Received: 8 April 2021 | Accepted: 27 January 2022

DOI: 10.1111/ene.15267

european journal of neurology
the official journal of the european academy of neurology

CONSENSUS STATEMENT

European Academy of Neurology guidance for developing and reporting clinical practice guidelines on rare neurological diseases

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This manuscript was handled by Prof. Dr Claudia Sommer and Prof. Dr Didier Leys was not involved at any stage of the review process.

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Abstract

Background and purpose: Rare diseases affect up to 29 million people in the European Union, and almost 50% of them affect the nervous system or muscles. Delays in diagnosis and treatment onset and insufficient treatment choices are common. Clinical practice guidelines (CPGs) may improve the diagnosis and treatment of patients and optimize care pathways, delivering the best scientific evidence to all clinicians treating these patients. Recommendations are set for developing and reporting high-quality CPGs on rare neurological diseases (RNDs) within the European Academy of Neurology (EAN), through a consensus procedure.

Methods: A group of 27 experts generated an initial list of items that were evaluated through a two-step Delphi consensus procedure and a face-to-face meeting. The final list of items was reviewed by an external review group of 58 members.

Results: The consensus procedure yielded 63 final items. Items are listed according to the domains of the AGREE instruments and concern scope and purpose, stakeholder involvement, rigour of development, and applicability. Additional items consider reporting and ethical issues. Recommendations are supported by practical examples derived from published guidelines and are presented in two tables: (1) items specific to RND CPGs, and general guideline items of special importance for RNDs, or often neglected; (2) items for guideline development within the EAN.

Conclusions: This guidance aims to provide solutions to the issues specific to RNDs. This consensus document, produced by many experts in various fields, is considered to serve as a starting point for further harmonization and for increasing the quality of CPGs in the field of RNDs.

KEYWORDS
AGREE, consensus, Delphi, guideline, neurology, rare diseases, recommendation

INTRODUCTION

Rare diseases (RDs) are characterized by their low prevalence (<5/10,000 persons in Europe), but when considered all together, as a group, they affect up to 29 million people in the European Union [1]. Therefore, it is not uncommon for clinical practitioners to be faced with the need to diagnose and treat patients with RDs. Neurologists are on the front line of this challenge since almost 50% of all RDs affect the nervous system and the muscles [2]. Due to the rare nature of these diseases, many clinicians lack enough expertise for diagnosing and treating people with RDs. Consequently, delays in the diagnosis and treatment onset and insufficient treatment choices are common [3–5]. The impact of delay on diagnosis and treatment of RDs can be significant, as people with RDs often experience progressive deterioration of their health-related quality of life. Furthermore, it represents a lost opportunity for the few RDs for which disease-modifying treatments are available [6].

High-quality clinical practice guidelines (CPGs) may improve the diagnosis and treatment of patients with RDs and optimize care pathways, delivering the best scientific evidence to all clinicians treating these patients, especially to those working outside tertiary specialized centres. In fact, the need for CPGs for RDs has been largely acknowledged and yielded an increase of CPGs published in the past years. Unfortunately, the existing guidelines do not always meet the highest quality criteria [7,8]. The lack of high-quality randomized controlled trials (RCTs) in RDs makes it demanding to implement the standard procedures for assessing the certainty of the evidence, as suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (https://www.gradeworkinggroup.org/). In addition, there are frequent methodological flaws in the existing guidelines on RDs, including the methodology followed to establish consensus amongst experts [7].

A few authors have proposed strategies to facilitate the process of CPG production on RDs [9,10]. However, clear guidance on producing specific CPGs for rare neurological diseases (RNDs) is missing. A survey of 62 CPG manuals found only sporadic references to or instructions on how to approach the field of RDs [11]. To promote the production of guidelines for RNDs within the European Academy of Neurology (EAN) and to improve their quality, a consensus procedure was conducted aiming to set recommendations for developing and reporting CPGs on RNDs. The results of this consensus are incorporated in this 'EAN Guidance for Developing and Reporting CPGs for RNDs'.

METHODS

Members of the consensus panel

Two separate groups were identified to be involved in the development of this guidance, a core group and an external review group. The core group included members from the EAN and the European Reference Networks (ERNs). EAN participants included the members of its Guideline Production Group, two patient representatives from the European Federation of Neurological Associations and Rare Diseases Europe, and 22 neurologists and methodologists with a special interest in RNDs, who were designated by the EAN Scientific Panels to attend the course 'European guidelines for RND—challenges' 2018 in Vienna. The ERN participants included members from its neurological networks: the European Reference Network for Rare and Complex Epilepsies, the European Reference Network for Rare Neurological Diseases and the European Reference Network for Rare Neuromuscular Diseases. In total, 33 persons were invited to join the core group and 30 of them agreed to participate.

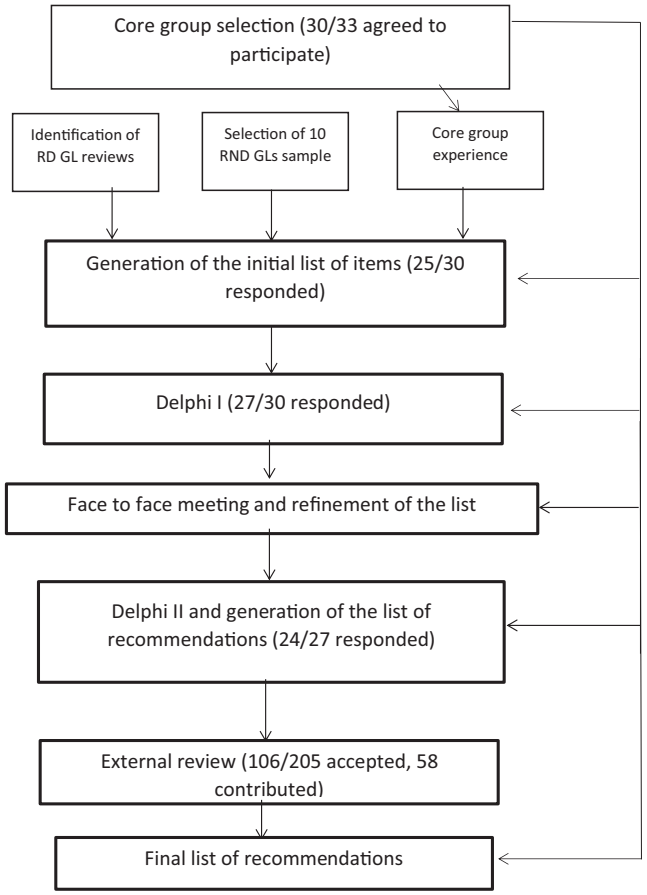

FIGURE 1 Flowchart illustrating the consensus process

A second larger group of CPG users and developers (the external review group) included two representatives from each of the 29 EAN Scientific Panels (https://www.ean.org/home/organisation/scientific-coordinating-panels), the members of the EAN Coordinating Panel on RDs, and other individuals suggested by the EAN guideline task forces, ERNs and patient organizations. On the whole, 205 potential participants were invited. Those who agreed to participate ($N = 106$) were included in the external review group.

This guidance was developed through several steps, following appropriate checklists and guidances [12,13] (Figure 1):

a. Retrieval of a sample of CPGs on RNDs
b. Generation of initial items

c. Two-round online Delphi consensus procedure and a face-to-face meeting
d. External review of the final draft

Retrieval of a sample of guidelines on RND

To provide an initial insight into the items to consider for this guidance, and to identify the methodological issues peculiar to RNDs, two authors (KA, TK) performed an informal review of CPGs on RNDs. PubMed (December 2018) was searched using the following string: ((guideline or guidelines or recommendations) AND (rare disease or rare diseases)) AND neurolog*. The search was limited to the last 5 years and manuscripts published in European languages. Additionally, the members of the EAN Guideline Production Group were asked to share high-quality CPGs on RNDs published in the last 5 years.

Generation of initial items

Our informal review retrieved 18 CPGs from which a convenience sample was selected of 10 CPGs with different qualities and methodologies that was sent to the core group, together with the two most recent reviews in the field, in order to provide the other experts with an insight into the various methodological problems in the RND CPGs [7,8,14–23]. The core group was requested to identify and define the methodological issues peculiar to the development of CPGs for RNDs and to generate an initial list of items, following a multistep process including assessment of the CPGs sample using the AGREE-II tool [24], reading the reviews and using insights from their own experience. An Excel sheet was prepared in advance that was sent to the core group to collect comments on the different steps of guideline production [25]. Two authors (KA, ML) gathered the answers from the core group and generated an initial list of recommendations by removing duplicates, summarizing answers and clustering similar responses. This initial list contained 93 items for scoring, seven yes/no questions and four 'discussion points'. 'Discussion points' were issues raised by the core group members which it was not possible to organize into structured items. The list was subjected to a two-round Delphi consensus survey.

Consensus procedure

A Delphi process was used to achieve consensus [26]. The advantages of this technique consist in involving content experts and ensuring anonymity, thus enabling balanced opinions amongst participants. The structured nature of the process enables efficiency in obtaining the desired aims.

- *Delphi phase I*

During Delphi phase I, the core group members were asked to rank each item in the initial list by its importance. A Likert scale from 1 to 9 was used, ranking questions as of low (1–3), medium (4–6) and high importance (7–9), except for the yes/no questions and the 'discussion points' that were not scored. The members were also requested to explain the answers when relevant, and to comment on the four discussion points. Respondents were allowed to add additional items and questions. At the end of this phase, the same two authors (KA, ML) categorized scores for each item as low, medium or high importance. The items assigned to the medium or high importance groups by at least 80% of the participants were included in the final list. The items considered of low importance by at least 80% of the participants were excluded. The rest of the items went to phase II.

- *Face-to-face meeting*

A meeting involving eight members of the core group was organized at the EAN Congress in Oslo (June 2019), to present the preliminary results of phase I and to suggest solutions to the discussion points.

- *Delphi phase II—agreement*

During Delphi phase II, the list of items that, based on a predefined threshold value, were neither included nor excluded in phase I were sent only to the first-round respondents for further assessment. The list also contained the related comments and the suggested solutions for each discussion point.

The same voting and prioritization procedures as in phase I were then followed, producing a new list, inclusive of items that passed both phases of the Delphi process. The possibility for another round was considered, but in our case it was not necessary.

External review

To evaluate the feasibility of the guidance, the external review group reviewed the draft of the manuscript and was allowed to suggest additional items. Two members of the core group (KA, ML) analysed their comments and referred to the core group that approved the final draft.

Study duration and participant withdrawal

The consensus procedure took place between 15 May 2019 and 15 September 2019. For each Delphi round, a 4-week period was given to the participants to answer the questions. Reminder emails were sent to the non-responders in the second week and 1 week before

the end of each round. Those participants who did not respond after the 4-week period were considered as withdrawn. Additionally, every participant was able to withdraw themselves upon request, in any phase, but none did.

RESULTS

The consensus process is illustrated in Figures 1 and 2.

a. *Generation of initial items*: Twenty-five out of the 30 members of the core group gave their proposals for the initial list of items. After removing duplicates and clustering similar responses, the initial list was formulated, containing 93 items for voting, seven yes/no questions and four discussion points.
b. *Delphi phase I*: Twenty-seven out of the 30 members of the core group voted, and 48 items were considered of high importance (Likert score 7–9) by more than 80% of the participants. None of the items was considered as of medium importance and none was considered as of low importance by more than 80% of participants. Two out of the initial seven yes/no questions were accepted by the majority of the voters and included in the list, together with the 48 items.
c. *Face-to-face meeting*: At this meeting, the solutions of the 'discussion points' were converted into eight new items that were added to the 45 items that did not reach the threshold in the first round.
d. *Delphi phase II—agreement*: Twenty-four out of 27 respondents to the first round responded to the second round. At this point, the core group participants were asked to rate the items that were not included/excluded at the first phase of the Delphi panel ($N = 45$), as well as the eight new items generated following the face-to-face meeting (53 items in total). Amongst these 53 items under evaluation, 26 were scored 7–9 (high importance) by at least 80% of the participants. Of the remaining 27 items, 25 were considered unimportant and discarded (listed in Appendix S1) and two were repetitive with those already accepted.
e. After the second Delphi phase, all the items that were considered important from the whole consensus process were collected. Thus, the final list included 48 items and two yes/no questions from the first round and 26 from the second round ($N = 76$). Finally, the refinement of the duplicates and similar topics yielded a total of 63 items.

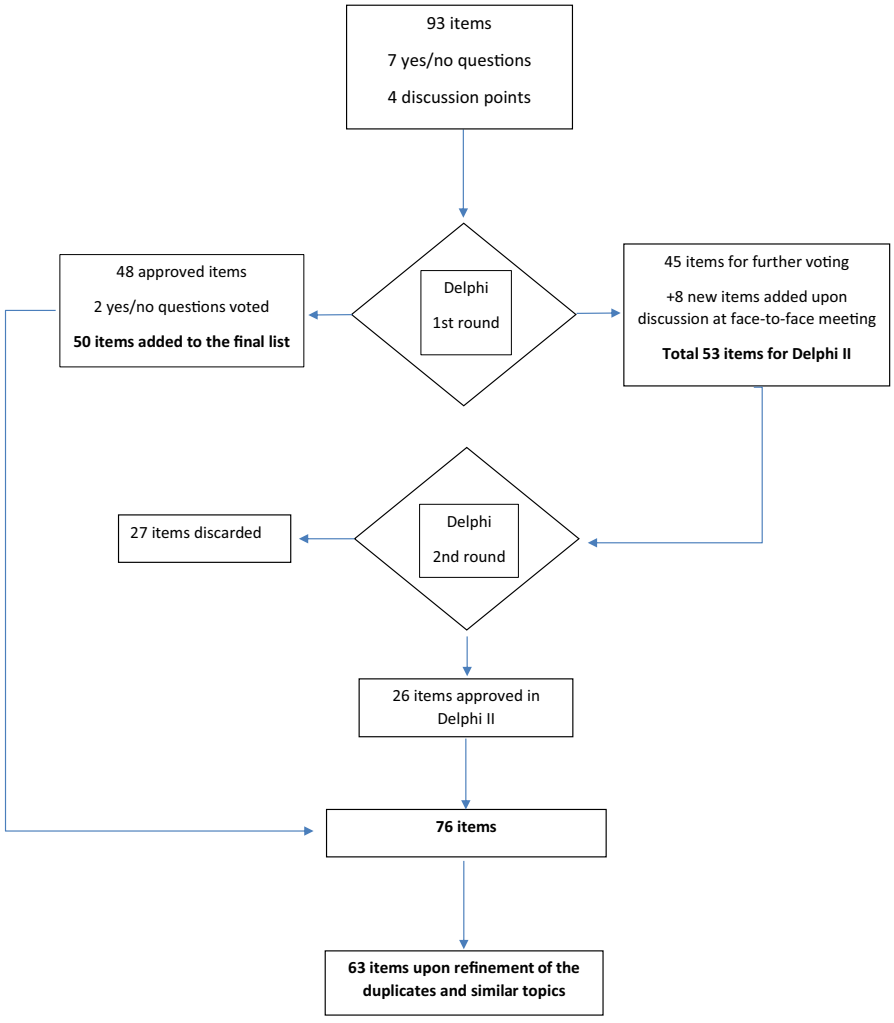

FIGURE 2 Flowchart illustrating the process of selection of items [Colour figure can be viewed at wileyonlinelibrary.com]

f. *External review*: The manuscript was drafted by KA and ML, repeatedly revised by the core group members, and eventually reviewed by the external group. Fifty-eight out of 106 external group participants responded, providing only minor suggestions regarding clarity of wording that were incorporated in the manuscript. Then, the final draft was sent to the core group for final approval.
g. *Final items*: The final items derived from the Delphi consensus and the external review are listed according to the AGREE reporting checklist (www.agreetrust.org), divided into two parts according to their content and aims:
h. Items specific to CPGs on RNDs and general guideline items that are of special importance or often neglected in CPGs on RNDs (Table 1)
i. Items for guideline development within the EAN (Table 2)

The items in Tables 1 and 2 are ordered by the AGREE domains of scope and purpose, stakeholder involvement, rigour of development, applicability and editorial independence. Additional items regard reporting (*in italics*) and ethical issues.

For educational purposes, in the following text suggestions are proposed for applying several items valid for guidelines in common diseases (listed in Table 1) to the specificity of RND, and these explanations are supported with examples.

Scope and purpose

The end-users of guidelines (usually not experts of RNDs but general neurologists or child-neurologists, geneticists, general practitioners, nurses or patients' organizations) desire to have a practical and useful instrument on their desk for everyday work, especially when information on disease management (diagnosis, therapy, rehabilitation) may be difficult to retrieve. Because of this, it is considered that a guideline on RND should usually cover a broad spectrum of disease management aspects and options, regarding diagnosis and treatment (Example 1) [27] (item 1 in Table 1).

Example 1 The aims of the consensus statement on "Stridor in multiple system atrophy" were to cover all aspects of the management of this condition. "An International Consensus Conference among experts with methodological support was convened in Bologna in 2017 to define stridor in MSA and to reach consensus statements for the diagnosis, prognosis, and treatment..... Unmet needs for research were identified."

One of the key points in guideline production is the formulation of the clinical questions using the PICO (Patient/Population, Intervention, Comparator/s and Outcome/s) format, which allows for a clear definition of the objectives and helps the guideline developers to focus on the main issues to be addressed [9,28]. The PICO format is often lacking in RND guidelines, sometimes because it may be difficult to make specific definitions of some of its elements [9]. Another reason is that guideline developers are more likely to skip a formal articulation of PICOs when they think the clinical question will be answered using a consensus process. Whatever the reason behind the lack of PICO formatting may be, this leads to recommendations or statements that are broad and unspecific and consequently very hard to implement by the end-users. Therefore, it is recommended that clinical questions should always follow the PICO format (Example 2) [29] (item 4).

Example 2 In a guideline on catastrophic antiphospholipid syndrome (CAPS), several diagnostic and therapeutic questions were formulated following the PICO format:

Diagnostic question:

- Should the preliminary criteria for classification of CAPS (Intervention) be used to diagnose CAPS (Outcome) in patients with features suggestive of CAPS (Population)? Compared to physician expertise (Comparator).

Therapeutic question:

- Should combination therapy with glucocorticoids, unfractionated heparin and plasmapheresis and/or IVIG be used as first-line therapy (I) for CAPS patients (P) compared to single agent (C), to prevent or improve the following outcomes (O): death, permanent organ dysfunction, permanent neurologic deficit, complete recovery, major bleeding, amputation, or thrombosis/thrombotic event.

The definition of the target population is another aspect of the RND CPG development that is considered highly important. RDs may differ considerably regarding the age of onset or clinical presentation. For this reason, an accurate definition of the clinically important characteristics of the target population is crucial to drive the whole guideline development process and inform the reader on the particular contexts in which the recommendations should be applied (Example 3) [30] (item 8).

Example 3 In the Consensus on clinical management guidelines for Niemann-Pick disease type-C (NPC) the Authors state:

"This document represents general guidelines, which in the opinion of the authors can inform care providers about the needs of patients with NPC in order to provide equitable and improved care, define standard of care for NPC patients, foster shared care arrangements between expert centres and family physicians, and empower patients. The guidelines refer to the management of patients suspected or diagnosed with NPC disease at any age."

Stakeholder involvement

Comprehensive stakeholder involvement is important for ensuring relevant recommendations [31]. Most RDs are multisystemic and multiple specialists may be involved in their diagnosis and management. Guideline developers must be aware of this and should include all medical specialists relevant to a particular guideline topic and population. In addition, it may be necessary to include biologists,

TABLE 1 Items specific to clinical practice guidelines (CPGs) on rare neurological diseases (RNDs) and general guideline items that are of special importance or often neglected in CPGs on RNDs

DOMAIN 1: SCOPE AND PURPOSE	
Objectives	
1	RND CPGs should be comprehensive, covering all aspects of the management of a disease, from diagnosis, natural history to therapy and rehabilitation. However, in selected cases, CPGs focused on specific topics concerning several RNDs can be accepted (e.g., rehabilitation in neuromuscular rare diseases, diagnosis of rare epilepsies)
2	The scope and purpose should be identified after discussion between experts and patients' representatives
3	*Scope and purpose should be clearly described*
Developing clinical questions	
4	The clinical questions should follow the PICO format
5	*When analysing biomarkers, clearly distinguish between those aimed for diagnostic, prognostic and therapeutic response*
6	*There should be a clear distinction between symptomatic treatment and disease-modifying therapies*
7	RND CPGs should contain no more than 10–15 clinical questions. Prioritize and start from the questions that are most relevant to the target group and audience
Population	
8	The target population must be clearly defined and reported (age group, disease variant etc.)
Target users	
9	*Target audience should be clearly described*
DOMAIN 2: STAKEHOLDER INVOLVEMENT	
Group membership	
10	Comprehensive stakeholder involvement is as important to the development of RND CPGs as it is for common diseases. Apart from clinicians from various specialties, the group should also involve methodologists with detailed knowledge about non-RCT designs and if appropriate also other relevant experts such as biologists, neuroscientists, geneticists, nurses, occupational therapists, nutritionists etc. Collaboration with ERNs should be sought
11	*There should be a clear description of the different stakeholders involved*
Target population preferences and views	
12	Patients' representatives should be designated by a European patients' association (e.g., European Federation of Neurological Associations). More than one patients' representative per guideline may be included
DOMAIN 3: RIGOUR OF DEVELOPMENT	
Systematic literature search and evidence selection criteria	
13	Collaboration with professional librarian/information specialist should be sought if needed. In the cases when this is not feasible, the recommendations from 15 to 19 should be followed
14	A survey of all published cases or from a registry if it exists should be included in the CPGs for RND with <100 published cases
15	More databases should be searched compared to common diseases, including special disease repositories. Where appropriate, longer time periods and literature search in languages different than English should be encouraged
16	RND CPGs must consider the best available evidence, according to the pyramid of evidence. This means that RCTs should be considered where possible, but in addition other study designs should be included. A systematic review of an RND should plan to identify observational data (including case reports and case series), in addition to experimental data
17	Special data collection forms may be used to obtain individual patient data from the experts participating in the CPG development
18	Do not put filters regarding the design on the database searches, but instead set up clearly defined inclusion and exclusion criteria
19	The systematic literature search should always be clearly reported in the CPG document, so the reader can verify that all available information has been considered
Reporting of the evidence from the individual studies (strengths and limitations of the evidence)	
20	*Since the sample sizes are often small, when reporting the results of the individual studies it is very important to report not just the effect sizes/p values but also corresponding measures of variability/uncertainty (e.g., confidence intervals, standard deviations, standard errors, range, interquartile range). Be as consistent as possible (e.g., if possible, extract the same measure of variability for all studies). Report evidence clearly and transparently, in predefined descriptive tables*
21	Avoid inclusion of studies with overlapping populations

(Continues)

TABLE 1 (Continued)

22	For evaluating individual studies' quality, follow standard reporting checklists for the main study types (e.g., ROB II, ROBINS, QUADAS-II, Newcastle Ottawa etc)
Quality appraisal of the overall body of evidence (strengths and limitations of the evidence)	
23	Besides all difficulties, GRADE should be the standard for all EAN RND CPGs. Evidence should be evaluated according to their level of certainty. Quality of evidence should be described transparently and using the GRADE outcome-centric methods
24	Beware of selection bias (studies may include patients only from tertiary centres, which may have a more severe clinical picture)
Evidence synthesis and analysis (link between recommendation and evidence)	
25	Guideline committees should promote individual participants' data meta-analysis to enrich scientific evidence by both asking authors to share data and searching and pooling case reports when possible
26	When no meta-analysis is possible, a systematic review of the individual studies must include detailed descriptive summaries (e.g., graphical or textual displays of effect sizes of individual studies, ideally accompanied by corresponding measures of variability)
27	*The evidence synthesis and analysis must be transparently reported in outcome-oriented summary tables*
28	*Evidence of benefits and harms (if available) should be adequately reported in the synthesis of the evidence*
29	The GRADE system should be used in the process of the formulation of the evidence and the rationale for each must be clearly discussed, following an evidence to decision (EtD) framework. In the cases where a good practice statement is more appropriate, the rationale behind the appropriateness of the corresponding statements must be reported and discussed openly
Consideration of benefits and harms	
30	Any recommendation should clearly explain the weights posed on balance of benefits and harms both from the patients' and clinicians' side
Creating recommendations (formulation of recommendations)	
31	Use GRADE (EtD frameworks) in addition to a predefined consensus process and a face-to-face meeting
32	The process should be methodologically sound and described in detail (process of voting, cut-off for acceptance, number of voters, people that voted against and their reasons, number of rounds etc.)
33	Provide advice in a form which is of clinical value, even if the evidence base falls short of the quality criteria required for more common disease, in a form of consensus statements. However, these statements should always be accompanied by adequate discussion of the statistical and the methodological limitations
34	*The key recommendations should be clearly reported in a concise summary document. They should be easy to follow but should always report the strength of recommendations. If the CPGs are multi-targeted, different summary documents may be provided (adapted for diverse audiences)*
35	An updating procedure should be planned and reported
36	Recommendations for future research are strongly encouraged
Adapting existing guidelines	
37	CPG and expert consensus eligible for adaptation should be (1) up to date and (2) of excellent methodological quality (AGREE II)
DOMAIN 5: APPLICABILITY	
38	*Tools for implementation (algorithms, advice for carers, emergency cards, guidance for critical care …) are useful and encouraged. A visual summary (e.g., a video or an infographic) of the main recommendations can be useful*
DOMAIN 6: EDITORIAL INDEPENDENCE	
39	*All COIs (commercial and non-commercial) and the methods used to deal with them must be clearly reported. This applies to every member of the task forces, including the patient representatives*
40	The recommendations should always be reviewed by multi-stakeholder external reviewers (non-physicians, patients, other specialists)
OTHER ISSUES	
Reporting	
41	*To facilitate retrieval of the CPGs, the term 'rare disease(s)' should be used (in title or in the abstract). For the same reason, the OMIM and ORPHA numbers should be reported*
42	*It is suggested that the AGREE reporting checklist be followed as methodological reference to meet the highest guideline development standards*

TABLE 1 (Continued)

Ethical issues	
43	Ethical issues need to be identified a priori and discussed; in particular, issues for genetic diagnosis and therapies
44	When relevant, always consider palliative care in the PICOs
45	A medical ethicist opinion may be valuable for individual recommendations, particularly in the areas dealing with end of life and with gene therapies. An ethical expert may be included in the membership when needed (e.g., guidelines about palliative care)

Notes: Italics indicate reporting recommendations. This table is aimed to be used as a list of items that should be considered in the development of RND CPGs and should be used to ease the implementation of the GRADE approach. For practical reasons, it is organized following the AGREE II tool but should not be used as its substitute for appraisal of CPGs.

Abbreviations: COI, conflict of interest; EAN, European Academy of Neurology; ERN, European Reference Network; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PICO, Patient/Population, Intervention, Comparator/s and Outcome/s;RCT, randomized controlled trial.

neuroscientists, physiotherapists, nurses, occupational therapists, nutritionists or other professionals who have expertise in the topic and population of interest. The guideline panels should also include methodologists from the beginning of the guideline development, because CPGs on RNDs pose additional methodological challenges, such as the type of data and the design of included studies (most frequently non-randomized, non-controlled data) (item 10).

Patients' representatives are needed to increase the transparency of the CPG development process. Furthermore, integration of patients' perspectives in CPGs is of great importance to make guidelines more patient-centred, and their natural experience in the diseases is a valuable 'add on' to the guidelines. The involvement of patients is recommended from the beginning of the guideline production process (e.g., definition of the guideline objectives), because their views about the relevance of some questions or outcomes may be different from those of the clinicians [31–36] (G-I-N Public Toolkit: Patient and Public Involvement in Guidelines—https://g-i-n.net/document-store/working-groups-documents/g-i-n-public/toolkit/toolkit-2015). The patients' representatives must be able to reflect the general opinion of the specific patient population. It is recommended that patients' representatives should be designated by a patient organization. Since guidelines may involve more than one disease and patient organizations are often formed around specific diseases, it is suggested that more than one representative is included, especially when the guideline covers different conditions (Example 4) [37] (items 2 and 12). In addition, authors may perform systematic reviews on patient preferences that could guide them in the selection of the clinical questions included in the guideline and selection of the outcomes.

Example 4 As a part of the multidisciplinary group developing the guideline on the management of idiopathic intracranial hypertension, patient representatives were involved: "…A Special Interest Group (SIG) was formed, including neurology, neurosurgery, neuroradiology, ophthalmology, nursing, primary care doctors and patient representatives. …An anonymous modified Delphi process was used to obtain consensus on guidance statements. All statements below obtained consensus of 75% or above from the SIG and wider Delphi group."

Apart from participating to the panel meetings and voting, the specific role of each task force member, including the patient representatives was reported: *"…KH (patient representative of Idiopathic Intracranial Hypertension, UK): design of the statement, interpretation of the survey results and critical review of the manuscript. MW (patient representative of Idiopathic Intracranial Hypertension, UK): design of the statement; interpretation of the survey results*

Rigour of development

Quality of evidence collection and synthesis

For each clinical question, a systematic search of the literature should be performed. Collaboration between clinicians and professional librarians/information specialists might be necessary and is strongly recommended. Guideline developers should take into consideration the following points to enhance the comprehensiveness of literature searches.

a. To facilitate the process, guideline developers usually define filters related to the study designs in the database searches. However, this carries the risk of missing evidence since, in the RND context, evidence may be found in various study designs. In addition, low-quality studies might not clearly report the study design and consequently be missed if a particular filter is used. It is recommended not to use study-design-related filters in electronic searches and to set up clearly defined inclusion/exclusion criteria.
b. Sometimes studies might include a subgroup of patients relevant to the PICO of interest but this information may not be available in the abstract. Therefore, guideline developers may consider not limiting the keyword search to title and abstract only but instead to use the automatic/all fields option, which enables the search engine to include both article keywords and MESH terms.
c. Extend the search to languages other than English.
d. Search more databases compared to common diseases and include databases of special interest for RNDs or CPGs (e.g., Orphanet [http://www.orpha.net/consor/cgi-bin/Disea

TABLE 2 Items specifically concerning EAN guideline development

DOMAIN 2: STAKEHOLDER INVOLVEMENT	
Group membership	
1	Members of the task force are selected amongst European countries. However, the task force may include up to four non-European members, if needed
2	A widespread and balanced geographic representation within Europe must be sought. EAN suggests to preferably include members from more than five European countries
3	The guideline panel should include 10 to 20 members, including all the stakeholders, one methodologist and up to four patients' representatives
DOMAIN 3: RIGOUR OF DEVELOPMENT	
Consensus process (formulation of recommendations)	
4	An individual having a COI in a specific area should have the right to speak on this topic but not to vote on the final acceptance of a recommendation (https://www.eanpages.org/2020/05/01/update-of-ean-guidance-for-guidelines/)
5	EAN suggests using the Delphi consensus process or its modifications
DOMAIN 6: EDITORIAL INDEPENDENCE	
Conflicts of interest	
6	The EAN 'Managing COI for the task forces' should be applied to RND
Facilitators and barriers	
7	The financial and feasibility aspects (if present) should be added in a separate section or at least clearly separated from other parts of the guideline document
External review	
8	The GLs will be published on the website and announced in EAN pages for an open comment period (external review by experts and patient representatives)
OTHER ISSUES	
Dissemination	
9	EAN creates libraries of existing GLs and consensus recommendations
10	Duplicate publication is allowed if GLs are jointly produced with other subspecialty scientific societies
11	National health economics studies are the correct context for cost evaluations and beyond the scope of this guidance. However, the task forces are strongly encouraged to give general suggestions for the best organization of healthcare and for implementation of GLs in different economic and social contexts. This should be organized in a specific paragraph of the GL
Guideline topic selection. How the topic should be prioritized?[a]	
12	Prioritize RND in which the diagnosis is possible, those requiring early diagnosis, diseases for which there are available treatments or where there is a potential loss of opportunity if wrongly managed
13	Prioritize diseases/conditions where the current practice is incongruent/different across European countries
14	A survey can be launched to assess the priority topics amongst EAN Scientific Panels, ERN members and patient organizations
15	If appropriate, EAN RD GLs may cover single RDs or multiple diseases grouped by aetiology (e.g., inherited movement disorders) or symptoms (e.g., ataxia). However, it is recommended that several independent systematic searches focused on a single disease or a symptom are made to obtain enough information on the practical disease-specific issues

Note: This table is aimed to be used as a list of items that should be considered in the development of RND CPGs and should be used to ease the implementation of the GRADE approach. For practical reasons, it is organized following the AGREE II tool, but should not be used as its substitute for appraisal of CPGs.

Abbreviations: COI, conflict of interest; EAN, European Academy of Neurology; GL, guideline; RD, rare disease; RND, rare neurological disease.

[a]A document regarding the prioritization of guideline topics within the EAN is under development.

se.php?lng=EN], G-I-N [http://www.g-i-n.net/], ECRI Guidelines Trust [https://guidelines.ecri.org], EuroGentest molecular testing [http://www.eurogentest.org/index.php?id=700]) or specific RND registries.

e. A systematic review on RND treatment should include non-randomized interventional studies in addition to RCTs. RCTs are often unavailable in RNDs for several reasons [38,39]: the low number of patients usually makes it impossible to achieve standard power requirements in sample size calculations; often there are no comparative or standard treatments available; and lastly, given that most RNDs are chronic in nature and RCTs usually have a short follow-up, the treatment effects could be underestimated because the true treatment results may require longer follow-up periods to be demonstrated. The certainty in the evidence can be higher in some high-quality observational studies than in poor-quality RCTs [40–42] (items 13–19).

Adopting these suggestions may result in an increase in the workload in this phase of CPG production, but it is considered that this is the only way one can be confident that all the evidence for a particular RND has been included in the guideline (Example 5) [18].

Example 5 In this guideline the panel combined various strategies in the literature search that enabled them to retrieve substantial amount of evidence:

- "A systematic literature review on Aromatic l-Amino acid DeCarboxylase (AADC) was performed through December 2015 on PubMed, Cochrane database, and the Cinahl database, using "aromatic (l) amino acid decarboxylase deficiency" and "AADC deficiency" as search terms."
- "No language or data filters were used."
- "The literature database on the official website of the AADC research trust was searched for applicable articles… The WHO registry for clinical trials and the NIH registry for clinical trials were searched."
- "The reference list of the large case series was screened for additional sources."
  - "reference lists from review articles and key case series were screened"

It is acknowledged that there are diseases or medical conditions for which even a broad comprehensive search strategy can only retrieve very few low-quality studies. In these cases, and for RNDs with less than 100 published cases, a review of all published cases and of data from registries, when available, should be added as available evidence. For example, a Belgian CPG on paroxysmal nocturnal haemoglobinuria used data from a patient registry of all reported cases in the country to describe the main clinical characteristics of the patients and to provide recommendations for screening of high-risk patients eligible for further diagnostic evaluations [43]. Furthermore, it is suggested that PICO-oriented, anonymized data collection forms are made to obtain individual patient data from the experts participating in the CPG development. This process allows for a structured and question-oriented data collection and prevents speculations in creating expert opinions (Example 6) [29] (item 17).

Example 6 The below CPG on CAPS is a good example of structured data-collection:

"… In addition, we collected standardized contributions from the panel prior to the panel meeting, elicited using a systematic observation form disseminated electronically. This expertbased evidence elicitation process sought to systematize the process of expert input based on personal experience, as it required data obtained from direct clinical care, and not personal opinions or anecdotes. Experts were required to indicate how many patients they had treated with a given intervention, and what the outcomes were for these patients. The number of CAPS cases seen, patient characteristics (e.g. age, sex, comorbid conditions such as Systemic lupus erythematosus, malignancy) and management (e.g. diagnostic approach, treatment adopted), and perceived effectiveness and harms of each therapy or diagnostic test were sought from each member, using Likert-type scales with the options as follows: "large or moderate benefit", "small benefit", "no benefit", "small harms", "moderate to large harms". Collated responses were presented for each question during the panel meeting. Expert panel members were informed that this was the only opportunity to bring in personal experience…"

Quality appraisal of the overall body of evidence (strengths and limitations of the evidence)

Almost always, in the case of RNDs, results will be presented in a narrative form. However, this should not preclude assessment of the certainty of the evidence, because the GRADE approach can also be applied to results that have been presented narratively. Evidence certainty is best assessed using pooled analyses, but when this is not feasible a comprehensive descriptive analysis of the results of the individual studies has been suggested (items 23, 25 and 26, Table 1).

For the first PICO in example 2, the panel combined two sources of evidence: systematic observations in which the panel members shared data from their patients, and evidence assessment tables using the published studies (Figure 3) [29].

One additional item is identified that should be considered in the evidence synthesis—the risk of selection bias towards more severe cases. This is due to the fact that studies may include patients only from tertiary academic centres that are highly specialized in the treatment of RNDs. This issue should be carefully assessed (item 24, Table 1).

Evidence synthesis and analysis

Primary studies in RNDs often differ in methods and measurements in such a way that summarizing the results through standard meta-analysis techniques is not feasible. In such cases, guideline developers should consider performing individual-participants'-data meta-analysis to synthesize the evidence, providing those data are available [44]. When data cannot be summarized through meta-analysis, the results of the individual studies included in the systematic review should be described in detail (e.g., outcome-oriented descriptive tables). This means that the guideline developers should not be limited to individual studies' summary tables, as is often done in RND CPGs, but provide summaries that are outcome-oriented (items 25–28, Table 1). In example 7 (Appendix S2) [45], the panel aimed to make recommendations on using intravenous immunoglobulin for Guillain-Barré syndrome in children, using four associated PICO questions. For each, they described the characteristics of the studies and the individual results and presented the conclusions narratively. With this kind of elaboration of the evidence, the rationale behind the recommendations is very clear [45].

Link between evidence and recommendation

In the RND context, often the evaluation of the evidence shows low or very low certainty and frequently only narrative synthesis is possible. Given these circumstances, and to support the relevance of the final recommendations, special attention must be given to the description of the link between the recommendations and the quality and the strength of the supporting evidence. This link should be clearly explained by the panel using the evidence to decision framework or the guidance for reporting good practice recommendations [46,47]. This means that even when the recommendations are based on consensus or when the certainty of the evidence is low or very low, the GRADE outcome-centric approach should be kept, and the consensus process and the recommendations should be transparently discussed (items 29, 31, 33, Table 1).

Benefits and harms

Due to the usual scarcity of primary studies, the balance between benefits and harms is hard to evaluate and is frequently neglected or unclearly reported in RND guidelines. Nevertheless, this is an important point that drives the final recommendations for the clinical practice (item 28, 30, Table 1).

In the following example (Example 7) [48], the authors acknowledge the absence of good-quality evidence to strongly support the recommendation for thymectomy (TE) in patients with myasthenia gravis. However, the existing (low-certainty) evidence, together with the considerations that TE is a safe procedure and that the tumour should be treated, allowed the guideline panel to recommend TE [48].

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ● Varies ○ Don't know		**Systematic observations** Number of responding experts: 7

2x2 table summary			
	T+	T-	
D+	28	10	38
D-	2	2	4
	30	12	42

Prevalence = (TP + FN) / total = 0.905
Sensitivity = TP / (TP + FN) = 0.737
Specificity = TN / (TN + FP) = 0.5
PPV = TP / (TP + FP) = 0.93
NPV = TN / (TN + FN) = 0.167

Question: Should the Preliminary Criteria for Classification of the Catastrophic Antiphospholipid Syndrome be used to diagnose CAPS in patients presenting with features suggestive of CAPS?

Sensitivity	0.90 (95% CI: -- to --)
Specificity	0.99 (95% CI: -- to --)

Prevalences	10%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 10%	
True positives (patients with CAPS)	1 studies 395 patients	case-control type accuracy study	serious [a,b]	serious [c]	not serious	not serious	none	90 (0 to 0)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having CAPS)								10 (100 to 100)	
True negatives (patients without CAPS)	studies patients	case-control type accuracy study						895 (0 to 0)	-
False positives (patients incorrectly classified as having CAPS)								5 (900 to 900)	

Explanations

a. Those applying the criteria were not blinded to the results of the reference standard
b. The reference standard of "expert opinion" could have been applied inconsistently
c. Control population does not include important mimickers of CAPS (e.g. sepsis, other thrombotic microangiopathies, thrombophilic disorders, etc)

FIGURE 3 Example for combining different ways of synthesis of evidence (upper half, individual patient data from systematic observation forms; lower half, analysis of studies retrieved with the literature search) [Colour figure can be viewed at wileyonlinelibrary.com]

Example 8 "Despite the absence of randomized, well-controlled studies, TE in MG patients with and without thymoma is widely practised…. In a controlled study, a 34% remission and a 32% improvement rate were achieved after TE compared with 8% and 16% for matched patients without the operation (class III evidence). The patient should be in a clinically stable condition before this elective intervention. The perioperative morbidity is very low and consists in wound healing disorders, bronchopneumonia, phrenic nerve damage and sternum instability…In MG patients with a thymoma, the main aim of TE is to treat the tumour rather than for any effect on the MG. Once thymoma is diagnosed, TE is indicated irrespective of the severity of MG (good practice point)"

Ethical issues

In the field of RDs, several specific ethical issues need to be considered, including genetic diagnosis, counselling and therapy, or the discussion of whether to apply the 'rule of rescue' (saving individual lives regardless of the costs) (https://philpapers.org/archive/VERHNT.pdf). Moreover, RDs often affect younger populations and are chronic in nature, which implies discussions for lifelong therapies, if they are improving the quality of life, or about palliative care. Ethical issues may be important for both patients and health services and, if applicable to a particular guideline, must be discussed from the initial steps of the guideline production (topic selection and definition of the CPG scope and purpose). If the guideline panels consider this necessary, an opinion from an ethics expert should be sought and s/he may even be included as a panel member (items 43–45, Table 1).

Furthermore, although the approach to the conflicts of interest (COIs) of the authors of the RND CPGs must follow the same principles as for common diseases (https://www.eanpages.org/2020/05/01/update-of-ean-guidance-for-guidelines/), in the RND context it may be difficult to find experts, and even patient representatives, without financial and intellectual COIs (guideline panellists are often authors of some of the included studies) [49]. Because of this difficulty, it is recommended that panellists with and without COIs are balanced and that the synthesis of evidence and the quality appraisal are performed by independent methodologists.

DISCUSSION

This guidance aims to provide recommendations to those researchers and clinicians willing to develop CPGs for RNDs within the context of EAN and the ERNs dedicated to RNDs. It was built on the recognition of an unmet need, considering the paucity of specific suggestions for RNDs in the guideline manuals and the literature. According to the hierarchical classification of the pyramid of evidence, the guideline methodology mostly relies on high-quality RCTs or large observational studies [42,50]—two conditions rarely met in RNDs. Thus, in practice, guideline developers in the field of RNDs encounter obstacles in applying consolidated methodologies and, because of this, they often abstain from guideline drafting or decide to make recommendations based solely on 'narrative' expert consensus. The idea that low prevalence equals low evidence must be contended; there can be convincing evidence in RDs coming from well-conducted studies based on pooled retrospective data, prospective observational studies and trials using alternative methods, as well as from correctly evaluated expert opinion.

The guideline production process in the field of RND CPGs could be supported by adding sections dedicated to RDs in the manuals of public organizations that produce guidelines. To promote further development of such guideline approaches, this guidance aims to provide solutions to the issues specific to RNDs. This guidance is not intended to set up new methods for guideline development, nor to establish new checklists for guideline appraisal, but instead it is aimed to make it easier for the guideline panels to implement the GRADE standard in the context of RNDs [40,41,51,52]. Similarly, the items provided in Tables 1 and 2 are not new checklists or guideline appraisal tools, but a list of items that should be considered in the development of RND guidelines.

The choice was made not to publish a separate paper with examples and explanations, as other guidances have done [53,54], considering the very practical nature of this document. Some good examples were selected from the literature, proposing solutions for the items more difficult to implement in RND CPGs, but this does not imply that the entire documents from which the examples were selected are of high quality. If the users need additional explanations, they can refer to publications from the GRADE group [28,40,41,46,52]. Some recommendations (listed in Table 2) are devoted to the process of guideline development within the EAN [51,55] but could also be considered by other scientific societies involved in RNDs. Taking into account the pan-European context of the EAN guidelines, applicability issues were not considered because of the difference in the organization of the health systems in various countries in Europe. Since this and the variable available resources across Europe may create barriers in the implementation of some recommendations, it is suggested that these issues and also considerations regarding costs and benefits of specific treatments should be taken into account when adopting/adapting the future EAN RND guidelines to individual countries.

This guidance has some limitations. First, the development items were not separated from the reporting items. The reason behind this was that many of the reporting items are to a large extent connected to the development process and, considering that the primary aim of this paper is to provide a practical tool for the guideline panels, it was considered more useful to report these two types of items together.

Second, being a consensus document, it is only based on the opinions of the participants and not on a systematic review of the quality of the RND guidelines. To compensate for this limitation, the task force involved in the consensus process of this guidance

was widespread, including experts from several RND fields, guideline methodologists, patients' representatives and external reviewers.

Also, as noted above, the main users of this guidance are intended to be the members of the EAN task forces and neurological ERNs. Because of this, experts outside the field of RNDs and Europe were not included. Future documents on similar topics could benefit from the inclusion of experts from wider fields, which could bring additional perspectives and increase the application of the proposed methods. In conclusion, it is considered that this consensus document, produced by a large number of experts in different fields, will serve as a starting point for further harmonization and for increasing the quality of guidelines in the field of RDs. Even more, it is hoped that the approaches that are recommended for guideline development will encourage improvements in original research in the RND field that are in line with this paper. This guidance is open to further suggestions and possible improvements in the next years.

CONFLICT OF INTEREST

The authors report no conflicts of interest regarding their contribution to this manuscript.

AUTHOR CONTRIBUTIONS

Katina Aleksovska: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); visualization (lead); writing—original draft (lead); writing—review and editing (equal). **Teia Kobulashvili**: Investigation (equal); methodology (equal); writing—review and editing (equal). **João Costa**: Methodology (equal); writing—review and editing (equal). **Georg Zimmermann**: Methodology (equal); writing—review and editing (equal). **Karen Ritchie**: Methodology (equal); writing—review and editing (equal). **Carola Reinhard**: Investigation (equal); methodology (equal); writing—review and editing (equal). **Luca Vignatelli**: Writing—review and editing (equal). **Alessandra Fanciulli**: Writing—review and editing (equal). **M Damian**: Writing—review and editing (equal). **Lucia Pavlakova**: Resources (supporting). **Jean-Marc Burgunder**: Writing—review and editing (equal). **Svetlana Kopishinskaya**: Writing—review and editing (equal). **Martin Rakusa**: Writing—review and editing (equal). **Norbert Kovacs**: Writing—review and editing (equal). **Fusun Erdogan**: Writing—review and editing (equal). **Lori Renna Linton**: Writing—review and editing (equal). **Massimiliano Copetti**: Writing—review and editing (equal). **Costanza Lamperti**: Writing—review and editing (equal). **Serenella Servidei**: Writing—review and editing (equal). **Teresinha Evangelista**: Writing—review and editing (equal). **Ayme Segolene**: Writing—review and editing (equal). **Davide Pareyson**: Writing—review and editing (equal). **Johann Sellner**: Writing—review and editing (equal). **Christian Krarup**: Writing—review and editing (equal). **Marianne de Visser**: Writing—review and editing (equal). **Peter van den Bergh**: Writing—review and editing (equal). **Antonio Toscano**: Writing—review and editing (equal). **Holm Graessner**: Writing—review and editing (equal). **Thomas Berger**: Writing—review and editing (equal). **Claudio L. A. Bassetti**: Writing—review and editing (equal). **Marie Vidailhet**: Writing—review and editing (equal). **Eugen Trinka**: Writing—review and editing (equal). **Guenther Deuschl**: Writing—review and editing (equal). **A Federico**: Conceptualization (equal); Writing—review and editing (equal). **Maurizio A. Leone**: Conceptualization (equal); methodology (equal); project administration (equal); resources (equal); supervision (lead); validation (equal); writing—original draft (supporting); writing—review and editing (equal).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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How to cite this article: Aleksovska K, Kobulashvili T, Costa J, et al. European Academy of Neurology guidance for developing and reporting clinical practice guidelines on rare neurological diseases. *Eur J Neurol*. 2022;29:1571–1586. doi:10.1111/ene.15267

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