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

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

Handbook #3: Adaptation and Adoption of Clinical Practice Guidelines and Clinical Decision Support Tools for Rare or Low-Prevalence and Complex Diseases

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This handbook includes a detailed explanation of the process for adapting or adopting CPGs or CDSTs for rare diseases, including:

- ✓ Assessment of their quality, currency, consistency, and acceptability/applicability
- ✓ Decision-making, where results for each recommendation, activity/procedure or indicator must be considered one by one.
- ✓ Adaptation, based on ADAPTE methodology.

Purpose:

To provide guidance for assessing and making decisions on the adoption or adaptation of existing CPGs and CDSTs.

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ABBREVIATIONS

AETSA	Andalusian Health Technology Assessment Department
CDSTs	Clinical Decision Support Tools
CPGs	Clinical Practice Guidelines
EASP	Andalusian School of Public Health
EC	European Commission
ERN	European Reference Network
EtD	Evidence to Decision
EU	European Union
FPS	Fundación Pública Andaluza Progreso y Salud
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IACS	Aragon Health Sciences Institute
ICD	International Classification of Diseases
ICHI	International Classification of Health Interventions
PREMs	Patient Reported Experience Measures
PROMs	Patient Reported Outcome Measures
QM	Quality Measures
RCT	Randomised Controlled Trial

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 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. The project also aims to provide a common methodology in order to harmonise the process for developing CPGs and CDSTs.

02.

AIM OF THIS DOCUMENT

The aim of this handbook on the Adaptation and Adoption of CPGs and CDSTs for Rare Diseases is to provide a framework for assessing and making decisions on the adoption or adaptation of existing CPGs and CDSTs. It defines the specific criteria and main activities for critically evaluating CPGs and CDSTs for ERN use.

2.1 | Scope

The Adaptation and Adoption of CPGs and CDSTs for Rare Diseases consists of a common framework for a more in-depth assessment than that defined previously in the Appraisal stage, and the decision-making phase in the documents covered by these projects (CPGs and CDSTs). The handbook provides specifications to apply to the different types of documents: Clinical Practice Guidelines; Diagnostic, Monitoring and Therapeutic Pathways; Evidence-based Protocols; Quality Measures, and Clinical Consensus Statements.

In the case of Evidence-Reports, the assessment would be restricted to the criteria in Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases, as it will be limited to the evaluation of the quality of the systematic search. If the evidence-report does not achieve the minimum required, a *de novo* development is suggested. Furthermore, Do's and Don'ts Factsheets and Patient Information Booklets are considered second-generation products based on CPGs or CDSTs, so no indications are provided for the assessment of these documents. It is suggested that the guidelines proposed for the documents on which they are based be applied.

The handbook also offers guidance on the adaptation process, when applicable, for each of the following documents:

- ✓ Clinical Practice Guidelines (CPGs)
- ✓ Diagnostic, Monitoring and Therapeutic Pathways
- ✓ Evidence-based Protocols
- ✓ Quality Measures (QMs)

03.

METHOD

The Adaptation and Adoption of CPGs and CDSTs for Rare Diseases handbook is based on well-founded and internationally recognised adaptation methodologies and resources, notably the ADAPTE process[2] and GRADE ADOLOPMENT[3].

The ADAPTE collaboration is an international group of researchers, guideline developers, and guideline implementers who proposed a framework and a systematic methodology for the adaptation of existing Clinical Practical Guidelines (CPGs), in order to promote the development and use of high-quality CPGs. The adaptation process described in the manual and toolkit were designed to ensure that the final recommendations address specific clinical questions relevant to the context of use and address the needs, priorities, legislation, policies, and resources in the target setting, without determining the validity of the resulting recommendations [2, 4].

The ADAPTE process has multiple applications. It was designed to be flexible, and not all chapters may be relevant to the users. The rationale behind the development of this Adaptation and Adoption of CPGs and CDSTs for Rare Diseases handbook is to facilitate the application of the ADAPTE process in the adoption or adaptation of a single CPG. It also offers guidance for the adoption and adaptation of CDSTs based on the ADAPTE process.

The GRADE-ADOLOPMENT approach was also considered for CPGs or CDSTs originally developed using GRADE (Grading of Recommendations Assessment, development and Evaluation) [3]. The use of GRADE Evidence to decision (EtD) frameworks facilitates the adoption or adaptation of documents to the setting, context, and culture of a specific region or country [3]. The most important basis for updating is the existence of a trustworthy systematic review that can then be used for judgement purposes by the working group. In addition, evidence and the associated judgements are presented transparently, allowing the adaptation working group to draw up recommendations appropriate to the ERN context.

04.

OVERVIEW OF THE PROCESS

Adoption and adaptation have two main aims: 1) using limited resources more efficiently by building on existing efforts to provide local, regional or national guidance, and 2) considering specific factors of these settings to enhance usability [3].

This handbook has been developed to ensure that CPGs or CDSTs are relevant in the ERN context, and address their needs and particularities (e.g. legislation, policies, resources, etc.), without compromising the validity of the resulting recommendations (CPGs, Clinical Consensus Statements); activities and/or procedures (Diagnostic, Monitoring and Therapeutic Pathways, Evidence-based Protocols), or indicators (QM) provided.

The process consists of two basic points: assessment and decision-making; and adaptation (Figure 1). It has been designed to provide a systematic approach to adopting or adapting existing CPGs or CDSTs for rare diseases to the ERN context and is based on ADAPTE methodology. The whole process must be transparent and well-documented, providing a rationale for the assessment made in order to promote confidence in decision-making.

Assessment and decision-making phases

This section provides a guide for a more detailed analysis of the following documents, in order to make a decision about their adoption or adaptation:

- ✓ Clinical Practice Guidelines (CPGs)
- ✓ Clinical Consensus Statements
- ✓ Evidence Reports
- ✓ Diagnostic, Monitoring and Therapeutic Pathways
- ✓ Evidence-based Protocols
- ✓ Quality Measures (QMs)

The unit of analysis considered in the assessment phase does not consist of the entire document, but:

- ✓ Each recommendation or set of recommendations (clinical question) comprising Clinical Practice Guidelines and Clinical Consensus Statements;
- ✓ Each activity or procedure comprising Diagnostic, Monitoring and Therapeutic Pathways and Evidence-based Protocols;

✓ Each indicator or set of indicators comprising a QM.

The same type of analysis is proposed for Diagnostic, Monitoring and Therapeutic Pathways and Evidence-based Protocols, focused on the activities or procedures. The instructions for both of them can be found in the same section.

The analysis focuses on four main factors: quality appraisal (already reviewed in Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases); currency; consistency; and acceptability/applicability. These factors must be reviewed individually for each recommendation, activity/procedure or indicator

Following the assessment phase, results for each recommendation, activity/procedure or indicator must be considered one by one. The working group will make a decision on their adoption or adaptation, following the algorithms proposed for each document.

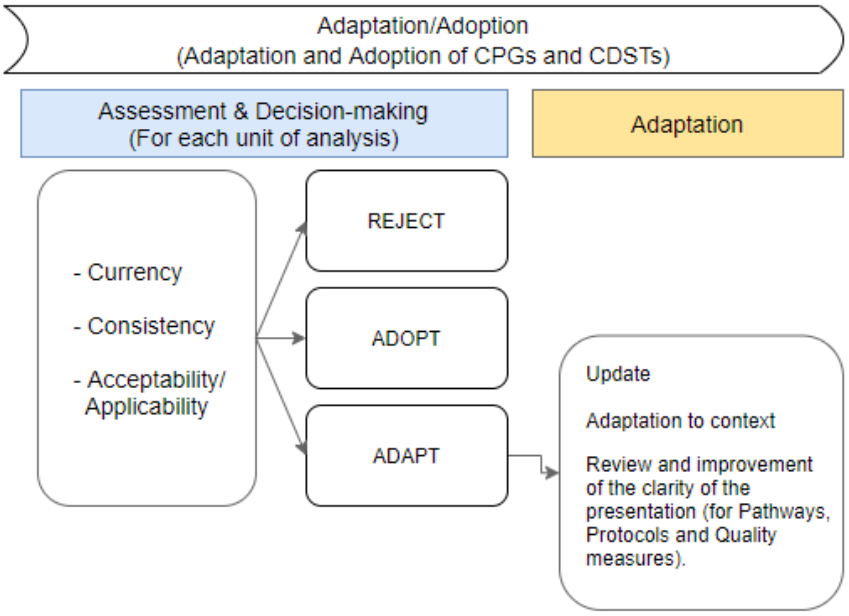
Adaptation phase

Adaptation refers to the systematic approach for considering the endorsement or modification of recommendations produced in one setting for application in another as an alternative to *de novo* development [5]. Based on the previous analysis, recommendations, activities/procedures or indicators may be adapted. This manual proposes three different approaches: updating, adaptation to the context and clarity of presentation (only for Diagnostic, Monitoring and Therapeutic Pathways, Evidence-based Protocols, and Quality Measures).

With regard to clinical consensus statements, no guidance is given on how to adapt them, since if they do not meet the minimum requirements for their adoption, a *de novo* development process is recommended. Depending on the extent to which the document is affected, the group should decide whether it can adopt part of the document or develop a *de novo* document as the most appropriate option.

In the case of evidence reports, no guidance is given on how to adapt them, since if they do not meet the minimum requirements for their adoption, a *de novo* development process is recommended.

Figure 1. Overview of the process



This process should follow the principle of efficiency, the working group should always consider time and other resources dedicated to the adaptation of documents, and determine whether a *de novo* development process would be more efficient. The adaptation process should be flexible in order to avoid duplication of work.

This guideline only applies to the decision to adopt or adapt a single CPG or CDST. In the field of rare diseases, the situation in which various CPGs or CDSTs are retrieved would be unusual, but

- ✓ When more than one CPG is suitable, the use of the ADAPTE Manual and Resource Toolkit (Version 2.0) [2] is recommended due to its suitability for comparing and building on information from different CPGs.
- ✓ When more than one suitable CDST is retrieved, since the content analysis for each document and its comparison usually requires a considerable effort, a new CDST should be prepared as the process will be more productive (see the respective Methodology for the development of CPGs or CDSTs).

To this end, it is essential that the working group always keep in mind all the options provided in the Methodological handbooks and toolkits, in order to be as efficient as possible.

05.

COMPOSITION OF THE ADAPTATION AND ADOPTION WORKING GROUP

The Adoption & Adaptation Working Group is the group of experts who participate in the adoption and adaptation process (assessment, decision-making and the adaptation itself). If possible, they shall be multidisciplinary and geographically representative to ensure an adequate analysis of the ERN context.

Although it is likely that one professional group may dominate, comprehensive stakeholder involvement is relevant and the group should include experts from among key stakeholders affected by the topic area addressed by the CPG or CDST. International expertise can be included in the panel.

The following profiles should be represented on the working group:

- ✓ Health professionals with clinical knowledge in the topic area addressed by the CPG or CDST (e.g. medical doctors, nurses, psychologists, physical therapists, etc.).
    - Ideally, members of the ERN should come from different parts of Europe, but this will be influenced by the expertise available.
    - If possible, it would be appropriate to involve at least one member of the working group that developed the existing CPG or CDST.
    - General practitioners, and/or paediatricians in the case of diseases revealed in childhood must be included in the group, as their contributions are very relevant. Besides, it may be necessary to cover the transition from paediatric to adult healthcare services [6].
    - For diseases revealed at paediatric age, the group should include specialists in childhood and adulthood care for the disease in question in order to cover the transition from paediatric to adult healthcare services.
    - Medical and surgical specialties should be involved in the working group, as well as diagnostic specialties (e.g. clinical laboratory sciences). Depending on the topic area, involving certain specialties may be more appropriate.
    - The working group should choose a clinical coordinator from among the experts in the group, with leadership capabilities and experience in evidence-based medicine.
- ✓ Patient, and/or carers, and/or patient representatives.

  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.

- ✓ Policy experts/decision makers with knowledge in different health systems.
- ✓ A technical team consisting of a methodologist with knowledge of critical appraisal and an information specialist with knowledge of databases and literature searching.

The number of participants included in the working group should include 7 to 15 members, apart from the clinical coordinator and the technical team. More than 15 participants may result in ineffective functioning, while less than 7 members may undermine representativeness. Throughout the assessment, the working group may deem it necessary to consult other expert contributors (e.g. policy makers).

The list of members of the working group is provided (name, discipline/content expertise, institution, geographical location, a description of the member's role and contact details).

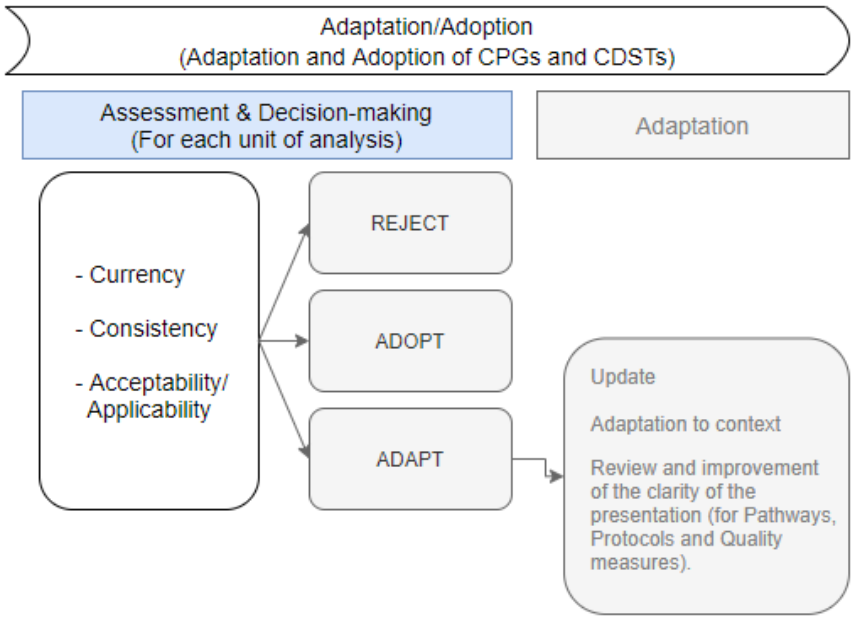
Potential conflicts of interests should be carefully identified and duly addressed, in accordance with the indications established by our partner FPS.

06.

ASSESSMENT & DECISION-MAKING

Determining whether recommendations, activities or procedures are valid involves two phases: assessment and decision-making. The aim of the assessment phase is to provide the adaptation working group with enough information to make a decision on whether to adopt or adapt a single CPG or a CDST (Figure 2).

Figure 2. Assessment and decision-making phases



Once the assessment has been completed, with the results of the assessment with regards to currency, consistency, acceptability/applicability and clarity of presentation in hand, the working group should consider all the factors, discuss and reach a consensus decision. Precise rules and firm solutions to this assessment cannot be provided. Working group members should undertake an analysis and make their own judgements, discussing the issues and the appropriateness of the conclusions (e.g. the group may consider that certain factors have a stronger influence and impact on their final decision). Above all, the process should be transparent and judgements involved explicit (see Annex 1).

The assessment and decision-making process for each of the following documents is explained below, taking into consideration their specificities:

- ✓ Clinical Practice Guidelines (GPCs)
- ✓ Evidence Reports
- ✓ Diagnostic, Monitoring and Therapeutic Pathways and Evidence-based Protocols
- ✓ Quality Measures (QM)
- ✓ Clinical Consensus Statements

6.1 | Clinical Practice Guidelines

6.1.1 / Assessment phase

The retrieved documents are assessed by analysing them in relation to the following aspects [2]:

6.1.1.1 | Quality appraisal

Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases provides the set of criteria for assessing the methodological quality of CPGs for Rare Diseases.

6.1.1.2 | Currency

As mentioned in Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases, the evidence supporting CPGs may evolve rapidly in certain fields, so no more than 3 years should generally have passed since the date of development and/or review or update to ensure that the most current evidence has been included [7].

In addition to this threshold, a CPG should be updated when there are relevant advancements in care or research in the areas of care related to the CPG or recommendations as to make them obsolete. The knowledge and expertise of the adaptation group, as well as that of other experts well-versed in the field and/or CPG developers who the working group may decide to consult, are key in identifying new, relevant evidence that could change or invalidate a recommendation. Nonetheless, if the CPG meets the 3-year threshold criterion, the working group should bear in mind that the likelihood of new relevant evidence emerging is low.

Furthermore, the CPG considered for adoption or adaptation should be subjected to a literature review [8]. This review will not be extensive, i.e. it will be limited to one or two of the main databases and specific studies (Randomised Control Trials and Systematic Reviews). Only studies that may modify the recommendations, based on the working group's judgement (qualitative analyses), will be taken into consideration for further analysis. For more information, consult Handbook #4: Methodology for the development of CPGs for Rare Diseases.

If the quality of the source document is good but relevant advancements and new evidence are identified which impact on the CPG recommendations or set of recommendations, the CPG will be considered as not current, either totally or partially. The working group should consider updating the CPG, together with the results of the assessment of consistency and applicability/acceptability items, in order to make a decision on whether to adopt or adapt.

6.1.1.3 | Consistency

Consistency refers to the link between the selected evidence and the summary and interpretation of this evidence, as well as how this interpretation is translated into the recommendations. In order for recommendations to be of high quality, they should be based on a thorough review of the available literature. The assessment of the consistency of a CPG includes the following evaluations[2,9] :

- ✓ The evidence has been generated via a systematic review (see Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases):
    - The literature search is shared and sufficiently comprehensive, as well as the databases in which it has been carried out. The risk that relevant evidence has been missed is low:
        - The authors had a clearly focused question (population, intervention, outcome).
        - Appropriate databases were searched.
        - Internet sites were searched.
        - Detailed search strategies are provided with the guideline.
        - A hand search of the reference lists was completed .
    - The criteria for selecting the evidence are explicit (inclusion and exclusion criteria). The excluded studies and the reasons for their exclusion are included in the annexes to the CPG.
    - The methodology for indicating the quality of the studies is described.
- ✓ The selected evidence and how the development working group summarised and interpreted this evidence is reported:
    - The evidence tables are provided and they reflect the main results and the evidence rating.
    - The adaptation working group must assess the outcome variables that have been considered in the PICO question(s).
    - Developers could have formulated a recommendation or set of recommendations based on the results of primary studies or systematic reviews, but also from clinical experience or clinical consensus statements, which must be explicitly reported.
    - The risk of bias, imprecision, inconsistency, indirectness and publication bias of the studies are analysed.
    - If applicable, the possibility of confounding factors is addressed.
    - When a meta-analysis has been performed, statistical analysis is explained and confirmed as appropriate.
    - The heterogeneity among studies is explained.
- ✓ The interpretation of the evidence and the recommendations are consistent in content.
    - The level of evidence is adequately described in tables of evidence.
    - The balance between risks and benefits is well justified.
    - Conclusions were supported by data and/or the analysis. When inconsistencies existed in data, considered judgement was applied and reported.
    - Conclusions and recommendations are written accordingly.
        - There is some justification to recommend/not recommend the intervention, even though the evidence is weak.
        - Recommendations are consistent in content and evidence-level, and the strength of recommendations is assigned .

6.1.1.4 | Acceptability/applicability

Acceptability and applicability refer to the fit of several context-dependent factors of the recommendations included in the retrieved CPG in the ERN context where they will be used. Each recommendation or set of recommendations (i.e. a clinical question) should be assessed. The following must be considered:

- ✓ Whether a recommendation or set of recommendations (clinical question) should put it into practice (acceptability).
- ✓ Whether an organization or group is able to put the recommendation or set of recommendations into practice (applicability).

The assessment of these aspects aims to identify any similarities and differences regarding contextual factors in the formulation of recommendations and those present in the ERN context in which the CPG would be used. Differences between contexts may introduce uncertainty, thus warranting re-evaluation of a recommendation or set of recommendations (clinical question) in the new context [10].

These factors are the following:

Worth

Does the benefit to be gained from implementing the recommendation make it worth implementing (acceptable)?

The working group should first consider whether the balance between risks and benefits to patients has been correctly taken into consideration in the recommendation or the set of recommendations, and whether their implementation will be useful in the ERN context. Issues related to complexity or ease of use should also be considered.

Population

Does the population described for eligibility match the population to which the recommendation is targeted in the local setting (acceptable)?

The working group should discuss whether the population addressed by each recommendation matches the population of interest which has been identified as in need by the ERN and which would be targeted in the local settings (age, childhood/adulthood, gender, high-risk population, a particular subgroup, etc.). Differences in the target patients should be noted.

- ✓ If the recommendation addresses different subgroups of population, the working group should consider the relevance of addressing these subgroups in the ERN context.
- ✓ If, on the other hand, the population identified as in need of a CPG is addressed as a subgroup in the retrieved CPG, the adaptation working group should consider the relevance of addressing the broader definition of the population. If the adaptation group does not consider it necessary to broaden the population, only the recommendations addressed for the initially defined population would be considered.

Patient perspectives

Does the intervention meet patient views and preferences in the context of use (acceptable)?

The working group should consider whether each recommendation is compatible with patient preferences and values in the setting where it is to be used.

Patients' perspectives may have been considered in different approaches when addressing the

clinical questions comprising the CPG. Different methods can be applied to obtain information about patients' perspectives, preferences and needs to enable a more in-depth analysis on patients' views and preferences, as explained in Handbook #4: Methodology for the Development of CPGs for Rare Diseases.

These methods can be mainly grouped into primary methods, which include surveys and other individual/ group techniques with patients and/or carers themselves (e.g. involving patients and/or carers in the development working group or include them as reviewers of the CPG), and/or primary research with health professionals involved in patient care (e.g. from a subjective judgement based on clinical experience of the development working group), and secondary methods, such as conducting a literature review on patients' views and preferences (see Handbook #4: Methodology for the Development of CPGs for Rare Diseases).

Intervention/ resources available

Are the intervention and/or equipment addressed in the recommendation available in the context of use (applicable)?

It should be considered whether each intervention targeted in the recommendations is available in the ERN context (e.g. equipment, diagnostic tests and/or treatments).

Explicit consideration should be given to the ERN context to ensure the relevance of a recommendation or set of recommendations.

Since CPGs are implemented locally, if the recommendation is finally adopted or adapted, the availability of the intervention/resource should be evaluated by a specialised local committe.

Expertise (knowledge and skills) available

Is there the necessary expertise (knowledge and skills) available in the context of use (applicable)?

It is necessary to determine whether health professionals involved in patient management in the given context have the necessary expertise to implement the recommendations proposed in the CPG. If the technical expertise does not yet exist, it should be considered whether specific training is possible and under what conditions it should be provided in the given context.

Barriers (legislation, organization, policies)

Are there any constraints, organisational barriers, legislation, policies, and/or resources in the health care setting of use that would impede the implementation of the recommendation (applicable)?

All possible barriers to the application of a recommendation or set of recommendations should be identified by the adaptation working group. If the board is not aware of this information, the working group should consult with management experts who are familiar with these particular organizations and European health contexts.

Potential organisational barriers to the implementation of a specific recommendation or set of recommendations should be explored at this point (e.g. resistance due to available resources, perception of effectiveness, etc.), so that the recommendation or set of recommendations provided by a CPG is accepted and relevant for health professionals.

Policy/decision makers and management experts can advise on possible adaptation to the given context with sufficient information on legislation/regulatory matters. It should be noted that the existence of constraints in legislation, policy or resources in local settings (e.g. countries, hospitals, etc.) that would prevent the implementation of the proposed interventions should be considered in a subsequent phase.

Compatible with the culture

Is the recommendation compatible with the culture and values in the setting where it is to be used (acceptable and applicable)?

Geographical, epidemiological, socio-cultural, socio-economic and ethical differences may be decisive for the correct implementation across countries and health systems of a particular recommendation or set of recommendations (clinical question). Hence, recommendations must be culturally appropriate and represent the norms and values of specific groups, communities, or populations, if needed, to ensure relevance for local practice. If the adaptation group considers that a recommendation does not address this factor correctly, the group itself can bring this information to the table as a subjective judgement, as they themselves are representatives of different countries and cultures.

6.1.2 / Decision-making phase

Once the assessment has been completed, the adaptation working group should consider the results and draw a conclusion for each recommendation (Annex 1). The decision for each recommendation should be reached by consensus and be well documented, so that the impact of the analysis and the feasibility of its adoption or adaptation can be determined.

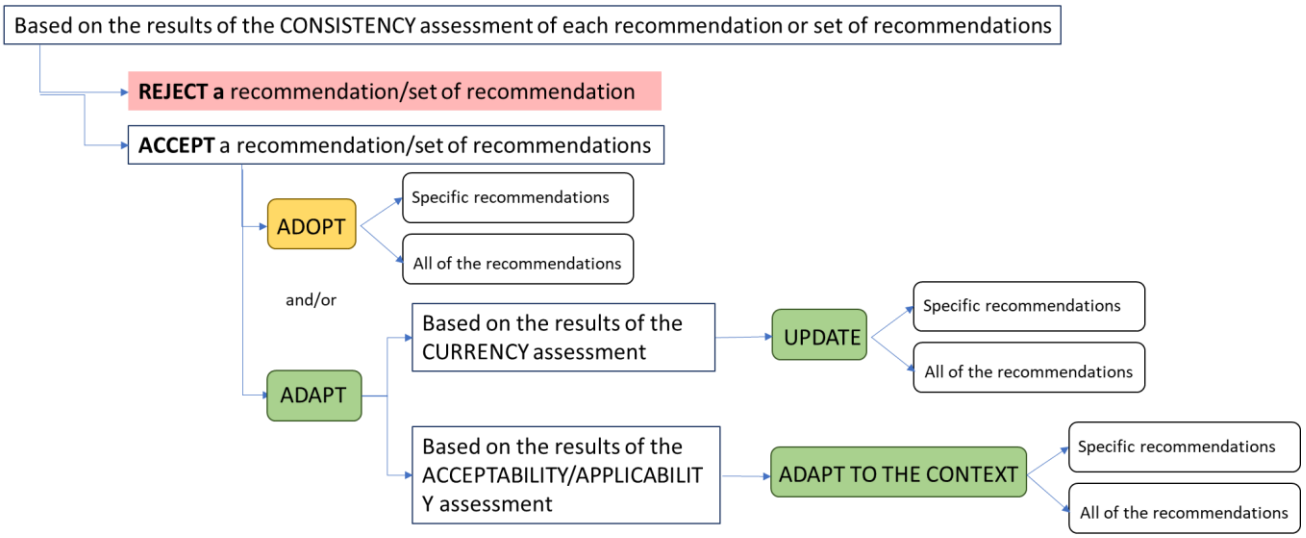
A decision-making algorithm is proposed below to reach a conclusion on the recommendations to create an adopted or adapted guideline, which may involve all or part of the guide (Figure 3). Hence the decision should be made for each recommendation or set of recommendations:

- ✓ Based on the results of previous consistency assessments, the CPG could be **accepted totally or partially**:
    - If a recommendation or a set of recommendations do not show consistency, they should be discarded and not included in the adopted or adapted CPG.
    - If a recommendation or a set of recommendations show consistency, specific recommendations from the CPG would be accepted.
    - If all of the recommendations show consistency, the whole guideline would be accepted.
- ✓ Then, the working group should decide whether an accepted recommendation could be **adopted** directly or whether it needs to be **adapted**.

  The results of the currency and acceptability/applicability assessment imply different approaches to adapt the CPG. It is also possible that certain recommendations can be adopted directly while others undergo an adaptation process. For this reason, each decision must be made with respect to each recommendation.
    - Based on the currency assessment, if more than 3 years have passed since its development, update or review or new evidence has been detected, and this is likely to affect the validity of the recommendations, the working group should update the affected recommendations.
    - Based on the acceptability/applicability assessment, and taking into consideration the ERN context, the adaptation to the context should be carried out (based on an adaptation plan).

Once the decision is made, the author of an existing CPG or CDST considered for adoption or adaptation will be contacted and informed.

Figure 3. Decision making algorithm for the acceptance of a recommendation or set of recommendations of an existing CPG for rare diseases



6.2 | Clinical Consensus Statements

Clinical consensus statements offer specific recommendations on a topic. They reflect opinions reached by consensus, using an explicit methodology to identify areas of agreement and disagreement. 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[11].

If after conducting the following analysis the working group considers that a recommendation or set of recommendations of the clinical consensus statements cannot be directly adopted and implemented in the ERN context, the working group should consider whether the rest of the document can be adopted or whether a *de novo* document would be preferable. To do this, the group should consider the degree to which the document is affected. If it is significantly affected, a *de novo* process is suggested. In that case, the retrieved clinical consensus can be used as one of the base documents for further development. Hence, no guidance is given to adapt clinical consensus statements.

6.2.1 | Assessment phase

The assessment of a Clinical Consensus Statement is performed by analysing the recommendations, one by one, with regards to the following aspects :

6.2.1.1 | Quality appraisal

Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases sets out the criteria for assessing the methodological quality of Clinical Consensus Statements for Rare Diseases.

6.2.1.2 | Currency

As stated in Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases, consensus statements provide a "snapshot in time" of the state of knowledge on a particular topic, so they must be periodically re-evaluated and re-published.

The date of development and/or review or update of the clinical consensus statement must be indicated in the document, but no more than 3 years should generally have passed since that date in order for it to be adopted.

If the working group is aware of new evidence or they have clinical experience that could change a recommendation, it would not be accepted.

6.2.1.3 | Consistency

In the case of Clinical Consensus Statements, consistency refers to the link between the selected evidence (if available) and clinical experience and their interpretation, as well as how that interpretation translates into recommendations. The assessment of the consistency of Clinical Consensus Statements includes the following evaluations:

- ✓ The method used to achieve consensus (e.g. Delphi method, nominal group technique/expert panel, consensus development conferences) must be described (see Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases).
- ✓ The process used to define the initial question or statement is described. The scope and the clinical questions are defined.
- ✓ A systematic approach has been used to search for evidence, and the selection criteria are clearly described:
    - A literature search for guidelines and systematic reviews (include narrative reviews) has been performed. The risk that relevant evidence has been missed is low to ensure that recommendations are not merely dependent on the subjective judgement of the experts.
        - Relevant databases have been consulted.
        - Internet sites were searched.
        - A hand search was performed (e.g. journals, websites, legislation, etc.).
        - Detailed search strategies are provided.
        - The search period is specified..
    - If necessary, another literature search has been conducted to retrieve other types of studies (randomised controlled trials and observational studies).
    - The criteria for selecting the evidence are explicit (inclusion and exclusion criteria).
    - The critical appraisal of the evidence and its interpretation should be indicated:
        - Selected CPGs have been evaluated using the AGREE-II instrument, rating the guideline as recommended or highly recommended.
        - The critical evaluation of systematic reviews has been performed following a pre-established system (Cochrane risk-of-bias assessment tool [12, 13], CASP [14], FLC 3.0 Critical Appraisal Tools Application [15], GRADE [16], etc.).
    - When insufficient information is available to make an evidence-based recommendation, due to the paucity of evidence, and the development working group reached a consensus on a statement based on their clinical experience, it would be identified and differentiated from those based on scientific evidence.

- ✓ The level of consensus of individual responses or consensus statements should be revealed. A clear definition of target "acceptable" level of consensus should be provided .

  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".

- ✓ There is an explicit relationship between each recommendation and the evidence on which it is based or the degree of agreement of the expert consensus.

6.2.1.4 | Acceptability/applicability

It is important to keep in mind that the scope of the clinical consensus statements should not be broad but rather focus on areas in which there is a clear paucity of evidence, opportunities for quality improvement, and variability in care or outcomes [11]. This section should consider the ERN context and the impact of a recommendation or set of recommendations (i.e. a clinical question) offered by the clinical consensus on same, considering:

- ✓ Whether a recommendation or set of recommendations (clinical question) should be implemented (acceptability).
- ✓ Whether an organization or group is able to put the recommendation or set of recommendations into practice (applicability).

Contextual factors must be assessed in order to identify similarities and differences in the formulation of a recommendation or set of recommendations, and those present in the ERN context. Differences between contexts may introduce uncertainty that justifies the rejection of the recommendation or set of recommendations (clinical question).

These factors are the following:

Worth

Does the benefit to be gained from implementing the recommendation make it worth implementing (acceptable)?

The working group should determine whether the recommendation has considered both health benefits and risks, and whether its implementation would be useful for patients in the ERN context. In other words, a recommendation should promote appropriate care, reducing inappropriate or harmful care. Experts should also consider issues related to complexity or ease of use.

Population

Does the population described for eligibility match the population to which the recommendation is targeted in the local setting (acceptable)?

The target population must be correctly defined. As mentioned previously, the working group should discuss whether the population addressed by each recommendation matches the population of interest in the ERN context (age, childhood/adulthood, gender, high-risk population, a specific subgroup, etc.). Differences in the target population should be noted.

- ✓ If the recommendation addresses different subgroups of population, the working group should consider the relevance of addressing these subgroups in the ERN context.
- ✓ If the population is addressed as a subgroup, the adaptation working group should consider the relevance of addressing the broader definition of the population. If the adaptation group does not consider it necessary to broaden the population, only the recommendations addressed for the initially defined population would be considered.

Patient perspectives

Does the recommendation meet patient views and preferences in the context of use (acceptable)?

The working group should consider whether each recommendation is compatible with patient preferences and values in the ERN context.

Ideally patients and/or carers will have been included in the group entrusted with developing the clinical consensus statements (see Handbook #5: Methodology for the Development of Clinical Consensus Statements for Rare Diseases).

Intervention/ resources available

Are the intervention and/or equipment addressed in the recommendation available in the context of use (applicable)?

A recommendation should improve access to care, so the working group should consider whether the intervention is available in the ERN context (e.g. equipment, diagnostic tests and/or treatments).

If a recommendation is finally adopted, the availability of the intervention/resource should be evaluated by a specialised committee for local implementation.

Expertise (knowledge and skills) available

Is there the necessary expertise (knowledge and skills) available in the context of use (applicable)?

It is necessary to determine whether health professionals involved in the treatment of patients in the given context have the necessary technical expertise. If not, it should be considered whether specific training is feasible and under what conditions it should be provided.

Barriers (legislation, organization, policies)

Are there any constraints, organisational barriers, legislation, policies, and/or resources in the health care setting of use that would impede the implementation of the recommendation (applicable)?

The potential organisational barriers (e.g. resistance due to available resources, perception of effectiveness, etc.) to the implementation of a recommendation should be described. If the working group is not aware of this information, management experts could be consulted.

If there are legislative or regulatory barriers at European level, policy/decision makers and management experts can inform accordingly. In the subsequent implementation phase, the existence of barriers in local settings that would impede the implementation of the proposed interventions should be considered.

Compatible with the culture

Is the recommendation compatible with the culture and values in the setting where it is to be used (acceptable and applicable)?

Cultural and ethical differences can be decisive for the proper implementation of a recommendation in the European context. Consequently, recommendations should represent the norms and values of specific groups, communities or populations to ensure their relevance to local practice. The adaptation group should consider whether a recommendation addresses this factor correctly in order to accept or reject it.

6.2.2 / Decision-making phase

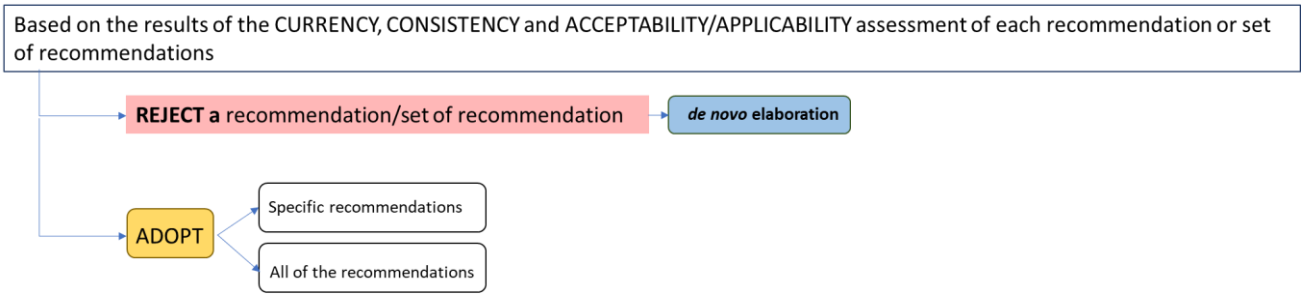
Once the assessment has been completed, the adaptation working group should ponder the results and draw a conclusion for each recommendation (Annex 1). The decision on each recommendation should be reached by consensus and be well documented, in order to be able to determine the impact of the analysis and the feasibility of its adoption.

A decision-making algorithm is proposed below to draw a conclusion on each recommendation or set of recommendations (clinical question). A clinical consensus statement can be adopted in whole or in part (Figure 4).

✓ Based on the results of the previous assessment (currency, consistency and acceptability/applicability), the clinical consensus could be **adopted in whole or in part**:

- If a recommendation or set of recommendations is not up to date/does not show consistency/is not acceptable or applicable, it should be discarded and not included in the adopted clinical consensus.
- If a recommendation or set of recommendations is up to date/does show consistency/is acceptable or applicable, specific recommendations would be adopted.
- If all of the recommendations are up to date/show consistency/ are acceptable and applicable, the clinical consensus would be adopted as a whole.

Figure 4. Decision making algorithm for the acceptance of a recommendation or set of recommendations of an existing Clinical Consensus



6.3 | Evidence Reports

The assessment of evidence reports would be based on the criteria set out in Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases, as it is limited to the quality of the systematic search. Therefore, if the evidence report does not meet the minimum requirements proposed in Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases, it will not be accepted by the working group, as a new evidence report would be prepared or sufficient (see Handbook #6: Methodology for the Development of Evidence Reports for Rare Diseases).

For a more in-depth quality assessment, AMSTAR 2 or ROBIS tools could be used [17, 18].

6.4 | Diagnostic, Monitoring and Therapeutic Pathways and Evidence-based Protocols

Due to the similarities between diagnostic, monitoring and therapeutic pathways (pathways) and evidence-based protocols, the same type of analysis is proposed below. Their assessment is focused

on activities or procedures as units of analysis.

Diagnostic, monitoring and therapeutic pathways and evidence-based protocols are not equivalent documents, but they share a common ground in their approach, as they focus on decision nodes (critical or routine) that help clinicians to make decisions. These activities or procedures are based on the best available evidence. They have a clearly differentiated utility and scope of application:

- ✓ The diagnostic, monitoring and therapeutic pathways must have been developed with the aim of sequencing and organizing clinical work in situations that present a predictable clinical course.
- ✓ The evidence-based protocol must have been developed with the aim of facilitating clinical work to address specific health problems.

The validity of pathways and evidence-based protocols is local, as they cover a specific scenario and may not be applicable to other clinical settings. Since both types of documents propose activities or procedures developed to achieve the maximum efficiency in patient care in a local setting, a common framework is proposed in this handbook for their assessment and decision-making.

6.4.1 / Assessment phase

The assessment of the retrieved documents is performed by analysing them with respect to the following aspects [2]:

6.4.1.1 | Quality appraisal

Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases provides a set of criteria for assessing the methodological quality of Diagnostic, Monitoring and Therapeutic Pathways and Evidence-based Protocols for rare diseases.

6.4.1.2 | Currency

As mentioned in Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases, no more than 3 years should generally have passed since the date of development and/or review or update of a diagnostic, monitoring and therapeutic pathway/evidence-based protocol in order to ensure that the content is up to date.

Pathways and evidence-based protocols should be designed through a rational combination of professional expertise and the best available scientific evidence. If the experts are aware of new evidence or they have personal experience that can improve the process and thus modify the proposed activities or procedures, the activities or procedures affected should be updated. The working group could decide whether other experts should be consulted.

Additionally, a literature review should be conducted if the diagnostic, monitoring and therapeutic pathway/evidence-based protocol is considered for adoption or adaptation. This review will be limited to one or two of the main databases and specific types of studies, preferably evidence that may come from other CPGs, pathways or evidence-based protocols. Only higher quality evidence that may modify an activity or procedure, based on the working group judgement (qualitative analyses), will be take into consideration for further analysis. For more information, consult Handbook #7: Methodology for the Development of Diagnostic, Monitoring and Therapeutic Pathways for Rare Diseases in the case of pathways and Handbook #8: Methodology for the Development of Evidence-Based Protocols for Rare Diseases for Evidence-Based Protocols.

When the quality of the original document is good but relevant advancements are identified, the activities or procedures affected will be considered as not current and the working group should consider updating the diagnostic, monitoring and therapeutic pathway/evidence-based protocol.

6.4.1.3 | Consistency

The activities or procedures proposed in the algorithm or diagram of a diagnostic, monitoring and therapeutic pathway/evidence-based protocol are mainly based on the result of the critical appraisal of one or more CPGs and systematic reviews. When these types of studies are not available, primary studies or consensus statements are considered. The consistency between the evidence included in the original document, its critical appraisal and its interpretation in the proposed activities and procedures should be reviewed.

The assessment of the consistency of an activity or a procedure includes the following evaluations:

- ✓ A systematic search of CPGs and systematic reviews has been performed. The risk that relevant evidence has been missed is low:
    - Relevant databases have been consulted.
    - Internet sites were searched.
    - A hand search was wade (e.g. journals, websites, legislation, etc.).
    - Detailed search strategies are provided.
    - The search period is specified.
- ✓ The criteria for selecting the CPGs and systematic reviews are explicit (inclusion and exclusion criteria).
- ✓ The critical appraisal of the evidence and its interpretation should be indicated:
    - Selected CPGs have been evaluated using AGREE-II instrument, rating the guideline as recommended or highly recommended.
    - The critical evaluation of systematic reviews has been performed following a pre-established system (Cochrane risk-of-bias assessment tool [12, 13], CASP [14], FLC 3.0 Critical Appraisal Tools Application [15], GRADE [16], etc.).
- ✓ When no CPGs or clearly acceptable systematic reviews existed, a literature search was conducted to retrieve other types of studies.
    - The literature search is shared and justified:
        - Appropriate databases were searched.
        - Internet sites were searched.
        - Detailed search strategies are provided.
        - A manual search of the reference lists was completed..
    - The criteria for selecting the evidence are explicit (inclusion and exclusion criteria).
    - The critical evaluation of the evidence has been performed following a pre-established system (Cochrane risk-of-bias assessment tool [12, 13], CASP [14], FLC 3.0 Critical Appraisal Tools Application [15], GRADE [16], etc.).
- ✓ 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 would be identified and differentiated from those based on scientific evidence.
- ✓ Activities or procedures are listed in chronological order.
- ✓ The algorithm, diagram or other supporting tools reflects the activities or procedures.
    - The algorithm, diagram or supporting tool provided are consistent with the evidence reviewed .

- ✓ Indicators have been established:
    - Indicators derive from activities or procedures.
    - For each objective of the diagnostic, monitoring and therapeutic pathway/evidence-based protocol, at least one indicator must be proposed.

6.4.1.4 | Acceptability/applicability

The impact of the diagnostic, monitoring and therapeutic pathway/evidence-based protocol on specific objectives would be evaluated in the ERN context [19]. The adoption and adaptation working group, together with other consultants, should consider:

- ✓ Whether an activity or a procedure should be implemented (acceptability.
- ✓ Whether an organization or group is able to put the activity or the procedure into practice (applicability).

The following analysis must be carried out for each activity or procedure listed, but limited to the European context. In some cases this may require consultation with management representatives and experienced experts in quality committees, as these profiles may not have been included in the working group.

Since the implementation of diagnostic, monitoring and therapeutic pathways and evidence-based protocols is local, it should be kept in mind that a further analysis of contextual factors will be necessary when the adopted or adapted document is implemented in a local context (e.g. its application in a particular hospital) (see Handbook #12: Implementation and Evaluation of the Uptake of CPGs and CDSTs for Rare Diseases

Differences between contexts may introduce uncertainty that justifies a re-evaluation of a recommendation, an activity or a procedure in the new context.

These factors are the following:

Worth

Does the benefit to be gained from implementing an activity or a procedure make it worth implementing (acceptable)?

The working group should consider the balance between risks and benefits to patients when proposing an activity or procedure, and whether their implementation will be useful in the ERN context. Issues related to complexity or ease of use should also be considered.

Population

Does the population described for eligibility match the population to which the activity or procedure is targeted in the local setting (acceptable)?

As mentioned earlier for CPGs, the working group should discuss whether the population addressed by each activity or procedure matches the population of interest in the ERN context (age, childhood/adulthood, gender, high-risk population, a particular subgroup, etc.). The working group should also consider the conditions in which the patient would receive the intervention (if inclusion and exclusion criteria exist).

- ✓ If the activity or procedure addresses different subgroups of population, the working group should consider the relevance of addressing these subgroups in the ERN context.
- ✓ If, on the other hand, the identified population is addressed as a subgroup in the activity or

procedure, the adaptation working group should consider the relevance of addressing the broader definition of the population. If the adaptation working group does not consider it necessary to broaden the population, only the activity or procedure addressed for the initially defined population would be considered.

Patient perspectives

Does the intervention meet patient views and preferences in the context of use (acceptable)?

The working group should consider whether each activity or procedure is compatible with patient preferences and values in the setting where it is to be used.

Patient perspectives may have been considered in different approaches. Values and preferences may have been reflected in the evidence on which the activity or procedures is based, e.g. when an activity or procedure is based on one or more CPGs, it should be noted whether patient perspectives have been considered. Patients may also have been involved as developers in the working group entrusted with developing the diagnostic, monitoring and therapeutic pathway/evidence-based protocol or as reviewers of the draft, and/or clinicians may have made a subjective judgement based on their personal experience in the management and interaction with patients.

Intervention/ resources available

Are the intervention and/or equipment addressed in the activity or procedure available in the context of use (applicable)?

The working group should assess whether each intervention targeted in an activity or procedure is available in the ERN context or whether it could be available in the near future (e.g. equipment, diagnostic tests and/or treatments).

As mentioned previously, since the implementation of the diagnostic, monitoring and therapeutic pathway/evidence-based protocol is local, if the activity or procedure is finally adopted or adapted, the availability of the intervention/resource will be evaluated by a specialised local committee.

Expertise (knowledge and skills) available

Is there the necessary expertise (knowledge and skills) available in the context of use (applicable)?

As mentioned previously with regard to CPGs, it is necessary to determine whether the required expertise exists among health professionals involved in patient management in the ERN context, in order to carry out the proposed activity or procedure. When the technical expertise does not yet exist, the working group should consider whether specific training is possible and under what circumstances it should take place in the ERN context.

Barriers (legislation, organisation, policies)

Are there any constraints, organisational barriers, legislation, policies, and/or resources in the health care setting of use that would impede the implementation of the recommendation (applicable)?

The working group should identify potential barriers to the implementation of an activity or procedure. If the adaptation working group is not aware of this information, management experts should be consulted to better understand the situation.

It is very important to analyse whether there are organisational barriers to implementing an activity or a procedure (e.g. resistance due to available resources, perception of effectiveness, etc.) for it to be accepted by health professionals.

At this point, ppolicy makers and management experts can advise the working group on European legislation and regulatory matters. It should be noted that the existence of constraints in legislation,

policy or resources in the local settings (e.g. countries, hospitals, etc.) that would impede the implementation of the proposed interventions should be considered in a subsequent phase (local adaptation and implementation), but not in this assessment (see Handbook #12: Implementation and Evaluation of the Uptake of CPGs and CDSTs for Rare Diseases).

Compatible with the culture

Are the activities or procedures compatible with the culture and values in the setting where it is to be used (acceptable and applicable)?

For the correct implementation of a diagnostic, monitoring and therapeutic pathway/evidence-based protocol across Europe, geographical, epidemiological, socio-cultural, socio-economic and ethical differences may be decisive. Each activity or procedure should be assessed. The working group should determine whether it is culturally appropriate and represents the norms and values of specific groups, communities, or populations, if needed, to ensure relevance for practice.

6.4.1.5 | Clarity of presentation

It should be noted that the description of the evidence and the activities or procedures should be accessible and concise [19]. The algorithm or diagram must reflect the activities and procedures properly. The working group shall consider whether these need to be clarified or refined.

6.4.2 | Decision-making phase

Once the assessment has been completed, the adaptation working group should consider the results and draw a conclusion for each activity or procedure (Annex 1). The decision for each one should be reached by consensus and be well documented, in order to be able to determine the impact of the analysis and the feasibility of its adoption or adaptation.

A decision-making algorithm is proposed below to reach a conclusion on the adoption or adaptation of a diagnostic, monitoring and therapeutic pathway/evidence-based protocol (Figure 5).

✓ Based on the results of the prior assessment of consistency:

- If all of the activities or procedures do not show consistency, the diagnostic, monitoring and therapeutic pathway/evidence-based protocol should be **discarded**.
- If one or more activities or procedures do not show consistency, the acceptance of the diagnostic, monitoring and therapeutic pathway/evidence-based protocol must be rated as a whole. The working group must assess whether they are interested in continuing with the **adaptation** of the diagnostic, monitoring and therapeutic pathway/evidence-based protocol or whether a ***de novo* development** process will be effective. If the group prefers to adapt the document, currency, acceptability/applicability and clarity of presentation factors will be taken into consideration.
- If all the activities or procedures show consistency, the whole diagnostic, monitoring and therapeutic pathway/evidence-based protocol would be accepted.

  Then, the working group should decide whether an accepted evidence-based protocol/ diagnostic, monitoring and therapeutic pathway could be **adopted** directly or whether it must follow an **adaptation process**.

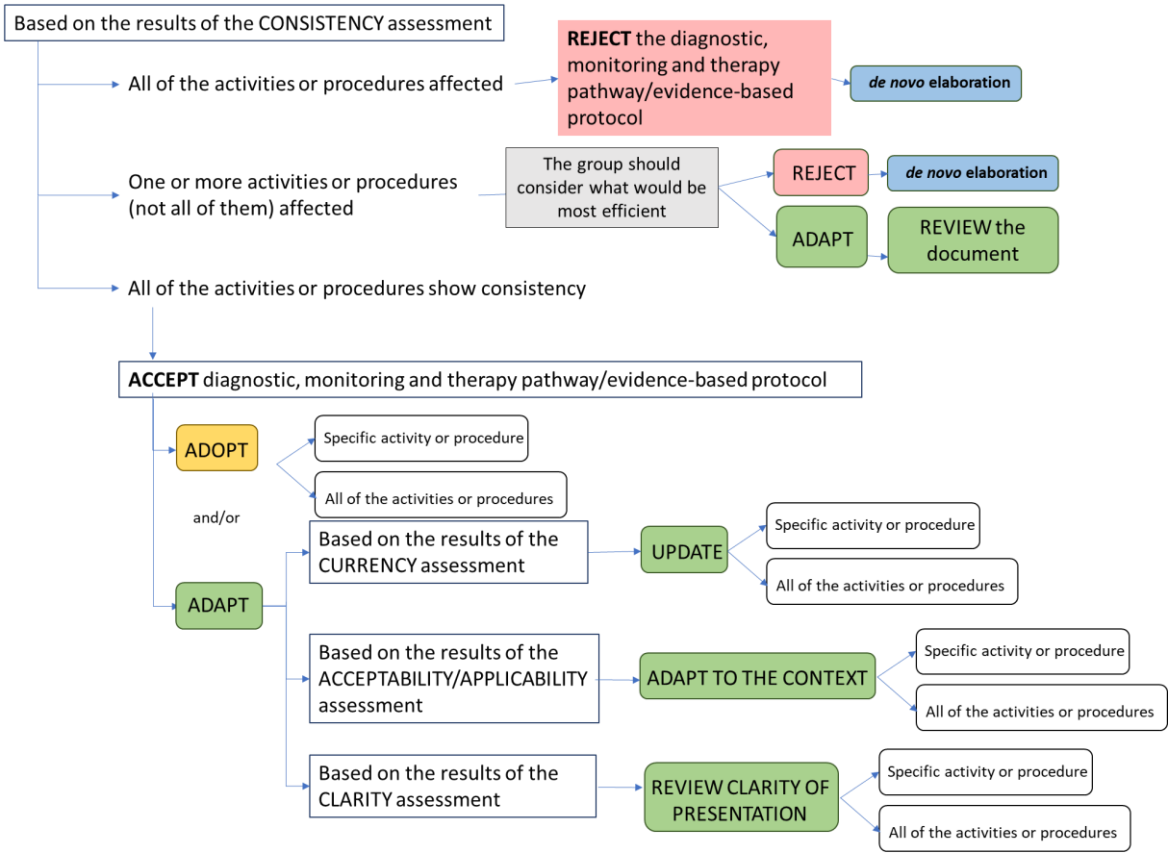
  The results of the currency and acceptability/applicability imply different approaches to adapt the diagnostic, monitoring and therapeutic pathway/evidence-based protocol. It is also possible that certain recommendations can be adopted directly while others need to be adapted.

  - Based on the currency assessment, if more than 3 years have elapsed since the

development, update or review of the document or new evidence has been detected, and this is likely to affect the validity of the activities or procedures, the working group should update them.

- Based on the acceptability/applicability assessment, and taking into consideration the ERN context, the adaptation to the context should be carried out (based on an adaptation plan).
- Based on the clarity assessment, it may be necessary to check the wording of the activities and/or procedures, and especially their integration in the algorithm/diagram, making it easier to read and/or more concise.

Figure 5. Decision-making algorithm for the acceptance of an activity or procedure of an existing Diagnostic, Monitoring and Therapeutic Pathway or an Evidence-Based Protocol for Rare Diseases.



6.5 | Quality measures

6.5.1 / Assessment phase

The retrieved Quality Measure (QM) tools is assessed by analysing them with regards to the following aspects [2]:

6.5.1.1 | Quality appraisal

Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases provides the set of criteria for assessing the methodological quality of QM tools for rare diseases.

6.5.1.2 | Currency

In the case of QM tools, no specific period for review or update is indicated. Nevertheless, indicators are elements that rely on data generated in clinical practice or reported by patients. For this reason, QM tools or sets of indicators that are being considered for adoption or adaptation should be in current use or have been pilot tested within the last three years. An indicator is in current use if at least one health care organization has used the measure to evaluate or report on quality of care within the previous three years [20]. Certain indicators may not be in current use, in which case it would be desirable for them to have been reviewed in line with a schedule that is commensurate with the rate of healthcare innovation [21].

There are several reasons why currency should be reviewed. QM tools or specific indicators need to be updated when there are:

- ✓ Relevant advances in care, based on new evidence.
- ✓ Relevant advances in the composition of information systems, codification and official standardised definitions.
- ✓ New methodologies or relevant innovation in the development of measurement artefacts.

Those QM tools considered for adoption or adaptation should be subjected to a literature review, since the evidence on which they are based may be outdated [22]. This review will not be extensive, i.e. it will be limited to one or two of the main databases and specific types of studies (RCT and Systematic Reviews). This review may include articles that discuss the outcome, event or process of interest. For instance, some articles may demonstrate effectiveness for a new indication for a treatment, this should be taken into account if an indicator measuring the rate of patients following a given treatment is to be adapted or adopted. Studies that may modify the subject of measurement or the relationships between components, based on the working group judgement (qualitative analyses), will be taken into consideration for further analysis. For more information, consult Handbook #10: Methodology for the Development of Quality Measures for Rare Diseases.

Additionally, QM tool inclusion/exclusion criteria are normally specified using internationally standardised definitions (ICD, ICHI, etc.); any update of these classifications or definitions should be reviewed with caution to verify the need to update the indicators that are intended to be adopted or adapted. For example, a new version of the ICD may be a reason to update an indicator defining its population with diagnosis codes, so the crossover to the new version should be reviewed.

Hence, the knowledge and expertise of the adaptation group, as well as that of other professionals well-versed in the field and quality of care experts who the working group may decide to consult, is key for identifying new relevant evidence that could modify the components, content or mathematical construction of a QM tool.

6.5.1.3 | Consistency

Consistency refers to the link between the selected evidence and the summary and interpretation of this evidence, as well as how this interpretation is translated into the QM tool. The assessment of the consistency of a QM includes the following evaluations [2]:

There should be a clearly documented scientific basis for the QM tool in literature. The evidence

supporting every indicator must cover the following aspects to ensure validity and reliability:

- ✓ QM tools and their indicators are linked to significant processes or outcomes of care and the causal relationship between them should be demonstrated by scientific studies. For example, the timely provision of diagnostic tests is a valid process indicator when supported by evidence that an early diagnosis is related with a better prognosis.
- ✓ The logical model that has been followed for every indicator in a QM tool must be duly justified. Does the indicator measure what it is intended to measure? To guarantee this, a correct interpretation of the mathematical instruments and their application to the indicator are necessary.
- ✓ According to reliability criteria, an indicator should produce similar results when repeated in the same population and setting, even when assessed by different people or at different times. Measure variability should result from changes in the subject of measurement rather than from artefacts of measurement.

For these consistency requirements to be met, it is necessary to review whether the following actions have been carried out:

- ✓ A systematic literature search has been performed. The risk that relevant evidence has been missed is low:
    - The research questions focused on the concept (what the measure is intended to capture), perspectives captured by the measure (patient, health professional, etc.) and specification (numerators, denominators and inclusion criteria) of the indicator.
    - Relevant databases were searched.
    - Relevant Internet sites were searched.
    - A hand search was performed (e.g. journals, websites, legislation, etc.).
- ✓ The criteria for selecting the evidence are explicit (inclusion and exclusion criteria) and coincide with the inclusion criteria considered for the indicator. For example, if the indicator is intended to measure the time to diagnosis for a paediatric condition, the systematic review should have selection criteria that exclude the adult population.
- ✓ The critical appraisal of evidence and its interpretation should be properly described and performed following a pre-established system (Cochrane risk-of-bias assessment tool [12, 13], CASP [14], FLC 3.0 Critical Appraisal Tools Application [15], GRADE [16], etc.).
- ✓ Other specific formal processes could be employed in which the measure has been accepted as a valid marker for quality, such as review by an expert panel. In that case, panel dynamics must be clearly established. For example, it is common to employ the modified RAND/UCLA Appropriateness Method to establish the consensual validity of the indicators..

6.5.1.4 | Acceptability/applicability

Acceptability and applicability refer to the fit that several context-dependent factors of the indicators included in a QM tool have in the ERN context in which they will be used. Each indicator or set of indicators should be assessed. The following must be considered:

- ✓ Whether a QM tool should be put into practice in a given context (organisation, group) (acceptability).
- ✓ Whether an organisation or group is able to put a QM tool or set of indicators into practice (applicability).

According to the principle of reliability, changes in the measurement subjects or in the context of

application of the QM tool should produce variability provided the measurement artefact and methodological characteristics are not modified. The acceptability and applicability assessment aims to identify similarities and differences between the contextual factors implicit in the original construction of a QM tool and those present in the ERN context in which the specific QM tool or set of indicators is to be implemented [23].

These factors are the following:

Worth

Does the benefit to be gained from implementing the indicator make it worth implementing (acceptable)?

Putting in practice a QM tool requires a significant effort on the part of the organisations (prepare information systems, ensure that professionals complete the necessary information about their practice, ensure periodic reports that are easily interpretable, etc.). The working group should consider whether the adaptation of an indicator or set of indicators would be useful in the context. An indicator should preferably address areas in which there is a clear gap between actual and potential levels of information. Indicators are to be adopted or adapted in areas that can be influenced by improvements in the quality of care monitoring.

Population

Does the population described for eligibility match the population to which the indicator is targeted in the local setting (acceptable)?

In the case of QM, it is possible to broaden the concept of population. The working group should discuss whether the subject of measurement addressed by the original indicator or set of indicators matches the subject of interest targeted in the local settings. The inclusion and exclusion criteria for each indicator in a QM tool are made explicit and include several dimensions (setting, unit, patient age, childhood/adulthood, gender, high-risk population, etc.).

The subject of measurement must be analysed according to the indicator type:

- ✓ For structure indicators, subjects of measurement are those resources available in the system. The working group should assess whether each indicator corresponds to the same level of care (primary care, hospital or a specific unit within the hospital).
- ✓ Process indicators may focus on measuring the execution of activities in a setting for a certain group of patients. It must be assessed whether each indicator corresponds to an equivalent level of care and whether the characteristics of the population included are similar.
- ✓ Outcome indicators focus specifically on health changes. Therefore, the working group should analyse whether the population of the original indicator and that of the application context are assailable.

For all cases, the inclusion criteria may be kept unchanged or adjusted and refined. For example, for a process indicator whose inclusion criterion is described as "paediatric population", the working group may refine the definition by establishing a specific age or considering an expanded population (young adults up to 20 years of age), according to the characteristics of the condition or operation of a specific hospital unit.

Patient perspectives

Does the indicator meet patient views and preferences in the context of use (acceptable)?

Patients' perspective may have been considered when addressing the construction of a QM tool. Ideally, every stakeholder, including those that are measured by a QM tool indicator, will have given

their feedback on the construction and criteria or, at least, those relevant stakeholders (including patients and/or carers) will have participated in the external review. Similarly, this feedback must be considered when adaptations are incorporated into the measure.

Intervention/ resources available

Are the structural and analytical resources available in the context of use (applicable)?

An indicator needs infrastructure for its implementation in the context. The working group should explicitly indicate the technological resources and information systems necessary to put an indicator or set of indicators into practice. Therefore, it is necessary to:

- ✓ Assess existing infrastructure resources (accessible databases, how they are connected to each other, whether there is enough memory capacity to produce the indicators, an IT team is in place and able to carry out the necessary implementation and maintenance).
- ✓ Analyse the need for data, for example, if international standardised definitions or codes are used in the setting, how these data are organised for collection, i.e. whether data are available at individual patient level or reports are produced with aggregate results, how often the databases are refreshed, etc.

Expertise (knowledge and skills) available

Is there the necessary expertise (knowledge and skills) available in the context of use (applicable)?

It is necessary to determine whether the necessary expertise exists among health professionals involved in patient management in the given context in relation to indicator monitoring. This requires being familiar with the quality of care models, information systems and data interpretation. If the technical expertise does not yet exist, it should be considered whether specific training is possible and under what conditions it should be provided in the given context.

Barriers (legislation, organization, policies)

Are there any constraints, organisational barriers, legislation, policies, and/or resources in the health care setting of use that would impede the implementation of an indicator (applicable)?

As indicated, potential barriers to the implementation of a QM tool may be identified (availability of adequate information systems, capacity for precise and constant monitoring, etc.) and it is important that they are properly identified and analysed at this point.

To achieve this, the working group may contact experts on regulatory matters and policy-makers to detect and analyse applicability in the ERN context involving multiple countries and different healthcare systems. For example, special attention should be given to existing constraints in legislation (e.g. those relating to confidentiality, data protection and cybersecurity) that would impede the implementation of the original QM tool.

Compatible with the culture

Is the indicator compatible with the culture and values in the setting where it is to be implemented (acceptable and applicable)?

Geographical, epidemiological, socio-cultural, socio-economic and ethical differences may be decisive for the correct implementation, across countries and health systems, of an indicator or set of indicators which comprise a QM tool or measuring instrument. The working group should assess and make a judgement on whether the data collected in standard practice to be included in an indicator or set of indicators is acceptable for the given cultural context. For example, in the case of PROMs, patients or their families/carers may be reluctant to declare particular conditions or

habits..

6.5.1.5 | Clarity of presentation

QM tools or indicators are mathematical and sometimes complex elements. It is important that the artefacts used are specified in an accessible and concise manner. Similarly, any reports extracted from their monitoring must be sufficiently understandable and informative (accompanied by legends, explanations of the calculations made, etc.), with a limited number of variables, so that they do not cause an information overload for its users. The working group shall consider whether these need to be clarified or refined..

6.5.2 / Decision-making phase

Once the assessment has been completed, the adaptation working group should consider the results and draw a conclusion on each indicator in a QM tool. The decision on each indicator should be reached by consensus and be well documented in order to determine the impact of the analysis and the feasibility of its adoption or adaptation.

A decision-making algorithm is proposed below for drawing conclusions on the creation of an adopted or adapted QM tool. The decision may affect all the indicators comprising the whole QM tool, a specific indicator or a set of indicators. It is recommended to approach decision making for each particular indicator also considering sets of indicators together (Figure 6):

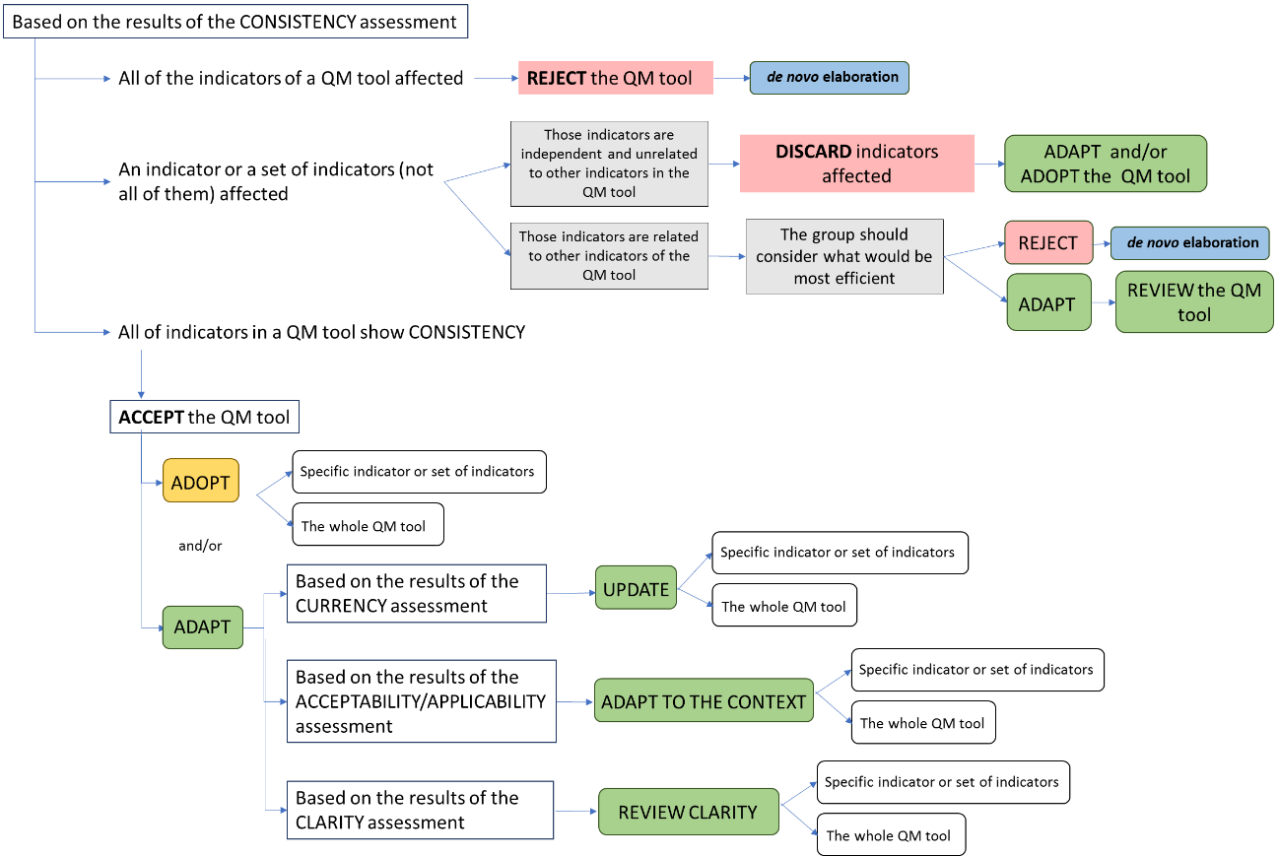
- ✓ Based on the results of the previous assessment of consistency, the QM tool could be **accepted totally or partially**:
    - If all indicators in a QM tool do not show consistency, the whole QM tool should be **rejected** and not adopted or adapted.
    - If one indicator or set of indicators does not show consistency, the acceptance of the whole QM tool must be rated:
        - First, it must be analysed whether the affected indicator or sets of indicators can be **discarded** without affecting the rest of the QM tool.
        - If the indicators affected by the lack of consistency are independent and unrelated to other indicators in the QM tool, these should be **discarded** and the QM tool adapted. Adaptation may also be considered for a single indicator, as long as it is independent.
        - If the indicators affected by the lack of consistency are related to other indicators in the QM tool, the working group must consider the QM tool as a whole and assess the appropriateness of continuing with the **adaptation** of the QM tool or whether a ***de novo* development** process will be more feasible/efficient. If the group prefers to adapt the QM tool, currency, acceptability/applicability and clarity of presentation factors will be taken into consideration.
    - If all indicators show consistency, the whole QM tool would be accepted.
- ✓ Then, the working group should decide whether a QM tool could be **adopted** directly or whether it needs to be **adapted**.

  The results of the currency and acceptability/applicability assessment imply different approaches to adapt the QM tool. It is possible that certain indicators can be adopted directly while others undergo an adaptation process.
    - Based on the currency assessment, if the working group detects important advances in care processes due to new available evidence, or an update of the international

standardised classifications is known or new approaches have been identified in relation to the internal calculations of an indicator that may be relevant, the working group should **update** the affected indicators.

- Based on the acceptability/applicability assessment, and taking into consideration the given context, an adaptation to the context should be carried out (based on an adaptation plan).
- Based on the clarity assessment, it may be necessary to check the usability of reports and the need for changes to make it more understandable or easy for users.

Figure 6. Decision making algorithm for the acceptance of an indicator or set of indicators of an existing QM tool for rare diseases

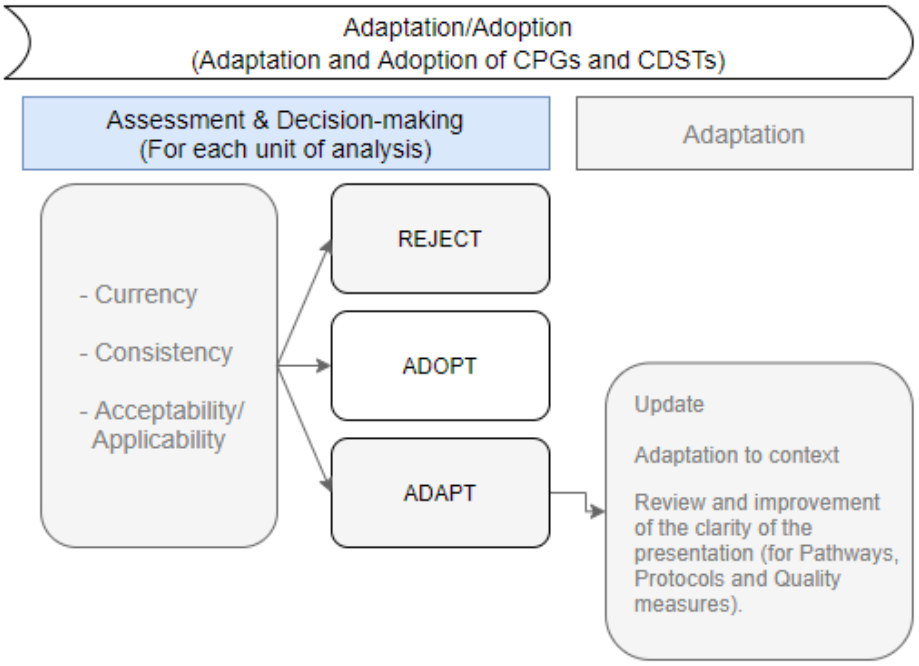


07.

ADOPTION

Once the decision to adopt the CPG or CDST has been made, the panel will proceed to the implementation phase (see Handbook #12: Implementation and Evaluation of the Uptake of CPGs and CDSTs for Rare Diseases) (Figure 7).

Figure 7. Adoption phase

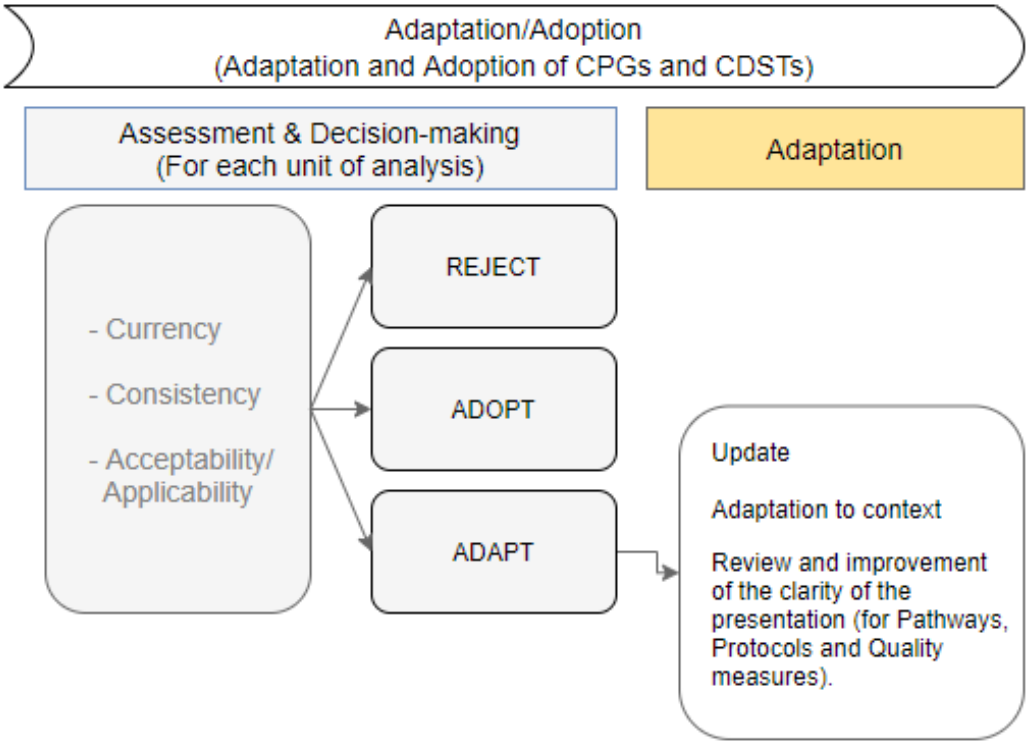


08.

ADAPTATION

If the working group considers that a recommendation, an activity or procedure, an indicator or set of indicators need to undergo an adaptation process (Figure 8), a decision should be taken on the extent to which they should be reviewed. When modifying an existing CPG or CDST, caution should always be taken not to modify recommendations to the extent that they no longer conform to the evidence on which they are based.

Figure 8. Adaptation phase



This information will be included in a plan, which will comprise details of the topic, membership of the working group, declaration of competing interests and a proposed timeline. It is desirable to set a standard of transparency, rigour and reproducibility. The adaptation plan shall be annexed to the draft of the adapted document, providing a detailed explanation of the process used to derive

recommendations (CPG), activities or procedures (evidence-based protocols, diagnostic, monitoring and therapeutic pathways) or indicators (QM) (see Annex 2).

It is important to highlight that:

- ✓ The working group should describe in detail the specific discrepancies that have been identified in the prior assessment and which have prompted the decision to adapt specific or all recommendations, activities, procedures or indicators: currency; consistency; acceptability/applicability in the ERN context (barriers, resources, expertise, cultural issues, language, etc.) and/or clarity of presentation (regarding algorithms, diagrams or other supporting tools). It is necessary to provide a description of concerns, their relevance and the new approach required.
- ✓ The adaptation working group, after having conducted the prior assessment of each recommendation (CPG), activity or procedure (evidence-based protocols, diagnostic, monitoring and therapeutic pathways) or indicator (QM), should consider whether more experts should be included in the adaptation group (e.g. medical specialties, surgical specialties, physical therapists, patients and/or carers, etc.) to continue with their adaptation.
- ✓ The adaptation process must be reliable and consistent to ensure the quality of the adapted CPG or CDST. The adapted CPG or CDST must meet the quality criteria provided in Handbook #2: Appraisal of Existing CPGs and CDSTs for Rare Diseases.
- ✓ For CPGs or CDSTs originally produced with GRADE, it is recommended to follow the "GRADE-ADOLOPMENT" approach. This model combines the advantages of selectively combining adoption, adaptation and *de novo* development of recommendations (updated or new) [3].
- ✓ At the end of the adaptation process, an external review should be performed. Health professionals, managers, policy-makers, and patients and/or carers should be consulted.
- ✓ The adaptation plan shall be annexed to the adapted CPG or CDST.
- ✓ Once adapted, the working group will proceed to the implementation phase (see Handbook #12: Implementation and Evaluation of the Uptake of CPGs and CDSTs for Rare Diseases).

8.1 | Update

According to the results of the assessment of CPG or CDST currency, the working group should update the content of the document. The corresponding section of Handbooks #4-11: Methodology for the Development of CPGs and CDSTs will be followed.

8.1.1 | Clinical Practice Guidelines

Below is an overview of the steps involved in the CPG updating process. For more information, see Chapter 11. Updating the CPG of Handbook #4: Methodology for the Development of CPGs for Rare Diseases.

- ✓ By means of the assessment performed in the previous chapter, the working group will decide which of the recommendations addressed by the CPG should be updated. Development of *de novo* recommendations involves formulating new questions.

  The group will decide (see Chapter 11. Updating the CPG of Handbook #4: Methodology for the Development of CPGs for Rare Diseases):

  - Clinical questions to be reviewed.

- Valid clinical questions
- New clinical questions, to be framed in accordance with the PICO format (Patient/Intervention/Comparison/Outcome), in order to help define the question.

✓ Relevant evidence identified in the assessment of currency (either provided by the experts or detected in the literature review) that may modify the recommendation will be the basis for the update.

The working group may consider that supplementary literature searches (e.g. patients' values and preferences, economic analysis relevant to the ERN settings) should be conducted to review certain clinical questions. In these cases, a restrictive literature search will be performed (see Chapter 11.3. Identification of New Evidence of Handbook #4: Methodology for the Development of CPGs for Rare Diseases).

✓ The evidence will be analysed and synthesised (see Appraisal and Synthesis of Scientific evidence of Handbook #4: Methodology for the Development of CPGs for Rare Diseases). The evidence will be summarised in evidence tables.

- When the method used to develop the original CPG was GRADE, information will be incorporated to evidence profiles [3]. Original EtD framework may have a role in the *de novo* development by making evidence syntheses available.
- When a different methodological approach to GRADE is used, it will necessary to elaborate *ex novo* the evidence profiles. Meaning, body of evidence of the original question and the new references should be assessed.

✓ EtD frameworks for each clinical question will be complete. The EtD frameworks facilitate the consideration of key context-specific factors (e.g. acceptability/applicability assessment) (see Appraisal and Synthesis of Scientific Evidence in Handbook #4: Methodology for the Development of CPGs for Rare Diseases). The EtD frameworks include the summary of evidence on the following [24]:

- Balance of desirable and undesirable consequences.
- Quality of evidence
- Resource use
- Patients' perspectives must be considered.
- Cost effectiveness ratio (economic model)
- Impact on equity

8.1.2 / *Diagnostic, Monitoring and Therapeutic Pathways and Evidence-based Protocols*

Because of the similarities between diagnostic, monitoring and therapeutic pathways and evidence-based protocols, whose rationale is detailed in the Assessment section above, the same type of update process is proposed for both.

✓ By means of the assessment performed in the previous chapter, the working group will decide which of the activities or procedures addressed by the diagnostic, monitoring and therapeutic pathway/evidence-based protocol should be updated. Development of *de novo* activities or procedures may involve formulating new questions. The group will decide on the following aspects:

- Activities or procedures to be reviewed. They will be reflected in clinical questions.
- Valid activities or procedures.

- New activities or procedures to be incorporated in the evidence-based protocol. They will be reflected in clinical questions.

Clinical questions will be framed, according to the PICO format (Patient/Intervention/Comparison/Outcome), in order to help define the question.

✓ Relevant evidence identified in the assessment of currency by the adaptation working group (either provided by the experts or detected in the literature review) that may modify the activity or procedure will be the basis for the update.

The working group may consider that a broader literature search should be conducted to review certain clinical questions or specific aspects (e.g. patients' values and preferences, economic analysis relevant to ERN settings). A restrictive literature search is suggested.

✓ The evidence will be analysed and synthesised. The evidence will be summarised in evidence tables (see Handbook #7: Methodology for the Development of Diagnostic, Monitoring and Therapeutic Pathways for Rare Diseases or Handbook #8: Methodology for the Development of Evidence-Based Protocols for Rare Diseases).

- When the method used to develop the original diagnostic, monitoring and therapeutic pathway/evidence-based protocol was GRADE, information will be incorporated to evidence profiles [3]. Original EtD framework may have a role in the *de novo* development by making evidence syntheses available.
- When a different methodological approach to GRADE is used, it will necessary to elaborate *ex novo* the evidence profiles. Meaning, body of evidence of the original question and the new references should be assessed.

✓ EtD frameworks for each clinical question will be complete. The EtD frameworks facilitate the consideration of key context-specific factors (e.g. acceptability/applicability assessment) (see Handbook #7: Methodology for the Development of Diagnostic, Monitoring and Therapeutic Pathways for Rare Diseases or Handbook #8: Methodology for the Development of Evidence-Based Protocols for Rare Diseases). The EtD frameworks include the summary of evidence on[24]:

- Balance of desirable and undesirable consequences.
- Quality of evidence
- Resource use
- Patients' perspectives must be considered.
- Cost effectiveness ratio (economic model)
- Impact on equity

✓ Once the activities and procedures have been updated, the working group will identify a list of specific, quantifiable evaluation criteria or indicators deriving from the new activities or procedures set out in the diagnostic, monitoring and therapeutic pathway/evidence-based protocol, which, in addition to the maintained and non-reviewed activities or procedures, will enable the achievement of the objectives in the context of use.

8.1.3 / Quality Measures

A QM tool indicator may be updated for different reasons, with a specific approach for each type of indicator .

✓ If the indicator is updated due to the identification of new healthcare processes resulting from the appearance of new evidence, the objective of the update will be to reconfigure the affected indicators that form part of a QM so that they continue to measure what is expected.

- Only relevant evidence identified in the assessment of currency by the adaptation working group (either provided by the experts or detected in the literature review) that may modify the indicator definition will be considered for the update.
- The evidence will be analysed and synthesised following a pre-established system.
- According to the new evidence obtained and analysed, the working group may decide to:
    - Update the construction of the indicator to capture new care procedures that were previously developed differently. For example, if there is evidence of the use of a new surgical approach, previously-designed process indicators may not collect information properly.
    - Modify the inclusion/exclusion criteria of the affected indicators according to the new evidence. For example, including new drug treatment codes which have been shown to be effective in process indicators related to a condition.

✓ When the QM tool update is due to relevant updates in the composition of information systems or codification based on the internationally standardised definitions (ICD, ICHI, etc.), the inclusion/exclusion criteria to adapt the indicator to the new established definitions should be modified.

✓ The working group can also identify areas for improvement in the composition of measurement artefacts that can provide higher efficacy to capture the phenomenon to be measured. For example, updating PROM instruments to improve their psychometric properties.

8.2 | Adaptation to the context

The adaptation to the context should be a systematically planned through a proactive process of modification to adapt the specific characteristics and needs and enhance intervention acceptability.

According to the aspects identified when assessing acceptability/applicability (population, patients' perspectives, resource availability or the proposed intervention, availability of required expertise, existence of barriers, cultural issues, worthiness), the working group should consider whether the recommendations, activities or procedures can be adapted to cover the weaknesses identified and to address clinical questions in the context.

This adaptation should abide by the efficiency principle explained at the beginning of this handbook. It should be performed taking care not to modify the recommendations to such an extent that the amount of time and other resources devoted to same match or surpass those required for the development of a CPG or CDST (or clinical questions) *de novo*.

The steps to follow will be those described in Handbooks #4-11: Methodology for the Development of CPGs and CDSTs.

8.2.1 | Clinical Practice Guidelines

✓ The working group will decide which of the recommendations addressed by the CPG should be reviewed and adapted to the given context.

✓ These gaps will be reflected in the adaptation plan.

✓ Relevant information, opinions, experiences and/or evidence identified in the assessment of acceptability and applicability in the ERN context will be used to inform and modify a recommendation or set of recommendations (e.g. clarify that training for health professionals is necessary; specify whether the recommendation would be culturally accepted, etc.).

The working group may consider that supplementary literature searches (e.g. patients' values and preferences, economic analysis relevant to the ERN settings) should be conducted to review certain clinical questions. In such cases, a restrictive literature search will be performed (see Chapter 11.3. Identification of New Evidence in Handbook #4: Methodology for the Development of CPGs for Rare Diseases).

- When the method used to develop the original CPG was GRADE, this information will be reflected in EtD frameworks.
- When a different methodological approach to GRADE was used, a qualitative assessment will be performed by the working group, reaching a consensus on how to express it in the recommendation.

8.2.2 / *Diagnostic, Monitoring and Therapeutic Pathways and Evidence-Based Protocols*

Because of the similarities between diagnostic, monitoring and therapeutic pathways and evidence-based protocols, whose rationale is detailed in the Assessment section above, the same type of adaptation to the context is proposed for both.

✓ The working group will decide which of the activities or procedures addressed by the diagnostic, monitoring and therapeutic pathway/evidence-based protocol should be reviewed and adapted to the given context.

✓ These needs will be reflected in the adaptation plan.

✓ Relevant information, opinions, experiences and/or evidence identified in the assessment of acceptability and applicability in the given context by the adaptation working group (either provided by the experts or detected in the literature review) that may modify the activity or procedure will be the basis for the adaptation.

The working group may consider that a broader literature review should be conducted to adapt certain clinical questions to the given context (e.g. patients' values and preferences, economic analysis relevant to the setting). In that case, restrictive literature searches are recommended.

- When the method used to develop the original diagnostic, monitoring and therapeutic pathway/evidence-based protocol was GRADE, this information will be reflected in EtD frameworks.
- When a different methodological approach to GRADE was used, a qualitative assessment will be performed by the working group, reaching a consensus on how to express it in the activity or procedure.

✓ After this review, the working group shall identify a list of specific, quantifiable evaluation criteria or indicators deriving from the activities or procedures set out in the adapted diagnostic, monitoring and therapeutic pathway/evidence-based protocol, which will enable the achievement of the objectives in the context of use.

8.2.3 / *Quality Measures*

The working group will decide which of the indicators in a QM tool should be reviewed and adapted to the given context; the following aspects should be taken into account:

✓ Modifying inclusion/exclusion criteria [23]

When a QM tool, a set of indicators or a single indicator is adapted to the given context, the inclusion/exclusion criteria will probably be modified. It must be verified that the adaptation meet face validity (measure what it should measure), construct validity (causal relationships between the indicator and the implications of its measurement), reliability (variability in results is due to variability in inputs) and usability (does not imply an information overload and data to process) requirements.

✓ Accounting for risk adjustment [25]

Risk adjustment allows for fair comparisons, particularly in the case of outcome indicators. Outcomes often vary due to factors outside the control of the system, such as comorbidities or condition severity. Standard risk adjustment development models include age and gender (and comorbidities when available). During the working group assessment for adaptation, potential risk factors or particular conditions should be identified and included within the risk adjustment model. Empirical testing should be done to reduce risk of bias in high-risk groups.

✓ Adapting the QM tool to the available data source [22]

The original QM tool or set of indicators may be entirely or partially defined using specific data sources (e.g. administrative databases), which are different from those available in the context in which the indicator is to be adapted (e.g. patient registries). In these cases, an equivalent definition using available data should be produced and tested empirically. For example, data from patient registries may follow a different codification than the ICD-10 for the conditions included; hence, similar definitions must be found in order to adapt the QM tool.

8.3 | Review and improvement of the clarity of presentation

As regards the clarity of presentation of a diagnostic, monitoring and therapeutic pathway and an evidence-based protocol, the wording of recommendations and how they are reflected in algorithms and diagrams may need to be clarified and refined.

Regarding the QM tool, the working group should review and analyse whether it is necessary to amend the presentation of results, use legends or provide more information on assumptions and calculations.

09.

EDITION OF THE FINAL ADOPTED OR ADAPTED DOCUMENT

After the adaptation process, both adapted CPGs and CDSTs must undergo an external review by recognised experts in the field and patient representatives to ensure their quality, validity and applicability, in order to guarantee the support of stakeholders.

In the case of adapted diagnostic, monitoring and therapeutic pathways and evidence-based protocols, diagrams or algorithms describing the sequence of established activities or procedures must be included.

If the document has been adopted or adapted, the format and style of the CPG or CDST should be considered. Final documents should be easily accessible to end-users, and it is desirable for a patient version to be provided. Final versions should also include a plan for future updates.

For further information on these aspects, please consult the respective chapters of Handbooks #4-11: Methodology for the Development of CPGs and CDSTs.

10.

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11.

ANNEXES

ANNEX 11.1 | Assessment and Decision-Making Phase Checklist

Type of document: Clinical Practice Guideline	
Name of the document	
ERN	
Working group	
Assessment Phase	
	Notes (recommendation, clinical question, section affected, proposed changes, etc.)
Currency	Have more than 3 years passed since the document was developed/reviewed/updated? Are you aware of any relevant new evidence which could affect a recommendation or set of recommendations? If so, please provide a reference for this new evidence. Is there any new evidence to invalidate any of the recommendations comprising the CPG?
Consistency	Has the evidence been generated via a systematic review? Is the selected evidence reported? Is the way in which the evidence has been summarised and interpreted reported? Is the interpretation of the evidence consistent with the formulation of recommendations?
Acceptability/Applicability Worth	Please indicate which recommendations are affected Does the benefit to be gained from implementing the recommendation make it worth implementing (acceptable)?

Population	Does the population described for eligibility match the population to which the recommendation is targeted in ERN context (acceptable)?
Patient perspective	Does the intervention meet patient views and preferences in the ERN context (acceptable)?
Intervention/resources available	Are the intervention and/or equipment addressed in the recommendation available in the ERN context (applicable)?
Expertise (knowledge and skills) available	Is the necessary expertise (knowledge and skills) available in the ERN context (applicable)?
Barriers (legislation, organization, policies)	Are there any constraints, organisational barriers, legislation, policies, and/or resources in the ERN context that would impede the implementation of the recommendation (applicable)?
Compatible with the culture	Is the recommendation compatible with the culture and values in the ERN context (acceptable and applicable)?

Decision-Making Phase	
Based on the consistency assessment, which recommendations need to be updated or adapted?	
Based on the currency assessment, which recommendations need to be updated?	
Based on the acceptability/applicability assessment, which recommendations need to be adapted?	

Type of document: Clinical Consensus Statements	
Name of the document	
ERN	
Working group	
Assessment Phase	
	Notes (recommendation, clinical question, section affected, proposed changes, etc.)
Currency	Have more than 3 years passed since the document was developed/reviewed/updated? Are you aware of any relevant new evidence which could affect a recommendation or set of recommendations? If so, please provide a reference for this new evidence. Is there any new evidence to invalidate any of the recommendations?
Consistency	Is the method used to reach consensus described? Is the process used to define the clinical question and recommendation described? Has the evidence been generated via a systematic review? Is the selected evidence reported? Is the level of consensus revealed? Is there an explicit relationship between each recommendation and the evidence on which it is based or the degree of agreement of the expert consensus?
Acceptability/Applicability	Please indicate which recommendations are affected
Worth	Does the benefit to be gained from implementing the recommendation make it worth implementing (acceptable)?
Population	Does the population described for eligibility match the population to which the recommendation is targeted in the ERN context (acceptable)?
Patient perspective	Does the intervention meet patient views and preferences in the ERN context (acceptable)?
Intervention/resources available	Are the intervention and/or equipment addressed in the recommendation available in the ERN context (applicable)?

Expertise (knowledge and skills) available	Is there the necessary expertise (knowledge and skills) available in the ERN context (applicable)?
Barriers (legislation, organization, policies)	Are there any constraints, organisational barriers, legislation, policies, and/or resources in the ERN context that would impede the implementation of the recommendation (applicable)?
Compatible with the culture	Is the recommendation compatible with the culture and values in the ERN context (acceptable and applicable)?

Decision-Making Phase	
Based on the consistency assessment, which recommendations would be adopted?	
Based on the currency assessment, which recommendations would be adopted?	
Based on the acceptability/applicability assessment, which recommendations would be adopted?	

Type of document: Diagnostic, Monitoring and Therapeutic Pathwa	
Name of the document	
ERN	
Working group	
Assessment Phase	
	Notes (recommendation, clinical question, section affected, proposed changes, etc.)
Currency	Have more than 3 years passed since the document was developed/reviewed/updated? Are you aware of any relevant new evidence which could affect an activity or a procedure? If so, please provide a reference for this new evidence. Is there any new evidence to invalidate any of the activities or procedures comprising the Diagnostic, Monitoring and Therapeutic Pathway?
Consistency	Has the evidence been generated via a systematic review? Is the selected evidence reported? Is the way in which the evidence has been summarised and interpreted reported? Does the algorithm, diagram or supporting tool properly reflect the activities or procedures? Have indicators been established?
Acceptability/Applicability	Please indicate which recommendations are affected
Worth	Does the benefit to be gained from implementing an activity or a procedure make it worth implementing (acceptable)?
Population	Does the population described for eligibility match the population to which an activity or a procedure is targeted in the ERN context (acceptable)?
Patient perspective	Does the intervention meet patient views and preferences in the ERN context (acceptable)?
Intervention/resources available	Are the intervention and/or equipment addressed in the recommendation available in the ERN context (applicable)?

Expertise (knowledge and skills) available	Is the necessary expertise (knowledge and skills) available in the ERN context (applicable)?
Barriers (legislation, organization, policies)	Are there any constraints, organisational barriers, legislation, policies, and/or resources in the ERN context that would impede the implementation of the activity or procedure (applicable)?
Compatible with the culture	Is the activity or procedure compatible with the culture and values in the ERN context (acceptable and applicable)?
Clarity of presentation	Are activities and procedures properly reflected in the algorithm, diagram of supporting tool provided?

Decision-Making Phase	
Based on the consistency assessment, which activities or recommendations need to be updated or adapted?	
Based on the currency assessment, which activities or recommendations need to be updated?	
Based on the acceptability/applicability assessment, which activities or recommendations need to be adapted?	
Based on the clarity of presentation assessment, which activities or recommendations need their wording to be reviewed? Does the algorithm, diagram or supporting tool need to be reviewed?	

Type of document: Evidence-Based Protocol	
Name of the document	
ERN	
Working group	
Assessment Phase	
	Notes (recommendation, clinical question, section affected, proposed changes, etc.)
Currency	Have more than 3 years passed since the document was developed/reviewed/updated? Are you aware of any relevant new evidence which could affect an activity or a procedure? If so, please provide a reference for this new evidence. Is there any new evidence to invalidate any of the activities or procedures comprising the evidence-based protocol?
Consistency	Has the evidence been generated via a systematic review? Is the selected evidence reported? Is the way in which the evidence has been summarised and interpreted reported? Does the algorithm, diagram or supporting tool properly reflect the activities or procedures? Have indicators been established?
Acceptability/Applicability	Please indicate which recommendations are affected
Worth	Does the benefit to be gained from implementing an activity or a procedure make it worth implementing (acceptable)?
Population	Does the population described for eligibility match the population to which an activity or a procedure is targeted in the ERN context (acceptable)?
Patient perspective	Does the intervention meet patient views and preferences in the ERN context (acceptable)?
Intervention/resources available	Are the intervention and/or equipment addressed in the recommendation available in the ERN context (applicable)?
Expertise (knowledge and skills) available	Is the necessary expertise (knowledge and skills) available in the ERN context (applicable)?

Barriers (legislation, organization, policies) Compatible with the culture	Are there any constraints, organisational barriers, legislation, policies, and/or resources in the ERN context that would impede the implementation of the activity or procedure (applicable)? Is the activity or procedure compatible with the culture and values in the ERN context (acceptable and applicable)?
Clarity of presentation	Are activities and procedures properly reflected in the algorithm, diagram of supporting tool provided?

Decision-Making Phase	
Based on the consistency assessment, which activities or recommendations need to be updated or adapted?	
Based on the currency assessment, which activities or recommendations need to be updated?	
Based on the acceptability/applicability assessment, which activities or recommendations need to be adapted?	
Based on the clarity of presentation assessment, which activities or recommendations need their wording to be reviewed? Does the algorithm, diagram or supporting tool need to be reviewed?	

Type of document: Quality Measures	
Name of the document	
ERN	
Adaptation group	
Assessment Phase	
	Notes (recommendation, clinical question, section affected, proposed changes, etc.)
Currency	Is the QM tool or set of indicators in current use or has it been pilot tested in the last 3 years? Are you aware of any relevant new evidence which could affect an indicator or set of indicators? If so, please provide a reference for this new evidence. Are you aware of any relevant advance in the composition of information systems, codification and official standardised definitions? Are you aware of any new methodologies or relevant innovation in the development of measurement artefacts?
Consistency	Construct validity: Has a clearly documented scientific basis for the QM tool been provided? Face validity: Does the indicator measure what it is intended to measure? Have the methodology and interpretation of the mathematical instruments been discussed properly? Reliability: Have the population and setting of the QM tool been adequately discussed and transferred to the indicator?
Acceptability/Applicability	Please indicate which recommendations are affected
Worth	Does the benefit to be gained from implementing the indicator make it worth implementing (acceptable)?
Population	Does the population described for eligibility match the population to which the indicator is targeted in the local setting (acceptable)?
Patient perspective	Does the indicator meet patient views and preferences in the context of use (acceptable)?
Intervention/resources available	Are the structural and analytical resources available in the context of use (applicable)?

Expertise (knowledge and skills) available	Is the necessary expertise (knowledge and skills) available in the context of use (applicable)?
Barriers (legislation, organization, policies)	Are there any constraints, organisational barriers, legislation, policies, and/or resources in the health care setting of use that would impede the implementation of an indicator (applicable)?
Compatible with the culture	Is the indicator compatible with the culture and values in the setting in which it is to be implemented (acceptable and applicable)?

Decision-making Phase	
Based on the results of the previous assessment of consistency, does the QM tool need to be updated or adapted?	
Based on the currency assessment, which indicators need to be updated?	
Based on the acceptability/applicability assessment, which indicators need to be adapted?	

ANNEX 11.2 | Checklist of Adapted Documents Content

Clinical Practice Guidelines

	Yes/No
Overview material: ○ Structured abstract ○ Date of adaptation ○ Status (original, adapted, revised, updated) ○ Print and electronic sources	
List of working group members and their credentials, declaration of conflicts of interest	
List of funding source(s)	
Key recommendations	
Introduction and background	
Scope and purpose	
Description of the target audience of the CPG	
Description of the target patients	
Methodology approach	
Clinical question(s), including an introduction to the chapter	
Recommendations ○ Risks and benefits associated with the recommendations ○ Specific circumstances under which to perform the recommendation ○ Strength of recommendation	
Supporting evidence and information for the recommendations ○ Rationale behind the recommendations ○ Presentation of additional evidence ○ How and why existing recommendations were modified	
Algorithm(s) of diagnostic and therapeutic strategies	

Plan for scheduled review and update	
External review and consultation process ○ Experts who participate as reviewers ○ What process was followed ○ Discussion of feedback ○ Feedback incorporated into the final document	
Summary document	
Version for patients	
Dissemination and implementation (potential barriers for the use of the CPG; development of quality measures) (see Handbook #12: Implementation and Evaluation of the Uptake of CPGs and CDSTs for Rare Diseases)	
Future research	
References	
Glossary (for unfamiliar terms)	
Annex describing the adaptation process: ○ Literature search and retrieval including the list of documents identified and whether they were included or excluded ○ Quality assessment including which assessments were undertaken and in which order, and a summary of results for each assessment ○ Decision process followed by working group ○ Results and decisions of each evaluation	

Diagnostic, Monitoring and Therapeutic Pathways

	Yes/No
Overview material: ○ Structured abstract ○ Date of adaptation ○ Status (original, adapted, revised, updated) ○ Print and electronic sources	
List of the working group members and their credentials, declaration of conflicts of interest	
List of funding source(s)	
Introduction and background	
Scope and purpose	
Description of the target audience of the Diagnostic, Monitoring and Therapeutic Pathway	
Description of the target patients	
Methodology approach	
Definitions of the clinical questions	
Recommendations ○ Risks and benefits associated with the recommendations ○ Specific circumstances under which to perform the recommendation ○ Strength of recommendation	
Supporting evidence and information for the recommendations ○ Rationale behind the recommendations ○ Presentation of additional evidence ○ How and why existing recommendations were modified	
Definition of the Diagnostic, Monitoring and Therapeutic Pathway (linked to evidence-based recommendations or consensus statements and listed in chronological order) ○ Safety issues ○ Entry, exit and marginal limits ○ Professionals involved	

○ Activities and good practices ○ Specific capabilities ○ Support units ○ Specific material resources	
Graphical representation: ○ General representation: ○ Patient's Roadmap	
Follow-up assessment plan	
Plan for scheduled review and update	
External review and consultation process ○ Experts who participate as reviewers ○ What process was followed ○ Discussion of feedback ○ Feedback incorporated into the final document	
Summary document	
Version for patients	
References	
Glossary (for unfamiliar terms)	
Acknowledgement of source guideline developers and permission granted	
Annex describing the adaptation process: ○ Literature search and retrieval including the list of documents identified and whether they were included or excluded ○ Quality assessment including which assessments were undertaken and in which order, and a summary of results for each assessment ○ Decision process followed by working group ○ Results and decisions of each evaluation	

Evidence-based Protocols

	Yes/No
Overview material: ○ Structured abstract ○ Date of adaptation ○ Status (original, adapted, revised, updated) ○ Print and electronic sources	
List of the working group members and their credentials, declaration of conflicts of interest	
List of funding source(s)	
Introduction and background	
Scope and purpose	
Description of the target audience of the evidence-based protocol	
Description of the target patients	
Methodology approach	
Definitions of the clinical questions	
Activities or procedures listed in chronological order (linked to evidence-based recommendations or consensus statements)	
Algorithm, diagrams or other supporting tools	
Indicators	
Plan for scheduled review and update	
External review and consultation process	
Glossary (for unfamiliar terms)	
References	
Acknowledgement of source guideline developers and permission granted	
Annex describing the adaptation process: ○ Literature search and retrieval including the list of documents identified and whether they were included or excluded	

○ Quality assessment including which assessments were undertaken and in which order, and a summary of results for each assessment ○ Decision process followed by the working group ○ Results and decisions of each evaluation	

Quality Measures

	Yes/No
Overview material: ○ Structured abstract ○ Date of adaptation ○ Status (original, adapted, revised, updated) ○ Print and electronic sources	
List of the working group members and their credentials, declaration of conflicts of interest	
List of funding source(s)	
Plan for scheduled review and update	
QM classification (measure domains for all indicators included)	
Brief abstract ○ Description ○ Rationale ○ Evidence for rationale	
Evidence supporting the QM ○ Information Supporting the need for the QM ○ Extent of Measure Testing	
State of use of the QM	
Application of the QM in the original use ○ Setting ○ Professionals involved ○ Acceptable minimum sample size ○ Target population (age, gender, condition, etc.)	
Data collection for the QM ○ Computation of the QM and its indicators ○ Inclusion/exclusion criteria for every indicator ○ Risk adjustment variables ○ Data sources ○ Interpretation of scores	
External review and consultation process ○ Experts who participate as reviewers ○ Process followed ○ Discussion of feedback ○ Feedback incorporated into the final QM	
References	
Glossary (for unfamiliar terms)	

Acknowledgement of original indicator developers and permission granted	
Annex describing the adaptation process: ○ Literature search and retrieval including the list of documents identified and whether they were included or excluded ○ Quality assessment including which assessments were undertaken and in which order, and a summary of results for each assessment ○ Decision process followed by working group ○ Results and decisions of each evaluation	

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