European Reference Networks | ERN GUIDELINES

D-B.1

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Report on the Literature Review and Expert Consultation

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Short Description:

Analysis of the state of the art on methodologies for CPGs and CDSTs for rare diseases, involving a systematic search in databases and a manual search in relevant organizations' and projects' websites.

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ABBREVIATIONS

ERNs	European Reference Networks
EU	European Union
EC	European Commission
CPGs	Clinical Practice Guidelines
CDSTs	Clinical Decision Support Tools
WP	Work package
PICO	Patient/Intervention problem, intervention, comparator, outcome
AQuAS	Agency for Health Quality and Assessment of Catalonia
IACS	Aragon Health Sciences Institute
FPS-AETSA	Health Technology Assessment Area of Fundación Pública Andaluza Progreso y Salud

01.

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 CDSTs and CPGs in the ERNs.

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

For this reason, Work Package B (WPB) of TENDER NºSANTE/2018/B3/030 pursues the development of methodologies for the prioritization, 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 prioritization, appraisal, adaptation, development and implementation of CPGs and CDSTs for rare diseases. This report summarizes the work undertaken on the first phase of WPB of TENDER NºSANTE/2018/B3/030.

02.

OBJECTIVE

The objective of this report is to provide information on how different organizations, methodologists, clinicians and other stakeholders in the field of RD address the development and use of Clinical Practices Guidelines (CPGs) and Clinical Decision Support Tools (CDSTs) for rare, low-prevalence and complex diseases (hereafter rare diseases (RD)).

For this purpose, an exhaustive analysis of the state of the art on methodologies for the prioritization, appraisal, adaptation, development and implementation of CPGs and CDSTs for rare diseases has been performed.

03.

METHODS

3.1 | Systematic Literature Review

A systematic literature search and review was performed with no time limit until January 2020, in seven databases, namely: PubMed, Embase, TRIP database, Web of Science, CINAHL, PsycINFO and CRD and Google Scholar. Only documents in English, French and Spanish were considered. See Annex 1 Search Strategy.

The studies were selected by means of a peer review involving four independent evaluators, based on a series of pre-defined inclusion and exclusion criteria that can be consulted in subsection 3.3 of this document. The screening was done in pairs, i.e., one pair of evaluators screened half of the retrieved documents (after duplicates where removed) and the other pair screened the remaining half.

In case of disagreement within the pair of evaluators, the discussion was extended to the other pair of evaluators plus another methodologist of the team, and the disagreement was solved by voting. The data were extracted using a form and summarised in evidence tables, included in the Results section of this report.

3.2 | Manual Literature Review

Since the subject of this search is an emerging area of knowledge, the existence of a considerable amount of relevant information outside the databases which can be consulted in a structured and systematic way, is to be expected. Thus, a manual search was conducted on the web pages of organizations and projects relevant to the matter of methodologies for CPGs and CDSTs for RD. Only documents in English, French and Spanish were considered. See Annex 2 List of organizations and projects reviewed.

The identification of organisations and projects started with those previously identified during the preparation of the proposal (See Annex 7.2) and continued through snowball technique until no more relevant organizations and projects were identified, thus the search was considered to have reached a saturation point. The snowball technique consisted on the revision of the summaries and documents available in the web pages with the aim of identifying potentially relevant information as well as other relevant projects and organisations.

The search was performed between December 2019 and January 2020. Three independent evaluators made the appraisal of the findings. Each evaluator was assigned an initial group of web organisations and projects from the list identified during the preparation of the proposal to review. Each of the evaluators reviewed the contents available of those organisations and projects and of

those identified therein through snowball technique and shared the preliminary results with the team, to reach common agreement.

The data were extracted using a form and summarised in evidence tables, included in the Results section of this report.

3.3 | Inclusion and Exclusion Criteria

For the screening of the documents found, the inclusion and exclusion criteria were predefined as follows:

Inclusion criteria:

- ✓ Methodological documents that provide a specific approach on how to perform the prioritization, appraisal, adaptation, development and implementation of CPGs and/or CDSTs for rare diseases.
- ✓ Documents that provide specific information on how to address the prioritization, appraisal, adaptation, development and implementation of CPGs and/or CDSTs for rare diseases.

Exclusion criteria:

- ✓ CPGs or CDSTs developed for specific conditions, e.g. a clinical practice guideline on a specific condition.

3.4 | Data Extraction, Synthesis and Classification

The extracted information was summarized descriptively and analysed. Evidence tables were produced by each couple in the case of the systematic literature review and by each evaluator in the case of manual literature review. In both cases, they were subsequently shared with the team. The following areas of analysis were specified:

- ✓ Type of document (CPGs or other type of CDSTs) to which the contribution refers or is applicable.
- ✓ Step in the development process of the CPGs or CDSTs for which is provided methodological information.
- ✓ Information on the specific contribution to the methodology for CPGs and CDSTs.

04.

RESULTS

The systematic literature search in databases identified 4,844 documents. Of these, 599 were duplicated within the databases and 3 had already been identified in the manual search.

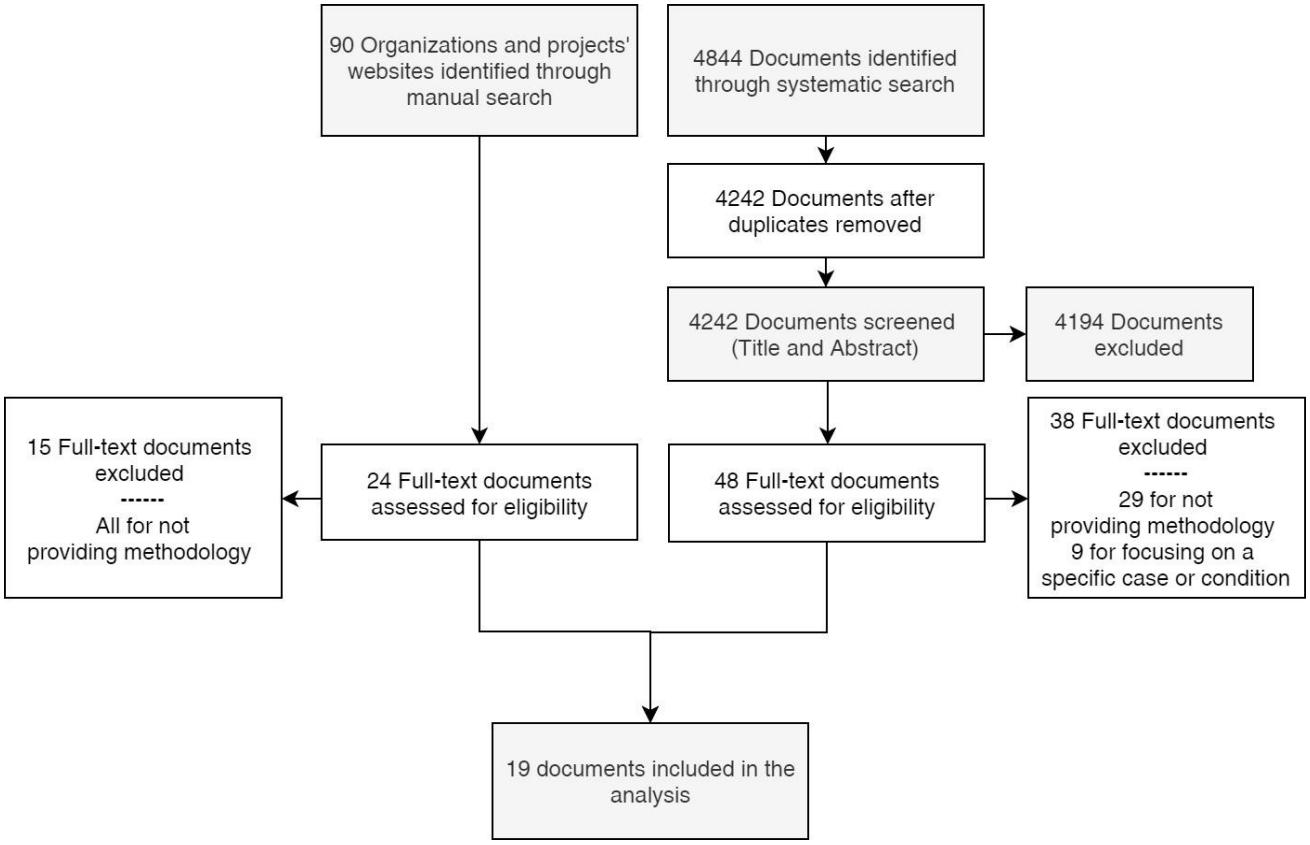
After the first screening (title and abstract), 48 documents were considered to be potentially relevant and eligible for a full text screening. After the full text screening, 38 documents were discarded: 29 for not providing methodology or specific information for methodological development for rare diseases and 9 for focusing on a specific case or condition, thus not providing information that could be translated to a general methodological approach. Ten documents were considered relevant after full text screening.

The manual search in organisations and projects' webpages identified 90 webpages. Given the heterogeneous formats of the texts reviewed in this first screening (some of them being the text in the webpage) the number of webpages reviewed are deemed more informative than the number of texts analysed by the research team.

After the first screening (summaries and abstracts), 24 documents were considered to be potentially relevant and eligible for a full text screening. After the second screening (full text), 15 documents were discarded for not providing methodology or specific information for methodological development for rare diseases. Nine documents were considered relevant after full text screening.

It should be noted that a document written in German (2), was identified through the manual search as potentially relevant after the analysis of a summary written in English (3). The document is a systematic review for existing approaches to handle evidence on rare diseases for the development of CPGs. The content of the executive summary indicates it could provide relevant information for the work of WPB of TENDER NºSANTE/2018/B3/030 and is currently being translated to English. The relevant findings will be used in the development of Deliverable B.2 of WPB of TENDER NºSANTE/2018/B3/030. Methodological manual and toolkit for the CPGs and CDSTs for rare disease.

Figure 1: Review flowchart



4.1 | Main Findings from the Systematic and Manual Literature Review

The findings of the literature review are organised as follows:

- ✓ Prioritization of conditions that require CPGs or CDSTs
- ✓ Appraisal of CPGs and CDSTs
- ✓ Adaptation of CPGs and CDSTs
- ✓ Development of CPGs and CDSTs
- ✓ Implementation of CPGs and CDSTs

No information related to the adaptation or implementation of CPGs or CDSTs was found.

Prioritization of Conditions that Require CPGs or CDSTs

Specific criteria for the prioritization of rare diseases that require a CPG is proposed in one document, including the burden of disease, variations in clinical practice and the impact of implementing the CPG. See Table 1.

TABLE 1: Prioritization of Conditions

Prioritization of Conditions				
Author	**Year**	**Title**	**Summary-Conclusions**	**Type of document**
Schüneman, H. (4)	2017	Methodology for Best Practices Guidelines on Rare Diseases	For the prioritization of topics, the burden of disease, variations in clinical practice or the impact of implementing the guide should be considered.	CPGs

Appraisal of CPGs and CDSTs

Four documents provide information on quality appraisal for CPGs and CDSTs for rare diseases. One document proposes a set of criteria for assessing CDSTs and AGREE II is proposed by three documents as a suitable tool for assessing the quality of CPGs on rare diseases, with some notes on specific areas of analysis. See Table 2.

TABLE 2: CPGs and CDSTs Quality Appraisal

CPGs and CDSTs Quality Appraisal				
Author	**Year**	**Title**	**Summary- Authors' Conclusions**	**Type of document**
Hilton Boon, M. et al. (5)	2015	Report of an international workshop to explore the utility of the AGREE II instrument for appraisal of rare disease guidelines	The AGREE-II instrument is applicable regardless of the small patient numbers, potentially small volume of evidence, and other limitations typically encountered in rare diseases guidelines. This study contributes with some notes for appraisers on the use of AGREE II instrument for guideline quality evaluation in rare diseases, that may be relevant for the Appraisal phase of existing CPGs and CDSTs within this project: - Stakeholder involvement: Although it is likely that one professional group may dominate, comprehensive stakeholder involvement is as important to the development of guidelines for rare diseases as it is for common diseases. - Rigour of development: External review by experts should include patients, carers, and/or patient groups. - There may not be a range of options for management of a rare condition. This item would be considered not applicable.	CPGs

			- Applicability: The extent to which a guideline can provide information on potential facilitators to guideline implementation and describe resource implications may be limited for rare disease guidelines where the implementation setting is likely to encompass diverse healthcare contexts. - Editorial independence: For many rare diseases there are likely to be only a small number of experts worldwide. This may limit the potential for editorial independence.	
Lindecker, V. et al (6)	2012	Méthode d'élaboration d'un protocole national de diagnostic et de soins pour les maladies rares	The criteria include issues related to the working group, the reference centre and coordinator involved, the synthesis of the evidence, scope of the document, its content, editorial independence and existence of a communication plan. Choice of Yes/ No, with no specific instructions on how to incorporate the results.	CDSTs
Pavan, S. et al (7)	2017	Clinical Practice Guidelines for Rare Diseases: The Orphanet Database	Regarding the application of AGREE II instrument to evaluate quality of rare diseases guidelines. - No differences or modifications with respect to the domains applicable to CPGs that do not address rare diseases: 23 items organised into six domains (scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence). They fit the evaluation process to the actual guideline quality, the original rating system of AGREE II that uses a 7-point scale for each item was simplified by yes/no answers. Methodological aspects (rigour of development, domain 3) are given particular weight: a poor methodological description leads to guideline rejection to be integrated to the Orphanet database, even if all other domains are outstanding. - "We often noticed insufficient information about the management of conflicts of interest, insufficient information about the methodology to establish recommendations, a lack of consideration of patients' preferences, and a lack of information about Implementation, dissemination and updating procedures." - "To overcome issues with variable quality, some national health institutions and medical	CPGs

			societies have established standardisation procedures. This methodology is implemented in the French National Diagnostic and Treatment Protocols (PNDS guidelines) for rare diseases. AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) has adopted a similar procedure based on DELBI, The German Instrument for Methodological Guideline Appraisal (AGREE II-derived) in order to provide a tool for the scientific medical societies to create and publish up-to-date and high-quality guidelines."	
RARE-BestPractices partners (8)	2017	Final Publishable Summary Report	AGREE II instrument is suitable to appraise quality of an existing guideline appropriate for rare diseases.	CPGs

Development of CPGs and CDSTs

Patients' Values and Preferences

Four documents addressed the issue of patients' values and preferences, three focus on patient-reported outcomes (PROs) and one on Patient-centred outcomes (PCOMs). Regarding the use of PROs for rare diseases, their limitations to capture the values and preferences of patients with rare diseases are stated, as well as proposing alternative measures, different means and tools for obtaining PROs. PCOMs are proposed as a suitable outcome measure to gather the values and preferences of patients with rare diseases. See Table 3

TABLE 3: Patients' Values and Preferences

Author	Year	Title	Summary- Authors' Conclusions	Type of Document
Basch, E. et al (9)	2014	Patient-Reported Outcomes in Clinical Trials of Rare Diseases	- Observer-Reported Outcomes (ObsROs) may be used to assess observable symptoms and functioning when patients are too young, too ill, or have cognitive impairments that make them unable to respond to PRO survey questions. - When patients are able to report their experience but have physical impairments to completing paper, computer, or automated phone surveys, PROs may be collected via an interviewer. - If there is substantial heterogeneity in how the disease presents, there may not be discrete outcomes that are measureable across the population. A multi-attribute questionnaire may be used in such cases.	All

Garrard, L. et al (10)	2015	A novel method for expediting the development of patient-reported outcome measures and an evaluation of its performance via simulation	Method for future PROMs development for small populations or rare diseases: - The Ordinal Bayesian Instrument Development (OBID) method integrates expert and participant data in a Bayesian item response theory (IRT) to overcome the small sample size challenge while maintaining psychometric soundness. - The overall performance of OBID (i.e., more reliable parameter estimates, smaller mean squared errors (MSEs) and higher predictive validity) is superior to that of classical approaches when the sample size is small (e.g. less than 100 subjects).	All
Morel, T. et al (11)	2017	Measuring what matters to rare disease patients - reflections on the work by the IRDiRC taskforce on patient-centered outcome measures	- Population (small samples size): Mixed methods psychometric research proposed as the best route to deliver fit-for-purpose PCOMs in rare diseases: "as this methodology brings together qualitative and quantitative research methods in tandem with the explicit aim to efficiently utilise data from small samples". - Election of the outcomes: Measure what matters to patients, is important to gain the patients' perspective. "In chronic, debilitating diseases such as most rare diseases, disease stabilisation 'is' improvement and may thus be considered as a meaningful outcome to patients." "Another hurdle to accurate outcome measurement relates to a phenomenon known as 'response shift', which in this case would refer to situations where rare disease patients adapt to their impairment leading to a 'new normal'; their self-reported health status becomes 'fine'." "Patient organisations can steer or even lead most of the work to map out the "context of use" (e.g. rare disease under consideration, stages of disease, sub-populations, healthcare system) and 'concepts of interest' (e.g. symptoms, functioning)" - An instrument which reflects outcomes of interest can either be selected, adapted or developed "The traditional psychometric data-driven approach to PCOM is inherently inappropriate in rare disease because, by definition, there are limited available data to drive the decisions. [...] mixed methods psychometric research is the best fit in rare diseases." To assess the measurement properties of PCOM for rare diseases, Rasch Measurement Theory (RMT) provides the most appropriate and scientifically defensible psychometric methods for use in small sample mixed methods research. - Limitations of existing PCOMs for rare diseases: There are few disease-specific PCOMs available for rare diseases. Traditional instruments do not relate specifically enough to	All

			rare diseases, which introduces 'noise'. "It is practically impossible to develop different specific outcome measures for every rare disease. Therefore, consideration of recycling existing instruments from one context of use to another is worth exploring. Of particular relevance would be considering concept-specific instruments, which may be applicable across a 'family of rare diseases."	
Rüther, A et al (12)	2016	Aspects of patient reported outcomes in rare diseases: A discussion paper	There remain challenges in the development and use of PROs, with contrasting concerns on the one hand regarding lack of responsiveness of generic measures and limited ability to capture all aspects that patients consider important, and on the other hand concern about optimal study design and risk of bias.	All

Evidence Synthesis

Five documents provide information on evidence synthesis for CDSTs and CPGs for rare diseases, including the definition of the PICO question. Regarding the PICO question, it is advised to use broad definitions of the population, intervention and comparator, in order to increase the chances of gathering relevant data. Furthermore, the appropriateness of considering composite and surrogate endpoints, non-experimental and non-comparative data as well as real-world data or reliable evidence on more common diseases, which may have some similarities with the rare condition on which the CPG or CDST focuses on are proposed as possible solutions for the evidence gap in rare diseases. See Table 4.

TABLE 4: Evidence Synthesis

Author	Year	Title	Summary- Authors' Conclusions	Type of document
EUnetHTA (13)	2015	GUIDELINE Endpoints used for Relative Effectiveness Assessment Composite endpoints	- A composite endpoint may be appropriate in cases where no single outcome is a suitable primary endpoint (e.g. some events in a given disease are of similar clinical importance), in case of very rare diseases/events, and for example, in the case of use of a combined safety endpoints. - Composite endpoints have been used in rare diseases where single endpoints are too rare or occur too late and therefore are not sufficiently informative. The use of composite endpoints can be considered if it allows for better assessment of overall benefit of the intervention than a single endpoint. - In general, the combination of objective and subjective components should be avoided (see recommendation6) to minimize problems with the interpretation of results. In some rare diseases (e.g. pulmonary arterial hypertension), use of such combined endpoints could be justified but has to be done in an explicit manner.	CPGs

EUnetHTA (14)	2015	GUIDELINE Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints	- Recommendation 6: The absence of data on clinical endpoints relevant for relative effectiveness assessment (REA) might be acceptable when a clinical endpoint is difficult or impossible to study (very rare or delayed) or target population is too small to obtain meaningful results on relevant clinical endpoints even after very long follow-up (very slowly progressive and/or rare diseases). However, these exceptions need to be carefully argued and agreed in advance of a REA. - The acceptability of a surrogate endpoint has also been based on other risk-benefit and/or public health considerations such as a serious life-threatening disease with no alternative therapy, large safety database available, difficult to study clinical endpoint (very rare or delayed). - In such situations, surrogate endpoints could be acceptable if they reliably predict rare and late clinical events.	CPGs
EUnetHTA (15)	2015	GUIDELINE Internal validity of non-randomised studies (NRS) on interventions	Possible reasons favouring the inclusion of non-randomised studies (NRS), include: The research question cannot (or only with the greatest difficulty) be answered in RCT (Randomized Control Trials). This may be the case because of organizational reasons (e.g. in public health interventions) or epidemiologic circumstances (e.g. very rare diseases).	All
Pai, M. et al. (16)	2015	Developing methodology for the creation of clinical practice guidelines for rare diseases: A report from RARE-BestPractices	- The PICO question: It might be practical to use broad definitions of the population (e.g., incorporate closely related disease entities), intervention and comparator (e.g., a class of medication) to potentially increase the amount of data relevant to the PICO question. - Evidence profiles (EP) and summary of findings (SoF) tables: EP and SoF tables for a rare disease may look very different from one for a common disease. Many studies in rare diseases have no comparator, so establishing relative effects is not possible.	CPGs
Pai, M. et al. (17)	2019	Strategies for eliciting and synthesizing evidence for guidelines in rare diseases	- Systematic reviews of evidence from similar, more common diseases can provide valuable comparative information to Guideline Panels. - Qualitative research has proven to be a viable data source for values and preferences, acceptability, feasibility, and equity. - Patient registries are a feasible source of information for guideline developers, capturing relevant long-term data that are difficult to capture in conventional experimental designs.	CPGs

			- To incorporate non-experimental and non-comparative data (including observational data and qualitative evidence) systematically collected in a usable way for guideline panel, can play a valuable role. AID (Appraising and Including Different Knowledge in Guideline Development) and GRADE-CERQual are actively exploring this topic.	

Economic Evaluation

Three documents provide information on the issues related to efficiency analysis and economic evaluation for CPGs and CDSTs for rare diseases and one provides an approach to obtain more accurate quality of life measures for rare diseases through a more thorough cultural adaptation. Overall, the adoption of the social perspective for the analysis is encouraged, also the use of QALYs as a key outcome, modelling techniques to simulate bigger study populations, Bayesian approach to data analysis and complementing the economic evaluation with a budget impact analysis are also recommended. See Table 5.

TABLE 5: Economic Evaluation

Author	Year	Title	Summary- Authors' Conclusions	Type of document
Cannizzo, S. et al (18)	2018	Rare diseases under different levels of economic analysis: current activities, challenges and perspectives	- Small samples and high heterogeneity among patients and in the evolution of the disease for each patient are the most relevant challenges in assessing the effectiveness and costs of treatments for rare diseases. Traditional approaches could not be appropriate for assessing the cost and effectiveness of rapidly changing conditions and high heterogeneity, as experienced in rare diseases. - Agent-based modelling is an alternative approach, which has the potential to capture the spectrum of consequences and effects produced by rare diseases. - The Big Data revolution is able to sustain the shift from the current to a new era of HTA indicated for a dynamic perspective in assessing the impact of therapies adapted for rare diseases. - The frequentist/classical approach can experience limits in case of rare diseases. The Bayesian perspective conceived probability distributions associated with a phenomenon as the model of our knowledge/ignorance for that phenomenon (updated according to the availability of novel evidence and information). It is closer to the concept of 'learning data'. - Need for criteria, methods and tools (far from a traditional measure of efficiency) which can be adopted to estimate the economic and social burden of a rare disease, and to compare alternative solutions in a budget constraint scenario.	All

Price, V.E. et al (19)	2009	Measuring disease-specific quality of life in rare populations: a practical approach to cross-cultural translation	- Tool adaptation in rare diseases is a challenge due to small samples: "[...] When the specific disease is rare, the cohort of patients is small and international collaboration is often necessary to accomplish meaningful research [...]." - The approach for development includes five steps: 1) forward translation by clinical expert, 2) backward translation by professional translator, 3) review of source and final translated version, 4) pretesting for equivalence in source and final documents in the format of cognitive debriefing, and 5) an international consensus meeting (consensus/synthesis).	All
Schlander, M. et al (20)	2014	Incremental cost per quality-adjusted life year gained? The need for alternative methods to evaluate medical interventions for ultra-rare disorders	There is a need for evaluation principles that had better reflect the public's social preferences (compared with the logic of cost–effectiveness using cost per QALY benchmarks). Examples for such approaches, which hold promise to overcome at least some of the weaknesses of the conventional logic, include (but are not limited to): - Methods combining traditional cost–effectiveness with budget impact analysis, or cost value analysis by means of adjusting cost per QALY benchmarks according to multiple contextual variables. - Using alternatives to QALY as a measure of benefit, such as 'capability-adjusted life years'. - Cost value analysis using the person trade-off method, or cost value (or social utility) analysis using the relative social willingness-to-pay (RS-WTP) instrument. - A multi-criteria decision analysis (MCDA) framework.	All
Zozaya, N., Villoro, R., Hidalgo, A., Sanz A. on behalf of RADEEV expert group (21)	2015	Guía metodológica de evaluación económica aplicada a medicamentos huérfanos	Relevant issues to be considered when developing economic evaluations of orphan drugs (main ideas): - It is recommended to establish very specifically the study population. - It is recommended to adopt a social perspective (especially patient's perspective). - Since the evidence may be scarce, multiple primary and secondary sources could be considered. Given the characteristics of clinical trials in the field of orphan drugs, modelling techniques will be a very useful tool for analysing the scarce evidence available and being able to extrapolate costs and long-term health outcomes. - QALY is a key health outcome measure for orphan drugs given the high impact rare diseases have on patients' quality of life. - It is advisable to carry out, together with an economic evaluation, a budget impact analysis, as it allows quantifying the real magnitude of the opportunity cost of the decision.	All

Other Topics Related to the Development of CPGs and CDSTs

There are other relevant topics within the development process of CPGs and CDSTs for which less information has been found. These are the following:

Scope of the Document

One document (4) recommends that the scope of the CPG should be based mainly on clinical, public health or policy needs. It also points at the existence of conflicts of interest in rare diseases as a critical issue, because the experts involved in the working group are more likely to be also involved in the development of therapeutic solutions.

Working Group and Update

Another document (6) provides specific guideline on the composition of a CDST working group, which should be multidisciplinary, including the different profiles involved in the care of a patient with a rare condition throughout time. This document also establishes a 5-year time threshold for the update of the CDST.

Recommendations

Furthermore, the elaboration of recommendations in a situation of scarce high-quality evidence is tackled in two documents (16) (22), in which the guideline developers (working group) are encouraged to adopt a pragmatic approach and make recommendations, even if they are weak. See Table 6

TABLE 6: Other topics

Author	Year	Title	Summary- Authors' Conclusions	Type of document
Scope of the document				
Schünemann, H. (4)	2017	Methodology for Best Practices Guidelines on Rare Diseases	Questions to be covered by the guideline should be identified based on clinical, public health or policy needs. Input from consumer or patient groups dealing with rare diseases will be very helpful but challenging.	CPGs
Conflicts of interests				
Schünemann, H. (4)	2017	Methodology for Best Practices Guidelines on Rare Diseases	The management of interest conflict is considered critical in developing guidelines for rare diseases. This is in part due to the nature of rare diseases in which many experts will be connected to those producing therapeutic solutions and conduct the relevant research.	CPGs
Working group				
Lindecker, V. et al (6)	2012	Méthode d'élaboration d'un protocole national de	Multidisciplinary working group, including at least 7-15 members, apart from the coordinator and the analysts involved. The profiles involved are:	CDSTs

		diagnostic et de soins pour les maladies rares	- Healthcare professionals that are involved in any stage of the care that the patients with a rare disease receive: · This implies including at least members of the reference and competence centres and, depending on the disease, any other professional, usually involved in the care of the patient. · If necessary, scientific societies or professional national councils concerned can be included. · Consultation/ participation of European or international experts can be useful, · The opinion of a general practitioner, and/ or a paediatrician in the case of a paediatric disease, is imperative · For diseases revealed in the paediatric age, the group must not only include professionals specializing in the care of the child but also professionals specialists in adults in order to organize the transition from paediatrics to adult medicine. - Other professionals (e.g., a psychologist) that are usually involved in the care of the patient with the rare condition - Patients and users' representatives, if necessary, in the absence of association of patients, patients themselves or their entourage.	
Recommendations				
Scharpf, J. (22)	2017	The Challenge of Guideline Development When Evidence Is Sparse	Application of GRADE system to rare disease GPCs: GRADE formalizes the evaluation of the factors based on the evidence to recommendation framework (overall quality of evidence, risk-benefit balance, and patient values and preferences), which is challenging in the light of lack of high-quality evidence for rare diseases. - "Although guideline developers often prefer to issue a recommendation based on opinion when evidence is scant and, although the GRADE working group encourages guideline workgroups to make recommendations when evidence is in low quality, future guidelines should explicitly state where the evidence is insufficient to make recommendations." - "Despite the lack of high-quality evidence, it is important that guideline panels do not abstain from making any recommendation the importance of making recommendations despite the lack of high-quality evidence. There needs to be a provision of some guidance even if it constitutes weak recommendations."	CPGs

			- "Rare disease guideline panels can also make research recommendations, including details of study design."	
Pai, M. et al. (16)	2015	Developing methodology for the creation of clinical practice guidelines for rare diseases: A report from RARE-BestPractices	Evidence to recommendation tables: For rare diseases, where high quality evidence is not always available, it is important that guideline panels take a pragmatic approach providing some guidance to end users, even if it is in the form of weak recommendations.	CPGs
Update timing				
Lindecker, V. et al (6)	2012	Méthode d'élaboration d'un protocole national de diagnostic et de soins pour les maladies rares	The possibility of updating the PNDS should be considered every 5 years at least.	CDSTs

4.2 | Expert Consultation

The preliminary report on the Literature Review was submitted to external review by the ERNs and other institutions with methodological or rare disease-related expertise to ensure no relevant information had been left out of the analysis.

The review was made by means of an online consultation in the EU Survey platform.

Recruitment of participants

Following the indications provided by the European Commission (EC) to the project coordination team at Fundación Progreso y Salud (FPS), the ERNs were previously contacted by FPS and asked to provide contact points to which the consultation would be sent. A total of 75 contact points were provided by 22 ERNs.

As for the institutions, 21 institutions were identified and contacted (see Annex 6. List of Institutions for Expert Consultation) by the project coordination team at FPS by email.

Expert consultation methods

The consultation was created and made available online with EU Survey. As per the EC's request, two surveys were created, one for the ERNs and the other for the institutions. These surveys differed in the questions regarding the personal information of the respondent but coincided in those referred to the consultation.

WP-B team at IACS contacted the previously identified contact points from the ERNs via a standard email. FPS contacted the institutions via a standard email.

In these emails, information on the consultation was provided, including the background of the TENDER, WP-B, the purpose of the consultation, the deadline and a contact point at IACS, as well as a link to the survey of the consultation. In the survey, the information on the consultation and practical information was provided together with the preliminary report on the literature review, i.e., D-B.1 before the addition of the information regarding the expert consultation. The participants were asked to review the preliminary report and answer whether relevant information was missing and, if so, which and where in the report. Participants were also invited to upload any relevant document. See Annex 7.7 Experts' Consultation Questionnaires for further information.

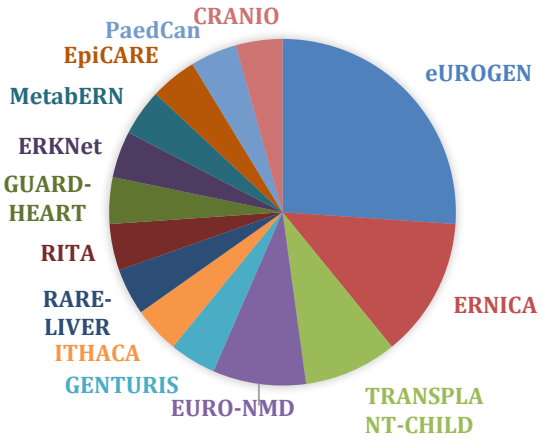
Expert consultation turnout

The consultation was opened from March 2nd- March 23rd.

One answer was received from the institutions, the participant was a healthcare professional from Institute Catalan of Oncology in Barcelona, Spain.

Twenty-three answers were received from 14 ERNs: eUROGEN (6), ERNICA (3), TRANSPLANT-CHILD (2), EURO-NMD (2), GENTURIS (1), ITHACA (1), RARE-LIVER (1), RITA (1), GUARD-HEART (1), ERKNet (1), MetabERN (1), EpiCARE (1), PaedCAN (1), ERN CRANIO (1). See Figure 1. ERN Turnout. Most of the ERN experts that participated in the consultation were healthcare professionals (19). Also two managers, two methodologists and one researcher participated.

Figure 1: ERN turnout



Results obtained from this consultation may not be fully representative, due to a low response rate from the institutions. This low rate of participation could be due to the fact that many of the initiatives identified are not currently active and that the consultation period coincided with the rising global crisis linked to COVID-19 pandemic. Anyhow, some of the initiatives and projects included in the manual search are linked to institutions and stakeholders of interest, so their views may also be reflected in this document.

Results from the Expert Consultation

Ten participants from 7 ERNs suggested new information to be considered in the report. These suggestions are very much appreciated and are enriching and valuable for WP-B team. However, none of the suggestions were finally included in the report because they were not methodological documents, i.e. addressed CDSTs and CPGs for specific conditions, or the methodologies proposed were not specific for rare diseases. Nonetheless, we will keep these suggestions in mind for future developments of this project. See Annex 7.6 Experts' Suggestions and answers.

05.

CONCLUSIONS AND RECOMMENDATIONS

This literature review aimed to identify methodological approaches that take explicitly into account the peculiarities of rare diseases. The findings of this analysis, however, ascertain the fact that there are few methodological approaches for the prioritization, appraisal, adaptation, development and implementation of CPGs and CDSTs specifically addressing rare diseases.

For the prioritization of conditions that require CPGs or CDSTs, only one document provided specific information, although the reason for using that criteria and the prioritization procedure are not clearly explained.

Regarding the appraisal of CPGs and CDSTs, the international appraisal instrument AGREE II to assess the quality of CPGs (with some specifications for rare disease) appears to be an appropriate approach for the case of rare diseases, according to the work develop through the RARE-Bestpractices project (5)

The development of CPGs and CDSTs is partially addressed by some documents, especially the inclusion of patients' values and preferences, evidence synthesis and economic evaluation. Some key points are raised and practical approaches are given, such as the consideration of composite endpoints in absence of a suitable primary outcome, the use of patient registries as a key tool in rare disease management or the use of modelling techniques to overcome the scarcity of robust economic data. In addition to this, the contribution of the European Union-funded project RARE-Bestpractices deserves to be highlighted. The project explored the use of GRADE in creating CPGs for rare diseases (16) and established the GRADE approach as the standard in CPGs development for rare diseases. The development of CPGs for three rare diseases in the framework of the project allowed to draw some practical conclusions from the author's experience (17). However, some questions around key issues in the development and use of CPGs and CDSTs need to be further investigated. For example, it has been emphasized the importance of making recommendations despite the lack of high-quality evidence (22), however, CPGs or CDSTs working groups need additional guidance to move from evidence to recommendations when evidence is scarce.

As for the adaptation and implementation of CPGs and CDSTs for rare diseases, no relevant information has been identified in this analysis. The multi-contextual care environment in which ERNs work, involving more than 900 highly specialised healthcare units from over 300 hospitals in 26 EU countries, poses a major challenge to the development of methodologies for the adaptation and implementation of CPGs and CDSTs, which are so closely linked to local circumstances and singularities.

GRADE is the methodology of choice for the development of CPGs and CDSTs in the ERNs, as established in the TENDER NºSANTE/2018/B3/030 specifications (23). Overall, this analysis highlights the need for further work in order to achieve an effective approach of GRADE

methodology to the idiosyncrasy and needs of rare diseases.

Although the focus of this review are the methodological approaches that address the challenges of rare diseases, it is important to mention that some methodological approaches with a wide international consensus will be considered and used for the development of the Methodological manual and toolkit for CPGs and CDSTs for rare diseases (Deliverable B.2). These include, for example, the Guidelines International Network (G-I-N) standards for guideline development (77), the ADAPTE methodology for guideline adaptation (78) (79) and the standards for guideline-based performance measures development and re-evaluation (80). As a matter of fact, many of these methodological approaches where also suggested by the ERN expert that took part in the expert consultation for this report explained in the Results section of this document.

WPB of TENDER NºSANTE/2018/B3/030 will incorporate the results summarized in this report to its ongoing work for the development of a Methodological manual and toolkit for CPGs and CDSTs for rare diseases (Deliverable B.2).

06.

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07.

ANNEXES

ANNEX 7.1 | Search Strategy (Systematic Literature Review)

Pubmed

#1 "Rare Diseases"[Mesh] OR (rare[tiab] diseases[tiab]) OR (rare[tiab] disease[tiab]) OR (orphan[tiab] diseases[tiab]) OR (orphan[tiab] disease[tiab]) OR (rare[tiab] conditions[tiab]) OR (rare[tiab] condition[tiab]) OR (rare[tiab] disorders[tiab]) OR (rare[tiab] disorder[tiab]) OR (unusual[tiab] diseases[tiab]) OR (unusual[tiab] disease[tiab]) OR ("low prevalence"[tiab] diseases[tiab])

#2 "Methods"[Mesh] OR "methods"[Subheading] OR methodology[ti] OR methods[ti] OR methodological[tiab] OR development[tiab] OR develop[tiab] OR developing[tiab] OR production[tiab] OR produce[tiab] OR creating[tiab] OR creation[tiab] OR procedures[tiab] OR procedure[tiab] OR elaboration[tiab] OR elaborating[tiab]

#3 "Practice Guidelines as Topic"[Mesh] OR "Guidelines as Topic"[Mesh] OR "Reference Standards"[Mesh] OR "Critical Pathways"[Mesh] OR "patient reported outcome measures"[Mesh] OR "quality indicators, health care"[Mesh]

#4 ((clinical decision support[tiab]) OR (clinical decision support[tiab])) AND (documents[tiab] OR tools[tiab]) OR CDSD[tiab] OR CDST[tiab] OR guidelines[tiab] OR (clinical[tiab] practice[tiab] recommendations[tiab]) OR (clinical[tiab] consensus[tiab] statements[tiab]) OR (consensus[tiab] reports[tiab]) OR (expert[tiab] consensus[tiab] reports[tiab]) OR (expert[tiab] committee[tiab] reports[tiab]) OR (consensus[tiab] statements[tiab]) OR (diagnostic[tiab] pathways[tiab]) OR (monitoring[tiab] pathways[tiab]) OR (therapy[tiab] pathways[tiab]) OR (clinical pathways[tiab]) OR (clinical paths[tiab]) OR (critical pathways[tiab]) OR (critical paths[tiab]) OR (patient pathways[tiab]) OR (care pathways[tiab]) OR (healthcare pathways[tiab]) OR (quality measures[tiab]) OR ((disease-specific outcome[tiab]) measures[tiab]) OR ((patient-reported outcome[tiab]) measures[tiab]) OR ((patient reported outcome[tiab]) measures[tiab]) OR (patient reported outcomes[tiab]) OR (self-reported outcomes[tiab]) OR ((self-reported outcome[tiab]) measures[tiab]) OR PROMs[tiab] OR ((patient reported experience[tiab]) measures[tiab]) OR ((patient reported[tiab]) experience[tiab]) OR PREMs[tiab] OR (quality standards[tiab]) OR (reference standards[tiab]) OR (quality indicators[tiab]) OR (health metrics[tiab]) OR ((patient information[tiab]) booklets[tiab]) OR ((patient education[tiab]) handouts[tiab]) OR ((patient information[tiab]) leaflets[tiab]) OR (evidence reports[tiab]) OR (Do's[tiab] Don'ts[tiab] factsheets[tiab]) OR (evidence-based[tiab] protocols[tiab]) OR (evidence[tiab] based[tiab] protocols[tiab])

#5 "Case Reports"[Publication Type] OR "Letter"[Publication Type] OR "Editorial"[Publication Type] OR "News"[Publication Type] OR "Historical Article"[Publication Type] OR "Anecdotes as Topic"[Mesh] OR "Comment"[Publication Type]

#1 AND #2 AND (#3 OR #4) NOT #5

Limits - language: English, French, Spanish

Embase

#1 'rare disease'/exp

#2 ((rare NEXT/1 diseases):ab,ti) OR ((rare NEXT/1 disease):ab,ti) OR ((orphan NEXT/1 diseases):ab,ti) OR ((orphan NEXT/1 disease):ab,ti) OR ((rare NEXT/1 conditions):ab,ti) OR ((rare NEXT/1 condition):ab,ti) OR ((rare NEXT/1 disorders):ab,ti) OR ((rare NEXT/1 disorder):ab,ti) OR ((unusual NEXT/1 diseases):ab,ti) OR ((unusual NEXT/1 disease):ab,ti) OR ((low NEXT/1 prevalence NEXT/1 disease):ab,ti)

#3 'methodology'/exp OR methodology:ti OR methods:ti OR methodological:ab,ti OR development:ab,ti OR develop:ab,ti OR developing:ab,ti OR production:ab,ti OR produce:ab,ti OR creating:ab,ti OR creation:ab,ti OR 'procedures'/exp OR procedures:ab,ti OR procedure:ab,ti OR elaboration:ab,ti OR elaborating:ab,ti

#4 'practice guideline'/exp OR 'consensus development'/exp OR 'clinical pathway'/exp OR 'patient information leaflet'/exp OR 'patient-reported outcome'/exp OR 'quality indicators'/exp OR 'clinical protocol'/exp

#5 ((clinical NEXT/1 decision NEXT/1 support NEXT/1 documents):ab,ti) OR ((clinical NEXT/1 decision NEXT/1 support NEXT/1 tools):ab,ti) OR cdsd:ab,ti OR cdst:ab,ti OR ((clinical NEXT/1 practice NEXT/1 guidelines):ab,ti) OR ((practice NEXT/1 guidelines):ab,ti) OR guidelines:ab,ti OR ((clinical NEXT/1 guidelines):ab,ti) OR ((clinical NEXT/1 practice NEXT/1 recommendations):ab,ti) OR ((clinical NEXT/1 consensus NEXT/1 statements):ab,ti) OR ((consensus NEXT/1 reports):ab,ti) OR ((expert NEXT/1 consensus NEXT/1 reports):ab,ti) OR ((expert NEXT/1 committee NEXT/1 reports):ab,ti) OR ((consensus NEXT/1 statements):ab,ti) OR ((diagnostic NEXT/1 pathways):ab,ti) OR ((monitoring NEXT/1 pathways):ab,ti) OR ((therapy NEXT/1 pathways):ab,ti) OR ((clinical NEXT/1 pathways):ab,ti) OR ((clinical NEXT/1 paths):ab,ti) OR ((critical NEXT/1 pathways):ab,ti) OR ((critical NEXT/1 paths):ab,ti) OR ((patient NEXT/1 pathways):ab,ti) OR ((care NEXT/1 pathways):ab,ti) OR ((healthcare NEXT/1 pathways):ab,ti) OR ((quality NEXT/1 measures):ab,ti) OR (('disease specific' NEXT/1 outcome NEXT/1 measures):ab,ti) OR (('patient reported' NEXT/1 outcome NEXT/1 measures):ab,ti) OR ((patient NEXT/1 reported NEXT/1 outcome NEXT/1 measures):ab,ti) OR ((patient NEXT/1 reported NEXT/1 outcomes):ab,ti) OR (('self reported' NEXT/1 outcomes):ab,ti) OR (('self reported' NEXT/1 outcome NEXT/1 measures):ab,ti) OR proms:ab,ti OR ((patient NEXT/1 reported NEXT/1 experience NEXT/1 measures):ab,ti) OR ((patient NEXT/1 reported NEXT/1 experience):ab,ti) OR prems:ab,ti OR ((quality NEXT/1 standards):ab,ti) OR ((reference NEXT/1 standards):ab,ti) OR ((quality NEXT/1 indicators):ab,ti) OR ((health NEXT/1 metrics):ab,ti) OR ((patient NEXT/1 information NEXT/1 booklets):ab,ti) OR ((patient NEXT/1 education NEXT/1 handouts):ab,ti) OR ((patient NEXT/1 information NEXT/1 leaflets):ab,ti) OR ((evidence NEXT/1 reports):ab,ti) OR 'do and don':ab,ti OR ((evidence NEXT/1 based NEXT/1 protocols):ab,ti) OR (('evidence based' NEXT/1 protocols):ab,ti)

(#1 OR #2) AND #3 AND (#4 OR #5)

Limits: [embase]/lim NOT "[embase]/lim AND [medline]/lim" AND "[article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [review]/lim OR [short survey]/lim" AND "[english]/lim OR [french]/lim OR [spanish]/lim"

TRIP database

(title:"rare diseases" OR "rare disease" OR "orphan diseases" OR "orphan disease" OR "rare conditions" OR "rare condition" OR "rare disorders" OR "rare disorder" OR "unusual diseases" OR "unusual disease" OR "low prevalence diseases")(title:methodology OR methods OR methodological

OR procedures OR procedure OR development OR develop OR developing OR production OR produce OR creating OR creation OR elaboration OR elaborating)

Web of Science

#1 (TS=("rare diseases" OR "rare disease" OR "orphan diseases" OR "orphan disease" OR "rare conditions" OR "rare condition" OR "rare disorders" OR "rare disorder" OR "unusual diseases" OR "unusual disease" OR "low prevalence diseases")) AND IDIOMA: (English OR French OR Spanish)

#2 (TS=(methodology OR methods OR methodological OR procedures OR procedure OR development OR develop OR developing OR production OR produce OR creating OR creation OR elaboration OR elaborating)) AND IDIOMA: (English OR French OR Spanish)

#3 (TS=("clinical decision support documents" OR "clinical decision support tools" OR CDSD OR CDST OR "clinical practice guidelines" OR "practice guidelines" OR guidelines OR "clinical guidelines" OR "clinical practice recommendations" OR "clinical consensus statements" OR "consensus reports" OR "expert consensus" OR "expert committee reports" OR "consensus statements" OR "diagnostic pathways" OR "monitoring pathways" OR "therapy pathways" OR "clinical pathways" OR "clinical paths" OR "critical pathways" OR "critical paths" OR "patient pathways" OR "care pathways" OR "healthcare pathways" OR "quality measures" OR "disease-specific outcome measures" OR "patient-reported outcome measures" OR "patient reported outcome measures" OR "patient reported outcomes" OR "self-reported outcomes" OR "self-reported outcome measures" OR PROMs OR "patient reported experience measures" OR "patient reported experience" OR PREMs OR "quality standards and indicators" OR "quality standards" OR "reference standards" OR "quality indicators" OR "health metrics" OR "patient information booklets" OR "patient education handout" OR "patient information leaflets" OR "evidence reports" OR "evidence based protocols" OR "Do and Don't")) AND IDIOMA: (English OR French OR Spanish)

#1 AND #2 AND #3

CINAHL

AB ("rare diseases" OR "rare disease" OR "orphan diseases" OR "orphan disease" OR "rare conditions" OR "rare condition" OR "rare disorders" OR "rare disorder" OR "unusual diseases" OR "unusual disease" OR "low prevalence diseases") AND AB (methodology OR methods OR methodological OR procedures OR procedure OR development OR develop OR developing OR production OR produce OR creating OR creation OR elaboration OR elaborating) AND AB ((clinical decision support documents) OR (clinical decision support tools) OR CDSD OR CDST OR (clinical practice guidelines) OR (practice guidelines) OR guidelines OR (clinical guidelines) OR (clinical practice recommendations) OR (clinical consensus statements) OR (consensus reports) OR (expert consensus) OR (expert committee reports) OR (consensus statements) OR (diagnostic pathways) OR (monitoring pathways) OR (therapy pathways) OR (clinical pathways) OR (clinical paths) OR (critical pathways) OR (critical paths) OR (patient pathways) OR (care pathways) OR (healthcare pathways) OR (quality measures) OR (disease-specific outcome measures) OR (patient-reported outcome measures) OR (patient reported outcome measures) OR (patient reported outcomes) OR (self-reported outcomes) OR (self-reported outcome measures) OR PROMs OR (patient reported experience measures) OR (patient reported experience) OR PREMs OR (quality standards and indicators) OR (quality standards) OR (reference standards) OR (quality indicators) OR (health metrics) OR (patient information booklets) OR (patient education handout) OR (patient information leaflets) OR (evidence reports) OR (evidence based protocols) OR "Do and Don't")

Limits - language: English, French, Spanish

PsycINFO

AB (“rare diseases” OR “rare disease” OR “orphan diseases” OR “orphan disease” OR “rare conditions” OR “rare condition” OR “rare disorders” OR “rare disorder” OR “unusual diseases” OR “unusual disease” OR “low prevalence diseases”) AND AB (methodology OR methods OR methodological OR procedures OR procedure OR development OR develop OR developing OR production OR produce OR creating OR creation OR elaboration OR elaborating) AND AB ((clinical decision support documents) OR (clinical decision support tools) OR CDSD OR CDST OR (clinical practice guidelines) OR (practice guidelines) OR guidelines OR (clinical guidelines) OR (clinical practice recommendations) OR (clinical consensus statements) OR (consensus reports) OR (expert consensus) OR (expert committee reports) OR (consensus statements) OR (diagnostic pathways) OR (monitoring pathways) OR (therapy pathways) OR (clinical pathways) OR (clinical paths) OR (critical pathways) OR (critical paths) OR (patient pathways) OR (care pathways) OR (healthcare pathways) OR (quality measures) OR (disease-specific outcome measures) OR (patient-reported outcome measures) OR (patient reported outcome measures) OR (patient reported outcomes) OR (self-reported outcomes) OR (self-reported outcome measures) OR PROMs OR (patient reported experience measures) OR (patient reported experience) OR PREMs OR (quality standards and indicators) OR (quality standards) OR (reference standards) OR (quality indicators) OR (health metrics) OR (patient information booklets) OR (patient education handout) OR (patient information leaflets) OR (evidence reports) OR (evidence based protocols) OR “Do and Don’t”)

Limits - language: English, French, Spanish

CRD

#1 "rare diseases" OR "rare disease" OR "orphan diseases" OR "orphan disease" OR "rare conditions" OR "rare condition" OR "rare disorders" OR "rare disorder" OR "unusual diseases" OR "unusual disease" OR "low prevalence diseases"

#2 “methodology OR methods OR methodological OR procedures OR procedure OR development OR develop OR developing OR production OR produce OR creating OR creation OR elaboration”

#3 (clinical decision support documents) OR (clinical decision support tools) OR CDSD OR CDST OR (clinical practice guidelines) OR (practice guidelines) OR guidelines OR (clinical guidelines) OR (clinical practice recommendations) OR (clinical consensus statements) OR (consensus reports) OR (expert consensus) OR (expert committee reports) OR (consensus statements) OR (diagnostic pathways) OR (monitoring pathways) OR (therapy pathways) OR (clinical pathways) OR (clinical paths) OR (critical pathways) OR (critical paths) OR (patient pathways) OR (care pathways) OR (healthcare pathways) OR (quality measures) OR (disease-specific outcome measures) OR (patient-reported outcome measures) OR (patient reported outcome measures) OR (patient reported outcomes) OR (self-reported outcomes) OR (self-reported outcome measures) OR PROMs OR (patient reported experience measures) OR (patient reported experience) OR PREMs OR (quality standards and indicators) OR (quality standards) OR (reference standards) OR (quality indicators) OR (health metrics) OR (patient information booklets) OR (patient education handout) OR (patient information leaflets) OR (evidence reports) OR (evidence based protocols)

#1 AND #2 AND #3

Google Scholar

(intitle:“rare diseases” OR intitle:“orphan diseases” OR intitle:“rare conditions” OR intitle:“rare disorders”) AND (intitle:methodology OR intitle:methods OR intitle:methodological OR intitle:procedures OR intitle:procedure)

ANNEX 7.2 | List of Organizations and Projects Reviewed (Manual Literature Review)

#	Organization - Project
	Identified during the preparation of the proposal
1	CIBERER: Undiagnosed Rare Diseases Programme
2	EUCERD Joint Action (N°2011 22 01) (Outputs & Deliverables)
3	EURORDIS: European Organisation for Rare Diseases
4	ICORD: International Conference on Rare Diseases and Orphan Drugs
5	ISPOR: Rare Disease Special Interest Group
6	RDCRN: Rare Diseases Clinical Research Network
7	Orphanet database
8	AHRQ: Agency for Healthcare Research and Quality
9	GIN: Guidelines International Network
10	GuíaSalud: Guías de Práctica Clínica del Sistema Nacional de Salud de España
11	SIGN: Scottish Intercollegiate Guidelines Network
12	COCHRANE (as organization)
13	NICE (National Institute for Health and Care Excellence)
14	CADTH (Canadian Agency for Drugs and Technologies in Health)
15	EUnetHTA (European Network for Health Technology Assessment)
16	RARE-BestPractices
17	EUROPLAN (European Project for Rare Diseases National Plans Development)
18	EPIRARE (European Platform for Rare Disease Registries)
19	BURQOL-RD
	Identified through snowball technique
20	FEDER (Federación Española de Enfermedades Raras)

21	Cancer Drugs Fund (CDF)
22	ECRI
23	Advance HTA (EU Project)
24	Centres of Expertise for RD Patients
25	EC Expert Group on Rare Diseases
26	RD-Action (joint action)
27	DEBRA International
28	EU RD Platform (European Platform on Rare Disease Registration)
29	EUROCAT Network (European network of population-based registries for the epidemiological surveillance of congenital anomalies)
30	VSOP (Dutch Patient Alliance for Rare and Genetic Diseases)
31	IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
32	ERA-Net E-Rare for Research Programmes on Rare Diseases
33	IRDiRC (International Rare Disease Research Consortium)
34	GRADE Working Group
35	EMA Committee for Orphan Medicinal Products
36	HAS (Haute Autorité de Santé)
37	Italian National Centre for Rare Diseases (CNMR)
38	Ireland National Rare Diseases Office (NRDO)
39	EUNENBS: European Network of Experts on Newborn Screening
40	European Conference on Rare Diseases & Orphan Products (ECRD)
41	CoCanCPG (Coordination of Cancer Clinical Practice Guidelines Research in Europe)
42	CARE-NMD project
43	IIER (Instituto de Investigación de Enfermedades Raras) - ISCII
44	CDR (CADTH Common Drug Review)
45	POLKA: Patients' Consensus on Preferred Policy Scenarii for Rare Disease
46	NewsRARE

47	Rare Disorders Denmark
48	EMA's Committee on Human Medicinal Products (CHMP) guidelines on the clinical investigation of orphan medicinal products
49	Programme for Expensive and Orphan Medicines (2007-2014)
50	RD-CONNECT
51	EJP RD (European Joint Programme for Rare Diseases)
52	ICBDSR (International Clearinghouse for Birth Defects Surveillance and Research)
53	Solve RD
54	OrphaNews
55	Office of Rare Diseases Research National Institutes of Health (NORD)
56	GARD Genetic and Rare Diseases Information Center
57	ENERCA European Network for Rare and Congenital Anaemias
58	Rare Voices Australia
59	European Organisation for Treatment & Rersearch on Cancer (EORTC)
60	Bulgarian Association for Promotion of Education and Science (BAPES)
61	Canadian Organization for Rare Disorders (CORD)
62	French Foundation for Rare Diseases
63	Advocacy Service for Rare and Intractable Diseases' multi-stakeholders in Japan (ASrid)
64	Karolinska Intitutet
65	RARECARE
66	RARECAREnet
67	JARC (Joint Action in Rare Cancers)
68	RARE DISEASES INTERNATIONAL (RDI)
69	RareConnect
70	New Zealand Organisation for Rare Disorders (NZORD)
71	Genetic Alliance (US)
72	Undiagnosed Diseases Network (UDN)

73	Undiagnosed Diseases Network International (UDNI)
74	Genetic and Rare Disease Network (GaRDN)
75	Genetic Alliance Australia (GA)
76	Genetic Support Network Victoria (GSNV)
77	Syndromes Without a Name (SWAN Australia)
78	Royal College of Physicians in Ireland
79	Rare Cancers Europe
80	Bridging Interventional Development Gaps (BrIDGs)
81	Rare Commons
82	Share4Rare
83	OHE (Office of Health Economics)
84	RareDis
85	NCPE Ireland (National Centre for Pharmacoeconomics)
86	Rare 2030
87	NGO Committee for Rare Diseases
88	Fundación Weber
89	Rare Share
90	EVIDEM

ANNEX 7.3 | Excluded Documents (Systematic Literature Review)

#	Authors	Year	Title	Reason
1	Bolignano, D. et al (24)	2014	Providing guidance in the dark: rare renal diseases and the challenge to improve the quality of evidence	It focuses on a specific case or condition, it does not provide information that could be translated to a general methodological approach
2	Brinduse, A. et al (25)	2014	METHODOLOGICAL ASPECTS IN ESTIMATING THE COST OF- ILLNESS FOR PATIENTS WITH RARE DISEASES	It does not provide methodology or specific information for methodological development for rare diseases
3	Tudur Smith, C. et al (26)	2014	Methodology of clinical trials for rare diseases	It does not provide methodology or specific information for methodological development for rare diseases
4	Whicher, D. et al (27)	2018	An overview of the impact of rare disease characteristics on research methodology	It does not provide methodology or specific information for methodological development for rare diseases
5	Gergely, P. (28)	2017	Challenges and opportunities of drug research and development in rare diseases	It does not provide methodology or specific information for methodological development for rare diseases
6	Haffner, M. E. (29)	1998	Designing Clinical Trials to study rare disease treatment	It does not provide methodology or specific information for methodological development for rare diseases
7	Joëlle Micallef (30)	2012	Méthodologie et gestion des essais cliniques à petits effectifs pour les maladies rares	It does not provide methodology or specific information for methodological development for rare diseases
8	Bharmal, M. et al (31)	2018	How to address the challenges of evaluating treatment benefits-risks in rare diseases? A convergent mixed methods approach applied within a Merkel cell carcinoma phase 2 clinical trial	It does not provide methodology or specific information for methodological development for rare diseases
9	Pillay, E. et al (32)	2018	Development of best clinical practice guidelines for epidermolysis bullosa	It focuses on a specific case or condition, it does not provide information that could be translated to a general methodological approach
10	Sancho Lopez, A. (33)	2018	New clinical trial designg applied to the study of orphan and rare diseases: feasibility of methodological guidance to clinical	It does not provide methodology or specific information for methodological development for rare diseases

			development of new treatments from a regulatory perspective	
11	Mosca, M. et al (34)	2018	Clinical practice guidelines: the first year of activity of the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET)	It does not provide methodology or specific information for methodological development for rare diseases
12	Gagne, J.J et al (35)	2014	Innovative research methods for studying treatments for rare diseases: methodological review	It does not provide methodology or specific information for methodological development for rare diseases
13	Wagner, M. et al (36)	2015	Can the EVIDEM Framework Tackle Issues Raised by Evaluating Treatments for Rare Diseases: Analysis of Issues and Policies, and Context-Specific Adaptation	It does not provide methodology or specific information for methodological development for rare diseases
14	Ayme, S. et al (37)	2018	État des lieux de la collecte et de l'exploitation des données pour la recherche et la prise de décision en santé dans les maladies rares en France [State of play of French data collections in the field of rare diseases]	It focuses on a specific case or condition, it does not provide information that could be translated to a general methodological approach
15	Babac, A. et al (38)	2019	Patient-reported data informing early benefit assessment of rare diseases in Germany: A systematic review	It does not provide methodology or specific information for methodological development for rare diseases
16	Cismondi, I.A. et al (39)	2015	Guidelines for incorporating scientific knowledge and practice on rare diseases into higher education: neuronal ceroid lipofuscinoses as a model disorder	It does not provide methodology or specific information for methodological development for rare diseases
17	Denger, B. et al (40)	2019	Patient and caregiver perspectives on guideline adherence: the case of endocrine and bone health recommendations for Duchenne muscular dystrophy	It does not provide methodology or specific information for methodological development for rare diseases
18	Ferrari, P. et al (41)	2019	My life with pulmonary arterial hypertension: a patient perspective	It does not provide methodology or specific information for methodological development for rare diseases
19	Ferrelli, R.M. et al (42)	2015	Exploring the usability of EUCERD core indicators for rare diseases	It does not provide methodology or specific information for methodological development for rare diseases

20	Fischbacher, C.M. et al (43)	2001	Improving the quality of communicable disease control: the example of meningococcal disease	It focuses on a specific case or condition, it does not provide information that could be translated to a general methodological approach
21	Garrison, L.P. et al (44)	2019	Value-Based Pricing for Emerging Gene Therapies: The Economic Case for a Higher Cost-Effectiveness Threshold	It does not provide methodology or specific information for methodological development for rare diseases
22	Goldin, A.B. et al (45)	2011	Guidelines for Surveys of the American Pediatric Surgical Association	It does not provide methodology or specific information for methodological development for rare diseases
23	Kessel, M. et al (46)	2012	Innovative work behavior in healthcare: The benefit of operational guidelines in the treatment of rare diseases	It does not provide methodology or specific information for methodological development for rare diseases
24	Le Cam, Y. (47)	2018	L'action de la France en Europe et ce que l'Europe peut inspirer à la France, du point de vue des malades [French model for Europe and Europe as a model for France in the field of rare diseases]	It does not provide methodology or specific information for methodological development for rare diseases
25	Pai, M. et al (48)	2016	Methodology for the development of the NHF-McMaster Guideline on Care Models for Haemophilia Management	It focuses on a specific case or condition, it does not provide information that could be translated to a general methodological approach
26	Pauer, F. et al (49)	2016	Adopting Quality Criteria for Websites Providing Medical Information About Rare Diseases	It does not provide methodology or specific information for methodological development for rare diseases
27	Péton-Klein, D. (50)	2014	[Inaugural conference - what stakes face rare diseases in the French health care system]	It does not provide methodology or specific information for methodological development for rare diseases
28	Sandberg, D.E. et al (51)	2015	Disorders of Sex Development (DSD): Networking and Standardization Considerations	It focuses on a specific case or condition, it does not provide information that could be translated to a general methodological approach
29	Roldan, U. B. et al (52)	2018	Multi-criteria decision analysis as a decision-support tool for drug evaluation: a pilot study in a pharmacy and therapeutics committee setting	It focuses on a specific case or condition, it does not provide information that could be translated to a general methodological approach
30	Salek, M.S. et al (53)	2019	Appraisal of patient-reported outcome measures in analogous	It focuses on a specific case or condition, it does not provide

			diseases and recommendations for use in phase II and III clinical trials of pyruvate kinase deficiency	information that could be translated to a general methodological approach
31	Torrent-Farnel, J. et al (54)	2018	The view of experts on initiatives to be undertaken to promote equity in the access to orphan drugs and specialised care for rare diseases in Spain: A Delphi consensus	It does not provide methodology or specific information for methodological development for rare diseases
32	Young, A. et al (55)	2017	Exploring patient and family involvement in the lifecycle of an orphan drug: a scoping review	It does not provide methodology or specific information for methodological development for rare diseases
33	Slade, A. et al (56)	2018	Patient reported outcome measures in rare diseases: a narrative review	It does not provide methodology or specific information for methodological development for rare diseases
34	Khodyakov, D. et al (57)	2017	Engaging Patients and Caregivers Managing Rare Diseases to Improve the Methods of Clinical Guideline Development: A Research Protocol	It focuses on a specific case or condition, it does not provide information that could be translated to a general methodological approach
35	Bullinger, M. et al (58)	2014	Cross-Cultural Equivalence of the Patient- and Parent-Reported Quality of Life in Short Stature Youth (QoLISSY) Questionnaire	It does not provide methodology or specific information for methodological development for rare diseases
36	Rapkin, B.D. et al (59)	2017	Distinguishing appraisal and personality influences on quality of life in chronic illness: introducing the quality-of-life Appraisal Profile version 2	It does not provide methodology or specific information for methodological development for rare diseases
37	Cheung, Y.B. et al (60)	2006	Developing health-related quality-of-life instruments for use in Asia: the issues	It does not provide methodology or specific information for methodological development for rare diseases
38	Facey, K. et al (61)	2014	Generating health technology assessment evidence for rare diseases	It does not provide methodology or specific information for methodological development for rare diseases

ANNEX 7.4 | Excluded Documents (Manual Literature Review)

#	Authors	Year	Title	Reason
1	EC Expert Group on Rare Diseases (62)	2015	Recommendation on cross border genetic testing of rare diseases in the European Union	It does not provide methodology or specific information for methodological development for rare diseases
2	Taruscio, D. et al (63)	2018	Primary prevention as an essential factor ensuring sustainability of health systems: The example of congenital anomalies (Policy Brief)	It does not provide methodology or specific information for methodological development for rare diseases
3	De Santis, M. et al (64)	2018	INTEGRATED CARE (Policy Brief)	It does not provide methodology or specific information for methodological development for rare diseases
4	Iskrov, G. et al (65)	2018	Health systems for rare diseases: Financial sustainability (Policy Brief)	It does not provide methodology or specific information for methodological development for rare diseases
5	E-Rare (66)	2008	Report of the Workshop on Clinical Trials and Natural History of Rare Diseases	It does not provide methodology or specific information for methodological development for rare diseases
6	Zozaya, N. et al (67)	2017	Enfermedades raras. Evaluación económica y financiación de los medicamentos huérfanos. (Rare diseases. Economic evaluation and reimbursement of orphan drugs)	It does not provide methodology or specific information for methodological development for rare diseases
7	Zozaya, N. et al (68)	2019	El Análisis de Decisión Multi-Criterio como herramienta para la toma de decisiones en medicamentos huérfanos: una revisión de la literatura. (Multicriteria Decision Analysis as a	It does not provide methodology or specific information for methodological

			tool for decision making in orphan drugs: a review of the literature)	development for rare diseases
8	Zozaya, N. et al (69)	2020	El Análisis de Decisión Multi-Criterio como modelo alternativo de evaluación de medicamentos huérfanos (Multicriteria Decision Analysis as an alternative model of orphan drug assessment)	It does not provide methodology or specific information for methodological development for rare diseases
9	Advance-HTA consortium (70)	2015	Advance HTA - Advancing and strengthening the methodological tools and practices relating to the application and implementation of HTA	It does not provide methodology or specific information for methodological development for rare diseases
10	López-Bastida, J. et al (71)	2016	Social/economic costs and health-related quality of life in patients with rare diseases in Europe	It does not provide methodology or specific information for methodological development for rare diseases
11	Sejersen, T. et al (72)	2014	Methodology for production of best practice guidelines for rare diseases	It does not provide methodology or specific information for methodological development for rare diseases
12	Yeung, C. H. T. (73)	2016	Methodological challenges in rare disease guidelines	It does not provide methodology or specific information for methodological development for rare diseases
13	Towse, A. et al (74)	2018	Appraising ultra-orphan drugs: is cost-per-QALY appropriate? A review of the evidence	It does not provide methodology or specific information for methodological development for rare diseases
14	National Institute for Health and Care Excellence (NICE) (75)	2017	Interim process and methods of the Highly Specialised Technologies Programme (Updated to reflect 2017 changes)	It does not provide methodology or specific information for methodological development for rare diseases

15	Henderson, N. et al (76)	2020	Ethical and economic issues in the appraisal of medicines for ultra-rare conditions	It does not provide methodology or specific information for methodological development for rare diseases

ANNEX 7.5 | List of Institutions for Expert Consultation

#	Institution
1	RARE-Bestpractices
2	EURORDIS
3	Orphanet
4	ISPOR - Rare Disease Special Interest Group
5	European Union Committee of Experts on Rare Diseases (EUCERD)
6	National Institute for Health and Care Excellence (NICE)
7	Guidelines International Network (G-I-N)
8	Institute of Medicine of the USA (IOM)
9	Haute Autorité de Santé (HAS)
10	Joint Action on Rare Diseases
11	Joint Action on Rare Cancers (JARC)
12	French Foundation for Rare Diseases (FFRD)
13	Rare Voices Australia (RVA)
14	Canadian Organization for Rare Disorders (CORD)
15	European Organisation for Treatment & Research on Cancer (EORTC)
16	GRADE Working Group
17	(Cochrane UK) Cochrane
18	HAS (FR) - French National Authority for Health *
19	McMaster University (CA)
20	Karolinska Institutet
21	Institute for Quality and Efficiency in Health Care (IQWiG)

* Same as #9.

ANNEX 7.6 | Experts' Suggestions and answers

ERN	Profile	Institution	Country	Inclusion/Exclusion and reason	Modifications in the document (if any)
ERN TRANSPLANT-CHILD European Reference Network on Transplantation in Children	Methodologist	Hospital La Paz Institute for Health Research (IdiPAZ)	Spain	The search focused on methodological documents, documents on specific conditions or CPG or CDST for specific conditions, do not meet the inclusion criteria. For this reason, the suggestion cannot be included.	Not applicable
ERN GENTURIS European Reference Network on genetic tumour risk syndromes	Manager	Radboudumc	Germany	- Suggestion regarding patient inclusion/ involvement methodologies: The methodologies suggested do not meet the inclusion criteria because they are not specific for rare diseases. For this reason, the suggestion cannot be included. However, WP-B will consider rigorous and commonly accepted patient inclusion/involvement methodologies for the development of WP-B Toolkit.	Not applicable
				- Suggestion regarding consensus building methodologies: The search did not retrieve any methodological document regarding consensus building on rare diseases. For this reason, the suggestion cannot be included.	

				However, WP-B will consider rigorous and commonly accepted consensus building methodologies for the development of WP-B Toolkit.	
				- Suggestion regarding ADAPTE: The methodologies suggested do not meet the inclusion criteria because they are not specific for rare diseases. For this reason, the suggestion cannot be included. However, WP-B will consider ADAPTE as one of its main references for the adaptation of CPG for the development of WP-B Toolkit.	
ERN TRANSPLANT-CHILD European Reference Network on Transplantation in Children	Methodologist	Other facility	Spain	The search focused on methodological documents, documents on specific conditions do not meet the inclusion criteria. For this reason, the suggestion cannot be included.	Not applicable
ERN ITHACA European Reference Network on congenital malformations and rare intellectual disability	Healthcare professional (nurse, medical doctor)	Amsterdam UMC	Netherlands	The scheme to which the comment refers to was not provided, so it cannot be reviewed or included during the consultation period. For this reason, the suggestion cannot be included. We would be very grateful if you could share it with us.	Not applicable
ERN EURO-NMD European Reference Network on neuromuscular diseases	Healthcare professional (nurse, medical doctor)	Sorbonne Université, INSERM U974, Institut Myologie, GH Pitié-	France	The documents suggested do not meet the inclusion criteria because they are not specific for rare diseases. For this reason, the suggestion	Not applicable

		Salpêtrière, Paris		cannot be included. However, WP-B will consider rigorous and commonly accepted methodologies for the development, adaptation and implementation of CPG and CDST for the development of WP-B Toolkit.	
ERN eUROGEN European Reference Network on urogenital diseases and conditions	Healthcare professional (nurse, medical doctor)	HCP NL09 Radboudumc	Netherlands	The information provided in the institutions and initiatives suggested do not meet the inclusion criteria because they do not provide specific methodologies for rare diseases. For this reason, the suggestion cannot be included.	Not applicable
ERN RITA European Reference Network on immunodeficiency, autoinflammatory and autoimmune diseases	Manager	Paediatrics	Netherlands	- Suggestion regarding consensus building methodologies: The search did not retrieve any methodological document regarding consensus building on rare diseases. For this reason, the suggestion cannot be included. However, WP-B will consider rigorous and commonly accepted consensus building methodologies for the development of WP-B Toolkit.	Not applicable
				- Suggestion regarding the document "EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees": It is not specific for rare diseases; thus it does	

				not meet the inclusion criteria. For this reason, the suggestion cannot be included.	
ERN RITA European Reference Network on immunodeficiency, autoinflammatory and autoimmune diseases	Healthcare professional (nurse, medical doctor)	Paediatrics depsrtment, University Hospital	Netherlands	- Suggestion regarding consensus methodologies: The search did not retrieve any methodological document regarding consensus building on rare diseases. For this reason, the suggestion cannot be included. However, WP-B will consider rigorous and commonly accepted consensus building methodologies for the development of WP-B Toolkit. - Suggestion regarding EULAR website: It is not specific for rare diseases; thus it does not meet the inclusion criteria. For this reason, the suggestion cannot be included.	Not applicable
ERN eUROGEN European Reference Network on urogenital diseases and conditions	Healthcare professional (nurse, medical doctor)	St George's University Hospitals NHS Trust, London UK	United Kingdowm	The search did not retrieve any methodological document regarding consensus building on rare diseases. For this reason, the suggestion cannot be included. However, WP-B will consider rigorous and commonly accepted consensus building methodologies, such as Delphi methodology, for the development of WP-B Toolkit.	Not applicable

ERN CRANIO	Healthcare professional (nurse, medical doctor)	Erasmus MC	Netherlands	The methodologies suggested do not meet the inclusion criteria because they are not specific for rare diseases. For this reason, the suggestion cannot be included. However, WP-B will consider rigorous and commonly accepted patient inclusion/involvement methodologies for the development of WP-B Toolkit.	Not applicable

ANNEX 7.7 | Experts' Consultation Questionnaires

Consultation with ERNs on the Literature on CPG and CDST Methodologies for Rare Diseases- WP-B TENDER N° SANTE/2018/B3 /030

Fields marked with * are mandatory.

Consultation with ERNs on the Literature on CPG and CDST Methodologies for Rare Diseases- WP-B TENDER N° SANTE/2018/B3 /030

INTRODUCTION

We would like to thank you for kindly agreeing to participate in this consultation.

You have received this survey because you have accepted to participate in the expert consultation for WP-B of the TENDER N° SANTE/2018/B3/030 "European Reference Network: Clinical Practice Guidelines and Clinical Decision Support Tools".

The aim of WP-B is to develop methodologies for the appraisal, adaptation, adoption, development and implementation of Clinical Practice Guidelines (CPG) and Clinical Decision Support Tools (CDST) for rare diseases to be used by ERNs. It comprises two main tasks: 1) Analysis of the state of the art on methodologies for CPGs and CDSTs for rare diseases and 2) Elaboration of methodological manual and toolkit for the appraisal, adaptation, adoption, development and implementation of CPG and CDST on rare diseases to be used by ERNs. WP-B is lead by IACS (Aragon Health Science Institute).

This is the first consultation of the two consecutive consultations. The subjects of the two consecutive consultations will be:

First: Literature Review on methodologies for CPG or a CDST on rare diseases. (March 2020).

Second: Criteria for prioritization of topics that require a CPG or a CDST and Criteria for the assessment of the quality of CPG or a CDST for rare diseases. (April 2020)

Regarding this consultation: Literature Review on methodologies for CPG or a CDST on rare diseases

We would like to know your views on the literature review on methodologies for CPG and CDST for rare diseases performed by WP-B of the TENDER. For this, we would like you to fill in this survey.

Your input will be used to complete this report and will be used in the ongoing work of WP-B of the TENDER N° SANTE/2018/B3/030 to develop a Methodological Manual and Toolkit for the development and use of CPG and CDST on rare diseases.

You can find the report here

NOTE THIS IS AND INTERNAL DOCUMENT, PLEASE DO NOT SHARE IT WITH ANYONE.

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You can find the annexes here

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280220_ERN_RD_D-B.1Annexes.pdf

Practical information

You can stop and resume the survey as many times as you want.

The **deadline** for this first consultation is **March 20th 2020**.

If you have any questions or concerns, please contact **hta.iacs@aragon.es**

PERSONAL INFORMATION

* Profile

- [ ] Healthcare professional (nurse, medical doctor)
- [ ] Manager
- [ ] Policy maker
- [ ] Methodologist
- [ ] Researcher
- [ ] Other

Please indicate which one (free text)

* Care unit in which you work (hospital or other facility)

* Country of residence

Member States (EU-28) + Norway

Austria	Finland	Lithuania	Slovak Republic
Belgium	France	Luxembourg	Slovenia
Bulgaria	Germany	Malta	Spain
Croatia	Greece	Netherlands	Sweden
Cyprus	Hungary	Norway	United Kingdom
Czechia	Ireland	Poland	
Denmark	Italy	Portugal	
Estonia	Latvia	Romania	

* Are you a member of an ERN?
- Yes
- No

Please, indicate of which ERN are you a member:
- ERN BOND European Reference Network on bone disorders
- ERN CRANIO European Reference Network on craniofacial anomalies and ear, nose and throat (ENT) disorders
- Endo-ERN European Reference Network on endocrine conditions
- ERN EpiCARE European Reference Network on epilepsies
- ERKNet European Reference Network on kidney diseases
- ERN-RND European Reference Network on neurological diseases
- ERNICA European Reference Network on inherited and congenital anomalies
- ERN LUNG European Reference Network on respiratory diseases
- ERN Skin European Reference Network on skin disorders
- ERN EURACAN European Reference Network on adult cancers (solid tumours)
- ERN EuroBloodNet European Reference Network on haematological diseases
- ERN eUROGEN European Reference Network on urogenital diseases and conditions
- ERN EURO-NMD European Reference Network on neuromuscular diseases
- ERN EYE European Reference Network on eye diseases
- ERN GENTURIS European Reference Network on genetic tumour risk syndromes
- ERN GUARD-HEART European Reference Network on diseases of the heart
- ERN ITHACA European Reference Network on congenital malformations and rare intellectual disability
- MetabERN European Reference Network on hereditary metabolic disorders
- ERN PaedCan European Reference Network on paediatric cancer (haemato-oncology)
- ERN RARE-LIVER European Reference Network on hepatological diseases
- ERN ReCONNET European Reference Network on connective tissue and musculoskeletal diseases
- ERN RITA European Reference Network on immunodeficiency, autoinflammatory and autoimmune diseases
- ERN TRANSPLANT-CHILD European Reference Network on Transplantation in Children
- VASCERN European Reference Network on Rare Multisystemic Vascular Diseases

CONSULTATION ON THE LITERATURE REVIEW

After having reviewed the report on literature review (see link above):

* Have you identified relevant information missing from the report?
- Yes
- No

Please, indicate where in the report and what information

Please, indicate relevant references, including websites, projects, or papers, that could help us completing this information

You can also upload documents here:

The maximum file size is 1 MB

Thank you for your time and valuable input.

Consultation on the Literature Review on CPG and CDST Methodologies for Rare Diseases – WP-B TENDER N° SANTE/2018/B3/030

Fields marked with * are mandatory.

Consultation on the Literature Review on CPG and CDST Methodologies for Rare Diseases – WP-B TENDER N° SANTE/2018/B3/030

INTRODUCTION

We would like to thank you for kindly agreeing to participate in this consultation.

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Regarding this consultation: Literature Review on methodologies for CPG or a CDST on rare Diseases (March 2020)
We would like to know your views on the literature review on methodologies for CPG and CDST for rare diseases performed by WP-B of the TENDER. For this, we would like you to fill in this survey.

Your input will be used to complete this report and will be used in the ongoing work of WP-B of the TENDER N° SANTE/2018/B3/030 to develop a Methodological Manual and Toolkit for the development and use of CPG and CDST on rare diseases.

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Practical information

You can stop and resume the survey as many times as you want.

The **deadline** for this first consultation is **March 15th 2020.**

If you have any questions or concerns, please contact hta.iacs@aragon.es

PERSONAL INFORMATION

* Profile

- [ ] Healthcare professional (nurse, medical doctor)
- [ ] Manager
- [ ] Policy maker
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- [ ] Other

Please indicate which one (free text)

* Organization in which you work

* Country of residence

Member States (EU-28) + Norway

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Croatia	Greece	Netherlands	Sweden
Cyprus	Hungary	Norway	United Kingdom
Czechia	Ireland	Poland	
Denmark	Italy	Portugal	
Estonia	Latvia	Romania	

CONSULTATION ON THE LITERATURE REVIEW

After having reviewed the report on literature review (see link above):

* Have you identified relevant information missing from the report?
  - Yes
  - No

Please, indicate where in the report and what information

Please, indicate relevant references, including websites, projects, or papers, that could help us completing this information

You can also upload documents here:

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Thank you for your time and valuable input.

European Reference Networks

European Reference Networks | ERN GUIDELINES

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