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

Handbook #8: Methodology for the Development of Evidence-Based Protocols for Rare or Low-Prevalence and Complex Diseases

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This handbook includes a detailed explanation of the process for developing Evidence-Based Protocols for rare diseases, including:

- ✓ Forming the EBP working group
- ✓ Selecting the topic
- ✓ Identifying the clinical question(s)
- ✓ Obtaining the evidence
- ✓ Evaluating the quality of the evidence
- ✓ Synthesising the evidence
- ✓ Development of a clinical algorithm
- ✓ Developing an evaluation plan or measurement strategy
- ✓ Updating the Evidence-Based Protocol

Purpose:

To provide guidelines for the development of Evidence-Based Protocols for rare diseases.

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ABBREVIATIONS

AMSTAR-2	A Measurement Tool to Assess Systematic Reviews-2
CDSTs	Clinical Decision Support Tools
CERQual	Confidence in the Evidence from Reviews of Qualitative research
CHEC	Consensus on Health Economic Criteria
CPGs	Clinical Practice Guidelines
DG	Development Group
EC	European Commission
ERN	European Reference Network
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
IACS	Aragon Health Sciences Institute
InterTASC-ISSG	InterTASC Information Specialists' Sub-Group
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RoB 2	Risk of Bias 2
ROBINS-I	Risk of Bias In Non-randomized Studies of Interventions-I
SoF	Summary of Findings

01.

BACKGROUND

There are a number of challenges surrounding the development of CPGs and CDST for rare diseases. One of the most relevant barriers is the lack of high-quality evidence, which cutting-edge 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 (CDSTs) for rare diseases. The project also aims to provide a common methodology to harmonise the development of CDSTs and CPGs.

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

1.1 | Context for the development of Evidence-Based Protocols for rare diseases

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

An Evidence-Based Protocol (EBP) is a document that seeks to organise and facilitate the clinical work of healthcare professionals, synthesizing the best available evidence and describing, in detail and step by step, the actions to follow in a specific healthcare situation. Therefore, the EBP describes how a procedure should be performed. It is approved among professionals on an "agree to comply" basis, and it adapts to the setting where it is applied and to the professionals who use it [2].

Evidence-based protocols involve combining healthcare professionals’ expertise with the best available evidence from published research in order to make decisions on what to do in response to a health intervention or problem. Therefore, protocols need to be periodically reviewed to reflect the most up-to-date evidence.

1.2 | 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).

02.

EVIDENCE-BASED PROTOCOL DEVELOPMENT GROUP

The Evidence-Based Protocol must include information on all the team members involved in its development, specifically: full name, position held or organisation he/she represents, and point-of-contact details of the person responsible for the protocol (for further clarification or questions) [2].

The protocol working group should be multidisciplinary, comprising healthcare professionals implicated in the delivery of care for the condition addressed. Patients and carers should be involved in at least 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 evidence review methods, and one information specialist with expertise on scientific literature searching.

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

Table 2 provides an example of how to present the information on the patients and carers involved in the development of the evidence-based protocol.

Table 2. Evidence-Based Protocol patients and carers involvement

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 among the members of the EBP development group should be carefully identified and duly addressed, following the indications established by our partner FPS.

03.

SELECTING THE TOPIC

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

- ✓ Evidence-based protocol on 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 the improvement of current care processes.
- ✓ 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.

04.

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? Who does it effect and how does it occur? Alternatively, what is the extent of the problem? 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 with the application of the EBP. They will answer the following 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: it is possible to quantify the benefits or purpose.
- ✓ Achievable: it is possible to achieve the objectives (with available resources and capacities) and thus lead to care improvements.

- ✓ Realistic: it is possible to obtain the level of change reflected in the objective; and
- ✓ Limited in time: it establishes the period in which each of objective must be achieved.

Objectives must start with an infinitive verb and they must be as operational as possible [i.e. reduction of the problem and the complications deriving from its application, benefits for people (increase in quality of life, decrease in morbidity and mortality, etc.), 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 newly diagnosed with Dravet Syndrome.

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

- ✓ Target population and exceptions: the 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 should 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).

05.

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 has relevant expertise and will also contribute significantly 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 Development of CPGs for Rare Diseases for additional information).

06.

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 development of EBPs 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. Table 3 provides specific details of databases that can be used to search for clinical guidelines.

Table 3. Main databases for identifying 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 Handbook #4: Methodology for the Development of CPGs for Rare Diseases.

07.

EVALUATING THE QUALITY OF THE EVIDENCE

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

✓ The methodological quality of CPGs 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 (Grading of Recommendations Assessment, Development and Evaluation) Working Group [1] (see Handbook #4: Methodology for the Development of CPGs for Rare Diseases for additional information).

In the absence of recommendations from CPGs to support a particular activity of the evidence-based protocol, it will be necessary to make recommendations based on 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 Handbook #4: Methodology for the Development 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 proves 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 a 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.

08.

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 activity indicated includes (when possible) the source of evidence that supports that activity [2].

Table 5 provides an example of 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 applicable)	**Exceptions**

The interpretation of the levels of evidence and grading of recommendation indicated in the activities should be included in the annexes of the protocol.

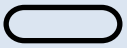
When activities are supported by expert consensus, this should be clearly stated.

09.

DEVELOPMENT OF A CLINICAL ALGORITHM

To facilitate their implementation in clinical settings, the activities previously listed can be represented in a diagram depicting the activities to follow step-by-step 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. The same arrow (or two at most) should be used for the entire flowchart. This keeps the diagram clean, but also allows certain steps in the process to be emphasized.
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 Development 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 to ensure that the EBP comprises the relevant elements and fulfils its purpose properly. Details of how to conduct the consultation process, including how to deal with and incorporate the suggestions made by the stakeholders, are provided in Handbook #4: Methodology for the Development 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 supporting them (see Table 5)
- ✓ Graphical representation
- ✓ Quality measures (set of indicators)
- ✓ Glossary

The methodological material may be included in annexes and it will contain information on:

- ✓ 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. The need for updating the EBP every three years should be evaluated [9].

Key issues

- The EBP working group should be multidisciplinary, comprising all relevant profiles involved in the delivery of care for the problem 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, the persons involved in its development and the scope and purpose of the protocol.
- The development of the protocol must be justified according to the current situation of the detected problem: What and where does it occur? Who does it effect and how does it occur? Alternatively, to what extent does it occur?
- The scope must be defined in terms of the target population covered and exceptions, professionals for 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 will have relevant expertise and will also make important contributions to this task.
- The activities of the protocol should be clearly listed and presented together with their respective levels of evidence, the grade of the recommendations and exceptions).
- An algorithm should be developed to depict the activities to be followed step-by-step to resolve a task.
- Relevant quality indicators have to be defined for each objective.
- 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 the absence of recommendations from CPGs, recommendations should be formulated using GRADE or consensus methods, if no evidence has been found or is scarce.

13.

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