and dates of the literature covered, and therefore it is reproducible.
     - Patient's preferences are included as evidence source.
     - The 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], CASP[27], 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 AGREE II instrument and rated as recommended or highly recommended.
     - If possible, a meta-analysis has been developed.
     - 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 Therapy Pathways

Definition:

Diagnostic, Monitoring and Therapy 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 therapy pathway [30].

Appraisal criteria:

The evaluation comprises two types of criteria: mandatory criteria that the diagnostic, monitoring and therapy 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 therapy pathways, in order to proceed to the next stage (Adoption & Adaptation Handbook). The document evaluated must fulfil all of the requirements [30].

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 therapy pathway 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 conflict of interest of 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 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 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], CASP[27], 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 AGREE II instrument and rated as recommended or highly recommended.
    - When there was insufficient information available to make an evidence-based recommendation, and the development working group reached a consensus about an activity or procedure based on their clinical experienced, it is identified and differentiated from those based on scientific evidence.
    - The diagnostic, monitoring and therapy pathway has been externally reviewed by relevant stakeholders, including patients, carers, and/or patient representatives.
7. It includes pictograms, matrices or diagrams that identify the main components, activities and time-frames of the healthcare process.
8. The proposed actions are evidence-based, and studies supporting them are identified. In the case of actions that have been reached by the consensus of the group, they are correctly identified and differentiated from those based on scientific evidence.
9. Process and outcome indicators are established in order to assess compliance and impact.

- Desirable characteristics of diagnostic, monitoring and therapy 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 incorporated in the development group.

4.4.5. Evidence-based Protocols

Definition:

Evidence-based protocols are an agreed detailed framework 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. It is adapted to the health care environment and the available resources [31]. In order to facilitate its use, evidence-based protocols usually include a flowchart in which the steps to be taken and the agents involved in the evidence-based protocols' workflow are clearly depicted.

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 (Adoption & Adaptation Handbook). The document evaluated must fulfil all of the requirements [31].
  1. The evidence-based protocol has been developed with the aim of facilitating clinical work in the face of 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 conflict of interest of 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 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], CASP[27], 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 AGREE II instrument and rated as recommended or highly recommended.
    - When there was insufficient information available to make an evidence-based recommendation, and the development working group reached a consensus about an activity or procedure based on their clinical experienced, 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 be incorporated 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 document evaluated 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 conflict of interest of authors, collaborators and reviewers is reported.
5. The methodology approach (development, adaptation or update) is transparent and explicit (consult appraisal criteria for CPG and the rest of CDST):
    - Either it is derived from an evidence-based document or clinical consensus statements, it is explained.
    - If it is based on a CPG or a CDST, the original document is in force.
    - 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 were incorporated in the development group.

4.4.7. Quality Measures

Definition:

Quality measures (QM) are tools that quantify healthcare processes, outcomes, patient perceptions, and organizational structure and/or systems. These instruments provide clinicians and policy makers with information associated with 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 document evaluated 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 (identification and selection of studies, data collection, study appraisal, synthesis and findings, judging risk of bias) [22].

      And/or
    - developed with consensus methods when evidence is scarce, by which 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, the measure is internally consistent and reproducible:
    - It is well defined and precisely specified so it can be implemented consistently within and across organizations and allows for comparability. Specifications are precise, unambiguous, and complete.
    - The method is described and appropiate 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
        - able to identify statistically significant and clinically meaningful differences missing data/non response
    - Regarding PROMs/PREMs, the document is internally valid and there is consistency of people's responses across the items on a multiple-item measure. The items reflect the same underlying construct, so 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 able to be collected without undue burden to the healthcare organization 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 to use it in multiple healthcare systems and/or healthcare services.
    - Format is adapted to the target audience (e.g., response scales, questions, visual analog scales, etc.).
    - Data are displayed in the most complete and understandable way. It is recommended using self-explanatory graphs or introducing interpretation legends for data, calculations or statistical concepts, etc.

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 that provides 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 to be 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 conflict of interest of 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 of a patient information booklet. Please read the *PEMAT User Guide* carefully [4].

   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 what score indicates exceptionally good or exceptionally poor materials; and reach a consensus about its recommendation for adoption or adaptation.

5. Abbreviations

AETSA	Andalusian Health Technology Assessment Department (Agencia de Evaluación de Tecnologías Sanitarias de Andalucía)
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
CPG	Clinical Practice Guideline
CDST	Clinical Descision Support Tool
ERN	European Reference Network
EU	European Union
FPS	Fundación Progreso y Salud
HTA	Health Technology Assessment
IACS	Aragon Health Sciences Institute (Instituto Aragonés de Ciencias de la Salud)
ICO	Catalan Institute of Oncology (Instituto Catalán de Oncología)
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 experiences
PROMs	Patient Reported Outcome Measures
QM	Quality Measures
SESCS	Evaluation Service of the Canarian Health Service (Servicio de Evaluación del Servicio Canario de la Salud)
SIGN	Scottish Intercollegiate Guidelines Network

WP	Work Package

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Annex 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 Canarian 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 2. Expert consultation - ERNs

Annex 3. Expert consultation - Institutions