D-B.2

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

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

Aragon Health Sciences Institute (IACS), June 2020

Handbook #5: Methodology for the elaboration of Clinical Consensus Statements for rare diseases

European Commission

European Reference Networks

IACS Instituto Aragonés de Ciencias de la Salud

Authorship:

Aragon Health Sciences Institute (IACS)

Authors:

Lucía Prieto Remón, BA in Business and Marketing
Aragon Health Sciences Institute (IACS, Spain)

Patricia Gavín Benavent, MD, PhD
Aragon Health Sciences Institute (IACS, Spain)

Internal reviewers (in alphabetical order):

María Bono Vega, BSc in Biochemistry
Aragon Health Sciences Institute (IACS, Spain)

María Soledad Isern de Val, BSc in Biochemistry, PhD
Aragon Health Sciences Institute (IACS, Spain)

Celia Muñoz Fernández, BA in Economics
Aragon Health Sciences Institute (IACS, Spain)

Collaborator:

María Pilar Blas Diez, Information Specialist
Aragon Health Sciences Institute (IACS, Spain)

Contents

This handbook provides the main steps and relevant considerations when developing a Clinical Consensus Statement for rare diseases, including the constitution of the coordination team, recruitment of participants (consensus panel), selection of the consensus method, development of the questions and edition of the final Consensus.

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 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 the Clinical Consensus Statements development in rare diseases

Clinical consensus statements reflect opinions drafted by subject matter experts for which consensus is sought using explicit method to identify areas of agreement and disagreement. In contrast to clinical practice guidelines, which are based primarily on high-level evidence, clinical consensus statements are more applicable to situations where evidence is limited or lacking, yet there are still opportunities to reduce uncertainty and improve quality of care[2,3]. It offers specific recommendations on a topic. It does not give specific algorithms or guidelines for practice.

Clinical consensus has different applications ranging from defining appropriateness of procedures to prioritisation of treatment options[4].

1.3 The development process of Clinical Consensus Statements: Main steps

TASK	DEFINITION
Consensus coordination team	• Constitution of the team that will lead and oversee the development of the consensus process.
Recruitment of participants	• Composition of the consensus panel (participants).
Clinical consensus method	• Selection of the method the method that will be used to reach consensus
Development of the questions	• Development of the questions that will be used to foster the initial discussions and develop the next ones.
Edition of the consensus	• Edition of the document that describes the consensus process and its results, including the clinical consensus statements.

2. Consensus coordination team

The consensus coordination team is a group of people, including 2-3 persons and the leader, who should have enough methodological expertise or at least include one methodologist. The main function of the coordination team is to lead and oversee the consensus process, which include the following main tasks[2]:

- Selection of the consensus method to be used.
- Preparation of the consensus process, including the configuration of the consensus panel (participants) and appointment of experts (only in CDC), development of the questions and questionnaires and definition of the consensus threshold.
- Act as main contact point for panellists and keep them informed.
- Facilitate the discussions and record the results during the discussions, when needed.
- Analysis and aggregation of results.
- Assist in the development of the final consensus statement.
- Edition of the consensus.

2.1 Coordination team leader

She or he will lead the work of the coordination team and the consensus process and should have knowledge of the topic, experience regarding consensus methods[2].

One of the tasks that the leader usually assumes if the facilitation of the discussions of the consensus, although it may be assumed by other member of the coordination team if necessary. The main objective of the facilitator is to ensure that the group makes the best quality decision possible. Nonetheless, the final decision is ultimately the group's responsibility. Other primary responsibilities as facilitator are the following[2]:

- Seek equal participation of all members during discussions
- Encourage constructive debate
- Keep deliberation and input within the scope of the consensus

3. Recruitment of participants (consensus panel)

3.1 Profiles

The participants should be experts on the subjects relevant to the topic and question(s) that the consensus addresses integrating the set of activities of all the professionals involved[5,6,7]. The following profiles should be considered:

- Care professionals relevant to the topic of the consensus, including healthcare, social care and others. For diseases revealed at paediatric age, the group should include specialists in childhood and adulthood management of the disease, to cover the transition from paediatric to adult healthcare services[8].
- Healthcare Managers relevant to the topic of the consensus.
- Patients and carers.
  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.

Other profiles may be considered if deemed relevant to the topic. If the topic is derived from a CPG or CDST, members from the development group have been involved in the development of the clinical consensus statements[5].

It is advisable that members from all countries present in the ERN are included in the panel.

3.2 Recruitment

There are some issues that should be considered when planning and conducting the recruitment of participants, in addition to those already indicated in the description of each method earlier in this handbook[2]:

- They represent their fields of expertise, enriched with their personal insight, knowledge and experience, not the organisation(s) they may be affiliated to. This should be explained and clarified during recruitment with them.
- They should be available to commit to participating in all the steps or phases of the consensus process, e.g. conferences, questionnaires or meetings.
- Participants with higher status are likely to exert more influences in the group[9].
- Homogeneous groups are appropriate if the aim is to define common ground and maximise areas of agreement, but risks arriving to polarized judgements due to polarized homogeneous views[4].
- Heterogeneous groups are suitable if the aim is to identify and explore areas of uncertainty, but risks not reaching consensus[10].

3.3 Management of conflicts of interest

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

4. Clinical Consensus Methods

4. 1 Formal Consensus

Formal consensus methods are structured process, with specific formal requirements. Certain reasons motivate the use of formal consensus methods[11]:

- Control of the process: by providing a structured process, formal methods can contribute to eliminate negative aspects of group decision-making. For example, avoid that group decision may be dominated by the opinion of one or a few members.
- Scientific credibility: formal consensus methods meet the requirements of scientific methods.

The three primary formal consensus methods are addressed in this handbook[10]: Delphi, Nominal Group Technique (NGT) and Consensus Development Conference (CDC).

These methods can be combined or modified and used in a two-step process, e.g. using one method as an initial approach to the consensus and the other method to reach final consensus[7].

4.1.1 Delphi

Delphi is an iterative technique based on successive rounds of questionnaires that aims at reducing the range of responses and help the group to arrive at something closer to expert consensus[12].

Delphi is more appropriate when the number of experts is high and/ or it is difficult to meet face-to-face for logistical or economic reasons, e.g. when the consensus panel (participants) are geographically dispersed[13].

Delphi process	
Preparation of the Delphi	- Definition of the question or questions that will be addressed in the Delphi[14], e.g., development of a set of diagnostic/ classification criteria (see section 5). - Recruitment/ invitation to the selected participants, providing clear information on the process and the purpose of the Delphi. The participants of the Delphi can be very numerous (even hundreds), but at least it should include 10-30 panellists (see section 3). - Definition of the level of consensus, i.e. the threshold that will determine that consensus has been reached over a given issue.
First round	The participants are asked to answer to the initial questionnaire, where they are also invited to provide additional information or suggest new items or modifications to the proposed ones, based on their opinions or experience. The results of the first round are analysed by the coordination team with simple descriptive statistics and summarized to generate a series of statements. Consensus may have been reached on some issues. The issues on which there is still no agreement are used to build the questionnaire that will be used in the second round.
Second round	The second questionnaire is sent to the participants, together with feedback from the first round, i.e. the overall results and his/her own previous reply/scores. Participants are then given the opportunity to reconsider their respective previous opinions and adjust the answer, e.g. by re-rating the level of agreement. The results of the second round are analysed and if there are still issues upon which no consensus has been reached, a third round will be done, repeating the process of the second round. Two to four rounds are usually necessary to develop the final consensus[7].
Development of the final consensus statement	A report on the development of the Delphi rounds is developed by the coordination team. In it, the results of each round are indicated, together with the final set of statements and level of agreement reached on them. This report is reviewed by the participants to ensure it reflects the views they shared during the consensus process. After this review, the final consensus document is produced.

4.1.2 Nominal Group Technique (NGT)

The nominal group technique (NGT) is a structured interaction based on silently and individually generated ideas that are discussed and ranked in a group session where all the consensus panel (participants) voice their opinions.

NGT process	
Preparation of the NGT	- Definition of the question or questions that will be addressed in the NGT, e.g., development of a set of diagnostic/ classification criteria (see section 5). - Recruitment/ invitation to the selected participants, providing clear information on the process and the purpose of the NGT. The group of participants should include 5–9 experts. Larger groups can be separated into different groups of 5–9 participants, which will work simultaneously on the same questions[15]. If several groups are formed, representativeness of profiles should be maintained in all of them (see section 2). - Definition of the level of consensus, i.e. the threshold that will determine that consensus has been reached over a given issue. Generally, 70– 80% consensus is required[16], although a lower threshold could be defined[17].
Phase 1	The participants are asked to record privately and independently on a piece of paper ideas to address the question(s), for 5-10 minutes.
Phase 2	One idea is collected from each individual in turn and listed in front of the group by the facilitator, continuing until all ideas have been listed. No discussion is conducted at this time.
Phase 3	A brief discussion on each idea is led by the facilitator with the aim of clarifying the ideas or statements[15].
Phase 4	After the discussions, the participants privately record their judgements or assign scores to the ideas and share them with the rest of the group in turn.
Final phase	Finally, the individual judgements or votes are aggregated statistically to derive the group judgement which will define the statement or statements. Each idea is privately ranked or rated on a scale of 1–5 or 1–10. The highest ranking solutions will be kept while the remaining solutions are discarded.
Development of the final consensus statement	A document with all the statements voted in the final phase and their respective score is developed by the coordination team. In it, those statements on which consensus has been reached are indicated, together with the level of agreement reached on them. This document is reviewed by the participants to ensure it reflects the views they shared during the consensus process. After this review, the final consensus document is produced.

NGT discussions can be influenced by strong personalities, to avoid or compensate this, the facilitator should make sure all participants speak. One way of doing this is that at each round the first person to speak is different from the previous one; this means that the first round will start with the first person to the left of the moderator, the second round with the second person to the left of the moderator etc. In this way all people will have the possibility to speak first and avoid the unduly influence of strong personalities[13].

4.1.3 Consensus Development Conference (CDC)

CDC is a semi-public process where consensus panel (participants) receive information from experts and interest groups and reach consensus after several rounds of discussion.

The CDC are frequently used to agreeing about on the safety, efficacy and/or appropriateness of using various medical procedures, drugs, and devices[18] that raise public interest. It is an appropriate method when the subject in question is of social relevance and/ or carries some controversy that transcends the professional field.

CDC Process	
Preparation of the CDC	- Definition of the question or questions that will be addressed in the CDC, e.g., the appropriateness of the use of a certain treatment for a given population (see section 5).

	- Recruitment/ invitation to the selected participants, providing clear information on the process and the purpose of the CDC. The CDC panel should have around 10 experts. The participants should be independent individuals highly regarded in their field of expertise but not closely aligned with the subject[7] (see section 3). - Appointment and invitation to the experts and other stakeholders that will present the evidence to the participants of the CDC. In the case of stakeholders, representativeness should be carefully regarded and patients and carers should be invited. - Definition of the level of consensus, i.e. the threshold that will determine that consensus has been reached over a given issue.
Presentation of the questions	The questions are publicly presented and explained to the CDC in the conference.
Presentation of the evidence	The experts and stakeholders appointed present the evidence to the CDC participants. The timing should be established in advance, including time for Question & Answer and discussion. The facilitator will oversee the presentations and Q&A and discussions, making sure that the pre-defined times are respected. The general public attending the conference is also welcomed to comment on the presentations during the Q&A and ask questions both to the experts and stakeholders and to the participants.
Private deliberation	After the presentations and the discussions, the participants of the CDC meet in a private session to further deliberate and reach a consensus, weighting the information received during the presentation of the evidence.
Presentation of consensus statement draft	The consensus statement is presented as a draft in a public session. The general public is invited to review and comment on it.
Development and dissemination of final consensus statement	The CDC participants meet in a private meeting where the draft consensus statement may be modified following the comments and suggestions received during the last presentation. The final consensus statement is made public and disseminated widely to achieve maximum impact on health care practice and medical research[7].

4.2 Informal consensus

Informal consensus is the process in which a group of individuals come to agree on a choice or choices without following any formal decision-making of any kind. Despite the lack of formal structure or methodology, the general n steps and considerations described in this handbook should be followed in order to ensure the consensus is relevant and valid.

Regarding the number of members of the consensus panel (participants), if there are more participants, the reliability of the statements is presumed to be higher[14]. At least, there should be six participants[19,4]. Nonetheless, a number higher than twelve may be more difficult to coordinate[14].

5. Development of the questions

In order to develop the questions, the following steps should be followed:

5.1 Definition of the scope and purpose

Covering:

- Target population: The characteristics of the population(s) of interest and any respective subgroups on which the consensus will focus, including the age, type of disease or condition, severity or comorbidities.
- Aspects to be covered: Care aspects that will be addressed in the consensus, e.g., effectiveness, safety, appropriateness.

5.2 Literature review

A literature review should be conducted to define the questions or preliminary set of items or statements. More information on the search of scientific evidence can be found in Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

Sources of information:

The sources of evidence should be considered in the following order: 1) CPGs and CDSTs; 2) Systematic Reviews (SR); 3) Health Technology Assessment (HTA) reports; 4) Original studies.

It is likely that there are no Systematic Reviews (SR) and/or CPG or CDSTs on the specific topic of the consensus, but those with a broader scope that includes the specific topic of the consensus should be considered, as they may assist in identifying specific areas of ambiguity or variations in practice. For example, a review or guideline on the broad topic of "sinusitis" may nonetheless have useful information on the narrower topic of "paediatric chronic sinusitis."[2].

More information on the search of the evidence can be found in Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

Synthesis of the evidence:

A synthesis of the evidence should be developed and handed to the participants before the consensus process starts. More information on the synthesis of the evidence can be found in Handbook #4: Methodology for the elaboration of CPGs for rare diseases.

5.3 Selection of the type of questions

a) If the consensus aims at developing a list of prioritised criteria, the questions will ask about the priority /e.g. relevance, appropriateness, etc.) of a set of items or statements[10].
b) If the consensus aims at developing recommendations, two type of questions can be used:
    - Technical questions, where judgement is needed because of insufficient data
    - Value questions, where judgement is needed about competing social goals

There can be no 'correct' answer for value questions, whereas for technical questions, there is a correct, if undiscovered, answer.

5.3. Formulation of questions

The questions should be clearly and concisely stated. In the case of Delphi questionnaires, the response elicited should be in a simple and straightforward fashion, e.g. the questions would require a yes/no answer or to provide the level of agreement or disagreement (by means of a Likert scale) with each item.

Ideally, participants should be given the opportunity to comment on the questions presented, correct them and/or add new ones. This should be done in the first phase of the consensus process[4].

6. Edition of the Clinical Consensus Statement

The consensus process and results should be documented and edited with the following information:

1. Rationale for using consensus method, including explicit and well-founded justification of the lack of the scientific evidence to formulate evidence-based recommendations
2. Consensus method used and rationale for choosing it.
3. Consensus panel, including the number of participants, profile, name, expertise, institution and geographical location.
4. Coordination team, including the number, profile, name, expertise, institution and geographical location.
5. Process for the development of questions, including the questionnaires and other material handed to the consensus participants.
6. Literature review conducted and its results.
7. Results of the consensus process at each step, including turnout. Significant dropouts should be analysed and substantiated.
8. Consensus statement(s), linked to the level of consensus reached at each statement.

Key issues

- The consensus coordination team leads and oversees the consensus process, from the selection of the method to the edition of the consensus. The leader of the team gathers expertise both technical and methodological and frequently acts as facilitator in the discussions.
- When planning the recruitment of the consensus participants, their profile, the capacity under which they participate, their commitment to finalising process, the homogeneity and heterogeneity of the group and potential conflicts of interests should be considered.
- Formal consensus offers a structured methodology, whereas informal consensus provides more flexible approach to reaching agreements. The appropriateness of each method may depend on the nature of the topic and the number of participants. Different methods may be combined.
- The scope and purpose of the consensus covers the target population addressed in the consensus and the aspects covered. The literature review to inform the development of the questions and the synthesis that will be shared with the participants should comprise CPGs, CDSTs, SR, HTA reports and original studies.

Abbreviations

CDST	Clinical Decision Support Tool
CDC	Consensus Development Conference
CPG	Clinical Practice Guideline
DG	Development Group
EC	European Comission
ERN	European Reference Networks
FPS	Fundación Progreso y Salud
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
IACS	Aragon Health Sciences Institute (Instituto Aragonés de Ciencias de la Salud)
NGT	Nominal Group Technique
SR	Systematic Reviews
WP	Work Package

Bibliography

1. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-94.

2. Rosenfeld RM, Nnacheta LC, Corrigan MD. Clinical Consensus Statement Development Manual. Otolaryngology-head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2015;153(2 Suppl):S1-S14.

3. Beighton D. Consensus Statements. Caries research. 2017;51(5):I-II.

4. Kea B, Sun BCA. Consensus development for healthcare professionals. Internal and emergency medicine. 2015;10(3), 373-383.

5. Kwong JS, Chen H, Sun X. Development of Evidence-based Recommendations: Implications for Preparing Expert Consensus Statements. Chinese Medical Journal. 2016;129(24):2998-3000.

6. Decamp M, Joffe S, Fernandez CV, Faden RR, Unguru Y. Chemotherapy drug shortages in pediatric oncology: a consensus statement. Pediatrics. 2014;133(3):e716-24.

7. Nair R, Aggarwal R, Khanna D. Methods of formal consensus in classification/diagnostic criteria and guideline development. Semin Arthritis Rheum. 2011;41(2):95-105.

8. Haute Autorité de Santé (HAS). Méthode d'élaboration d'un protocole national de diagnostic et de soins pour les maladies rares: Guide Methodologique [Internet]. 2012 [cited 15/06/2020]. Available from : https://www.has-sante.fr/jcms/c_1342513/fr/guide-methodologique-pnds

9. Vinokur A, Burnstein E, Sechrest L, Wortman PM. Group decision making by experts: field study of panels evaluating medical technologies. Journal of Personality and Social Psychology. 1985; 49:70-84.

10. Black N, Murphy M, Lamping D, et al. Consensus development methods: a review of best practice in creating clinical guidelines. J Health Serv Res Policy. 1999;4(4):236-248.

11. Janis I. Groupthink. In E. Griffin (ed.) A First Look at Communication Theory. New York: McGrawHill; 1991. p. 235-246.

12. RAND Corporation [Internet]. [cited 15/06/2020]. Delphi Method. Available from: https://www.rand.org/topics/delphi-method.html.

13. Delbecq AL, Van de Ven AH, Gustafson DH. Group techniques for program planning: A guide to nominal group and delphi processes. Middleton, WI: Green Briar Press; 1975.

14. Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CF, Askham J, et al. Consensus development methods, and their use in clinical guideline development. Health Technology Assess. 1998;2: 1–88.

15. Ruperto N, Meiorin S, Iusan SM, Ravelli A, Pistorio A, Martini A. Consensus procedures and their role in pediatric rheumatology. Curr Rheumatol Rep. 2008;10(2):142–146.

16. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum. 1997;40(7):1202–1209.

17. Khanna D, Lovell DJ, Giannini E, Clements PJ, Merkel PA, Seibold JR, et al. Development of a provisional core set of response measures for clinical trials of systemic sclerosis. Ann Rheum Dis. 2008 ;67(5):703–709.

18. Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods: characteristics and guidelines for use. Am J Public Health. 1984;74(9):979-983.

19. Hogarth R. A note on aggregating opinions. Organizational Behavior and Human Performance. 1978; 21:40–46.