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ORIGINAL RESEARCH

Prioritizing topics for a clinical practice guideline on SATB2-associated syndrome: methodological rigor vs clinical usability

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Abstract

Objectives: SATB2-associated syndrome (SAS) is a rare genetic condition characterized by developmental delay and typical features. Currently, an evidence-based clinical practice guideline (CPG) is being developed by European Reference Network ITHACA in close collaboration with the patient community. To ensure that the guideline addresses the most pressing concerns of affected individuals, families, and clinicians, while remaining feasible to produce, a prioritization process was carried out.

Study Design and Setting: The prioritization process aimed to minimize the relevant clinical questions to a maximum of 12, based on criteria that were defined beforehand and based on input from a large patient community. The prioritization process included a SAS community-wide survey that collected all patient-relevant topics, a prioritization round using a tool that helps to calculate the items that were most voted on, and a final consensus round with the guideline core group.

Results: In the first round, a total of 376 topics was collected based on input from over 20 families. These were combined and refined into 48 clinical topics. A total of 269 valid responders filled in their prioritization on these topics in an online survey. Of these respondents, 234 identified as representative/family/carer, 30 identified as clinician, and 5 individuals identified as both. Rather than prioritizing a subset of 12 topics, that each would be answered with a systematic review, the core group decided on a final set of 22 questions and only 1 systematic review.

Conclusion: Despite using a rigorous, community-driven process with input from many parents, carers, and global clinical experts, the guideline core group could not agree on a final set of 12 clinical topics. The group concluded that completeness and clinical usability of the guideline should take precedence over adhering to 12 prioritized clinical topics that could each be answered with a systematic search in the literature. We concluded that completeness and usability, vs methodological rigor, are competing interests in CPG development. This methodological issue is a pressing matter in the field of rare disease CPG development, and possibly also beyond the context of rare diseases, for which no clear solution currently exists.

Keywords: Clinical practice guidelines; Rare diseases; Prioritization; Guideline methodology; Systematic reviews; European reference network

1. Introduction

SATB2-associated syndrome (SAS) is a rare genetic condition characterized by developmental delay, such as limited or absent speech development and mild to profound intellectual disabilities (IDs); craniofacial abnormalities,

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Plain Language Summary

SATB2-associated syndrome (SAS) is a rare genetic condition that causes developmental delays and other characteristic features. A new clinical practice guideline (CPG) for SAS is currently being developed by the European Reference Network ITHACA, together with families, caregivers, and health-care professionals. To make sure the guideline focuses on the most important needs of the SAS community, a structured process was used to decide which clinical topics should be included. First, families across the SAS community were asked to share their concerns. This resulted in 376 topics, which were combined into 48 broader clinical themes. Next, 269 people completed an online survey to rank these topics. Most respondents were family members or caregivers, and some were clinicians. Finally, the guideline development team reviewed the results and discussed which topics should be prioritized. Although the original goal was to select 12 questions to answer through systematic reviews, the team decided that limiting the guideline to only 12 topics would leave out important issues. Instead, they agreed on 22 key questions, which would be addressed with only 1 systematic review. The CPG recommendations would then be more complete but supported with less systematically searched evidence. This experience highlights an ongoing challenge in rare disease guideline development: balancing completeness and practicality with strict methodological standards.

including palatal and dental anomalies; dysmorphic features; skeletal anomalies; and osteopenia [1,2]. Population-based studies estimate the prevalence of SAS to be approximately 3.5−4.9 per 100,000 live births, with over 200 cases described in the literature to date [3−6].

The patient organization SATB2 Europe has connected the patient community globally, facilitating a global clinical network specifically for SAS, which previously did not exist. Within the SAS patient community, there is a strong and ongoing demand for accessible information to support daily care needs and to guide the management of the medical and functional challenges associated with SAS throughout the lifespan. Both caregivers and clinicians feel this need. In response, several initiatives have been launched to address these informational gaps, including international patient surveys [7] and establishing a global patient registry. However, no evidence-based clinical practice guideline (CPG) involving international consensus specific to SAS has been developed to date, although some general recommendations have been published [8,9].

In March 2017, 24 European Reference Networks (ERNs) were launched. These clusters of rare diseases have been assigned to develop, update, and appraise CPGs for the diseases they represent.

ERN ITHACA, which covers rare malformation syndromes as well as intellectual and other neurodevelopmental disorders, has initiated the development of CPGs for SAS, among other CPGs for the conditions it represents. The development of the SAS CPG was launched through the advocacy of SATB2 Europe and is being carried out in close collaboration with the organization.

The development and implementation of high-quality, evidence-based CPGs—particularly for rare conditions such as SAS—is a complex, resource-intensive endeavor, often requiring more than 3 years to complete [10−12]. Given the considerable efforts and (often limited) resources required to develop, implement, and update guidelines, guideline developers must prioritize what topics and questions to address [13,14]. This involves selecting both overarching guideline themes [15] and specific clinical questions within each guideline [16].

In the development process of a CPG, a thorough systematic review is performed per clinical question, even when little literature or only low-quality evidence is expected [17]. According to the GRADE methodology, a systematic search and selection is performed per clinical question, after which the articles are summarized and the relevant outcomes are evaluated and graded on the quality of evidence [18,19]. Then, recommendations can be formulated after consultation with the guideline panel, following the Evidence-to-Decision Framework [20]. In the context of rare diseases, this set-up may help search for broader literature, for example, on conditions that may be similar to the condition of topic, as long as the clinical question remains well-defined and not too broad. In the GRADE methodology, such recommendations based on a wider defined population may be downgraded for indirectness, or applicability [21]. When no evidence is found, the Evidence-to-Decision Framework and input from all relevant stakeholders may still yield useful recommendations for the field, albeit with a low or very low level of evidence [20].

A structured prioritization process was established to ensure that the SAS guideline reflects the most pressing concerns of affected individuals and families. Through a multistep approach, involving all relevant stakeholders, we aimed to allocate the limited time and resources of the CPG initiative to the issues of highest importance to health-care providers, individuals with SAS, and their families and carers. In this paper, we will describe the methodology and results of this thorough process and discuss the final outcome of the priority-setting exercise in the context of CPG methodology for rare diseases.

What is new?

Key findings

- We present a list of most important topics for a clinical practice guideline (CPG) for a rare genetic condition: SATB2-associated syndrome.
- The methodology for producing this list was rigorous, but the assignment of prioritizing to only 12 topics could not be met.
- The competing interests of completeness and usability of a CPG, on the one hand, vs methodological rigor, on the other, are pressing matters in the field of rare disease guideline development, for which no clear solution currently exists.

What this adds to what is known?

- The prioritization of guideline topics is particularly difficult for rare diseases, and the CPG methodology may need to be evaluated for rare diseases specifically.

What is the implication and what should change now?

- CPG methodology for rare diseases needs more research and a wider scientific debate, since currently no clear guidance exists for this particular field.

2. Materials and methods

We conducted an international priority-setting exercise using input from patient representatives/families/carers and an interdisciplinary group of clinicians. The priority-setting assessment was carried out in several steps:

2.1. Setting the infrastructure

A guideline core group was established, consisting of a patient representative and clinical pharmacist (E.S., also the chair of the project), an ID physician and patient representative (B.T.), a clinical geneticist (Y.Z.) and a pediatric neurologist (D.O.) with expertise in SAS, two guideline methodologists (C.G., M.K.H.), and a project manager. This group was established through the network of ERN ITHACA, and the network of the chair of the guideline core group (A.v.E.).

2.2. Collecting important clinical topics

A group of patient representatives in the guideline Consortium (Parent Forum) was asked to provide the most urgent topics regarding their day-to-day living, which could be improved with recommendations in a guideline. In total, 20 families were invited to collect all these topics and send them to the guideline core group.

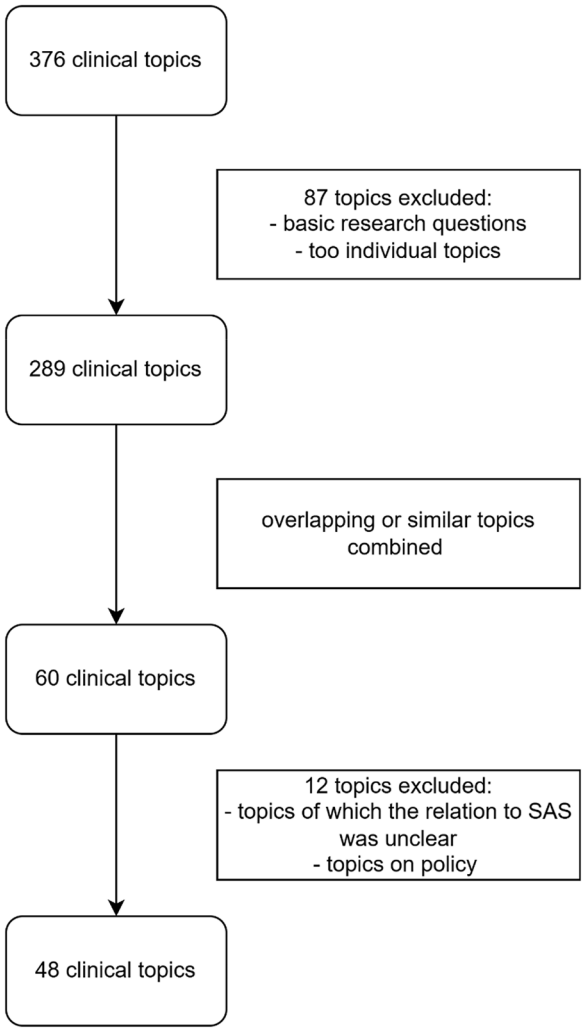

Figure 1. Flow diagram of excluding and combining topics that were collected from parents/carers.

2.3. Combining and refining the clinical topics

A total of 376 topics raised by parents/carers were collected. The two guideline methodologists (C.G. and M.K.H.) evaluated the topics, combined topics that were very similar or complementary, and disregarded questions that were not suitable for a CPG, such as very specific individual questions, and basic research questions. The list was refined to 60 clinical topics. After consultation with the guideline core group and the Parent Forum, it was further refined to 48 topics. Topics on health policy were beyond the clinical scope of the project, and of some topics the relation to SAS was unclear (see Fig 1 for the flow diagram on excluding and combining topics, and Appendix I for the final list of topics).

2.4. Translating the clinical topics

Of the 48 clinical topics that remained, volunteers of the SAS patient community made translations in seven additional languages based on the original English questions: Spanish, Portuguese, Polish, Italian, German, French, and Dutch. The first translation of the clinical topics and the survey text was done using OpenAI ChatGPT (2024). All translations were then checked by native-speaking parents who speak English as well, and a second volunteer double-checked them to make sure no content changes were made in any of those seven additional languages.

2.5. Prioritizing the clinical topics

In December 2024, the final list of topics was sent to European SAS patient organizations, who have disseminated the list to their communities: SATB2 Europe, Association Française Du SATB2 (France), SATB2 Stichting Nederland en België (the Netherlands and Belgium), Asociación del Síndrome Asociado al SATB2-SAS (Spain), SATB2 Italia associazione onlus (Italy), SATB2 Gene trust (UK), SATB2 Gene Foundation (USA), and SATB2 Connect (Australia). The list was also shared through global SAS social media groups, and to clinicians working with SAS patients, using the networks of SATB2 Europe and European Reference Network ITHACA. A Google Form format was used, and it remained open for 2 weeks in total. The large panel of both clinicians and patient representatives was asked to evaluate the priority of the topics. The panel members were instructed that a score of 0 meant ''no priority'' and 5 meant ''highest possible priority,'' based on the following criteria (that were based on discussions within the guideline core group):

- High prevalence of a specific symptom
- High care need/burden either for the affected individuals or for their close relatives
- Local variance in the clinical management of SAS that may be improved by international consensus recommendations

Panel members could abstain from scoring an item when they had no specific opinion or expertise on that item. For patient representatives/families/carers, the question on age group of the individual they represented was added, with six possible answers: 0−3 years, 4−11 years, 12−17 years, 18−24 years, 25−39 years, or 40 years and older. Survey results were used by the guideline methodologist (C.G.) as input for the RE-weighted Priority-Setting (REPS) tool. This tool is developed specifically to calculate prioritized topics, particularly in the setting of CPG development, [22]. When a certain group of stakeholders is larger and therefore may have a more heavy influence on the final prioritization outcome, the tool may be able to diminish the influence of this group with adding or distracting weights (reweighted range voting). This may increase the democratic value of the final choice of topics. The REPS-tool was used to calculate the sum score of the prioritized topics and make a list of prioritized topics.

2.6. Selecting the final clinical topics

For the priority-setting assessment in the guideline development project, the REPS-tool's output was obtained under the condition of mean scores per subgroup (input format), and after discussion with the core group, the tool was used without the reweighted range voting (weighting method). This was decided because the largest group that participated in this part of the prioritization process was the group of patient representatives/families/carers, and it was decided that we did not want to punish their larger influence as their voice was most important in this stage of the process. The output of the REPS-tool was discussed within the guideline core group, with a main focus on the top-20 topics as calculated by the tool, through a 1.5-hour virtual meeting and further email correspondence. The goal was to select a maximum of 12 clinical questions, since the time and resources to perform more than 12 systematic reviews for the guideline project were limited.

3. Results

3.1. Prioritizing clinical topics

The survey was completed by 270 respondents. One respondent was excluded from further analysis as the person ticked all listed expertise, and ranked all clinical topics as highest priority. Of the remaining 269 respondents, 234 identified as representative/family/carer, 30 identified as clinical expert, and 5 individuals identified as both. In Table 1 all the specific expertise that was mentioned by the respondents is listed. In Table 2, the number of

Table 1. Number of respondents and their expertise

Respondent's expertise	Frequency
Behavioral specialist	4
Clinical geneticist	8
Genetic counselor	1
Clinical psychologist	1
Dental expert	2
ENT specialist	1
ID specialist	1
Neurologist	4
Neuropsychologist	2
Patient representative/parent	234
Pediatrician	2
Speech and language therapist	4
Both clinician and patient representative	5

ID, intellectual disability; ENT, Ear, Nose, and Throat.

Table 2. Number of respondents per survey language

Language	Nr of respondents	Clinical experts	Parents	Both clinical and patient expert
English	115	26	85	4
		Clinical geneticist: 8		
		Genetic counselor: 1		
		Neurologist: 4		
		Pediatrician: 2		
		Speech and language therapist: 4		Speech and language therapist: 1
		Dental expert: 2		
		Clinical psychologist: 1		
		Behavioral specialist: 1		Behavioral specialist: 1
		ID-specialist: 1		ID physician: 1
		Neuropsychologist: 1		
		ENT specialist: 1		
				Nurse practitioner: 1
French	28	2	26	
		Behavioral specialist: 2		
Italian	25	2	23	
		Behavioral specialist: 1		
		Neuropsychologist: 1		
Dutch	31	0	31	
Spanish	20	0	20	
Portuguese	15	0	14	Clinical geneticist: 1
German	18	0	18	
Polish	17	0	17	

ID, intellectual disability.

respondents is shown per language and per expertise. The age groups of the individuals that were represented by patient representatives/families/carers are shown in Figure 2. The priorities identified through the survey were mainly the needs of individuals in the age group of 4–11 years of age.

The sum scores of the prioritization of all clinical topics are shown in Appendix I. The top-20 that was calculated based on these sum scores was identical for the overall group and for the group of patient representatives/carers/families alone. The group of respondents that represented both the clinical and patient expertise was included in all three analyses (overall group, patient representatives/carers/families alone and clinicians alone). The top-20 and the order of the items of the smaller group of clinicians differed slightly from the overall group. Both the top-20's of the overall group and of the clinicians alone were used as a basis for discussion. See Tables 3 and 4 for the top-20 questions that were identified for the overall group and for the group of clinicians alone.

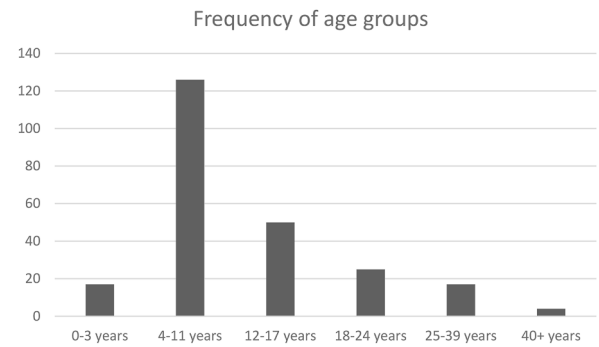

Figure 2. Frequency of reported age groups of patients represented by representatives/families/carers.

3.2. Selecting the final clinical topics

The final clinical topics selected by the guideline core group (E.S., B.T., Y.Z., D.O.) are shown in Table 5. The core group decided to not prioritize 12 topics based on the aforementioned methodology, but to aim for a more useable and complete document, cutting corners on the standard CPG methodology of performing a systematic review per topic. Instead, 1 overall search on the topic of SAS was chosen over 12 individual searches, and 22 questions were chosen instead of 12.

Two top-20 questions were disregarded: those on education (Tables 3 and 4, rank 14) and on puberty (Tables 3 and 4, rank 20). The question on education was considered outside of the

Table 3. Clinical topics ranked by the overall group of clinicians and patient experts (numbered as in the survey)

Rank number	Clinical topic as numbered in the survey
1	34. What interventions are best to improve and support communication in individuals with SAS?
2	39. What should the multidisciplinary team of an individual with SAS look like?
3	32. What is the nature of speech disorders in individuals with SAS and how should they be diagnosed and treated?
4	13. How should the occurring dental health problems in individuals with SAS be prevented, monitored and treated?
5	35. What challenging behaviors occur in individuals with SAS and what are recommendations for assessment and interventions?
6	27. What therapies and interventions are recommended for individuals with SAS to stimulate development in different areas (motoric, cognitive, sensory, social etc)?
7	33. Which assessments/tools are suitable to assess language comprehension in individuals with SAS?
8	40. How should the transition of care of individuals with SAS from pediatric to adult best be done?
9	46. How can pain be identified, measured and treated in individuals with SAS, considering a higher pain threshold?
10	17. How and when should screening and diagnostics for bone health be done in individuals with SAS?
11	18. What interventions are best to keep or improve bone health in individuals with SAS?
12	38. How may the family of an individual with SAS best be counseled and supported in regard to their well-being?
13	28. How and in what frequency should the development of individuals with SAS be monitored? (Intelligence, motor skills, adaptive functioning, social and emotional)
14	29. What should the education of an individual with SAS look like?
15	3. What neurological diagnostic examinations are recommended for individuals with SAS?
16	9. What types of sleep issues are most common in individuals with SAS and what interventions may improve sleep in individuals with SAS?
17	1. What is the recommended diagnostic route for individuals with neurodevelopmental disorders to establish the diagnosis of SATB2-Associated syndrome (SAS)?
18	41. What are the more common comorbid (accompanying) diagnoses associated with SAS, the recommended screening, and treatment? (For e.g. Hearing, vision, urologic and other issues)
19	8. What is the recommended diagnostic pathway for sleep issues in individuals with SAS?
20	30. How may puberty of individuals with SAS best be counseled?

scope of a CPG, and the question on puberty was too broad and partly covered in other subquestions (behavior, transition of care, bone health related to contraceptives).

Three questions outside of the overall top 20 but ranked in the top 15 by clinicians alone were included, concerning psychiatric management, autism, and genetic counseling.

Finally, 1 question that was not ranked among either top 20 was included, namely the question on epilepsy, as it was considered relevant by the core group and fell within the scope of a topic (Neurology) where two other questions were already clustered.

4. Discussion

In this priority setting exercise, we have made use of a thorough methodology to come to a community-driven prioritization of clinical questions, making use of input from a large group of parents/carers of SAS individuals and clinical experts across the globe, and prioritizing according to the criteria that were seen as relevant by the guideline core group. In the end, however, the guideline core group decided that the completeness and clinical usability of the CPG superseded a list of 12 prioritized topics, and consequently selected the 22 questions shown in Table 5. The priority-setting exercise was therefore useful, but did not obtain the expected results of a 12-item list of clinical questions. The possibility of dividing the project in multiple parts, thus allowing for more prioritized topics to be included, was discussed in the guideline core group. However, the financial support from the ERN only allowed for 1 project with 1 final consensus meeting and 1 final end product. It was also concluded that several products could also hamper usability from a clinical point of view, due to the lack of 1 complete overview of topics and solutions. It was therefore decided that 1 overarching search strategy would be used to obtain all relevant literature on SAS, thereby reducing the underlying methodological rigor of the recommendations formulated in the final CPG.

The methodology of including a large group of parents/carers in the priority setting may be exemplary of the CPG context of rare diseases. The strong patient community that was involved in this endeavor, and in the entire process of CPG development, is often a driving force in demanding and producing information in the field of rare diseases [23,24], although the level of funding and degree of professionalization among such groups may vary depending on the condition [25].

However, the final results of the exercise and their diversion from the initial goal of prioritizing a maximum of 12

Table 4. Clinical topics ranked by clinicians alone (numbered as in the survey)

Rank number	Clinical topic as numbered in the survey
1	34. What interventions are best to improve and support communication in individuals with SAS?
2	39. What should the multidisciplinary team of an individual with SAS look like?
3	35. What challenging behaviors occur in individuals with SAS and what are recommendations for assessment and interventions?
4	32. What is the nature of speech disorders in individuals with SAS and how should they be diagnosed and treated?
5	37. What psychiatric disorders should professionals be alert to in individuals with SAS, and what are recommendations for assessment and treatment?
6	46. How can pain be identified, measured and treated in individuals with SAS, considering a higher pain threshold?
7	1. What is the recommended diagnostic route for individuals with neurodevelopmental disorders to establish the diagnosis of SATB2-Associated Syndrome (SAS)?
8	27. What therapies and interventions are recommended for individuals with SAS to stimulate development in different areas (motoric, cognitive, sensory, social etc)?
9	41. What are the more common comorbid (accompanying) diagnoses associated with SAS, the recommended screening, and treatment? (for e.g. hearing, vision, urologic and other issues)
10	13. How should the occurring dental health problems in individuals with SAS be prevented, monitored and treated?
11	38. How may the family of an individual with SAS best be counseled and supported in regard to their well-being?
12	9. What types of sleep issues are most common in individuals with SAS and what interventions may improve sleep in individuals with SAS?
13	2. What are the genetic counseling recommendations after the SAS diagnosis has been made?
14	36. How may autism spectrum disorder best be treated in individuals with SAS?
15	40. How should the transition of care of individuals with SAS from pediatric to adult best be done?
16	3. What neurological diagnostic examinations are recommended for individuals with SAS?
17	33. Which assessments/tools are suitable to assess language comprehension in individuals with SAS?
18	8. What is the recommended diagnostic pathway for sleep issues in individuals with SAS?
19	28. How and in what frequency should the development of individuals with SAS be monitored? (intelligence, motor skills, adaptive functioning, social and emotional)
20	17. How and when should screening and diagnostics for bone health be done in individuals with SAS?

clinical topics based on defined criteria may be exemplary of the CPG context of rare diseases as well. Where topic prioritization for rare disease research may be challenging as well, methodologies for this exist and yield useful results [26]. For CPG development, an extra dimension comes into play; when the final CPG document is not user-friendly and complete, it will not be used by clinicians, undermining the main goal of a CPG. A complex interplay exists between stakeholder priorities: rigorous CPG development methodology, on the 1 hand, as is prescribed by CPG methodologies such as GRADE and a need for complete and holistic guidance when information is scarce, on the other hand, as is wanted by clinicians and patient representatives. In the context of rare diseases, when a CPG is started, often nothing is available on that condition yet in terms of formal evidence-based information. Therefore, any guideline that does not answer any of the questions that a clinician or patient may have at 1 particular point may be regarded as insufficient or even irrelevant by that clinician or patient. Therefore, completeness is mentioned as an important quality criterion for a rare disease CPG by users, maybe even more so for multisystem conditions such as SAS [27]. Also, when the literature of a condition is so scarce, 1 systematic search instead of 1 per prioritized topic may suffice. However, no clear guidance on when and how this may be decided exists, even though this issue may extend to topics where evidence is very scarce, beyond the context of rare diseases.

The global guideline on Down syndrome is a good example of a rare disease CPG where prioritization has taken place, PICOs have been developed and systematic reviews have been performed according to standard CPG methodology, but where a complete overview of care for these individuals is not described [28]. However, the question arises whether touching on all possible topics and interventions is feasible in CPGs, for which the methodology is structured around clinical questions, and if a complete description of care may still be called a CPG.

The competing interests of completeness and clinical usability on one hand, and methodological rigor on the other is a pressing matter in the field of rare disease CPG development, and possibly also beyond the context of rare diseases, for which currently no clear solution exists. Methodological rigor cannot be found when there is no acceptance and support from a guideline panel, consisting of mainly clinicians and patient representatives/parents/carers who, understandably, want to see a product that they can use in their daily practice and addresses all clinical

Table 5. Clinical topics selected by guideline core group

Selected questions (nonhierarchical order)	Ranking in overall group	Ranking in clinician's group
1. Genetic diagnostics and counseling		
What is the recommended diagnostic route for individuals with neurodevelopmental disorders to establish the diagnosis of SATB2-Associated Syndrome (SAS)?	17	7
What are the genetic counseling recommendations after the SAS diagnosis has been made?	23	13
2. Development		
How and in what frequency should the development of individuals with SAS be monitored? (intelligence, motor skills, adaptive functioning, social and emotional)	13	19
What therapies and interventions are recommended for individuals with SAS to stimulate development in different areas? (motor, cognitive, sensory, social etc)	6	8
3. Speech, language, and communication		
What is the nature of speech disorders in individuals with SAS and how should they be diagnosed and treated?	3	4
Which assessments/tools are suitable to assess language comprehension in individuals with SAS?	7	17
What interventions are best to improve and support communication in individuals with SAS?	1	1
4. Mental health, behavior and sleep		
What challenging behaviors occur in individuals with SAS and what are recommendations for assessment and interventions?	5	3
What psychiatric disorders should professionals be alert to in individuals with SAS, and what are recommendations for assessment and treatment?	22	5
How may autism spectrum disorder best be treated in individuals with SAS?	29	14
What types of sleep issues are most common in individuals with SAS and what interventions may improve sleep in individuals with SAS?	16	12
What is the recommended diagnostic pathway for sleep issues in individuals with SAS?	19	18
5. Neurology		
What neurological diagnostic examinations are recommended for individuals with SAS?	15	16
Which types of epilepsy can occur in individuals with SAS and what are the recommendations for diagnostics and treatment?	38	27
How can pain be identified, measured and treated in individuals with SAS, considering a higher pain threshold?	9	6
6. Bone health		
How and when should screening and diagnostics for bone health be done in individuals with SAS?	10	20
What interventions are best to keep or improve bone health in individuals with SAS?	11	23
7. Oral health		
How should the occurring dental health problems in individuals with SAS be prevented, monitored and treated?	4	10
8. Comorbidities and miscellaneous		
What are the more common comorbid (accompanying) diagnoses associated with SAS, the recommended screening and treatment? (for e.g. hearing, vision, urologic and other issues)	18	9
9. Organization of care		
What should the multidisciplinary team of an individual with SAS look like?	2	2
How should the transition of care of individuals with SAS from pediatric to adult best be done?	8	15
10. Family support		
How may the family of an individual with SAS best be counseled and supported in regard to their well-being?	12	11

questions in a patient's journey. However, limited resources often constrain efforts to answer all these clinical questions with methodological rigor [29]. Especially for rare diseases, clear and structured prioritization of topics in a CPG to allocate time and effort is important [30]. When no clear prioritization has been done, this may leave a guideline project potentially with a complete overview of topics, but without individual evidence-based recommendations based on proper underlying systematic reviews [31]. On the other hand, it may be argued that the ultimate goal of a CPG is to help clinicians treat patients better; strict methodology will ensure valid recommendations are being made, but if that methodology leads to a very limited set of recommendations, then the ultimate goal is not met and is being sacrificed in favor of methodological perfection.

In light of this discussion, we suggest more debate on topic prioritization vs completeness of rare disease CPGs, research on different stakeholders' views on this topic, and a wider scientific debate on CPG methodology for topics with little to no evidence in general, for which currently no clear guidance exist. CPG development and implementation for rare diseases in many aspects can be more challenging than CPG development for more common diseases [19], whereas the context of rare diseases is in extra need of more evidence-based knowledge, since this is currently lacking in many conditions.

CRediT authorship contribution statement

Charlotte M.W. Gaasterland: Writing − original draft, Methodology, Formal analysis, Conceptualization. **Mirthe J. Klein Haneveld:** Writing − review & editing, Methodology, Conceptualization. **Barber M. Tinselboer:** Writing − review & editing, Methodology. **Yuri A. Zarate:** Writing − review & editing, Supervision, Conceptualization. **Damjan Osredkar:** Writing − review & editing, Conceptualization. **Agnies M. van Eeghen:** Writing − review & editing, Supervision, Funding acquisition. **Erika Stariha:** Writing − review & editing, Supervision, Project administration.

Declaration of competing interest

C.M.W. Gaasterland reports financial support was provided by ITHACA European Reference Network. C.M.W. Gaasterland reports a relationship with ITHACA European Reference Network that includes: employment. M.J. Klein Haneveld reports a relationship with ITHACA European Reference Network that includes: employment. There are no competing interests for any other author.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2026.112187.

Data availability

The data that has been used is confidential.

References

[1] Zarate YA, Perry H, Ben-Omran T, Sellars EA, Stein Q, Almureikhi M, et al. Further supporting evidence for the SATB2-associated syndrome found through whole exome sequencing. Am J Med Genet A 2015;167a(5):1026−32.
[2] Döcker D, Schubach M, Menzel M, Munz M, Spaich C, Biskup S, et al. Further delineation of the SATB2 phenotype. Eur J Hum Genet 2014;22(8):1034−9.
[3] López-Rivera JA, Pérez-Palma E, Symonds J, Lindy AS, McKnight DA, Leu C, et al. A catalogue of new incidence estimates of monogenic neurodevelopmental disorders caused by de novo variants. Brain 2020;143(4):1099−105.
[4] Gillentine MA, Wang T, Eichler EE. Estimating the prevalence of de novo monogenic neurodevelopmental disorders from large cohort studies. Biomedicines 2022;10(11):2865.
[5] Zarate YA, Bosanko KA, Caffrey AR, Bernstein JA, Martin DM, Williams MS, et al. Mutation update for the SATB2 gene. Hum Mutat 2019;40(8):1013−29.
[6] Zarate YA, Bosanko KA, Thomas MA, Miller DT, Cusmano-Ozog K, Martinez-Monseny A, et al. Growth, development, and phenotypic spectrum of individuals with deletions of 2q33.1 involving SATB2. Clin Genet 2021;99(4):547−57.
[7] Zarate YA, Bosanko KA, Caffrey AR. SATB2-associated syndrome in adolescents and adults. Am J Med Genet A 2021;185(8):2391−8.
[8] Zarate YA, Fish JL. SATB2-associated syndrome: mechanisms, phenotype, and practical recommendations. Am J Med Genet A 2017;173(2):327−37.
[9] Zarate YA, Bosanko K, Fish J. SATB2-Associated syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews(®). Seattle (WA): University of Washington, Seattle Copyright © 1993-2025, University of Washington, Seattle; 1993. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.
[10] Stoller JK. The challenge of rare diseases. Chest 2018;153(6):1309−14.
[11] 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.
[12] World Health O. WHO handbook for guideline development. 2nd ed. Geneva: World Health Organization; 2014.
[13] 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.
[14] Oxman AD, Schünemann HJ, Fretheim A. Improving the use of research evidence in guideline development: 2. Priority setting. Health Res Policy Syst 2006;4(1):14.
[15] Klein Haneveld MJ, Oerbekke MS, Szakszon K, Cornel MC, Gaasterland CMW, Van Eeghen AM. Priority-setting criteria for

clinical practice guideline development on rare genetic neurodevelopmental disorders: a Delphi study within the European Reference Network ITHACA. J Clin Epidemiol 2025;182:111761.

[16] Richter Sundberg L, Garvare R, Nyström ME. Reaching beyond the review of research evidence: a qualitative study of decision making during the development of clinical practice guidelines for disease prevention in healthcare. BMC Health Serv Res 2017;17(1):344.

[17] Schünemann HJ. Using systematic reviews in guideline development: the GRADE approach. In: Egger M, Davey Smith G, Altman DG, editors. Systematic Reviews in Health Research: Meta-Analysis in Context. 2nd ed. Hoboken: Wiley; 2022:424−48.

[18] Zhang Y, Akl EA, Schünemann HJ. Using systematic reviews in guideline development: the GRADE approach. Res Synth Methods 2019;10(3):312−29.

[19] Pai M, Iorio A, Meerpohl J, Taruscio D, Laricchiuta P, Mincarone P, et al. Developing methodology for the creation of clinical practice guidelines for rare diseases: a report from RARE-Bestpractices. Rare Dis 2015;3(1):e1058463.

[20] Neumann I, Brignardello-Petersen R, Wiercioch W, Carrasco-Labra A, Cuello C, Akl E, et al. The GRADE evidence-to-decision framework: a report of its testing and application in 15 international guideline panels. Implementation Sci 2016;11(1):93.

[21] Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. J Clin Epidemiol 2011;64(12):1303−10.

[22] Oerbekke MS, Gaasterland CMW, van der Laan MJ, Hooft L. Introducing re-weighted range voting in clinical practice guideline prioritization: development and testing of the re-weighted priority-setting (REPS) tool. PLoS One 2024;19(4):e0300619.

[23] Aymé S, Kole A, Groft S. Empowerment of patients: lessons from the rare diseases community. Lancet 2008;371(9629):2048−51.

[24] Klein Haneveld MJ, de Mortier CA, Hugon A, Cornel MC, Gaasterland CMW, van Eeghen AM. "We are the engine": a focus group study on clinical practice guideline development with European patient advocates for rare congenital malformations and/or intellectual disability. Orphanet J Rare Dis 2025;20(1):169.

[25] Patterson AM, O'Boyle M, VanNoy GE, Dies KA. Emerging roles and opportunities for rare disease patient advocacy groups. Ther Adv Rare Dis 2023;4:26330040231164425.

[26] Mickute G, Staley K, Delaney H, Gardiner O, Hunter A, Keen R, et al. Rare musculoskeletal diseases in adults: a research priority setting partnership with the James Lind Alliance. Orphanet J Rare Dis 2020;15(1):117.

[27] Aleksovska K, Kobulashvili T, Costa J, Zimmermann G, Ritchie K, Reinhard C, et al. European Academy of Neurology guidance for developing and reporting clinical practice guidelines on rare neurological diseases. Eur J Neurol 2022;29(6):1571−86.

[28] Tsou AY, Bulova P, Capone G, Chicoine B, Gelaro B, Harville TO, et al. Medical care of adults with Down Syndrome: a Clinical Guideline. JAMA 2020;324(15):1543−56.

[29] 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.

[30] Hieltjes IJ, Gaasterland CMW, Bakx R, van Breukelen SCW, Ensink RJH, van Esch C, et al. An additional Criterion to Appraisal of Guidelines for research and evaluation II might increase the efficiency in Guideline development for rare diseases: results of a national Delphi Study. Clin Public Health Guidel 2025;2(4):e70040.

[31] Shaneyfelt TM, Centor RM. Reassessment of clinical practice guidelines: go gently into that good night. JAMA 2009;301(8):868−9.