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ORIGINAL RESEARCH

Priority-setting criteria for clinical practice guideline development on rare genetic neurodevelopmental disorders: a Delphi study within the European Reference Network ITHACA

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Abstract

Objectives: The prioritization of clinical practice guideline (CPG) efforts is particularly challenging for rare genetic neurodevelopmental disorders given the large number of (ultra)rare conditions and limited resources. We aimed to establish criteria for the priority-setting of CPG topics within the European Reference Network (ERN) Intellectual disability, TeleHealth, Autism, and Congenital Anomalies (ITHACA) based on stakeholder input.

Study Design and Setting: Sets of priority-setting criteria for etiology-specific CPGs and shared health topic CPGs (across etiologies) were generated using a 2-phase consensus process. The first phase consisted of initial criteria generation, internal feedback from the ERN ITHACA Executive Committee and Patient Advisory Board, and stakeholder input through an open survey. The second phase consisted of a 2-round modified Delphi and consensus meeting with an expert panel consisting of patient advocates, clinicians, and methodologists.

Results: The final sets of priority-setting criteria included absence of existing guidance, high burden for affected individuals and families, and specific health risks requiring adaptation from usual care. In addition, complexity and treatment availability were included for etiology-specific CPGs and common occurrence and societal burden were included for CPGs for shared health topics. Availability and interest of clinical experts and patient organizations were considered required to produce CPGs; shared health topics addressed through dedicated CPGs need to be universal across etiologies.

Conclusion: Aligning with stakeholder perspectives in priority-setting is required to allocate scarce resources to the development of high-priority CPGs for rare conditions. Priority-setting criteria specific to the rare condition context were identified. CPG development was considered a particular priority important for complex conditions and/or health care and where care is nonstandard. Practice variation was not selected as a priority-setting criterion.

Keywords: Clinical practice guidelines; Rare disease; Prioritization; Stakeholders; European reference network; Genetic syndromes

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Plain Language Summary

What was the research about?

Guidelines are documents with recommendations on how to treat and manage medical conditions. Many rare conditions do not have guidelines available. We are a European network that aims to improve health care for people who have rare conditions with malformations or intellectual disability. We want to make guidelines for conditions and health problems that have most priority, because we do not have resources to develop guidelines for all conditions in our network. The aim of this research was to develop criteria that help to choose for which conditions or health problems to make a guideline.

What were the results?

Conditions and health problems without any guidelines, with a high burden for people and their families, and with specific health risks due to the rare condition(s) have priority. Complex conditions and conditions with new treatments have priority. Health problems that commonly occur in people with these rare conditions and have a high societal burden have priority.

Who was in the study?

Health care providers, patient advocates, and guideline methodologists were in the study.

What did the research team do?

First, we made a long list of criteria. To do this, we read literature, listened to a discussion with patient advocates and health care providers, asked feedback from experts, and did a survey in our network.

Then, we asked a group of experts to choose from these criteria. The experts were health care providers, patient advocates, and methodologists. We asked them to discuss and vote on these criteria multiple times.

What were the limits of the study?

We tried to involve all important experts. In our network, we have mostly health care providers who work in clinical genetics. Although people from many different countries participated, not all European countries were equally represented.

How can people use the results?

The criteria can be used to help choose between potential guideline topics for rare conditions with malformations or intellectual disability.

1. Introduction

Providing and accessing evidence-based care is challenging for health care providers and individuals dealing with rare conditions, affecting less than 1 in 2000 people [1]. For rare genetic neurodevelopmental disorders (RGNDs), health care is complex due to rare and emerging etiologies (eg, genomic variants associated with developmental disabilities), unfamiliarity among health care providers, and somatic and psychiatric comorbidities requiring specialized multidisciplinary care [2–5]. Clinical practice guidelines (CPGs) are used to improve quality of health care; in the context of rare conditions, CPG development and implementation can be challenging due to scarce published evidence, limited resources, and small expert groups [6]. For RGNDs (high-quality), CPGs are often unavailable, and existing CPGs are clustered around a small subset of syndromes [7].

European Reference Network (ERN) Intellectual disability, TeleHealth, Autism, and Congenital Anomalies (ITHACA)[1] is one of the 24 virtual expertise networks for rare and complex conditions, uniting health care providers and family support organizations across Europe [8,9]. The ERNs aim to improve access to highly specialized health care, for which the development of CPGs and clinical decision-support tools is one of the core activities [9]. ERN ITHACA covers a large number of diagnosed and undiagnosed rare (multiple) malformation syndromes

[1] ERN: European Reference Network. ITHACA: Intellectual disability, TeleHealth, Autism and Congenital Anomalies. OMIM: Online Mendelian Inheritance in Man.

What is new?

Key findings

- We established priority-setting criteria for European rare condition guidelines.

What this adds to what is known?

- Complexity and need to deviate from usual care indicated guideline priority.
- Practice variation and feasibility of implementation were not selected.

What is the implication and what should change now?

- Priority-setting is shaped by the context and goals of guideline development

and intellectual and other neurodevelopmental disorders, including but not limited to those caused by >1500 identified primary intellectual disability genes [2,3]. ERN ITHACA develops CPGs both for specific etiologies (ie, particular (genetic) conditions with Online Mendelian Inheritance in Man (OMIM) numbers) and for topics shared across etiologies (eg, transition to adult health care or challenging behavior), addressing gaps where etiology-specific CPGs are unavailable but health issues overlap. It is important to select CPG topics carefully given the significant resource requirements for typically multiyear CPG development processes [10,11]. The resources required for CPG development, combined with the large number and heterogeneous manifestations of RGNDs, necessitate prioritization of CPG development efforts.

As a publicly funded network, ERN ITHACA aims to allocate its resources in a manner that is transparent and considered fair and appropriate by its stakeholders. In this Delphi study, we established priority-setting criteria for both types of CPGs developed by ERN ITHACA based on input from health care providers, affected individuals and families,

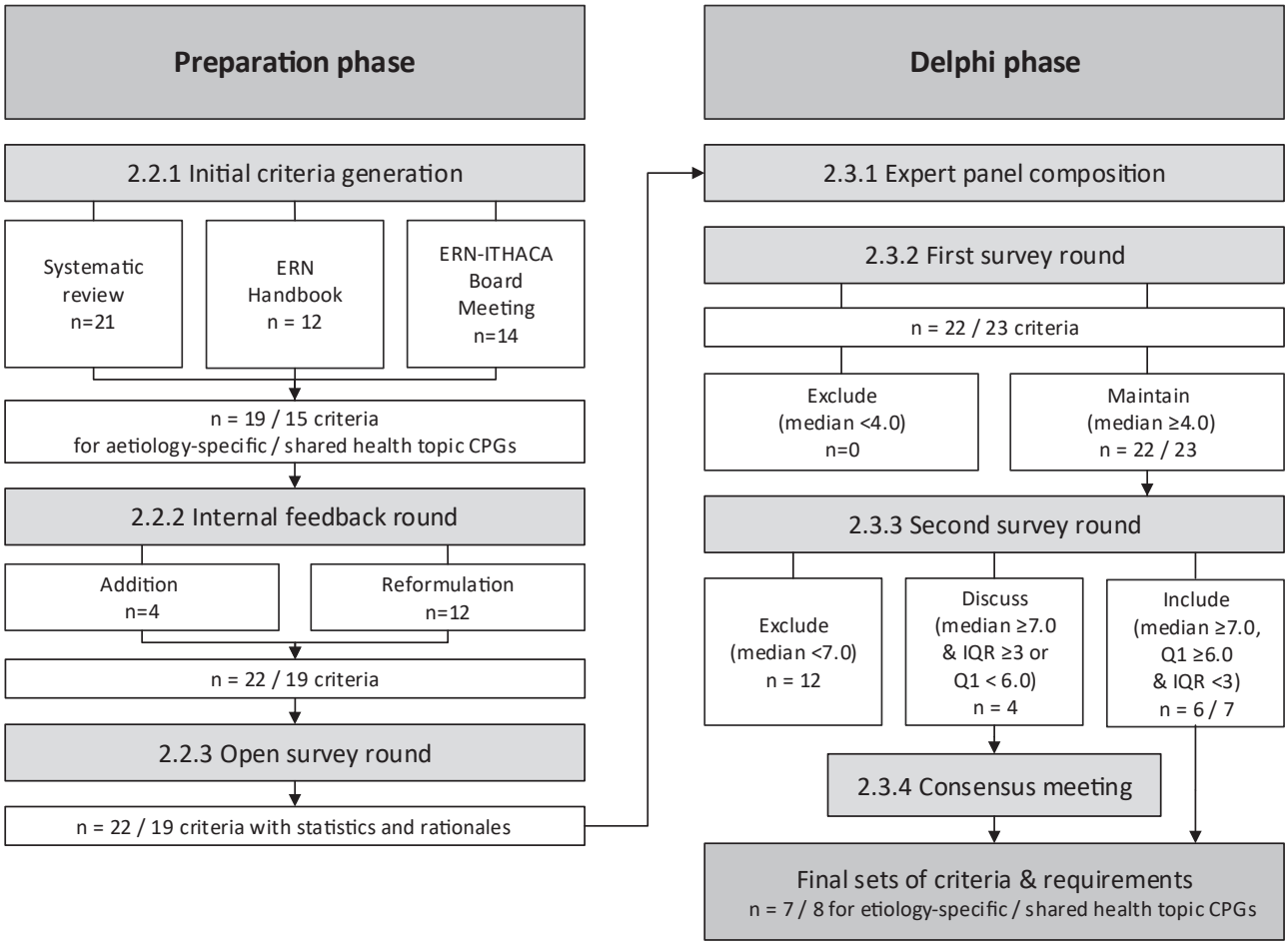

Figure. Study design.

and methodological experts. Through developing a priority-setting strategy, we aim to ensure that limited resources will be allocated to topics with the highest priority for health care professionals and affected individuals and families.

2. Methods

2.1. General overview

The study design consisted of the following two phases (Fig): a preparation phase to generate candidate criteria and a two-round modified Delphi and consensus meeting with an expert panel to reach consensus on priority-setting criteria. Separate sets of priority-setting criteria were developed for etiology-specific and for shared health topic CPG development by ERN ITHACA. The study was conducted by M.J.K.H. (PhD candidate on guideline methodology) in consultation with the ERN ITHACA guideline working group leadership (A.M.V.E., K.S., C.M.W.G.) and supported by M.S.O. as an external methodological advisor. Reporting was guided by the ACcurate COnsensus Reporting Document checklist for consensus methods in biomedicine [12]; no protocol was registered.

2.2. Preparation phase

2.2.1. Initial criteria generation

The initial list of candidate criteria was generated iteratively by M.J.K.H. in consultation with C.M.W.G., A.M.V.E., and K.S. based on the following 3 sources (Appendix A): (i) priority-setting criteria as summarized in the systematic review by El-Harakeh et al [11] (n = 21), (ii) priority-setting criteria described in the ERN's Prioritization of Rare or Low-Prevalence and Complex Rare Diseases that Require CPGs or Clinical Decision Support Tools handbook [13] (n = 14), and (iii) priority-setting criteria that were mentioned during the 1.5 hour interactive discussion on CPG development during the 2022 ERN ITHACA board meeting (n = 14).

2.2.2. Internal feedback round

Anonymous written feedback was solicited through an online form disseminated to all members of the ERN ITHACA Executive Committee and Patient Advisory Board. Members were shown the initial sets of criteria and asked to propose additional criteria and/or share any feedback. All responses were reviewed by M.J.K.H. and discussed with C.M.W.G., A.M.V.E., and K.S.; criteria were merged in case of redundancy and/or reformulated wherever necessary (Appendix A). All resulting criteria were conveyed in the open survey round.

2.2.3. Open survey round

A digital and openly accessible survey was created in Castor Electronic Data Capture [14]. The survey was disseminated through dedicated ERN ITHACA newsletters, social media posts, and leaflets at the annual ERN ITHACA board meeting in Dublin in December 2023. The survey was open from November 21, 2023, until December 31, 2023. Respondents were asked to share their country, role, and area of expertise. First, they voted on the desired balance between etiology-specific and shared health topic CPGs to be developed by ERN ITHACA. Then, they were asked to rate the importance of the proposed criteria on a 1 to 9 Likert scale for both CPG types, where 1 indicated no importance and nine, high importance. There was opportunity for comments on the content and phrasing of the criteria with open fields in the survey. Descriptive statistics (median and IQR) for each criterion were calculated for all respondents and stratified for patient representatives and health care professionals. Open-field responses were reviewed and summarized by M.J.K.H. in preparation for the modified Delphi.

2.3. Modified Delphi

A two-round modified Delphi followed by a consensus meeting was conducted to achieve consensus on sets of priority-setting criteria with an expert panel. A priori, it was determined to use two survey rounds with predetermined cut-off values for conveying criteria to the next round. Surveys were developed, disseminated using Castor Electronic Data Capture, and analyzed by M.J.K.H. and were pretested and reviewed by M.S.O. The surveys are available in Appendices C and D.

2.3.1. Expert panel composition

An expert panel was composed in January to February 2024, representing the ERN ITHACA CPG stakeholder groups of patient representatives, health care providers, and policy and methodological experts. Panel selection was based on relevant content expertise, affinity with the ERN context, and geographic diversity, in consultation with the ERN ITHACA coordination team. Patient representatives were members of the ERN-ITHACA Patient Advisory Board with leadership roles in (inter)national patient organizations and lived experience as (a parent of) an individual with a condition covered by the network. Health care providers had relevant clinical expertise, were involved with ERN ITHACA network activities, and represented diverse medical specialties in both pediatric and adult health care. Methodology and policy experts had previous experience advising in CPG development for rare conditions within the ERN context. Selected experts were invited through email. No reimbursement was provided to the panelists.

2.3.2. First Delphi round

The candidate criteria conveyed from the preparation phase were divided into a set of priority-setting criteria, which indicate the priority of the etiology or shared topic for CPG development, and a set of requirements, which represent practical and organizational conditions that need to be in place to allow

for CPG development. Four criteria that were proposed for etiology-specific CPGs but could potentially be applicable to both types of CPGs were presented for evaluation to the expert panel in both candidate criteria sets.

The aims and context of the project and the input from the preparation phase were presented to the expert panel in an online meeting on March 12, 2024. Subsequently, panelists completed a digital survey before March 24, 2024 in which they were asked to score the importance of all candidate priority-setting criteria and requirements separately for both etiology-specific and shared health topic CPGs on a 1−9 Likert scale [15]. In addition, panelists were asked to explain their rating and provide any comments on the phrasing and content of each item in an accompanying free-text field.

The median and IQR for each criterion were calculated and comments were reviewed and summarized. The predetermined threshold for conveying items into the next round was a median of ≥4.0. Criteria with a median <4.0, reflecting at least half of expert panelists rating the criterion on the lowest end [1−3] of the 1−9 scale, were discarded.

2.3.3. Second Delphi round

The digital survey in the second Delphi round contained feedback on the conveyed items from the first survey round. This feedback included both statistics (median and IQR of panel responses on each criterion) and considerations or rationales from the expert panel (ie, anonymized bullet-point summaries of proarguments and/or contra-arguments). Each criterion in the survey was presented with the expert panel's feedback, accompanied by a personalized document including the panelist's own scores. Panelists were asked to complete the survey between April 2, 2024, and May 5, 2024. The median and IQR for each item were calculated and comments were reviewed and summarized. The predetermined threshold for conveying items into the next round was a median of ≥7.0, reflecting at least half of expert panelists rating the criterion on the highest end [7−9] of the 1−9 scale. Consensus was defined as median ≥7.0 in combination with decrease in variance (Q1 ≥6.0 and IQR <3) [13]; items with median ≥7.0 but high variance indicating disagreement within the panel were presented for discussion in the consensus meeting. Criteria with a median <7.0 were discarded.

2.3.4. Consensus meeting

An online consensus meeting was held on May 21, 2024 to achieve consensus about the criteria and requirements with median ≥7.0 but high variance. One week in advance of the meeting, panelists received a written overview of all criteria and requirements conveyed from the second survey round with descriptive statistics and rationales. Discussions for each criterion or requirement were moderated by M.J.K.H. according to the following steps: (i) providing an overview of all arguments in favor and against the criteria from the survey rounds; (ii) voting for or against inclusion; (iii) asking the minority voters what they would need to agree with the majority decision; (iv) open discussion, followed by revoting; and (v) repetition if necessary, based on the steps of the Lewis method.[2]

3. Results

3.1. Preparation phase

3.1.1. Initial criteria generation

The initial sets of criteria based on the literature and ERN ITHACA board meeting discussions contained 19 and 15 items for etiology-specific and shared health topic CPGs, respectively (Appendix A).

3.1.2. Internal feedback round

Internal feedback was provided by 20 members of the ERN ITHACA Executive Committee and Patient Advisory Board. Eight respondents suggested additional criteria and eight provided comments, resulting in the addition of four new criteria and the reformulation of 12 criteria (Appendix A). The resulting sets contained 22 and 19 criteria for etiology-specific and shared health topic CPGs, respectively.

3.1.3. Open survey round

The survey was completed by 81 respondents from 21 European countries, including 22 patient representatives, 53 health care providers, and six other stakeholders (eg, scientists, methodologists, and health care network management), of which 75% were members of ERN ITHACA. Full respondent characteristics and results are available in Appendix B.

The preferred balance of CPG development efforts between specific etiologies and shared health topics according to the respondents was 50%/50% (IQR 25%−60% for shared health topics).

All proposed candidate criteria were considered important (median ≥5.0), although for both types of CPGs, five items were perceived as highly important (median ≥8.0). These included complexity, high burden for affected individuals, and absence of guidance for both types of CPGs (criterion 4, 2, and 8 in Table 2); availability of new or targeted treatments and specific health risks for etiology-specific CPGs (criterion 13 and 15); and prevalence and universality for shared health topic CPGs (criterion 1 and requirement 7).

[2] This method is described by Myrna Lewis (Deep Democracy) and applied for decision-making in corporate settings. The method was taught to C.G. during a course in advising for CPG development at the Knowledge Institute of the Dutch Federation of Medical Specialists.

Table 1. Expert panel with respective content expertise and country

Name	Content expertise	Country of residence	Survey participation	Consensus meeting participation
Dorica Dan	Chair Patient Advisory Board (PAB) with lived experience as a parent; psychologist	Romania	Both surveys	Views submitted in writing
Tanja Zdolšek Draksler	Cochair PAB with lived experience as a parent	Slovenia	Both surveys	In attendance
David Ross	Member PAB with lived experience of having a rare condition	United Kingdom	Both surveys	Unable to attend
Davide Vecchio	Pediatrician	Italy	Both surveys	In attendance
Katalin Szakszon	Pediatrician & clinical geneticist	Hungary	Both surveys	In attendance
Sofia Douzgou Houge	Clinical geneticist	Norway	Both surveys	In attendance
Andrew Stanfield	Psychiatrist	United Kingdom	Both surveys	In attendance
Stéphanie Miot	Geriatrician & psychiatrist	France	Both surveys	Unable to attend
Marta López-Argumedo	Guideline methodologist ERN Guidelines Project	Spain	Both surveys	In attendance
Charlotte Gaasterland	Guideline methodologist ERN ITHACA	The Netherlands	Both surveys	In attendance
Matt Bolz-Johnson	EURORDIS-Rare Diseases Europe health care advisor	Germany	Both surveys	Unable to attend

ERN, European Reference Network; ITHACA, Intellectual disability, TeleHealth, Autism, and Congenital Anomalies.

Table 2. Candidate criteria

Priority-setting criteria

1 Prevalence of the condition/prevalence of the health problem in individuals with congenital malformations and/or intellectual disability
2 High burden for affected individuals and families (eg, morbidity, mortality, and/or disability)
3 High burden on societal level (eg, health system, economy)
4 Complexity of the condition/health problem and/or required health care (eg, due to multiorgan comorbidity)
5 Unwanted practice variation (differences in treatment and quality of care between regions) for the condition/health problem
6 Impact on equity/access to health care (including affordability of medication, accessibility of medical and paramedical care, and medical devices)
7 Addresses a societal need related to the condition/health problem (eg, societal awareness, stigma)
8 Absence of guidelines and other clinical decision support tools for the health problem
9 Information need expressed by affected individuals and families or patient organizations
10 Information need expressed by health care professionals, including expert centers or professional organizations
11 Diversity of conditions/health problems addressed by ERN ITHACA
12 Possibility to *adolop*[a] existing (inter)national guideline for more efficient development
13 Availability of new and/or targeted treatments for the condition/health problem
14 Recognizability of the condition (ie, potential for health impact when availability of genetic diagnostic modalities is limited)
15 Specific health risks associated with the condition requiring adaptation from usual care
16 Possibility to address multiple related conditions in one guideline (eg, RASopathy)

Requirements for CPG development

1 Availability of sufficient scientific evidence for the condition/health problem
2 Availability of measures to assess health (care) for the condition/health problem (eg, PROMs, PREMs, and/or measures)
3 Availability and interest of clinical experts with knowledge of the condition/health problem
4 Availability and interest of any patient organization(s) interested in the condition/health problem
5 Availability and interest of a patient organization(s), at the European level, interested in the condition/health problem
6 Feasibility of implementation
7 Universality of the health problem across (genetic) conditions *(for shared health topic CPGs only)*

CPG, clinical practice guideline; ERN, European Reference Network; ITHACA, Intellectual disability, TeleHealth, Autism, and Congenital Anomalies; PROMs, patient-reported outcome measures; Qol, quality of life; PREMs, patient-reported experience measures.

[a] ''The GRADE-ADOLOPMENT approach to guideline production combines adoption, adaptation, and, as needed, de novo development of recommendations [16].

Table 3. Final sets of priority-setting criteria for etiology-specific CPGs and for shared health topic CPGs

Criterion	Source criterion	Etiology-specific CPGs	Shared health topic CPGs
Priority-setting criteria			
Absence of guidelines and other clinical decision support tools for the condition/health problem	Board + SR	X	X
Specific health risks (associated with the condition) requiring adaptation from usual care	Board	X	X
High burden for affected individuals and families (eg, morbidity, mortality, and/or disability)	SR + Handbook	X	X
Availability of new and/or targeted treatments for the condition	Board + Handbook	X	
Complexity of the condition and/or required health care (eg, due to multiorgan comorbidity)	Board	X	
High burden on societal level (eg, health system, economy)	SR +Handbook		X
Health problem commonly shared in individuals with congenital malformations and/or intellectual disability	Board + SR		X
Requirements			
Availability and interest of clinical experts with knowledge of the condition	Board + SR + Handbook	X	X
Availability and interest of any patient organization(s) interested in the condition	Board + SR +Handbook	X	X
Universality of the shared health topic across (genetic) conditions	Internal feedback		X

CPG, clinical practice guideline; SR = systematic review (by El-Harakeh et al, 2019) [3]; see 2.2.1 Initial criteria generation and Appendix A.

3.2. Modified Delphi

3.2.1. Panelists and response rate

Out of 12 invited experts, 11 participated in the Delphi (Table 1). One expert initially agreed to participate but did not attend the kick-off meeting nor did complete the first survey round. All 11 experts completed both survey rounds. Seven panelists participated in the online consensus meeting, with one representative from each stakeholder group absent from the discussion and one panelist sharing their views in writing.

3.2.2. Survey rounds

In the first survey round, 16 candidate criteria and seven candidate requirements were assessed by the panel (Table 2). All had median scores exceeding the cut-off of $\geq$4.0 in the first survey round and were conveyed into the second survey round.

In the second round, five criteria and four requirements for etiology-specific CPGs and five criteria and five requirements for shared health topic CPGs had median scores of $\geq$7.0 and were conveyed into the next stage. Among those, consensus was lacking for two criteria and two requirements, which were discussed during the consensus meeting.

Descriptive statistics and rationales from both survey rounds are available in Appendices E and F.

3.2.3. Consensus meeting

After discussion, the criterion on complexity of the condition (criterion 4 in Table 2) was included in the criteria set for etiology-specific CPGs. The criterion on prevalence for shared health topics (criterion 1) was rephrased to "Commonly shared health problem among individuals with congenital malformations and/or intellectual disability", to reflect frequent occurrence without focusing on prevalence statistics that may be unavailable or inapplicable, before inclusion.

The requirements on availability and interest of patient organization(s) at the European level and feasibility of implementation (requirements five and six) were excluded; although these were both considered important by the panelists, these were ultimately not deemed necessary for CPG topic priority-setting.

3.2.4. Final criteria sets

The final sets of priority-setting criteria and requirements for CPG development are presented in Table 3.

4. Discussion

4.1. Main findings and interpretation

We established sets of priority-setting criteria for etiology-specific and shared health topic CPG development for RGNDs by ERN ITHACA based on stakeholder input (Table 3). Although some of the criteria were consistent with previous literature on CPG prioritization (eg, absence of existing guidance and burden of the condition) [10,11,13], newly identified priority-setting criteria reflect the unique context of the ERN target population. These refer to topics for which care is nonstandard, e.g. due to unique pathophysiological processes related to the underlying genetic etiology requiring proactive surveillance or

alternative management, and for complex conditions and/or required health care, for example with co-occurrence of multiorgan comorbidity and intellectual disability.

Unexpectedly, the presence of unwanted practice variation was not selected as a priority-setting criterion [17]. Although some panelists considered practice variation a core argument for CPG development to reduce health disparities, others viewed practice variation as inevitable due to differences between national health care systems, heterogeneity in clinical presentations, and individual clinical decision-making in the rare condition context (see Appendices E and F). Similar attitudes were found in a survey among health care providers for the general population, where reducing practice variation was considered desirable but not necessarily feasible [18].

Our panel did not reach consensus on feasibility of implementation as a requirement for CPG development; arguments included the differing health care systems across Europe, as well as large perceived gaps between ideal and currently feasible care. CPG development was considered by panelists as a potential first step toward health care improvement, where the collaborative development process and CPG publication may pave the way toward eventual implementation.

Several other goals for health care improvement were reflected in candidate criteria proposed by stakeholders, which included meeting information needs of affected individuals and families, improving equity and access to health care, and decreasing stigma related to intellectual disability and/or congenital malformations. No consensus was reached for these criteria, as panelists did not consider CPGs as a suitable instrument to address these challenges (see Appendices E and F).

Our results confirm that priority-setting assessments are shaped by the context of CPG development, in our case, European CPG development for rare and complex conditions, where standardized care is challenging to achieve. The influence of context is also demonstrated in previous prioritization assessments; these earlier studies applied the same priority-setting criteria in different contexts, in which the predictive values of these criteria varied per context [19,20].

4.2. Strengths and limitations

This study used an elaborate preparation phase to generate candidate priority-setting criteria and subsequently involved an international and interdisciplinary panel with relevant content expertise. ERN ITHACA is strongly rooted in expertise centers for rare conditions, often with a focus on clinical genetics, which may have shaped the response to our survey and the discussions of the expert panel. Although there is significant geographic diversity among survey respondents and expert panel members, not all countries were represented equally.

The Delphi was conducted in a semianonymous manner. Many panelists have met and collaborated within and/or outside of ERN ITHACA, such that full anonymity was not considered feasible or desirable; these previous contacts might have influenced panelist input. Feedback from survey rounds was anonymized to allow panelists to assess the collective reasoning without being aware of the individual proposing the arguments.

Elaborate feedback was provided, consisting of summary statistics, rationales, and panelist's own scores, to stimulate vicarious thinking [21,22]. Previous empirical research found that experts who receive their initial ratings as part of the feedback are less likely to change their opinion; it is unknown if this difference reflects underlying psychological mechanism(s) related to opinion change or decreased random error, with the latter implying an advantage in terms of reliability resulting from providing initial ratings [22].

4.3. Implications for further research and practice

The sets of priority-setting criteria will be used by a dedicated committee to select topics for CPG development within ERN ITHACA; the insights gained might also benefit other (inter)national rare disease networks including ERNs. Next steps may involve evaluating the application of these criteria in a priority-setting assessment and evaluating satisfaction with the prioritized topics according to various stakeholders. In addition, future work could expand on how the aims of guideline development may differ across contexts and stakeholder groups [23].

5. Conclusion

In this Delphi study, involving clinicians, patient advocates, and methodologists working in the European Reference Network context, priority-setting criteria specific to rare conditions were identified. CPG development was considered a priority for complex conditions and/or required health care and where care is nonstandard. Practice variation and feasibility of implementation were not selected in the criteria sets. These results support that priority-setting assessments are dependent on the context of CPG development and related to what stakeholders see as desirable and feasible goals of CPG development.

Ethics statement

On March 27, 2023, the Medical Ethics Review Committee Amsterdam Medical Center declared that the Dutch Medical Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek met mensen) does not apply to this study and that official ethical approval is not required. Survey respondents provided written informed consent.

Glossary

OMIM number: Online Mendelian Inheritance in Man (OMIM, available from https://www.omim.org/) is a continuously updated catalog of human genes and genetic disorders and traits, with particular focus on the molecular relationship between genetic variation and phenotypic expression. Each OMIM entry is given a unique 6-digit identifier i.e. number.

CRediT authorship contribution statement

Mirthe J. Klein Haneveld: Writing − original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Michiel S. Oerbekke:** Writing − review & editing, Methodology, Investigation. **Katalin Szakszon:** Writing − review & editing, Conceptualization. **Martina C. Cornel:** Writing − review & editing, Supervision. **Charlotte M.W. Gaasterland:** Writing − review & editing, Supervision, Methodology, Conceptualization. **Agnies M. Van Eeghen:** Writing − review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

M.J.K.H. reports financial support was provided by European Reference Network on rare congenital malformations and rare intellectual disability (ERN ITHACA). There are no competing interests for any other author.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2025.111761.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its appendices. The participants of the open survey did not give written consent for their data to be shared publicly, such that only the descriptive analysis of these data is provided in the appendices.

References

[1] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Available at: http://data.europa.eu/eli/dir/2011/24/oj. Accessed July 29, 2024.
[2] Maia N, Nabais Sa MJ, Melo-Pires M, de Brouwer APM, Jorge P. Intellectual disability genomics: current state, pitfalls and future challenges. BMC Genomics 2021;22(1):909. https://doi.org/10.1186/s12864-021-08227-4.
[3] Jansen S, Vissers L, de Vries BBA. The genetics of intellectual disability. Brain Sci 2023;13(2). https://doi.org/10.3390/brainsci13020231.
[4] Young-Southward G, Rydzewska E, Philo C, Cooper SA. Physical and mental health of young people with and without intellectual disabilities: cross-sectional analysis of a whole country population. J Intellect Disabil Res 2017;61(10):984−93. https://doi.org/10.1111/jir.12422.
[5] Rosenberg AGW, Pater MRA, Pellikaan K, Davidse K, Kattentidt-Mouravieva AA, Kersseboom R, et al. What every internist-endocrinologist should know about rare genetic syndromes in order to prevent needless diagnostics, missed diagnoses and medical complications: five years of 'internal medicine for rare genetic syndromes'. J Clin Med 2021;10(22). https://doi.org/10.3390/jcm10225457.
[6] Gittus M, Chong J, Sutton A, Ong ACM, Fotheringham J. Barriers and facilitators to the implementation of guidelines in rare diseases: a systematic review. Orphanet J Rare Dis 2023;18(1):140. https://doi.org/10.1186/s13023-023-02667-9.
[7] Klein Haneveld MJ, Hieltjes IJ, Langendam MW, Cornel MC, Gaasterland CMW, van Eeghen AM. Improving care for rare genetic neurodevelopmental disorders: a systematic review and critical appraisal of clinical practice guidelines using AGREE II. Genet Med 2024;26(4):101071. https://doi.org/10.1016/j.gim.2024.101071.
[8] Directive 2011/24/EU of the European parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. Available at: http://data.europa.eu/eli/dir/2011/24/oj. Accessed July 29, 2024.
[9] 'Who we are': ern-ithaca. Available at: https://ern-ithaca.eu/about-us/who-we-are/. Accessed July 29, 2024.
[10] Aleksovska K, Bassetti CLA, Berger T, Carvalho V, Costa J, Deuschl G, et al. Prioritization process for European Academy of Neurology clinical practice guidelines. Eur J Neurol 2023;30(2):305−20. https://doi.org/10.1111/ene.15608.
[11] El-Harakeh A, Morsi RZ, Fadlallah R, Bou-Karroum L, Lotfi T, Akl EA. Prioritization approaches in the development of health practice guidelines: a systematic review. BMC Health Serv Res 2019;19(1):692. https://doi.org/10.1186/s12913-019-4567-2.
[12] Gattrell WT, Logullo P, van Zuuren EJ, Price A, Hughes EL, Blazey P, et al. ACCORD (ACcurate COnsensus Reporting Document): a reporting guideline for consensus methods in biomedicine developed via a modified Delphi. Plos Med 2024;21(1):e1004326. https://doi.org/10.1371/journal.pmed.1004326.
[13] Handbook #1. Prioritisation of rare or low-prevalence and complex rare diseases that Require CPGs or CDSTs. Zaragoza, Spain: Aragon Health Sciences Institute (IACS); 2020.
[14] Castor EDC. Castor Electronic Data Capture. [online]. 2019. Available at: https://castoredc.com. Accessed November 1, 2023.
[15] De Meyer D, Kottner J, Beele H, Schmitt J, Lange T, Van Hecke A, et al. Delphi procedure in core outcome set development: rating scale and consensus criteria determined outcome selection. J Clin Epidemiol 2019;111:23−31. https://doi.org/10.1016/j.jclinepi.2019.03.011.
[16] Schunemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol 2017;81:101−10. https://doi.org/10.1016/j.jclinepi.2016.09.009.
[17] Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, editors. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US); 2011.

[18] Cook DA, Pencille LJ, Dupras DM, Linderbaum JA, Pankratz VS, Wilkinson JM. Practice variation and practice guidelines: attitudes of generalist and specialist physicians, nurse practitioners, and physician assistants. PLoS One 2018;13(1):e0191943. https://doi.org/10.1371/journal.pone.0191943.

[19] Wiercioch W, Nieuwlaat R, Zhang Y, Alonso-Coello P, Dahm P, Iorio A, et al. New methods facilitated the process of prioritizing questions and health outcomes in guideline development. J Clin Epidemiol 2022;143:91−104. https://doi.org/10.1016/j.jclinepi.2021.11.031.

[20] Zaror C, Deana NF, Espinoza-Espinoza G, Aravena-Rivas Y, Muñoz-Millán P, Pineda P, et al. Questions and health outcomes prioritization for the development of a COVID-19 dental clinical practice guideline: a case study. J Eval Clin Pract 2022;28(3):404−10. https://doi.org/10.1111/jep.13658.

[21] Fish R, MacLennan S, Alkhaffaf B, Williamson PR. "Vicarious thinking" was a key driver of score change in Delphi surveys for COS development and is facilitated by feedback of results. J Clin Epidemiol 2020;128:118−29. https://doi.org/10.1016/j.jclinepi.2020.09.028.

[22] Meijering JV, Tobi H. The effects of feeding back experts' own initial ratings in Delphi studies: a randomized trial. Int J Forecast 2018;34(2):216−24.

[23] Wieringa S, Dreesens D, Forland F, Hulshof C, Lukersmith S, Macbeth F, et al. Different knowledge, different styles of reasoning: a challenge for guideline development. BMJ Evid Based Med 2018;23(3):87−91. https://doi.org/10.1136/bmjebm-2017-110844.