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

Handbook #7: Methodology for the elaboration of Diagnostic, Monitoring and Therapy Pathways for Rare Diseases

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Handbook #7: Methodology for the elaboration of Diagnostic, Monitoring and Therapy Pathways for Rare Diseases.

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ABBREVIATIONS

AETSA	Andalusian Health Technology Assessment Department
AGREE II	Appraisal of guidelines for research & evaluation II
AMSTAR	A Measurement Tool to Assess Systematic Reviews
CDSTs	Clinical Decision Support Tools
CPGs	Clinical Practice Guidelines
DG	Development Group
EC	European Commission
ER	Evidence Reports
ERN	European Reference Network
FPS	Fundación Progreso y Salud
GDD	Global Developmental Delay
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health technology assessment
IACS	Aragon Health Sciences Institute
LD	Learning Disability
PDSA	Plan Do Study Act
PICO	Population, Intervention, Comparator, Outcome
PROs	Patient Reported Outcome
SR	Systematic Reviews
WP	Work Package

This handbook provides the main steps and relevant considerations when developing a Diagnostic, Monitoring and Therapy Pathway for rare diseases, including the constitution of the development group, definition of the scope, the development of the clinical questions, the formulation of recommendations based on the evidence, the definition of the pathway, it graphical representation and the design of a follow-up assessment. In addition to this, the update and external consultations process and edition of the final pathway are explained.

01.

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 barrier 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 (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 Diagnostic, Monitoring and Therapy Pathways development in rare diseases

Diagnostic, monitoring and therapy pathways (Pathways) are multidisciplinary care management tools, which describe the procedure for the care and treatment of a disease, condition or complex process. Their aim is to improve the care and management of patients, while enhancing the coordination of healthcare around the patient[2]. Pathways standardise care so that all patients are provided with the same high quality evidence-based care, that is timely and cost-effective and enable the documentation of changes in care, as a result of the patient's health status[3].

Pathways have demonstrated higher impact on healthcare quality and safety in complex conditions, such as rare diseases. Complex conditions require a multidisciplinary use and organisation of resources[4]. For example, in the case of patients that have to undergo a complex major surgical procedure, a myriad of care procedures has to be coordinated to optimise preoperative preparation, surgical recovery and postoperative rehabilitation.

Multidisciplinary and care-intensive procedures are resource-consuming and prone to safety hazards. By outlining the sequence and timing of interventions and defining desired outcomes within a specified period of time, pathways can help make a more efficient use of care resources, i.e. rationalise the use of resources without compromising care quality[4].

The use of pathways is associated with several specific advantages and benefits, such as[3]:

- ✓ Promoting patient centred-care, organising the care around the patient and enhancing communication with patients and carers.
- ✓ Fostering patient education and the provision of information regarding care provided
- ✓ Facilitating collaboration within the multidisciplinary team in the continuum of care
- ✓ Maximising the use of resources, for example minimise unnecessary tests or procedures.

1.3 | The development process of Diagnostic, Monitoring and Therapy Pathways: Main steps

TASK	DEFINITION
Pathway Development Group	• Constitution of the team that will develop the pathway and lead its final edition.
Definition of the scope	• Selection of a procedure or activity to develop the pathway • Objectives, target population and aspects to be covered
Identification of uncertainty, variability and formulation of questions	• Evaluation of current care processes •Formulation of clinical questions
Search, selection and appraisal of the scientific evidence	• Selection of the sources of information •Appraisal and synthesis of the evidence
Formulation of recommendations	• Based on the evidence/ consensus
Definition of the pathway	• Considering safety issues, entry, exit and marginal limits, professionals involved, activities and good practices, specific capabilities, support units, specific material resources
Graphical representation	• Task-time matrix/ Pathway flowchart/ Patient's Roadmap
Follow-up assessment	•Development of indicators •Continuous improvement cycles
Update Process	•Updating of the pathway every 3 years (minimum)
Consultation Process	•External review and incorporation of suggestions and comments
Edition of the pathway	•Complete pathway •Methodological material

02.

DIAGNOSTIC, MONITORING AND THERAPY PATHWAY DEVELOPMENT GROUP

The pathway development group (pathway DG) is a multidisciplinary group of professionals and users' and/or patients' representatives responsible for the development of the pathway.

2.1 | Composition of the Diagnostic, Monitoring and Therapy Pathway Development Group

The diagnostic, monitoring and therapy pathway development group (pathway DG) should include individuals from all relevant professional groups, with representation of the expertise and views relevant to the scope of the pathway, including those of the patients. The following roles should be included in the pathway DG.

- ✓ Chair/ coordinator with leadership capabilities and experience in evidence-based diagnostic, monitoring and therapy pathway.
- ✓ Specialists:
  - Healthcare professionals that are involved at any stage of the pathway, including members of the corresponding ERN. Ideally, members of the ERN should be drawn from different parts of Europe, but this will be influenced by the expertise available. In the case of paediatric diseases, general practitioners and/or paediatricians should be included. For diseases revealed at paediatric age, the group should be involved specialists in childhood and adulthood management of the disease, to cover the transition from paediatric to adult healthcare services[5].
  - Methodologist(s) with expertise in the methods to review evidence and develop pathways.
  - Information specialist with expertise on scientific literature searching[6].
- ✓ Users' and/or patients and carers: They are essential in order to ensure a comprehensive perspective is adopted throughout the implementation and relevant objectives are established.

  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.

Ideally, the number of participants include 4 to 10 members, apart from the chair/coordinator, the

methodologist(s) and the information specialist. Members of the ERN from different parts of Europe should be considered.

2.2 | Management of conflict of interest

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

03.

DETERMINING THE SCOPE OF THE DIAGNOSTIC, MONITORING AND THERAPY PATHWAY

The scope of the pathway lays the foundations for the definition of the clinical questions and development of recommendations that will make up the pathway.

3.1 | Selection of a procedure or activity to develop the pathway

The first step for determining the scope of the pathway is to identify the procedure or activity within the condition[i] for which the pathway will be developed, i.e. the procedure or activity were a pathway is required to improve quality of care and/or efficiency.

There are different criteria to select the procedure or activity, such as the high risk or level of complexity the procedure or activity entails, the existing (unwarranted) variability of clinical practice or use of resources and costs. An example of procedure could be first line metabolic, genetic and radiological testing for children and adults with unexplained global developmental delay (GDD).

Based on these criteria, the pathway DG should discuss and agree on a procedure or activities that will be the focus of the pathway.

3.2 | Definition of the objectives, target population and aspects to be covered

Once the care procedures or activities that will be tackled have been decided, the specific objectives of the pathway should be defined. The objectives of the pathway are aligned with the main benefits for quality of care and/ or efficiency that the pathway aims at achieving. For example, to address the condition at an earlier stage, hence promoting clinical effectiveness and better risk management, to foster clinical audit, to improve multidisciplinary communication, teamwork and care planning, to provide explicit and well-defined standards for care, among others[7].

Furthermore, the target population and the aspects of the procedure that will be covered by the

[i] The condition that is the subject of the pathway is decided in the prioritisation process developed in WP-A and WP-B. See Handbook #1: Prioritisation of the rare diseases that require CPGs or CDSTs for more information on the prioritisation process.

pathway should be defined with regards to the following aspects:

- ✓ Target population: The characteristics of the population of interest and any subgroups that will be subject to enter the pathway, including the age, type of disease or condition, severity or comorbidities.
- ✓ Aspects to be covered: The situations or activities that will be addressed in the pathway (e.g. screening, monitoring), and those that will not be covered, although they are part of the usual process.

Both will be further specified with the establishment of entry, exit and marginal limits of the pathway in chapter 7.

04.

IDENTIFICATION OF UNCERTAINTY AND UNWARRANTED CLINICAL VARIABILITY AND FORMULATION OF THE CLINICAL QUESTIONS

4.1 | Evaluation of the current care process

Uncertainty areas are those care areas where there is lack of evidence-based, robust and clear guidance on the most appropriate way to proceed. Unwarranted clinical variability occurs when it cannot be explained by illness, medical need, or evidence-based guidance in relation to the condition. The identification of uncertainty areas and clinical variability areas is the first step for determining the clinical questions that will be addressed in the pathway.

It can be done by mapping out the care pathway that the target population currently follows from admission to discharge. While doing the mapping, it is important to consider all aspects of the patient pathway through the continuum of care, e.g. from the emergency department to inpatient admission and transition back to community or reviewing the preoperative process for the surgical population[8].

Different data sources where the information on the flow of the patient are collected should be consulted. These data sources can be health system data (computerised hospital files where the patient diagnosis is coded usually using the International Classification of Diseases (ICD)), healthcare provider's databases (permanent registrations of patient information in a systematic way, carried out by one healthcare provider or specific regional healthcare system on the basis of their referrals) or the ERN's patient registries, amongst others. More information on data sources can be found in the Handbook #10: Methodology for the elaboration of Quality Measures for rare diseases Besides, existing pathways, protocols and other internal procedures currently being used should be reviewed[6].

Once the uncertainty areas and clinical variability areas have been identified, they should be prioritised according to their relevance and urgency in tackling them. The pathway DG should discuss and/or go through a formal or informal consensus process in order to prioritise the uncertainty areas and clinical variability areas, and determine which ones will be addressed in the pathway.

4.2 | Formulation of clinical questions

Based on the uncertainty and clinical variability areas prioritised, generic clinical questions should be formulated. For example: What are the criteria for referral to genetic testing when hypermobile subtype Ehlers-Danlos syndrome is suspected?

These generic questions will then be transformed into structured clinical questions, through the PICO format.

4.2.1 | Structuring clinical questions (PICO format)

PICO format is the most common structure used to articulate questions in terms of its four anatomic parts (population, intervention, comparison, and outcomes), according to the PICO format:

- ✓ Definition of the **population** of interest, specifying the health condition or stages of disease, characteristics of the population such as age, gender, comorbidities or risk profiles and care setting (Hospital and/or community). When the rare disease does not have clear diagnostic criteria, it may be helpful to use a broad definition of the population by incorporating closely related disease entities to potentially increase the amount of data relevant to the PICO question[9].
- ✓ Description of the **intervention** to be evaluated (i.e. the procedure or activity on which the pathway focuses). When the patterns of practice differ within a given rare disease or treatments are not used in a consistent way, thus making it difficult to give a standardised definition of the intervention, the use of broad definitions may be an adequate approach (e.g., a class of medication instead of a particular medication)[9].
- ✓ Description of the **comparator** or intervention to be compared. Comparisons of interest may include alternative options.
- ✓ Specify all potential clinically relevant and patient important **outcomes** and decide on the measures or variables according to which these outcomes will be assessed or monitored, or on the estimators of performance or diagnostic reliability. Outcomes may include survival (mortality), clinical events (e.g. strokes or myocardial infarction), patient-reported outcomes (e.g. symptoms, quality of life), adverse events, burdens (e.g. demands on caregivers, restrictions on lifestyle) and economic outcomes (e.g. cost and resource use). Indirect or surrogate outcome measures, such as laboratory results are potentially misleading and should be avoided or interpreted with caution because they may not predict clinically important outcomes accurately. Surrogate outcomes may provide information on how a treatment might work but not whether it actually does works[10]. Relying on surrogate outcomes can be even more problematic in rare diseases because the pathophysiology and empiric evidence linking them to patient important outcomes are less likely to be well-understood[9].

05.

SEARCH, SELECTION AND APPRAISAL OF THE SCIENTIFIC EVIDENCE

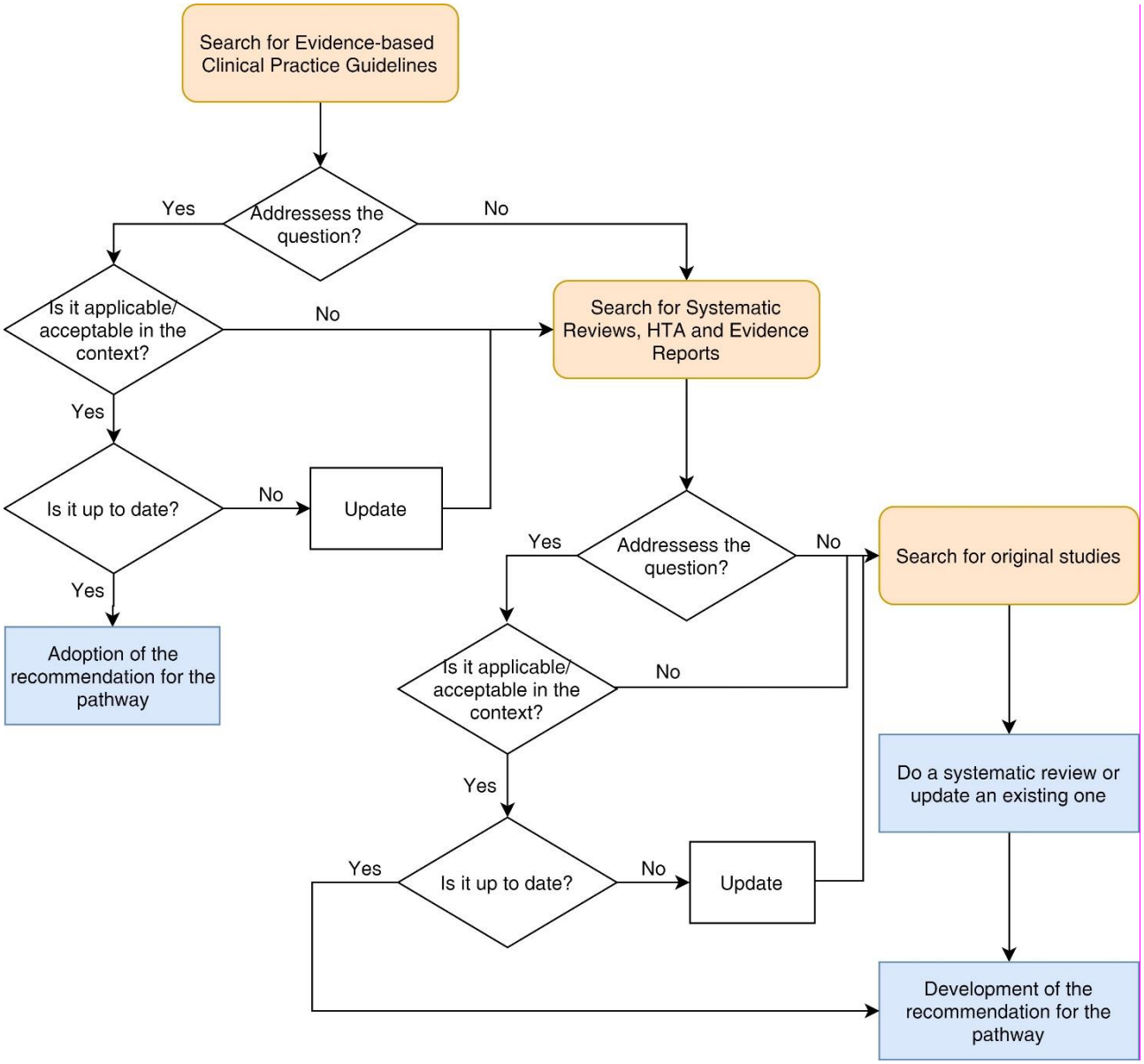
The best available evidence should guide every activity of the pathway. The objective of this step is to identify recommendations from Clinical Practice Guidelines (CPGs) or, if necessary, Systematic Reviews (SR), Health Technology Assessment reports and Evidence reports or original research studies that may be used to develop recommendations, or as supporting evidence directly linked to the decision or activity.

Different sources of evidence can be used for the development of the pathway. CPGs are the source of choice, however, other sources should also be considered, especially in the context of rare diseases, where there may be less CPGs available than in that of common diseases.

The search and selection of the scientific evidence that will be the basis for the pathway should be done following an explicit search strategy, according to the inclusion and exclusion criteria that were agreed for each clinical question (components of the PICO format).

Herein are depicted (Figure 1) and explained the steps that the pathway DG should take in order to select the scientific evidence according to the different sources considered and to appraise its quality, acceptability/ applicability and currency.

Figure 1. Search, selection and appraisal of the scientific evidence



A) Recommendations from Clinical Practice Guidelines (CPGs)

CPGs are the most common source of evidence for the development of pathways and should be considered in the first place. When a CPG on the condition of the pathway is retrieved its methodological quality should be appraised using the AGREE II tool[11], as mentioned in Handbook #2: Appraisal of existing CPGs and CDSTs for rare diseases. Preferably, no more than 3 years should generally have passed since the date of the elaboration and/or review or update of the CPG. Detailed information on the sources of information that should be consulted when searching CPG can be found in the update chapter of the Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

If the CPG is considered to have enough quality and currency, the acceptability/ applicability of the recommendations that address the procedure/ activities of the pathway will be assessed separately. This assessment is based on the judgement of the pathway DG, informed by their experience and knowledge of the context.

- ✓ Acceptability refers to whether the recommendation should put it into practice (e.g. is it worthy, does it suit the target population of the pathway, are patients' and carers' views and preferences met).
- ✓ Applicability refers to the ability of organisation or group to put the recommendation into practice (e.g. availability of the resources required available, existence of constraints, organisational barriers, legal barriers, policies).

The recommendation adopted should be presented with its strength of recommendation, indicated in the system used to develop the CPG (e.g. SIGN[12], GRADE[1], etc.).

If no CPG that addresses the question is found or the methodological quality of the CPG found is questionable, SR, HTA reports should be considered as the second-best source of information.

B) Systematic Reviews, Health Technology Assessment reports and Evidence Reports

In order to select and appraise the evidence from SR/HTA reports/ evidence reports[ii] for the pathway, these steps should be completed:

- ✓ Search and selection of SR, HTA reports and evidence reports: Detailed information on the design of the search strategy and the sources of information that should be searched can be found in Handbook #4: Methodology for the elaboration of CPGs for rare diseases.
- ✓ Methodological quality appraisal: This should be done used using GRADE, which provides a reproducible and transparent framework for grading certainty in evidence[13], according to five domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias. In the case of SR, the risk of bias should be assessed using AMSTAR[14]. More information on the use of GRADE can be found in Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

If no SR, HTA reports or evidence reports are found or if the methodological quality is not acceptable, original studies should be considered as the source of information.

C) Original research studies

In order to select and appraise the evidence from original studies for the pathway, these steps should be followed:

- ✓ Search and selection of original studies: Detailed information on the design of the search strategy and the sources of information that should be searched can be found in Handbook #4: Methodology for the elaboration of CPGs for rare diseases.
- ✓ Appraise the methodological quality: Using GRADE, which provides a reproducible and transparent framework for grading certainty in evidence[13], according to five domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias. More information on the use of GRADE can be found in Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

[ii] Within the scope of this Handbook, Evidence reports are understood as systematic reviews that summarise the best available evidence on a topic. Evidence reports are generally used by clinical professional organisations to support the development of clinical practice guidelines or by policy makers to inform their programme planning and research priorities. More information can be found in Handbook #6: Methodology for the elaboration of Evidence Reports for rare diseases

If the methodological quality is not acceptable, or no studies are found, group consensus should be considered as the source of information (see chapter 6).

Together with these sources of evidence, the pathways, protocols, procedures and other relevant information currently in use in the countries of the ERN should also be reviewed. The pathway DG can gather this information from the representatives of the countries present in the ERNs and consult with the Working Group on Knowledge Generation.

06.

FORMULATION OF RECOMMENDATIONS

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[15,16]. More information on the formulation of recommendations can be found in Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

Alternatively, the pathway DG 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 pathway are well founded.

6.1 | Formulation of recommendations based on consensus

As mentioned in chapter 5, if no evidence is retrieved, the pathway DG should use consensus methodologies to formulate recommendations.

The consensus can be either formal or informal. If it is informal, it is important to ensure that each individual view is presented and debated in an open and constructive manner at the pathway DG meeting. In both cases, it must be made explicit justified properly that the scientific evidence is insufficient or limited for formulating evidence-based recommendations[17].

Besides, the formal or informal method used to achieve consensus should be clearly stated (e.g., Delphi method, nominal group technique/expert panel, consensus development conferences)[18]. More information on the development of consensus can be found in Handbook #5: Methodology for the elaboration of Clinical Consensus Statements for rare diseases.

07.

DEFINITION OF THE PATHWAY

The pathway DG should clearly define the actions of the process or processes comprised in the pathway. These actions are considered the core activities of the pathway and should be defined as a sequence and the points at which coordination and/or simultaneity is required, should be made explicit. The care areas and professional profiles involved and responsible for each action should also be made explicit

7.1 | Safety

Safety is a key element in the definition of Pathways. The definition of a new care procedure entails the appearance of new potential risks, as well as those inherent to the actions covered by the Pathway and that were already identified.

These risks should be identified beforehand by the Pathway DG and clearly indicated in the Pathway, including the actions to avoid the risk and the procedure that should be followed in case the safety issue occurs.

The identification of risks within a Pathway requires specific expertise and knowledge on safety. It is recommended that the Pathway DG includes this expertise or consults with experts on the subject.

7.2 | Entry, marginal and exit limits

In order to facilitate the clear identification of the beginning and the end of the sequence of activities that make up the pathway, certain limits have to be defined. These limits should be defined explicitly and unequivocally.

Entry limits: It refers to the specific criteria that the target patients should meet in order to be included in the pathway. These criteria can be symptoms-related, treatment-related or others.

Example of entry limits (cervical cancer pathway)[19]:

- ✓ Women included in a cervical cancer screening program in primary care using cervical-vaginal cytology.
- ✓ Women with clinical symptoms: genital bleeding, bloody leucorrhoea, bleeding during intercourse.
- ✓ Women who, after gynaecological examination performed at any level of care, present signs of clinical suspicion and/ or pathological diagnosis (based on cytology, biopsy) of precursor lesions / invasive cervical cancer.

Marginal limits: Those aspects, situations or activities that will not be addressed although they are part of the process.

Example of marginal limits (breast cancer pathway)[19]:

- ✓ Male breast cancer
- ✓ Non-epithelial breast tumours (lymphoma, sarcoma, melanoma).
- ✓ Metastatic breast tumours.

Exit limits: These comprise the specific criteria that the target patients included in the pathway should meet in order to exit the pathway. It is possible and likely that the exit to the pathway is reached from numerous points within the pathway.

Example of exit limits (paediatric asthma pathway)[19]:

- ✓ Asthma diagnosis not confirmed.
- ✓ Not paediatric age (e.g. > 14 years).
- ✓ Previous diagnosis but remained without symptoms, with normal lung function (inactive asthma), without background for at least two years.

7.3 | Professionals involved

The human resources required for the development of the activities of the pathway should be defined, taking into account that professionals from healthcare, social care, managerial, administrative and information and communication technologies areas may be required.

The professionals involved, the activities carried out and the good practices related to their profiles will be defined and chronologically shown in the flowchart of the pathway (see chapter 8).

7.4 | Activities and good practices

The specific activities that define the pathway are described, together with the good practices related to them.

The good practices are those indications aimed at improving care quality and are based on the recommendations of the pathway.

The definition of the activities should follow a WHO-WHAT-WHEN-WHERE-HOW structure.

- ✓ Who: The professional or professionals involved in the activity.
- ✓ What: The specific activity to be performed
- ✓ When: The moment in which it is performed, according to the sequence and timing of the pathway.
- ✓ Where: The setting or settings where it takes place.
- ✓ How: The specific procedure or technique that should be followed.

All activities and good practices must be based on the recommendations (see chapter 6), thus responding to the needs identified and that motivated the development of the pathway. The activities and good practices will be clearly indicated in their corresponding sections of the graphical

representation of the pathway (see chapter 8), in order to facilitate the identification of the activities and good practices that each professional is responsible for at each step of the pathway.

Example of the description of the activity and some of the corresponding good practices (unexplained global developmental delay (GDD)/ learning disability (LD)[20]):

Professional responsible	Paediatrician
Activity	Development of a comprehensive medical history, including a three generation family tree.
Good practices	Establish age of onset of development/learning problems, the presence/absence of regression and distinguish between congenital and acquired micro/macrocephaly.
	Ascertain the possibility of a possible hereditary component if recurrent miscarriages, stillbirths, neonatal or childhood deaths are noted or if other live born children with DD/LD exist amongst first and second degree relatives.
	In males with GDD/LD, male relatives on the maternal side with learning or developmental difficulties should be noted which may indicate an X-linked cause of GDD/LD.

7.4.1 | Red flags

Red flags are the decision nodes where several options that lead to different sequences of activities are presented. Red flags may lead, for example, to suspicion on the disease, condition or complex procedure.

7.5 | Specific capabilities

The specific capabilities are the observable and measurable technical or functional abilities that the professionals involved in the pathway must have in order to perform the activities and good practices of which they are responsible.

The specific capabilities have to be oriented to the development of the activities and good practices, and therefore to the achievement of the objectives of the pathway. They can be related to different types of activities, such as technical preventive or for the promotion of health.

Example of description of capabilities (cervical cancer[19]):

Capabilities		
Professional	Knowledge	Abilities
Primary Care nurse	Cytology sampling technique	Use of cervical and vaginal cytology sampling techniques

Endoscopy nurse	Uterus	Use of electrosurgical technique

7.6 | Support units

The support units are those professionals that are responsible for the provision of support processes. The support processes are those through which the pathway receives logistic or administrative support or specific material resources or information needed, (e.g. laboratory, pharmacy, personnel, radiology, Information and Communication technologies, etc.). They are represented as such in the graphical representation of the pathway (see chapter 8).

The support processes are subject to the compliance of quality standards, which should be aligned with the good practices of the pathway as well as with those of the organisation in which the pathway will be deployed.

7.7 | Specific material resources

The specific material resources are those required to perform the activities and good practices of the pathway, such as equipment or consumables. They are specific of the pathway, and do not include those that are usually available for regular care practice.

When planning the specific material resources needed, the technical characteristics required should be made explicit, as well as the quality standards that have to be met. These standards should be aligned with the good practices of the pathway as well as with those of the organisation in which the pathway will be deployed.

08.

GRAPHICAL REPRESENTATIONS

The graphical representations of the pathway are the main documents produced when developing a pathway and, therefore, a key tool for its deployment. In them, the pathway DG depicts the coordinated sequence of actions comprised in the pathway. More specifically the graphical representation can outline:

- ✓ Entry and exit limits of the pathway
- ✓ Care settings involved (primary care, hospital care, social care)
- ✓ Individuals involved (e.g., users, patients, professionals)
- ✓ Activities and tasks required at each point, including the red flags
- ✓ Time for each activity
- ✓ Resources required at each point
- ✓ Responsibilities, roles and capabilities of the individuals involved
- ✓ Key safety points, where risks have been identified
- ✓ Information and communication points, where the patient and/or carer has to be informed or a specific communication activity will be carried out with her or him.
- ✓ Assessment points, where the corresponding expected outcome can be measured.

Diagnostic, monitoring and therapy pathways are complex processes with a great deal of information at macro, meso and micro level; therefore, the graphical representation should be done at different levels and from different perspectives. It is recommended that at least two main graphical representations are produced, namely: The task-time matrix/ flowchart and the patient roadmap.

The task-time matrix and the flowchart provide a view on the specific activities and tasks. The patient roadmap represents the pathway from the patient's perspective, i.e. the pathway the patient follows until she or he exits the pathway.

8.1 | Task-time matrix

The task-time matrix of the pathway is the basic graphic representation of the pathway. It indicates the corresponding actions for each time point.

For example, the X axis of the matrix depicts the time and patient's location is indicated. Time is

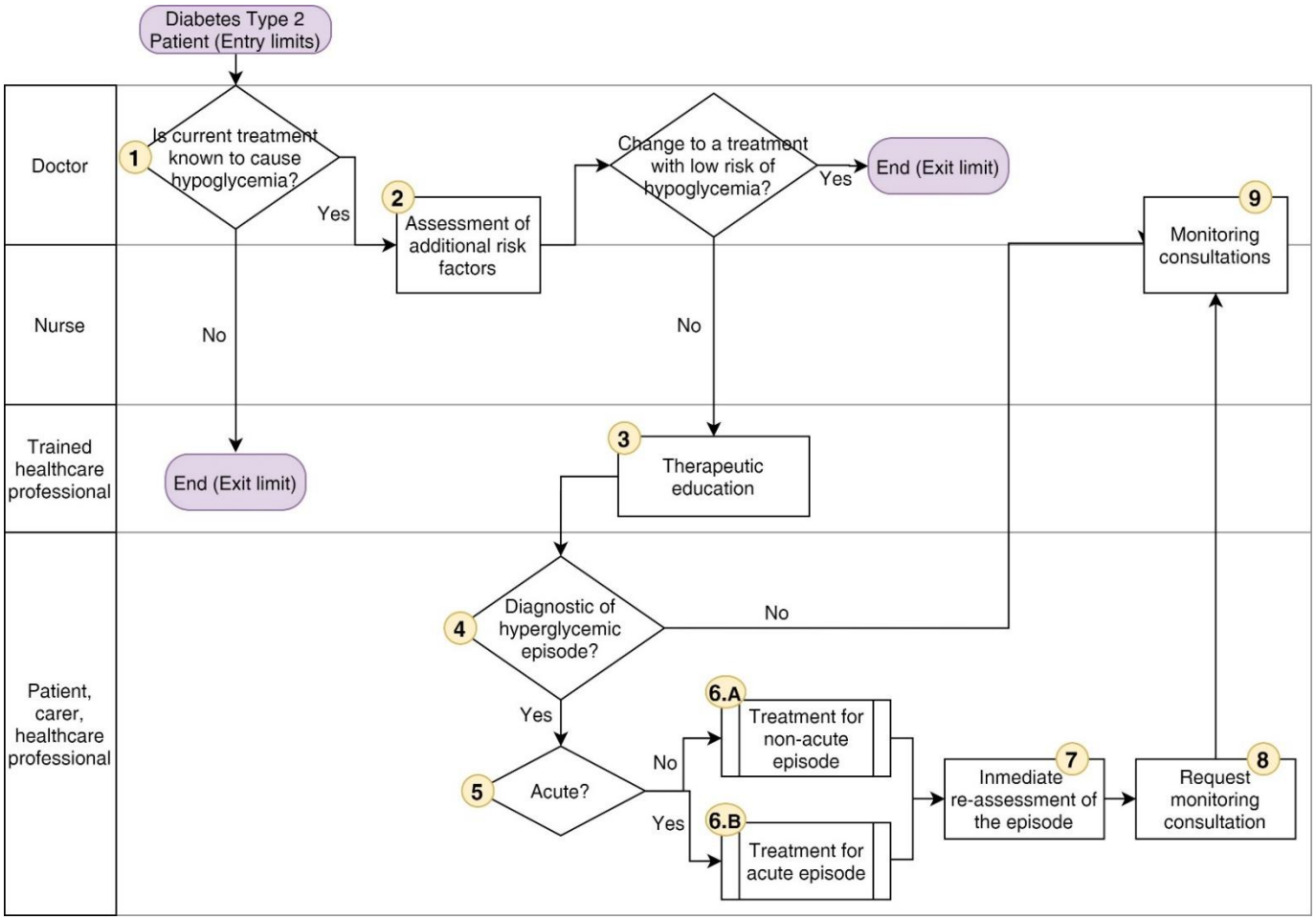
divided into days or even hours. In the Y axis are distributed all the corresponding (evaluations, care interventions, laboratory tests, medical treatments, nursing care, medication, physical therapy, diet, information and support for the patient and / or carer, admission or discharge criteria).

Another option would be to show the medication, activity, consultations, laboratory tests and monitoring activities in the X axis and different pre-defined status of the patient, (e.g. transition phase, discharge phase)[21]. See Template 1. Task-time matrix.

8.2 | Pathway flowchart

The flowchart offers a detailed sequenced representation, based on the WHO-WHAT-WHEN-WHERE-HOW structure used to define the activities and good practices. All the decision nodes (red flags) are represented, as well as the different activities linked to the different possible decisions, the timing for each activity, the responsible and the resources and/or support activities required. Classic flowcharts may be a useful tool to do this representation, an example can be seen in Figure 2[22].

Figure 2. Example of Pathway Flowchart (Type 2 Diabetes with treatment prone to cause hypoglycaemia)

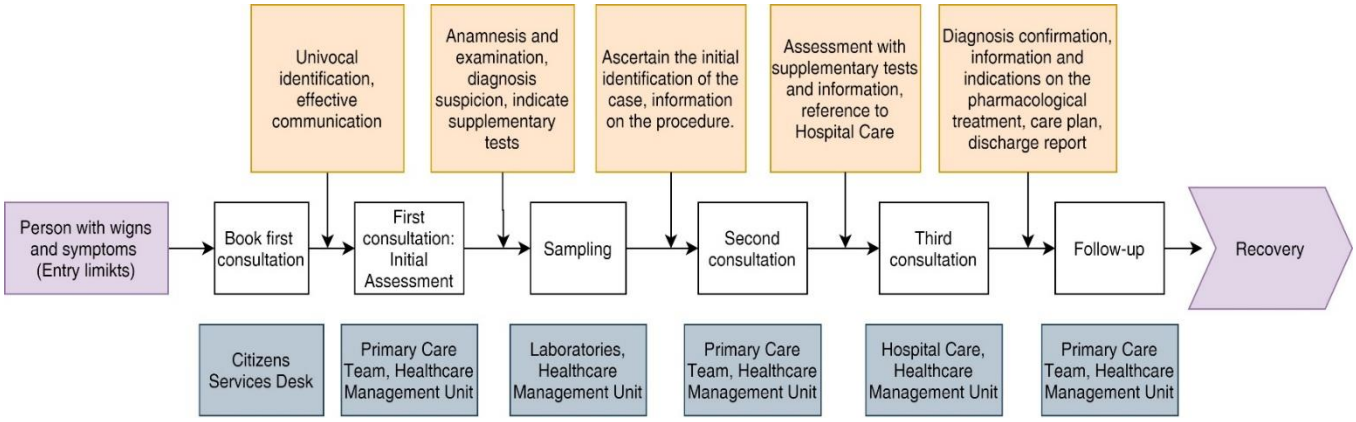


8.3 | Patient's roadmap

The patient's roadmap provides a general overview of what the patients may expect as they move through their care journey[23] . It shows the path that the patient follows throughout all the phases of the care process, helping visualise the continuum of care around the patient (see Figure 3). The following elements are present in this graphic representation:

- ✓ Care setting where the services are delivered
- ✓ Professionals involved and the activities that each one performs
- ✓ Good practices
- ✓ Key safety points
- ✓ Information and communication points

Figure 3. Example of Patient's Roadmap



More information on the development of information for patients and carers and patient versions of diagnostic, monitoring and therapy pathways can be found in Handbook #11: Methodology for the elaboration of Patient Information Booklets for rare diseases.

09.

FOLLOW-UP ASSESSMENT

In order to follow-up on the compliance with the pathway and assess the level of fulfilment of the objectives, a follow-up assessment strategy has to be established. For this, structure, process and outcome indicators relevant to the pathway have to be defined.

- ✓ Structure indicators focus on the setting in which pathway is delivered and its attributes with regards to material resources, human resources and organisational structure. For example, the number of healthcare professionals trained in a certain activity delivered in the pathway, the availability of the required health technology.
- ✓ Process indicators refer to the approaches or means of providing health care along the pathway, which includes the services and treatments the patients receive. For example, the time between the different activities of the pathway.
- ✓ Outcome indicators refer to the result or impact of the pathway on the health status of the patients. It may also involve improvements in patient's knowledge & behaviour and degree of patient satisfaction. In this sense, Patient-Reported Outcomes (PROs), defined by the National Quality Forum as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a healthcare professional or anyone else.", should be included in the outcome measures.

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.

9.1 | Continuous Improvement

In order to ensure that the pathway stays relevant, it is advisable to revisit and refine it on a periodic basis. A commonly used method is the Plan-Do-Study-Act (PDSA) cycle, a model that consists of a logical sequence of four iterative steps for continuous improvement, specific activities and recommendations regarding every step. More information on the continuous improvement cycles can be consulted in Handbook #12: Implementation and Evaluation of the Uptake of CPGs and CDSTs for rare diseases.

10.

UPDATE PROCESS

The evidence that supports the recommendations and the activities and good practices that constitute the pathway, should be reviewed to ensure it stays current as often as, at least, every 3 years, or following the emergence of ground-breaking evidence or an important change in clinical practice[24]. For this, the specific steps detailed in Handbook #4: Methodology for the elaboration of CPGs for rare diseases and Handbook #3: Adaptation and Adoption of CPGs and CDSTs should be followed.

11.

CONSULTATION PROCESS AND DEALING WITH STAKEHOLDERS' COMMENTS

The preliminary version of the pathway should undergo an exhaustive external review by the stakeholders. The aim of this consultation is ensuring that the pathway 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.

DOCUMENTS ANNEXED TO THE DIAGNOSTIC, MONITORING AND THERAPY PATHWAY

There are two documents that should be produced to enable the operationalisation of the pathway. The documents are the following:

- ✓ Pathway Checklist: A checklist for the effective operationalisation of the care processes, including all the activities, good practices, support activities and the safety procedures applicable at each step of the pathway. This checklist is to be used by the responsible of the pathway, in order to follow-up on the compliance of the activities of the pathway.
- ✓ Variations registry: The variations are the difference between what was done and what was planned or expected according to the pathway. Variations can have many causes, such as unexpected complications or adverse events, reconsideration of the case after new clinical data or unexpected unavailability in resources.

  A registry should be kept where all the variations will be registered, described and tagged as follows[25]:

  - Nature: Avoidable/ Not avoidable/ Mixed.
  - Dependent on: The condition of the patient/ Family/ Health personnel/ Institution or health organisation.

  Variations will be analysed by the pathway DG and used in the continuous improvement.

13.

EDITION OF THE DIAGNOSTIC, MONITORING AND THERAPY PATHWAY

The pathway can have different versions and format according to the audience and the intended purpose:

- Complete pathway
- Methodological material: Provides all the information related to the methodological development of the pathway

Each version includes the following content:

Complete pathway:

✓ Introduction

✓ Pathway development group

✓ Objective, target population and aspects covered

✓ Recommendations, linked to the evidence that sustains them.

✓ Description of the main elements of the Pathway:

- Safety issues, potential risks identified and the strategies to avoid them.
- Entry, marginal and exit limits
- Professionals involved
- Activities and good practices, including red flags
- Specific capabilities
- Support units
- Specific material resources

✓ Pathway:

- Graphical representation
- Patient Roadmap

- Pathway checklist
- Variations registry

✓ Assessment framework

✓ Glossary

Methodological material:

✓ Clinical questions addressed in the pathway

✓ 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

Key issues

- Pathways can help make a more efficient use of care resources and are appropriate in the context of complex interventions.
- The pathway DG should include individuals from all relevant professional groups, and patients and carers.
- The identification of uncertainty areas and clinical variability areas is the first step for determining the clinical questions that will be addressed in the pathway.
- The recommendations should be based on the best evidence available and formulated using GRADE. Clinical Practice Guidelines (CPGs) or Systematic Reviews (SR), Health Technology Assessment reports and Evidence reports or original research studies should be searched, appraised and synthesized. If no evidence has been found, consensus methods will be used.
- The recommendations are the basis for the actions, good practice and other elements of the pathway.
- Two graphical representations of the pathway should be produced, including the Patient's Roadmap.

14.

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15.

ANNEXES

ANNEX 15.1 | Template 1. Task-time matrix

TIME	*Day 1 (example)*	*Day 2*	*Day 3, 4, 5*	*Day 6*
STATUS	*Admission Ward*	*Recovery room Ward*	*Ward*	*Discharge Ward*
TYPE OF ACTIVITIES	*Evaluations, care interventions*			
	Laboratory tests			
	Medical and nurse care procedures			
	Medication			
	Diet			
	Information to the patient/ carer			
	Discharge criterion			

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