D-B.2

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

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

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Handbook #3: Adaptation and Adoption of CPGs and CDSTs

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Document Information

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

This document contains the methodological manual for the adaptation and adoption of CPGs and CDSTs for rare diseases.

Short Description

This document comprises the methodological basis and procedure for the assessment and decision-making phases for the adaptation and adoption of existing CPGs and CDSTs for the rare diseases.

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1. Background

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

Nonetheless, there are a number of challenges surrounding the development of CPGs and CDSTs for rare diseases. One of the most relevant barriers is the lack of high-quality evidence, in which the foremost methodological frameworks like GRADE [1] rely on.

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

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

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

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

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

2. Aim of this document

The aim of this Adaptation and Adoption of CPGs and CDSTs for rare diseases is to provide a framework for assessing and making decisions on adoption or adaptation of existing CPGs and CDSTs. The manual consists on specific criteria provided to critically evaluate CPGs and CDSTs for ERN use and it provides the main activities to do so.

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 that the previously made in the Appraisal stage, and a decision-making phase of the documents covered by these project (CPGs and CDSTs). Throughout the manual, specifications are provided to apply to the different types of documents: Clinical Practice Guidelines; Diagnostic, Monitoring and Therapy Pathways; Evidence-based Protocols; Quality Measures, and Clinical Consensus Statements.

In the case of Evidence-Reports, the assessment would be restricted to the criteria of the 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 would not achieve the minimum required, a *de novo* elaboration 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 manual also offers guidance on the adaptation process, when applicable, for each of the following documents:

- Clinical Practice Guidelines (GPCs)
- Diagnostic, Monitoring and Therapy Pathways
- Evidence-based Protocols
- Quality Measures (QM)

3. Method

The Adaptation and Adoption of CPGs and CDSTs for rare diseases has been based on well-founded and internationally recognised adaptation methodologies and resources, especially 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 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.

GRADE-ADOLOPMENT approach has also been 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 be then used for the judgements by the working group. In addition, evidence and the associated judgements are transparently presented, allowing the adaptation working group to create recommendations appropriate to the ERN context.

4. 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 the CPG or CDST 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 Therapy Pathways, Evidence-based Protocols), or indicators (QM) provided.

The process consists of two basic points: assessment & 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 it 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 & 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 (GPCs)
  - Clinical Consensus Statements
  - Evidence Reports
  - Diagnostic, Monitoring and Therapy Pathways
  - Evidence-based Protocols
  - Quality Measures (QM)

  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 Therapy Pathways and Evidence-based Protocols;
  - Each indicator or set of indicators comprising QM

  The same type of analysis is proposed for Diagnostic, Monitoring and Therapy 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 review in the 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 each 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.

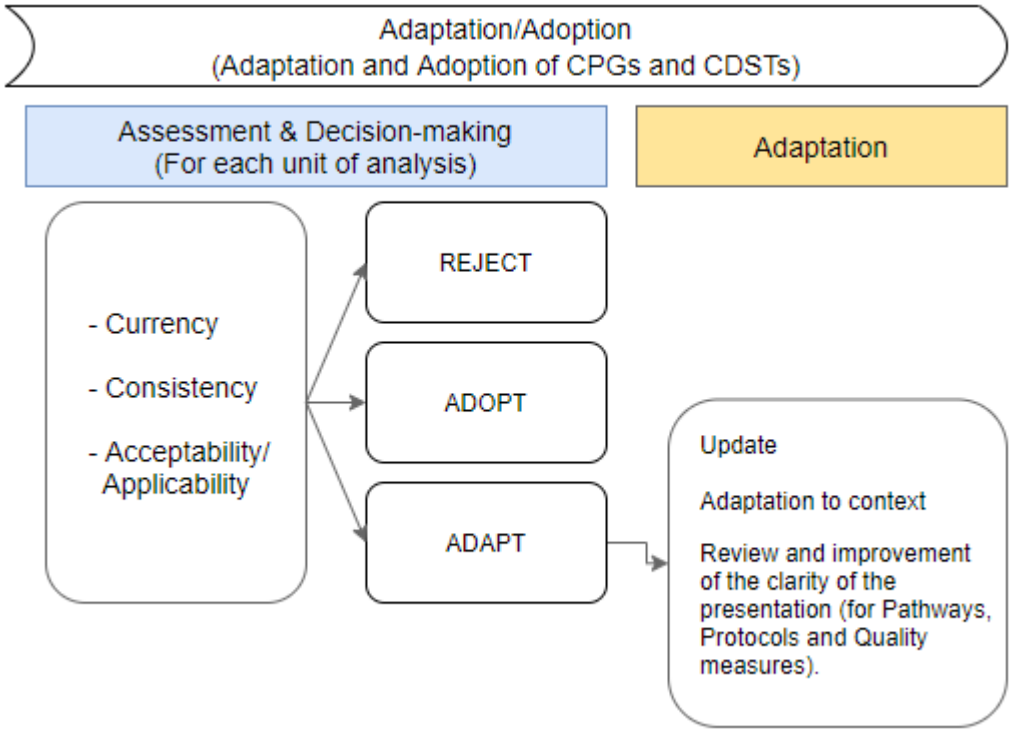
- Adaptation phase

  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 Therapy Pathways, Evidence-based Protocols, and Quality Measures).

With regard to clinical consensus statements, no information on their adaptation is provided. Depending on the extent to which the document is affected, the group should decide whether it can adopt part of the document or a *de novo* elaboration is the 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* elaboration 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 pondering over whether a *de novo* elaboration would be more efficient. The adaptation process should be flexible in order to avoid duplication of efforts.

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

- In the case of more than one CPG are suitable, it is recommended to use ADAPTE Manual and Resource Toolkit (Version 2.0) [2] for its suitability for comparing and building on information from different CPGs.
- In the case of having retrieved more than one suitable CDST, since the content analysis for each document and its comparison usually requires a considerable effort, it is recommended to elaborate a new CDST, as the process will be more productive (see the respective Methodology for the elaboration 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.

5. 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). They shall be multidisciplinary and geographically representative, if possible, in order to make 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 the CDST.

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 include at least a member of the elaboration working group of 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 could be necessary to cover the transition from paediatric to adult healthcare services [6].
    - For diseases revealed at paediatric age, the group should be involved specialists in childhood and adulthood care of the disease, 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 some specialties may be more appropriate.
    - The working group should choose a clinical coordinator from among the experts on the group, with leadership capabilities and experience in evidence-based medicine.
- Patient, and/or carers, and/or patient representatives with personal experience in the topic area

  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 in 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, whereas less than 7 members may threaten representativeness. Throughout the assessment, the working group may deem necessary to consult other expert contributors (e.g., policy makers).

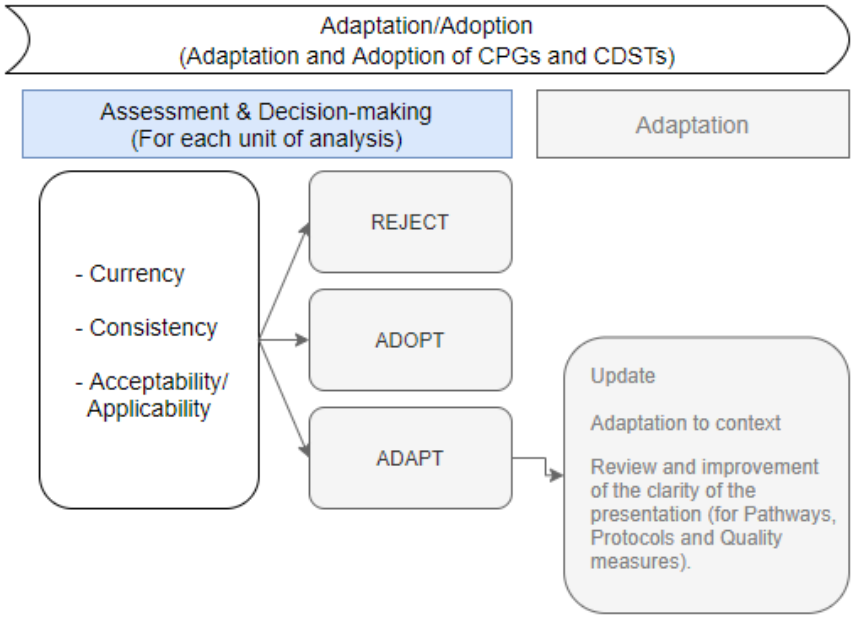
The list of members of the working group is provided (name, discipline/content expertise, institution, geographical location, a description of the member's role and contact details).

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

6. Assessment & Decision-making

Determining whether a recommendation, an activity or procedure is 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 & Decision-making phases



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

The Assessment & Decision-making process for each of the following documents is explain below, taking into consideration their specificities:

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

6.1. Clinical Practice Guidelines

6.1.1. Assessment phase

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

6.1.1.1. Quality appraisal

The 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 the Handbook #2: Appraisal of existing CPGs and CDSTs for rare diseases, the evidence that supports CPGs may evolve rapidly in some fields, so no more than 3 years should generally have passed since the date of the elaboration and/or review or update in order 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 GPC developers that the working group may decide to consult, is 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 probability that new relevant evidence has emerged 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 type of studies (Randomised Control Trials and Systematic Reviews). Only studies that may modify the recommendations, based on the working group judgement (qualitative analyses), will be take into consideration for further analysis. For more information, consult the Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

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

1. 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 of their exclusion are included in the annexes of the CPG.

- The methodology for indicating the quality of studies is described.

2. 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 a 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 metanalysis has been performed, statistical analysis is explained and appropriate.
    - The heterogeneity among studies is explained.
3. 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 strength of recommendations is assigned.

6.1.1.4. Acceptability/applicability

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

- Whether a recommendation or a 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 at identifying the similarities and differences regarding contextual factors in the formulation of recommendations and those present at the ERN context where the CPG would be used. Differences between contexts may introduce uncertainty that justifies a re-evaluation of a recommendation or a set of recommendations (clinical question) in the new context [10].

These factors are the following:

A. 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.

B. 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 if 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 deem relevant to broaden the population, only the recommendations addressed to the initially defined population would be considered.

C. Patient perspectives

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

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

Patients' perspective may have been considered in different approaches when addressing the clinical questions that comprise the CPG. Different methods can be applied to obtain information about patients' perspectives, preferences and needs that enable a more in-depth analysis on the patients' views and preferences, as explained in Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

These methods can be mainly grouped into primary methods, which includes 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 the patients' views and preferences (see Handbook #4: Methodology for the elaboration of CPGs for rare diseases).

The adaptation working group should give careful consideration to the need to incorporate patient's values and preferences into a recommendation. In that case, a subjective judgement should be done by the working group. On one hand, patient and/or carers included in the adaptation working group could offer their particular experiences and insights; on the other hand, health professional experts may contribute based on the patient management experience and their personal relationship with them. Also, the working group may consider to carry out a restrictive literature search which could highlight other type of situations for which they have no information.

D. 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 ERNs context to ensure relevance of a recommendation or a set of recommendations.

Since the implementation of a CPG is local, in case of the recommendation is finally adopted or adapted, the availability of the intervention/resource should be evaluated by a specialised local committee.

E. 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 ERN context, in order to carry out the recommendations proposed by 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 take place in the ERN context.

F. 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 in the application of a recommendation or a set of recommendations in the ERNs framework 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.

Possible organisational barriers to its implementation should be explored especially at this point (e.g., resistance due to available resources, perception of effectiveness, etc.), so that a recommendation or a 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 ERN context with sufficient information about European legislation/regulatory affairs. The ERN framework involves very different countries and health systems, and therefore different policies. So, 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.

G. 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 determinant for a correct implementation across countries and health systems of a particular recommendation or a set of them (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.

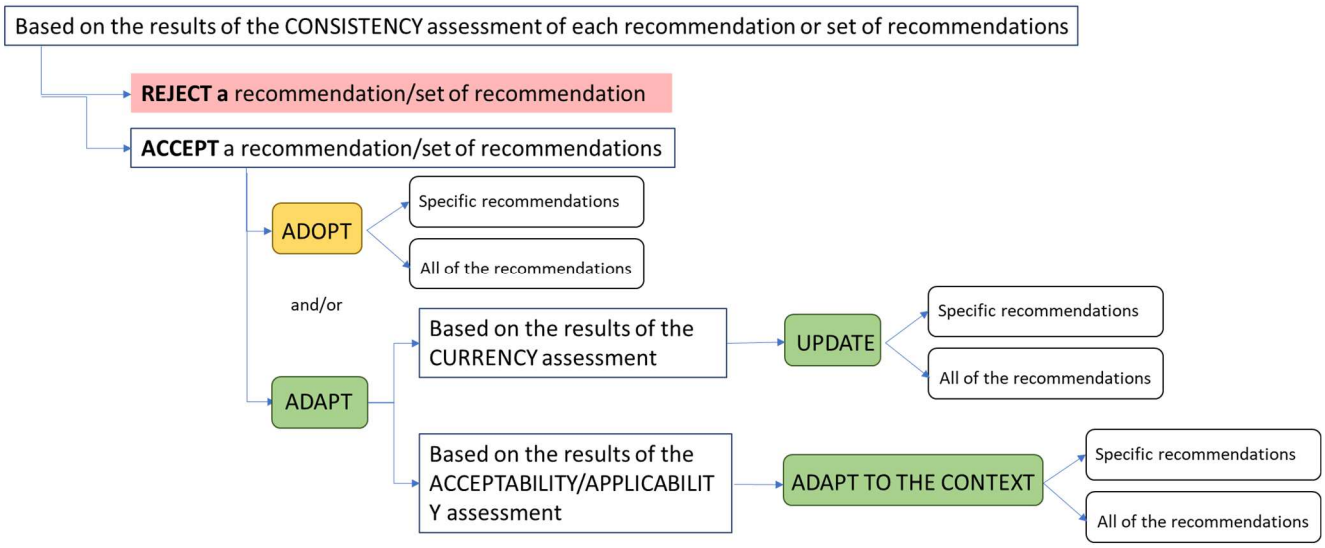
6.1.2. Decision-making phase

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

A decision-making algorithm is proposed below to reach a conclusion about 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:

1. Based on the results of previous assessment of consistency 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.
2. Then, the working group should decide if an accepted recommendation could be **adopted** directly or it needs an **adaptation process**.
   The results of the currency and acceptability/applicability imply different approaches to adapt the CPG. It may also happen that some recommendations can be adopted directly while others undergo an adaptation process. That is why each decision must be made with respect to each recommendation.
    - Based on the currency assessment, if more than 3 years since its elaboration, update or review has passed or new evidence has been detected, and likely this affects the validity of the recommendations, the working group should update the affected recommendations.
    - Based on the acceptability/applicability assessment, and taken into consideration the ERN context, the adaptation to the context should be carried out (based on an adaptation plan).

Figure 3. Decision making algorithm for the acceptance of a recommendation or set of recommendations of an existing GPC 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 a set of recommendations of the clinical consensus statements cannot be directly adopted and implemented in the ERN context, the working group should consider if the rest of the document can be adopted or a *de novo* elaboration 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 done by analysing the recommendations, one by one, with regards to the following aspects:

6.2.1.1. Quality appraisal

The Handbook #2: Appraisal of existing CPGs and CDSTs for rare diseases provides the set of criteria for assessing the methodological quality of Clinical Consensus Statements for rare diseases.

6.2.1.2. Currency

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

The date of elaboration 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 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), clinical experience and interpretation of it, as well as how that interpretation translates into recommendations. The assessment of the consistency of Clinical Consensus Statements includes the following evaluations:

1. 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).
2. The process used to define the initial question or statement is described. The scope and the clinical questions are defined.
3. A systematic approach has been used to search for evidence, and the selection criteria are clearly described:
   3.1. A literature search for guidelines and systematic reviews (include narrative reviews) has been performed. The risk that relevant evidence has been missed is low, in order to recommendations are not the result merely dependent on the subjective judgement of the experts.
      - Relevant databases have been consulted.

- Internet sites were searched.
- A manual search was wade (e.g., journals, websites, legislation, etc.).
- Detailed search strategies are provided.
- Search period is given.

3.2. If necessary, another literature search has been conducted to retrieve other types of studies (randomised controlled trials and observational studies).

3.3. The criteria for selecting the evidence are explicit (inclusion and exclusion criteria).

3.4. 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-establish system (Cochrane evaluation tool for assessing risk of bias [12, 13], CASP [14], FLC 3.0 Critical Appraisal Tools Application [15], GRADE [16], etc.).

3.5. When there was insufficient information available to make an evidence-based recommendation, due to the paucity of the evidence, and the development working group reached a consensus about a statement based on their clinical experienced, it would be identified and differentiated from those based on scientific evidence.

4. 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".
5. 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 a set of recommendations (i.e., a clinical question) offered by the clinical consensus on it, considering:

- Whether a recommendation or a 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).

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

These factors are the following:

A. Worth

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

The working group should assess if the recommendation has considered both health benefits and risks, and if its implementation would be useful for patients in the ERN context. That is, a recommendation should

promote appropriate care, reducing inappropriate or harmful care. Experts should consider as well the issues related to complexity or ease of use.

B. 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 if the population addressed by each recommendation matches the population of interest in the ERN context (age, childhood/adulthood, gender, high-risk population, a particular 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 deem relevant to broaden the population, only the recommendations addressed to the initially defined population would be considered.

C. Patient perspectives

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

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

Ideally patients and/or carers have been included in the development group of the clinical consensus statements (see Handbook #5: Methodology for the elaboration of Clinical Consensus Statements for rare diseases).

D. 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 if the intervention is available in the ERN context (e.g., equipment, diagnostic tests and/or treatments).

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

E. 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 ERN context has the technical expertise required. If not, it should be considered whether specific training is feasible and under what conditions it should be carried out.

F. 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 in the ERNs framework 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 the European level, policy/decision makers and management experts can warn about them. In the subsequent implementation phase, the existence of barriers at local settings that would impede the implementation of the proposed interventions should be considered.

G. 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 a 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 if a recommendation does address this factor correctly in order to accept it or not.

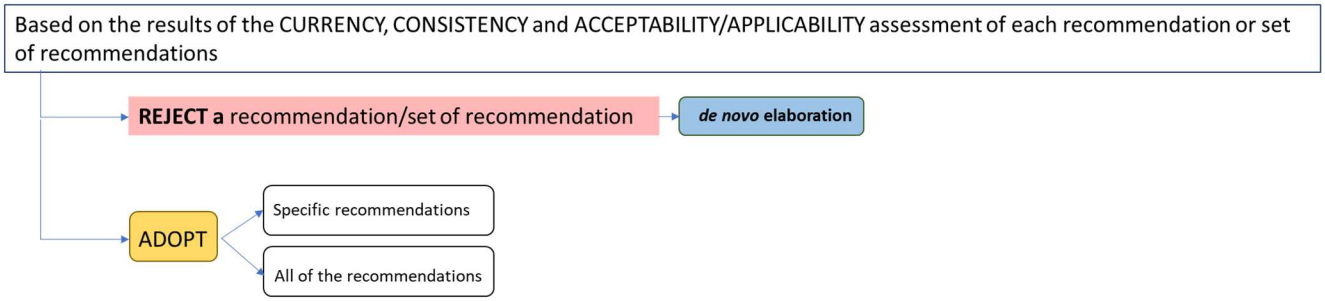
6.2.2. Decision-making phase

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

A decision-making algorithm is proposed below to reach a conclusion about each recommendation or set of recommendations (clinical question). A clinical consensus statement can be adopted totally or partially (figure 4).

1. Based on the results of the previous assessment (currency, consistency and acceptability/applicability) the clinical consensus could be **adopted totally or partially**:
    - If a recommendation or a set of recommendations is not up to date/does not show consistency/is not acceptable or applicable, they should be discarded and not included in the adopted clinical consensus.
    - If a recommendation or a 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 of the 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 by the 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 efficient to elaborate (see Handbook #6: Methodology for the elaboration 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 Therapy Pathways and Evidence-based Protocols

Because of the similarities between diagnostic, monitoring and therapy pathways (pathways) and evidence-based protocols, the same type of analysis is proposed below. Their assessment is focused on activities or procedures as unit of analysis.

Diagnostic, monitoring and therapy pathways and evidence-based protocols are not equivalent documents, but they share a common ground in their approach, as they focused attention on decision nodes (critical or routine) that help clinicians in the decision making. 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 therapy pathways must have been developed with the aim of sequencing and organising 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 in the face of 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 done by analysing them with regards to the following aspects [2]:

6.4.1.1. Quality appraisal

The 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 Therapy Pathways and Evidence-based Protocols for rare diseases.

6.4.1.2. Currency

As mentioned in the Handbook #2: Appraisal of existing CPGs and CDSTs for rare diseases, no more than 3 years should generally have passed since the date of the elaboration and/or review or update of a diagnostic, monitoring and therapy 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 hence modify the proposed activities or procedures, the activities or procedures affected should be updated. The working group could decide if other experts should be consulted.

Additionally, a literature review should be conducted if the diagnostic, monitoring and therapy 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 type of studies, preferably evidence that may come from others CPGs, pathways or evidence-based protocols. Only evidence with higher quality 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 elaboration of Diagnostic, Monitoring and Therapy Pathways for rare diseases in the case of pathways and Handbook #8: Methodology for the elaboration of Evidence-based Protocols for rare diseases for evidence-based protocols.

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

6.4.1.3. Consistency

The activities or procedures proposed in the algorithm or diagram of a diagnostic, monitoring and therapy 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 into the proposed activities and procedures should be reviewed.

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

1. 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 manual search was wade (e.g., journals, websites, legislation, etc.).
    - Detailed search strategies are provided.
    - Search period is given.
2. The criteria for selecting the CPGs and systematic reviews are explicit (inclusion and exclusion criteria).
3. 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-establish system (Cochrane evaluation tool for assessing risk of bias [12, 13], CASP [14], FLC 3.0 Critical Appraisal Tools Application [15], GRADE [16], etc.).
4. 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 hand 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 preestablish system (Cochrane evaluation tool for assessing risk of bias [12, 13], CASP [14], FLC 3.0 Critical Appraisal Tools Application [15], GRADE [16], etc.).
5. 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.
6. Activities or procedures are listed in chronological order.
7. The algorithm, diagram or other supporting tools reflects the activities or procedures.
    - The algorithm, diagram or supporting tool provided is consistent with the evidence review.
8. Indicators have been established:
    - Indicators are derived from activities or procedures.
    - For each objective of the diagnostic, monitoring and therapy pathway/evidence-based protocol must be proposed at least one indicator.

6.4.1.4. Acceptability/applicability

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

- Whether an activity or a procedure should put it into practice (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. Possibly, in some cases this would require a consultation with management representatives and experienced experts in quality committees, as these profiles may not have been included into the working group.

Since the implementation of diagnostic, monitoring and therapy pathways and evidence-based protocols is local, it should be kept in mind that a further analysis regarding contextual factors will be necessary when the adopted or adapted document is implemented at 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:

A. Worth

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

The balance between risks and benefits to patients should be considered by the working group 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.

B. 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 if 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 consider as well under what conditions 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 population identified 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 deem relevant to broaden the population, only the activity or procedure addressed to the initially defined population would be considered.

C. Patient perspectives

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

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

Patients' perspective 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 if patients' perspective has been considered. in addition, patients may also have been involved as developers in the elaboration working group of the diagnostic, monitoring and therapy 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.

D. 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 it could be in near future (e.g., equipment, diagnostic tests and/or treatments).

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

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

F. 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 possible barriers in the application of an activity or procedure in the ERNs framework. If the adaptation working group is not aware of this information, management experts should be consulted, in order to understand better the situation.

It is very relevant 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.), so that it is accepted by health professionals.

At this point, policy makers and management experts can advise the working group on European legislation and regulatory affairs. As stated above, ERN framework involves very different countries and health systems, and therefore different policies. So, 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 on this assessment (see Handbook #12: Implementation and Evaluation of the Uptake of CPGs and CDSTs for rare diseases).

G. 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 a correct implementation of a diagnostic, monitoring and therapy pathway/evidence-based protocol across Europe, geographical, epidemiological, socio-cultural, socio-economic and ethical differences may be determinant. Each activity or procedure should be assessed. The working group should determine if is culturally appropriate and represent the norms and values of specific groups, communities, or populations, if needed, to ensure relevance for ERN 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 if there is a need to clarify or refine them.

6.4.2. Decision-making phase

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

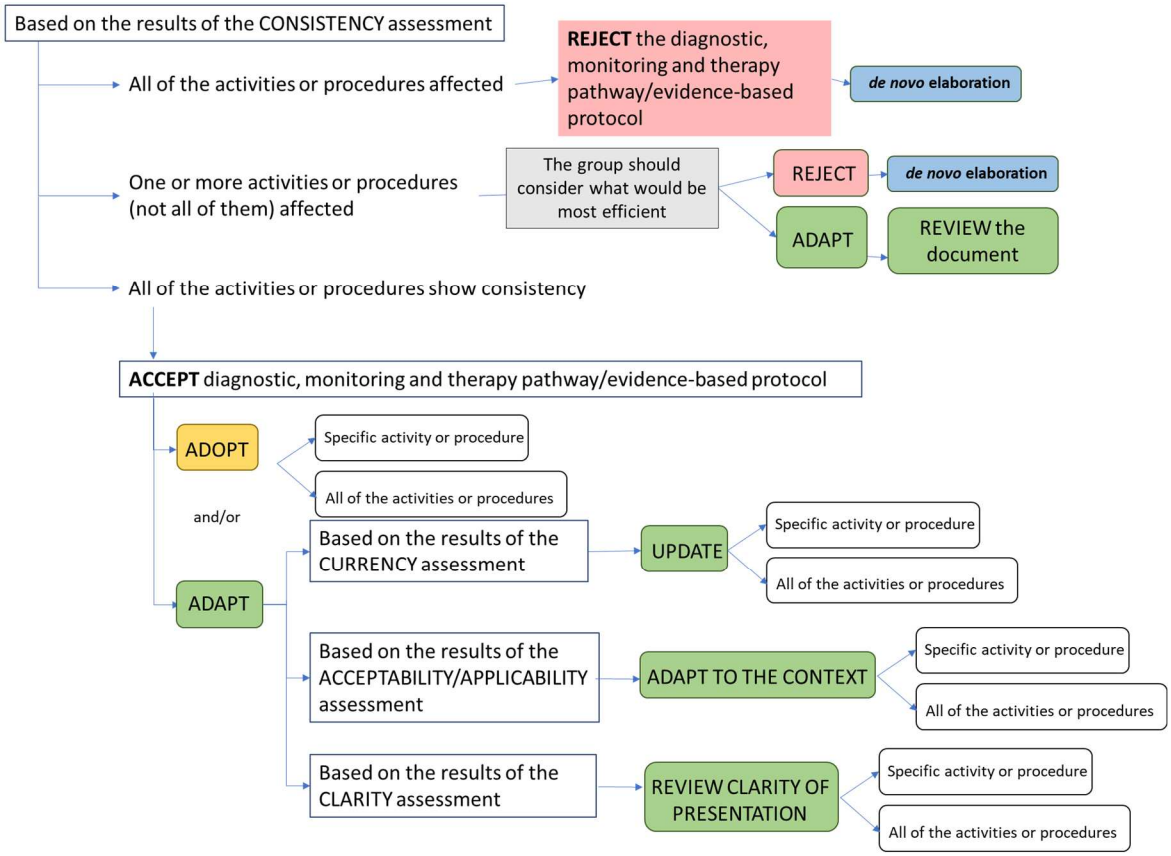
A decision-making algorithm is proposed below to reach a conclusion to adopt or adapt a diagnostic, monitoring and therapy pathway/evidence-based protocol (figure 5).

1. Based on the results of previous assessment of consistency:
   1.1. If all of the activities or procedures do not show consistency, the diagnostic, monitoring and therapy pathway/evidence-based protocol should be **discarded**.
   1.2. If one or more activities or procedures does not show consistency, the acceptance of the diagnostic, monitoring and therapy 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 therapy pathway/evidence-based protocol or a ***de* novo elaboration** process will be efficient. If the group prefers to adapt the document, currency, acceptability/applicability and clarity of presentation factors will be taken into consideration.
   1.3. If all of the activities or procedures show consistency, the whole diagnostic, monitoring and therapy pathway/evidence-based protocol would be accepted.
   Then, the working group should decide if an accepted evidence-based protocol/ diagnostic, monitoring and therapy pathway could be **adopted** directly or it must follow an **adaptation process**.

   The results of the currency and acceptability/applicability imply different approaches to adapt the diagnostic, monitoring and therapy pathway/evidence-based protocol. It may also happen that some recommendations can be adopted directly while others undergo an adaptation process.

   - Based on the currency assessment, if more than 3 years since the elaboration, update or review of the document has passed or new evidence has been detected, and likely this affects the validity of the activities or procedures, the working group should update them.
   - Based on the acceptability/applicability assessment, and taken 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 into 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 Therapy Pathway or an Evidence-based Protocol for rare diseases



6.5. Quality measures

6.5.1. Assessment phase

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

6.5.1.1. Quality appraisal

The Handbook #2: Appraisal of existing CPGs and CDSTs for rare diseases provides the set of criteria for assessing the methodological quality of QM for rare diseases.

6.5.1.2. Currency

In the case of QM tools, there is no specific period in which to review or update. Nevertheless, indicators are elements that rely on data generated in clinical practice or reported by patients. For this reason, QM tools or set 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]. There is a possibility that indicators are not in current use, in which case it would be desirable that they have undergone a review process on 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 the 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 have been outdated [22]. This review will not be extensive, i.e., it will be limited to one or two of the main databases and specific type 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 measures the rate of patients following a given treatment is to be adapted or adopted. Those 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 elaboration of Quality Measures for rare diseases.

Additionally, inclusion/exclusion criteria of QM tools are usually 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 that defines its population with diagnosis codes, so the crosswalk 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 that the working group may decide to consult, is key in 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 foundation for the QM tool in the literature. The evidence supporting every indicator must cover the following aspects to ensure validity and reliability:

- QM tools and its 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 provision of diagnostic tests in a timely manner 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? For ensuring 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:

1. A systematic literature search has been performed. The risk that relevant evidence has been missed is low:
    - The research questions were focus 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 made (e.g., journals, websites, legislation, etc.).
2. The criteria for selecting the evidence are explicit (inclusion and exclusion criteria) and coinciding 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.
3. The critical appraisal of the evidence and its interpretation should be properly described and performed following a pre-established system (Cochrane evaluation tool for assessing risk of bias [12, 13], CASP [14], FLC 3.0 Critical Appraisal Tools Application [15], GRADE [16], etc.).
4. Some other formal process could be employed by which the measure has been accepted as a valid marker for quality, such as review by an expert panel. In that case, dynamics of the panel must be clearly established. For example, it is common to employ 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, where they will be used. Each indicator or set of indicators should be assessed. It 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 QM tool or a 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, as long as the measurement artefact and the methodological characteristics are not modified, should produce variability. The assessment of acceptability and applicability aims at identifying the similarities and differences regarding contextual factors implicit in the original construction of a QM tool and those present at the ERN context where that QM tool or set of indicators is to be implemented [23].

These factors are the following:

A. 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 by 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 a set of indicators will be useful in the context of ERNs. Preferably, an indicator should address those areas in which there is a clear gap between the actual and potential levels of information. Indicators are to be adopted or adapted in those areas that can be influenced by improvements in the quality of care monitoring.

B. 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 extend the concept of population. The working group should discuss if the subject of measurement addressed by original indicator or set of indicators matches the subject of interest which would be targeted in the local settings. Inclusion and exclusion criteria of 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, subject 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 particular unit within the hospital).

- Process indicators may be focused 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 especially 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, it can be decided to keep the inclusion criteria unchanged or make adjustments and refinements. 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 consider an expanded population (young adults up to 20 years old), according to the characteristics of the condition or operation of an specific hospital unit.

C. 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 an indicator of a QM tool, have given their feedback about

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

D. 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 of ERNs, given their nature. The working group should make explicit the needs in terms of technological resources and information systems that are required to put an indicator or a 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, that is, if data is available at individual patient level or reports are produced with aggregate results, how often the databases are refreshed, etc.

E. 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 ERN 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 take place in the ERN context.

F. 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, possible barriers to the implementation of a QM tool may be found (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.

In order to carry out this, the working group may access to experts on regulatory affairs and policy makers to detect and analyse applicability in the ERN context with multiple countries and different healthcare systems involved. For example, it should be noted that the existence of constraints in legislation (e.g. those in relation to confidentiality, data protection and cybersecurity) that would impede the implementation of the original QM tool.

G. 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 determinant for a correct implementation across countries and health systems of an indicator or a set of indicators, which comprise a QM tool or measure 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, there may be reluctance to declare particular conditions or habits by patients or their families/carers.

6.5.1.5. Clarity of presentation

QM tools or indicators are mathematical elements, sometimes complex. It is important that the artefacts used are specified in an accessible and concise manner. In the same way, the reports that are extracted from their monitoring must be understandable and informative enough (accompanied by legends, explanations of the calculations made, etc.), with a limited number of variables, so that they do not cause an information overload to its users. The working group shall consider if there is a need to clarify or refine them.

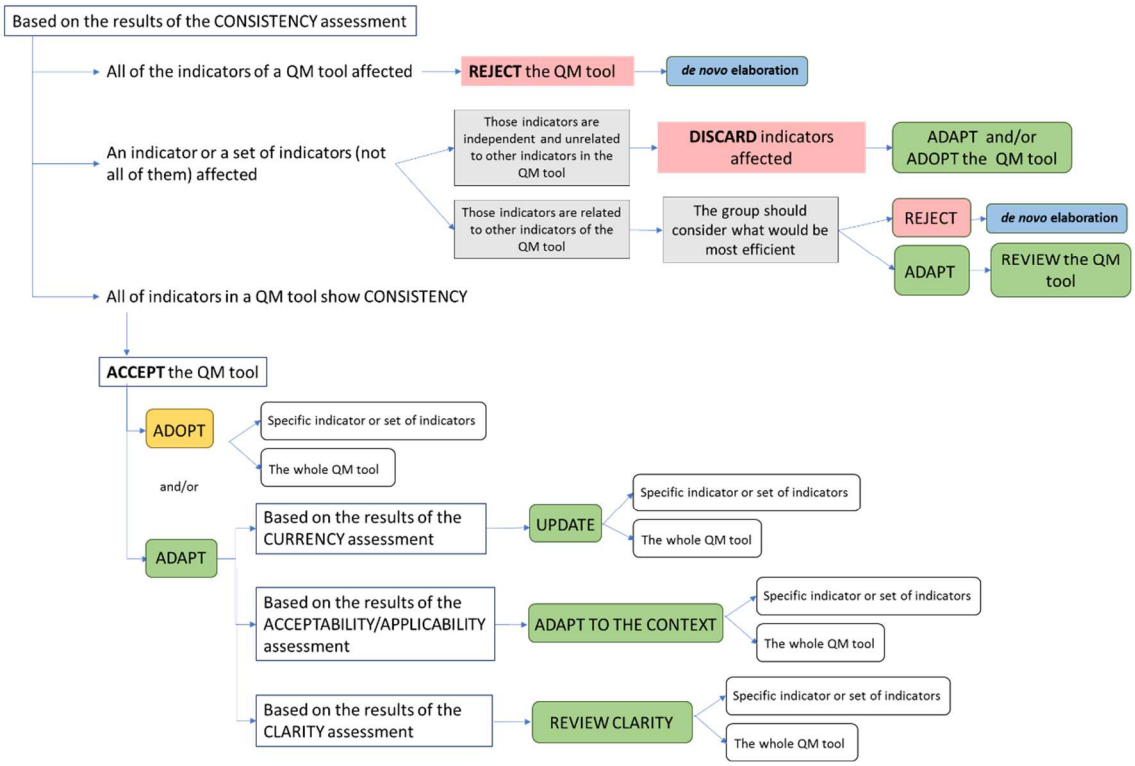
6.5.2. Decision-making phase

Once the assessment has been completed, the adaptation working group should consider the results and obtain a conclusion for each indicator part of a QM tool. The decision for each indicator should be reached by consensus and be well documented, so that it can be determined the impact of the analysis and the feasibility of its adoption or adaptation.

A decision-making algorithm is proposed below to reach a conclusion about creating an adopted or adapted QM tool. Decision can affect all the indicators that make up 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):

1. Based on the results of 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 a set of indicators do 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 be also considered for a single indicator, as long as it independent.
        - If the indicators affected by the lack of consistency are related to other indicators of 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 a ***de novo* elaboration** 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.
2. Then, the working group should decide if a QM tool could be **adopted** directly or it requires an **adaptation**. The results of the currency and acceptability/applicability imply different approaches to adapt the QM tool. It may also happen that some indicators can be adopted directly while others undergo an adaptation process.
    - Based on the currency assessment, if the working group detects important advances in the 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 ERN 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 to make changes to make it more understandable or easy for users.

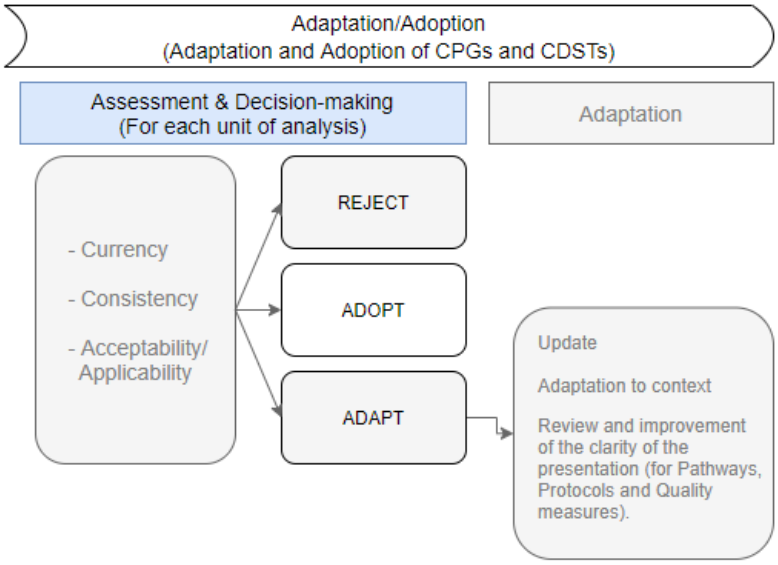
Figure 6. Decision making algorithm for the acceptance of an indicator or set of indicators of an existing QM tool for rare diseases



7. 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).

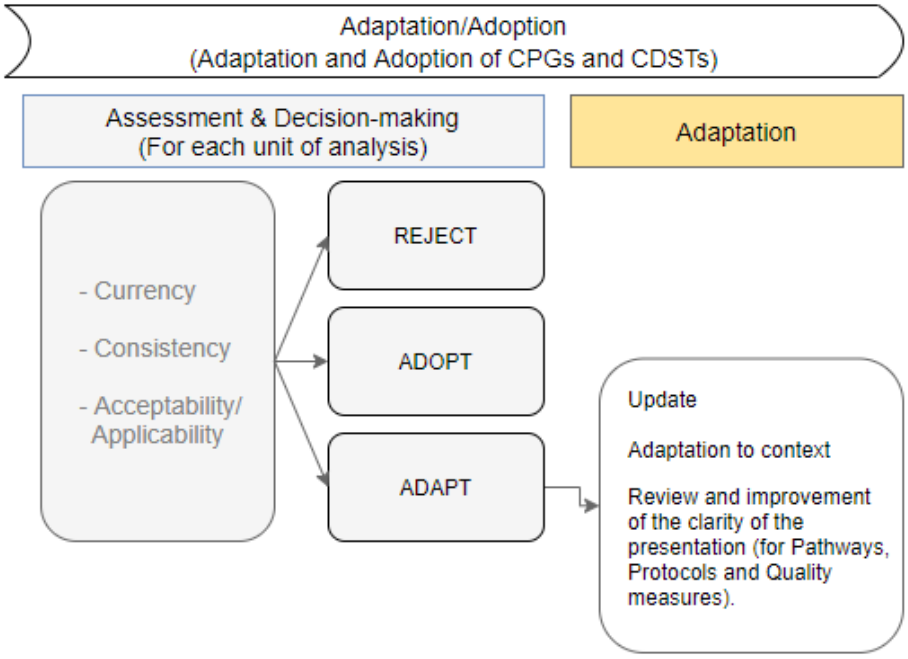
Figure 7. Adoption phase



8. Adaptation

If the working group considers that a recommendation, an activity or procedure, an indicator or a set of them need to undergo an adaptation process (figure 8), it should be decided to what extent it should be reviewed. When modifying an existing CPG or CDST, caution should always be taken not to modifying recommendations to the extent that they are 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 being transparent, rigorous and reproducible. 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 therapy pathways) or indicators (QM) (see Annex 2).

It is important to highlight that:

1. The working group should describe in detail the specific discordances that have been identified in the previous assessment and which have led to the decision to adapt specific or all the recommendations, activities, procedures or indicators: currency; consistency; acceptability/applicability in 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 describe what the concerns are, their relevance and the new approach required.
2. The adaptation working group, after having conducted the previous assessment of each recommendation (CPG), activity or procedure (evidence-based protocols, diagnostic, monitoring and therapy pathways) or indicator (QM), should consider if more experts should be included in the adaptation group (e.g., medical specialties, surgical specialties, physical therapists, patients and/or carers, etc.) to continue to their adaptation.
3. 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 the Handbook #2: Appraisal of existing CPGs and CDSTs for rare diseases.

4. 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].
5. At the end of the adaptation process, an external review should be carried out. Health professionals, managers, policy-makers, and patients and/or carers should be consulted.
6. The adaptation plan shall be annexed to the adapted CPG or CDST.
7. 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 the CPG or CDST currency, the working group should update the content of the document. The corresponding section of the Handbooks #4-11: Methodology for the elaboration of CPGs and CDSTs.will be followed.

8.1.1. Clinical Practice Guidelines

Below is an overview of the steps involved in the updating process of a CPG. For more information, see chapter 11. Updating the CPG of Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

1. 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 elaboration of CPGs for rare diseases):
   a. Clinical questions to be reviewed.
   b. Valid clinical questions
   c. New clinical questions, which will be framed, according to the PICO format (Patient/Intervention/Comparison/Outcome) in order to help define the question.
2. Relevant evidence identified in the assessment of the 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 some clinical questions. In such a case, a restrictive literature search will be performed (see chapter 11.3. Identification of new evidence of Handbook #4: Methodology for the elaboration of CPGs for rare diseases).
3. The evidence will be analysed and synthesised (see Appraisal and synthesis of the scientific evidence of Handbook #4: Methodology for the elaboration of CPGs for rare diseases). The evidence will be summarised in evidence tables.
   a. 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.
   b. When the methodological approach was other than GRADE approach, 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.
4. 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 in the ERN framework) ((see Appraisal and synthesis of the scientific evidence of Handbook #4: Methodology for the elaboration of CPGs for rare diseases). The EtD frameworks includes the summary of evidence about [24]:

a. Balance of desirable and undesirable consequences.
b. Quality of evidence
c. Resource use
d. Patients' perspectives must be considered.
e. Cost effectiveness ratio (economic model)
f. Impact on equity

8.1.2. Diagnostic, Monitoring and Therapy Pathways and Evidence-based Protocols

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

1. 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 therapy pathway/evidence-based protocol should be updated. Development of *de novo* activities or procedures may involve formulating new questions. The group will decide:
    a. Activities or procedures to be reviewed. They will be reflected in clinical questions.
    b. Valid activities or procedures.
    c. New activities or procedures to be incorporated to 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.

2. Relevant evidence identified in the assessment of the 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 some clinical questions or some particular aspects (e.g., patients' values and preferences, economic analysis relevant to the ERN settings). A restrictive literature search is suggested.
3. The evidence will be analysed and synthesised. The evidence will be summarised in evidence tables (see Handbook #7: Methodology for the elaboration of Diagnostic, Monitoring and Therapy Pathways for rare diseases or Handbook #8: Methodology for the elaboration of Evidence-based Protocols for rare diseases).
    a. When the method used to develop the original diagnostic, monitoring and therapy 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.
    b. When the methodological approach was other than GRADE approach, 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.
4. 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 in the ERN framework) (see Handbook #7: Methodology for the elaboration of Diagnostic, Monitoring and Therapy Pathways for rare diseases or Handbook #8: Methodology for the elaboration of Evidence-based Protocols for rare diseases). The EtD frameworks includes the summary of evidence about [24]:
    a. Balance of desirable and undesirable consequences.
    b. Quality of evidence
    c. Resource use
    d. Patients' perspectives must be considered.
    e. Cost effectiveness ratio (economic model)
    f. Impact on equity
5. Following the updating of the activities and procedures, the working group shall identify a list of specific, quantifiable evaluation criteria or indicators derived from the new activities or procedures set out in the diagnostic, monitoring and therapy pathway/evidence-based protocol, which, in addition to the activities or procedures maintained and non-reviewed, will enable the achievement of the objectives in the context of use.

8.1.3. Quality Measures

Updating an indicator from a QM tool can be due to different, for each type the approach will be specific.

- If the case is the identification of new healthcare processes caused by the appearance of new evidence. The objective of the update will be to reconfigure the affected indicators that are part of a QM so that they continue to measure what is expected.
    - Only relevant evidence identified in the assessment of the 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-stablished system.
    - According to the new evidence obtained and analysed, the working group may decide:

        a) Update the construction of the indicator to capture new care procedures that previously developed differently. For example, if there is evidence of the use of a new surgical approach, process indicators previously designed may not collect information properly.

        b) Modify the inclusion/exclusion criteria of the affected indicators according to the new evidence. For example, including new drug treatment codes that have been shown to be effective in process indicators related to a condition.

- When QM tool update is due to relevant updates in the composition of information systems or codification from the internationally standardised definitions (ICD, ICHI, etc.), changes in the inclusion/exclusion criteria to adapt the indicator to the new established definitions should be done.
- 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 and a proactive process of modification with the aim to suit the specific characteristics and needs and enhance intervention acceptability.

According to the issues identified when assessing acceptability/applicability (population, patients' perspective, availability of resources or the intervention proposed, availability of the expertise required, existence of barriers, cultural issues, worthiness), the working group should consider whether it is possible to adapt the recommendations, activities or procedures in order to cover the weaknesses identified and to address clinical questions in the context of the ERNs.

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

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

8.2.1. Clinical Practice Guidelines

1. The working group will decide which of the recommendations addressed by the CPG should be reviewed and adapted to the ERN context.
2. These gaps will be reflected the adaptation plan.
3. 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 a set of them (e.g., clarify that a training to the 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 some clinical questions. In such a case, a restrictive literature search will be performed (see chapter 11.3. Identification of new evidence of Handbook #4: Methodology for the elaboration of CPGs for rare diseases).
   a. When the method used to develop the original CPG was GRADE, this information will be reflected in EtD frameworks.
   b. When the methodological approach was other than GRADE, a qualitative assessment will be made by the working group, reaching consensus on how to express it in the recommendation.

8.2.2. Diagnostic, Monitoring and Therapy Pathways and Evidence-based Protocols

Because of the similarities between diagnostic, monitoring and therapy 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 of them.

1. The working group will decide which of the activities or procedures addressed by the diagnostic, monitoring and therapy pathway/evidence-based protocol should be reviewed and adapted to the ERN context.
2. These necessities will be reflected in the adaptation plan.
3. Relevant information, opinions, experiences and/or evidence identified in the assessment of acceptability and applicability in the ERN 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 some clinical questions to the ERN context (e.g., patients' values and preferences, economic analysis relevant to the ERN settings). In that case, restrictive literature searches are recommended.
   a. When the method used to develop the original diagnostic, monitoring and therapy pathway/evidence-based protocol was GRADE, this information will be reflected in EtD frameworks.
   b. When the methodological approach was other than GRADE, a qualitative assessment will be made by the working group, reaching consensus on how to express it in the activity or procedure.
4. After this review, the working group shall identify a list of specific, quantifiable evaluation criteria or indicators that are derived from the activities or procedures set out in the adapted diagnostic, monitoring and therapy 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 part of a QM tool should be reviewed an adapted to the ERN 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 ERN 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 where 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, similar definitions must be found in order to adapt the QM tool.

8.3. Review and improvement of the clarity of the presentation

With regard to clarity of the presentation of a diagnostic, monitoring and therapy 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 QM, working group should review and analyse whether it is necessary to amend the presentation of the results, use legends or provide more information about the assumptions and calculations made.

9. Edition of the final adopted or adapted document

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

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

Either the document has been adopted or adapted, the format and style of the CPG or CDST should be considered. The final documents should be easily accessible to end-users, and it is desirable that a patient version is provided. In addition, the final version should include a plan for a future updating.

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

10. Abbreviations

CPG	Clinical Practice Guideline
CDST	Clinical Descision Support Tool
ERN	European Reference Network
EtD	Evidence to Decision
EU	European Union
GRADE	Grading of Recommendations Assessment, development and Evaluation
IACS	Instituto Aragonés de Ciencias de la Salud (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
RCT	Randomised Controlled Trial
QM	Quality Measures

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Annex 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	Has it been more than 3 years since the date of elaboration/review/update of the document? Are you aware of any new evidence relevant which could affect to a recommendation or a set of them? 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? How the evidence has been summarised and interpreted is reported? Is the interpretation of the evidence consistent with the formulation of recommendations?
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 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 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	Has it been more than 3 years since the date of elaboration/review/update of the document? Are you aware of any new evidence relevant which could affect to a recommendation or a set of them? 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 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 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 Therapy Pathway	
Name of the document	
ERN	
Working group	
Assessment Phase	
	Notes (recommendation, clinical question, section affected, proposed changes, etc.)
Currency	Has it been more than 3 years since the date of elaboration/review/update of the document? Are you aware of any new evidence relevant which could affect to 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 Therapy Pathway?
Consistency	Has the evidence been generated via a systematic review? Is the selected evidence reported? How the evidence has been summarised and interpreted is reported? Does the algorithm, diagram or supporting tool reflect properly the activities or procedures? Have indicators been stablished?
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 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 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 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 to be wording reviewed? Is the algorithm, diagram or supporting tool in 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	Has it been more than 3 years since the date of elaboration/review/update of the document? Are you aware of any new evidence relevant which could affect to 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? How the evidence has been summarised and interpreted is reported? Does the algorithm, diagram or supporting tool reflect properly the activities or procedures? Have indicators been stablished?
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 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 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 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 to be wording reviewed? Is the algorithm, diagram or supporting tool in 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 have been pilot tested within the last 3 years? Are you aware of any new evidence relevant which could affect to an indicator or a set of them? If so, please provide a reference for this new evidence. Are you aware of any o relevant advance in the composition of the 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 clearly documented scientific foundation for the QM tool been provided? Face validity: Does the indicator measure what it is intended to measure? Has the methodology and interpretation of the mathematical instruments been discussed properly? Reliability: Has the population and setting the QM tool 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 there 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 where it is to be implemented (acceptable and applicable)?
Decision-making Phase	
Based on the results of previous assessment of consistency 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 2. Checklist of Adapted Documents Content

Clinical Practice Guidelines

	Yes/No
Overview material: o Structured abstract o Date of adaptation o Status (original, adapted, revised, updated) o Print and electronic sources	
List of the working group members and 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 o Risks and benefits associated with the recommendations o Specific circumstances under which to perform the recommendation o Strength of recommendation	
Supporting evidence and information for the recommendations o Rationale behind the recommendations o Presentation of additional evidence o 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 o Experts who participate as reviewers o What process was followed o Discussion of feedback o 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: o Literature search and retrieval including the list of documents identified and whether they were included or excluded o Quality assessment including which assessments were undertaken and in which order, and a summary of results for each assessment o Decision process followed by working group o Results and decisions of each evaluation	

Diagnostic, Monitoring and Therapy Pathways

	Yes/No
Overview material: o Structured abstract o Date of adaptation o Status (original, adapted, revised, updated) o Print and electronic sources	
List of the working group members and 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 Therapy Pathway	
Description of the target patients	
Methodology approach	
Definitions of the clinical questions	
Recommendations o Risks and benefits associated with the recommendations o Specific circumstances under which to perform the recommendation o Strength of recommendation	
Supporting evidence and information for the recommendations o Rationale behind the recommendations o Presentation of additional evidence o How and why existing recommendations were modified	
Definition of the Diagnostic, Monitoring and Therapy Pathway (linked to evidence-based recommendations or consensus statements and listed in chronological order) o Safety issues o Entry, exit and marginal limits o Professionals involved o Activities and good practices o Specific capabilities o Support units o 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: o Structured abstract o Date of adaptation o Status (original, adapted, revised, updated) o Print and electronic sources	
List of the working group members and 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: o Literature search and retrieval including the list of documents identified and whether they were included or excluded o Quality assessment including which assessments were undertaken and in which order, and a summary of results for each assessment o Decision process followed by the working group o Results and decisions of each evaluation	

Quality Measures

	Yes/No
Overview material: o Structured abstract o Date of adaptation o Status (original, adapted, revised, updated) o Print and electronic sources	
List of the working group members and 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 o Description o Rationale o Evidence for rationale	
Evidence supporting the QM o Information Supporting the need for the QM o Extent of Measure Testing	
State of use of the QM	
Application of the QM in the original use o Setting o Professionals involved o Acceptable minimum sample size o Target population (age, gender, condition, etc.)	
Data collection for the QM o Computation of the QM and its indicators o Inclusion/exclusion criteria for every indicator o Risk adjustment variables o Data sources o Interpretation of scores	
External review and consultation process o Experts who participate as reviewers o Process followed o Discussion of feedback o Feedback incorporated into the final QM	
References	
Glossary (for unfamiliar terms)	
Acknowledgement of original indicator developers and permission granted	
Annex describing the adaptation process: o 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	