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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 #8: Methodology for the elaboration of Evidence-Based Protocols for rare diseases

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Contents

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This handbook provides information about key issues related to developing an Evidence-Based protocol (EBP), including the composition of the EBP working group, the selection of the topic, search and critical appraisal of the evidence, and development of the clinical algorithm.

1. Background

With the launching of the first European Reference Network (ERN) in 2017, a care model based on the concentration of knowledge and resources in highly specialised 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 (CPG) and Clinical Decision Support Tools (CDST) to ensure the safest and most efficient care is provided to patients with rare diseases and carers through the EU.

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

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

1.1. Work Package B: Methodologies for CPGs and CDSTs for Rare Diseases

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 WP-B 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 handbook and toolkit for the prioritisation, appraisal, adaptation, development and implementation of CPGs and CDSTs for rare diseases.

It is worth noting that within the scope of WP-B, “rare diseases” is the term used to refer to rare diseases as well as low prevalence complex diseases.

1.2. Context for Evidence Based Protocols for rare diseases development

In real-world settings, health care can be inconsistent from one healthcare professional to the next to the same situation.

An Evidence-Based protocol (EBP) is a document aimed at organising and facilitating the clinical work of the healthcare professionls, developed by a synthesis of the best available evidence and it describes in detail and step by step, the actions to follow on a specific healthcare situation; so the EBP describes how a procedure should be performed. It is approved among professionals with the character of "agree to comply", and it adapts to the setting where it is applied and to the professionals who use it [2].

Evidence-based protocols involves combining healthcare professionals' expertise with the best available evidence from published research in order to make decisions about what to do in response to a presenting health intervention or problem. Therefore, protocols need periodically review to reflect the most up-to-date evidence.

1.3. The development process of Evidence Based Protocols for Rare Diseases: Main Steps

TASK	DEFINITION
Forming the EBP working group	•Describing the composition of the GDG •Managing the conflict of interest
Selecting the topic	•The process and criteria for selecting and prioritizing topics
Identifying the clinical question(s)	•Developing clinical questions according to the PICO framework
Obtaining the evidence	•Systematic searches of bibliographic databases using sensitive key words
Evaluating the quality of the evidence	•Appraising identified evidence using objective instruments
Synthesising the evidence	•Summarizing the results and quality of evidence.
Development of a clinical algorithm	•Representing the evidence-based activities in a diagram that depicts them step-by-step
Developing an evaluation plan or measurement strategy	•Defining relevant quality indicators
Updating the EBP	•Planning future updating (process and timeline).

2. Evidence-Based Protocol Development Group

It is necessary that the Evidence Based Protocol includes information about all the team members involved in its development, specifically: full name, position held or organisation that represents, and point of contact details of the person responsible of the protocol (for further clarification or questions) [2].

The protocol working group should be multidisciplinary, comprising healthcare professionals implicated in the care delivery of the issue addressed. Depending on the topic, patients and carers should be involved at least in one stage of the development process, as part of the working group or as external reviewers. When the term 'patients and 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.

It also should include at least one methodologist with expertise in the methods to review evidence, and one information specialist with expertise on scientific literature searching.

Although there are no hard and fast rules about how many people to include in the working group, although experience suggests that large groups can become unwieldy. In addition, it should be considered that the involvement of the staff responsible for the hands-on delivery of care is essential to the successful development and implementation of the protocol. In table 1 there is an example of how to present the EBP development group.

Table 1: Evidence Based Protocol Development Group

Evidence Based Protocol Development Group			
Coordinator Name and Surname	**Position held**	**Workplace**	**Phone / e-mail**
Other members of the team			
Name and Surname	**Position held**	**Workplace**	**E-mail**

In table 2 there is an example of how to present the information about the patients and carers involved in the development of the evidence-based protocol.

Table 2: Evidence Based Protocol patients and carers involment

Evidence Based Protocol Involvement and users group			
Name and Surname	**Role held**	**Organisation**	**Phone / e-mail**

2.1. Management of conflicts of interest

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

3. Selecting the topic

EBP focus on the diagnosis and management of specific clinical situations. Some examples are listed below:

- Evidence-based protocol on the urinary catheter cares in intensive care units [3].
- Evidence-based protocol for structural rehabilitation of the spine and posture [4].
- Evidence-based protocol on wound drain management for total joint arthroplasty [5].

The topic to be covered by the EPB should be selected based on different situations. For example:

- Identification of opportunities for improvement in current processes of care.
- Care situations requiring standardisation due to inappropriate variability among healthcare professionals.
- A new care intervention to be implemented for the first time in the care setting.
- The topic represents a high risk for the organisation and clinical governance considerations indicate that actions are needed.
- New evidence has become available.
- Patients and carers express interest in a particular issue or area.
- The procedure is low volume which may generate uncertainty and variability.

It is important to consider the context in which the protocol will be implemented and used, because this will determine the topic to be covered, who will be involved in its development and the scope and purpose of the protocol.

4. Justification, scope and purpose of the Evidence-Based Protocol

4.1. Justification

This section must explain the causes and reasons why the EBP is needed. It must provide information on the current situation of the detected problem: what and where does it occur? To whom and how does it happen? Alternatively, how much happens? For example, the information included could be [2]:

- Definition of the detected problem.
- Existence of data about the problem and its social impact.
- People affected by the problem.
- Prevalence and incidence of the disease.
- Morbid-mortality of the problem.
- Existence of scientific studies that corroborate what we want to study etc

4.2. Scope and purpose

The objectives are the intended results to be achieved because of the application of the EBP. They will answer the question: what do we want to achieve? The patient perspective may also be useful.

It is important that any EBP should be associated with clear objectives that are [2]:

- Specific: clear on what, where, when and how the situation will change
- Measurable: that it is possible to quantify the benefits or purpose
- Achievable: that it is possible to reach the objectives (with available resources and capacities) to lead to care improvements.
- Realistic: that it is possible to obtain the level of change reflected in the objective and
- Limited in time: establishing the period in which each of them must be completed.

Objectives must start with an infinitive verb and they must be as operational as possible [i.e. reduction of the problem and the complications derived from its application, benefits for people (increase in quality of life, decrease in morbidity and mortality ...), for staff and organisation (standardisation of clinical interventions, reduction of variability etc.).

Example:
Increase the number of parents who receive information on non-pharmacologic strategies to reduce seizure risk in children new diagnosed with Dravet Syndrome.

The scope of the evidence-based protocol includes the following components:

- Target population and exceptions: characteristics of the population and any subgroups to which the protocol applies should be described (age group, type of disease or condition, disease or condition severity, or comorbidities). Any exception shoud also be stated (i.e. presence of characteristics in patients that make the application of the protocol unnecessary because it does not solve the health problem, does not prevent the risk, or aggravates the problem or risk).
- Professionals to whom the protocol is intended: the potential healthcare and non-healthcare professionals (and department or unit if necessary) users of the protocol should be indicated.
- Context of application: the health care setting to which the protocol applies is described, including the health system level (e.g. primary care, acute care) and clinical stage (e.g. prevention, screening, assessment, treatment, rehabilitation or monitoring).

5. Identifying the clinical questions

The definition of the clinical questions of interest may be informed by a preliminary search of the literature. The EBP working group have relevant expertise and will also contribute importantly to this task. Clinical questions will be developed according to the PICO format (Patients, Intervention, Comparison and Outcomes) (see the Handbook #4: Methodology for the elaboration of CPGs for rare diseases for additional information).

6. Obtaining the evidence

The systematic identification of evidence is an essential step in evidence-based protocol development. Hence, the EBP must include the search strategies used, databases consulted, search period established, and inclusion/exclusion criteria for the selection of the studies. This information should be accurately described to ensure transparency and reproducibility.

The sources of evidence should be considered in the following order: clinical practice guidelines (CPGs), systematic reviews, and original research studies.

The existence of clinical guidelines can facilitate the elaboration of EBP because they include a series of recommendations based on a systematic review of best available evidence that can be used as a source of evidence

to determine the activities of the protocol. In table 3, there are some especific databases to search for clinical guidelines.

Table 3: Main databases to identify clinical practice guidelines.

ECRI Guidelines Trust®	https://guidelines.ecri.org/
G-I-N international guideline library	www.g-i-n.net/library/international-guidelines-library
GuíaSalud	www.guiasalud.es
NICE (National Institute for Health and Care Excellence) clinical guidelines	www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines/nice-clinical-guidelines
Orphanet	www.orpha.net
RARE-Bestpractices	www.rarebestpractices.eu
Scottish Intercollegiate Guidelines Network (SIGN)	www.sign.ac.uk
CMA Infobase: Clinical Practice Guidelines Database (CPGs)	www.cma.ca/En/Pages/clinical-practice-guidelines.aspx
Australia's Clinical Practice Guidelines Portal	www.clinicalguidelines.gov.au
Tripdatabase	www.tripdatabase.com
MEDLINE and EMBASE by using methodological filters	

A detailed description of the development of search strategies and information sources for the retrieval of systematic reviews and individual research studies can be consulted in the Handbook #4: Methodology for the elaboration of CPGs for rare diseases).

7. Evaluating the quality of the evidence

Once retrieved, the CPGs, systematic reviews or clinical research papers, it is necessary to establish its methodological quality.

- The methodological quality of CPG should be appraised using the AGREE II tool [6].
    - The methodological quality of systematic reviews and individual research studies has to be appraised and the results summarised by applying the methodology developed by the GRADE Working Group [1] (Grading of Recommendations Assessment, Development and Evaluation)(see the Handbook #4: Methodology for the elaboration of CPGs for rare diseases for additional information).

In abscense of recommendations from CPGs to support a particular activity of the evidence-based protocol, it will be necessary to make recommendations from the retrieved evidence, i. e. systematic reviews or individual research studies. The recommendations should be formulated using GRADE. According to this system, the strength of recommendations is based not only on the quality of the evidence, but also on a series of factors such as the risk/benefit balance, values and preferences of the patients and carers and professionals, and the use of resources or costs [7, 8]. More information on the formulation of recommendations can be found in the Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

Alternatively, the EBP development group could choose not to formulate recommendations and use directly the information retrieved and analysed from systematic reviews or from a pool of original studies. Nonetheless it should be noted that this is a less robust methodological approach and can only be done if, after a thorough appraisal of the

evidence, the size of the effect proofs to be relevant enough, and the applicability and acceptability of the findings to the scope and purpose of the EBP are well founded.

When evidence is scarce or absent, expert consensus should be considered as the source of information, either within the EBP development group or obtained from published literature. Any activity based on the consensus of experts should be clearly stated and the rationale for this provided.

8. Step-by-step activities to be followed

The next step will be to list the relevant activities to be followed in the protocol, which have been identified in the scientific evidence and the clinical experience of the EBP development group, following the logical sequence to perform in the clinical practice. It is important that each activitiy indicated includes (when possible) the source of evidence that supports that activity [2].

In table 5, there is an example about how to present the activities in the protocol.

Table 5: Activies to follow in the Evidence-Based Protocol

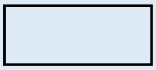
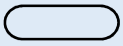
Activity	**Level of evidence**	**Grade of recommendation** (if proceed)	**Exceptions**

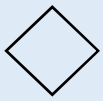
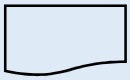
The interpretation of the levels of evidence and grading of recomendation indicated in the activities should be included in the annexes of the protocol.
When activities are supported by expert consensus, this should be clearly stated.

9. Development of a clinical algorithm

To facilitate its implementation in clinical setting, the activities previously listed can be represented in a diagram that depicts the activities step-by-step to follow to solve a task. The diagram is developed using different shapes. The six basic flowchart shapes and their meaning are represented in table 6. Depending on the activity to describe, additional shapes can be added [2].

Table 6: Common Flowchart Symbols

Flowchart Symbol	Name	Description
Process		This shape represents a step in the flowcharting process, action, or function. It is the go-to symbol once the flowcharting has started. It represents any step in the process.
Start/End		This symbol represents the start points, endpoints, and potential outcomes of a path.

Decision		Indicate that a decision is required to move forward. This could be a binary, this-or-that choice or a more complex decision with multiple choices.
Arrow		Indicate Directional Flow. The arrow is used to guide the viewer along their flowcharting path. It is recommended sticking with the same arrow (or two at most) for the entire flowchart. This keeps the diagram looking clean, but also allows emphasising certain steps in the process.
Document		It shows that there are additional points of reference involved in your flowchart

10. Development of an evaluation plan or measurement strategy

In order to follow-up on the compliance with the protocol and assess the level of fulfilment of the objectives, a follow-up assessment strategy has to be established. These include the definition of relevant quality indicators. For each objective, there must be at least one indicator. Indicators can highlight potential quality improvement areas and track changes over time.

Handbook #10: Methodology for the elaboration of Quality Measures for rare diseases provides more detailed information on the characteristics and steps in the development and deployment of indicators.

11. Consultation process and dealing with stakeholders' comments

The preliminary version of the EBP should undergo an exhaustive external review by the stakeholders. The aim of this consultation is ensuring that the EBP comprises the relevant elements and that it addresses appropriately its purpose. How to conduct the consultation process, including how to deal and incorporate the suggestions made by the stakeholders are detailed in Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

12. Edition of the final document

The final document should be easily accessible to end-users. The information must be structured to facilitate its reading and understandability. The final document should include the following content:

- Introduction
- Evidence-based development group
- Justification, scope and purpose
- Table with the activities to be followed and the evidence behind them (see table 5)
- Graphical representation
- Quality measures (set of indicators)
- Glossary

The methodological material may be allocated in annexes and it will contain information about:

- Clinical questions addressed in the EBP

- Search of the scientific evidence: search strategies and sources of information
- Methods for the selection and appraisal of the scientific evidence
- Methods for the selection or formulation of recommendations (if applicable)

In addition, it should include a plan for a future updating. It is recommended to evaluate the need for updating the EBP every three years [9].

Key issues

- The EBP working group should be multidisciplinary, comprising all relevant profiles implicated in the care delivery of the issue addressed, including healthcare professionals, patients and carers and a methodologist.
- It is important to consider the context in which the protocol will be implemented and used, because it will determine the topic to be covered, who will be involved in its development and the scope and purpose of the protocol.
- The elaboration of the protocol must be justified on the current situation of the detected problem: what and where does it occur? To whom and how does it happen? Alternatively, how much happens?
- The scope must be defined in terms of the target population covered and exceptions, professionals to whom the protocol is intended and the context of application.
- the clinical questions of interest may be informed by a preliminary search of the literature. The EBP working group have relevant expertise and will also contribute importantly to this task.
- The sources of evidence should be considered in the following order: clinical practice guidelines (CPGs), systematic reviews, and original research studies. The evidence retrieved should be appraised.
- In absence of recommendations from CPGs, recommendations should be formulated using GRADE or consensus methods, if no evidence has been found or is scarce.
- The activities of the protocol should be clearly listed and presented together with its respective level of evidence, grade of the recommendations and exceptions).
- An algorithm should be developed to depict the activities step-by-step to follow to solve a task.
- Relevant quality indicators have to be defined for each objective.

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