Protocol for the European Academy of Neurology Guideline on

**“*Title*”**

***Title structure***

*The title should succinctly state the scientific societies involved, the intervention(s) (in the broad or narrow sense) to be considered, and the problem (disease/population) at which the intervention is directed. In some cases, the title may also indicate a specific population or setting. EAN guideline titles should follow the structure shown in the Table in supporting document A.*

*Number version*

*Date of approval by the Guideline Task Force*

****

**Table of Contents**

*Please provide a table of contents*

**1. Guideline task force members and roles of members**

*Indicate name and affiliations of all task force members and role in the development of the guideline (e.g. representative of other organizations involved in the guideline, Task force chair, patient representative, members of other EAN Scientific Panels, involvement of sub-specialties within neurology, other specialties outside neurology)*

**2. Introduction and objectives**

*The brief introduction should inform the reader about why it is important to develop an EAN guideline on the specific topic. The overarching objective(s) should be stated. Please report any existing guidelines (EAN guidelines or others) which address overlapping (in part or completely) or related areas which will also be addressed in the present guideline. Please provide documentation to the fact that a reasonable effort to identify any relevant guidelines have been carried out (e.g. through a systematic literature search). If overlapping EAN guidelines (or guidelines endorsed by the EAN) have been identified, please provide justification for carrying out the present guideline, e.g. new evidence, in other ways outdated.*

**3. Selection of the Guideline Task Force**

*Please present the timeline for Task Force formation, how the Task Force was selected (e.g. who were invited, criteria for selection, method of selection), which EAN Scientific Panels were invited to participate, other organisations, specialties of the included members, patient representatives, other experts if relevant (e.g. geneticists, physiotherapists… etc), methodologists, etc. geographical and gender distribution. For most guidelines a Guideline Task Force of no more than 20 members will be appropriate to ensure that the necessary capabilities are present within the Task Force while balancing the need for a smooth operation of the Task Force (e.g. in terms of meetings, consensus forming etc.). In rare circumstances, it may be necessary with a larger Task Force but the reverse is likely to be more commonly occurring (i.e. a smaller Task Force)*

**4. Patient and public involvement**

*Please present when and how patient representatives have been or will be involved in the guideline production process. If and how the patient representative will exchange information between the guideline developers and the public and promote dissemination of the guideline. For practical advice on involving patients and the public in guideline activities you can refer to the “GIN Public Toolkit” (https://g-i-n.net/toolkit/)*

**5. Development and prioritization of guideline scope, guideline questions and evidence review questions (PICO questions)**

*Please provide a description on how the guideline scope and guideline questions were developed. This should include who participated, how the process was carried out (e.g. Face-to-face, online), a timeline and any methodology used (e.g. voting, Delphi, discussions, consensus). Specific care should be taken to describe how the ranking of outcomes (not important, important, critical) was achieved.* Indicate how you define consensus (e.g. 80% threshold, all must be in agreement) in terms of members of the TF.

**6. Scope**

*The purpose of the scope is to set the boundaries of what the clinical guideline will include in terms of key clinical issues and what will not be covered. The framework provided will inform the development of the detailed guideline questions, the evidence review questions (PICOs), and the search strategy.*

*The scope should define the aspects of care that the guideline will cover in terms of the following:*

* + *Target populations to be included – Describe the population to whom the guideline is meant to apply. For example, age groups or people with certain types of disease or condition. Equality groups that may merit specific consideration (for example, specific ethnic groups or people with learning disabilities) are identified. Specific sub-groups that should be excluded are specified.*
	+ *The different types of interventions and treatments to be included and excluded – for example, diagnostic tests, surgical treatments, medical and psychological therapies, rehabilitation and lifestyle advice.*
	+ *The main outcomes that will be considered.*
	+ *The target audience and healthcare setting – for example, the intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) in which setting (e.g. primary, secondary or tertiary care), and how the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care).*

*(Adapted from* [*https://www.nice.org.uk/process/pmg6/chapter/the-scope*](https://www.nice.org.uk/process/pmg6/chapter/the-scope)*)*

**7. Guideline questions and evidence review questions**

*The guideline questions derive from the scope. They are “should” questions: e.g. “Should treatment/test X (vs treatment/test Y) be used for people with Z?”. These questions define the population, interventions and, possibly, the comparison. Another way to think about guideline questions is that each recommendation will provide the answer to the specific guideline question (“should”) question: e.g. “The treatment with A should be used for people with Z”, “The treatment with B might be used for people with Z”.*

*Please provide the list of the evidence review questions. Evidence review questions should take the format of PICO(S) questions. Often PICO(S) questions are not in the form of a question, but rather the breakdown of the Guideline questions into PICO(S) components. In other words, the PICO(S) questions derive from and detail the guideline questions, in terms of Population/patients, Intervention, Comparator, Outcomes. Additionally, a PICO question may include the setting – hence the S in parenthesis.* See supporting document B for examples of guideline questions and evidence review questions.

**Introduction to Guideline questions 1:**

*Please provide short intro to each guideline question and components of the evidence review questions that reflect the motivation for including the specific question in the guideline.In the below table PICO questions have been formulated as “Should” questions. However, other formats may be equally relevant.*

|  |
| --- |
| **Guideline Q1**  |
|  | **Interven-tion/diagnostic test** |  | **Comparator***(may be no intervention or an alternative treatment)* |  | **Population** |
| **all people/ subgroup** | **health condition** |
| ***Should*** |  | ***vs*** |  | ***be used*** |  |  |
| ***Outcomes:***  |  ***Critical:*** |
| ***Important:*** |
| ***Not important*** |
| ***Time (optional):*** |
| ***Setting (optional):*** |

**8. Methods of the systematic review, meta-analysis and development of the Guideline**

*Include a paragraph clearly stating that the GRADE methodology and the methods papers published by the EAN with regards to how guidelines should be developed. E.g.:”The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [CITE e.g. XXX ] will be used in the development of the present guideline as the preferred rating system for development of EAN Guidelines [34]. The methodology described in [34,35] will be followed.” Consider providing a time table (see Appendix B)*

*8.1 Information sources and search*

*Describe search strategy including databases, how search strings were developed, backwards and forwards citation search, call for evidence etc* Describe which sources of information (e.g. PubMed/MEDLINE, EMBASE, Cochrane, Scopus and possible subject-specific databases, e.g. Orphanet) will be used to ensure adequate coverage of relevant references. *Include the search strings in an appendix (e.g. 1 search string which is illustrative of the search strings to be used. All search strings should be published with the finished gruideline). Define the inclusion and exclusion criteria, mentioning which study designs will be included/excluded, define additional characteristics of the studies to be included and excluded . If relevant, define the length of follow-up in the eligible studies and the dose of the medications included in the PICOs. Describe which publication dates will be sought and the languages of the studies that will be included. Provide a rationale for the inclusion and exclusion criteria (e.g. “We will include studies published from XXXX-XXXX because the intervention of interest was not available before those dates”) See supporting document B for examples from other guidelines*

*The authors can decide if they want to report the search strategy using the following table:*

|  |  |
| --- | --- |
| **Study design**  |  |
| **Inclusion criteria** |  |
| **Exclusion criteria** |  |
| **Languages and publication dates** |  |
| **Database to be searched** |  |

*8.2 Study selection*

*Describe how studies will be screened and selected (e.g. title and abstract screening followed by full-text screening, who will do it, whether consensus was strived for). Plan the screening to be done by two authors independently and a third author to be involved/consulted if inconsistencies emerge. Plan to document the literature search process using PRISMA flowcharts.*

*8.3 Data collection process*

*Describe how will you collect the data (e.g., two persons from the TF). Describe which data items will be extracted. You may also report which data handling system you plan to use (e.g. piloted excel sheet, software tool for conducting SRs ) See supporting document D for examples*

*8.4 Risk of bias assessment of the individual studies*

*Describe the procedure and the tools that you will use for the assessment of the risk of bias for various study designs. For example “RCTs will be assessed with the Cochrane ROB tool, the ROBINS tool will be used for observational studies, QUADAS-2 for diagnostic accuracy studies etc. See supporting document E for example.*

*8.5 Synthesis of results*

*Describe whether meta-analysis will be carried out, or other approaches to data synthesis (e.g. network meta-analysis, individual patient data meta-analysis etc.), whether you will use fixed or mixed effect meta-analysis. Describe how will you perform heterogeneity analysis; and whether you will attempt any subgroup analysis. Provide a rationale for your strategy. See supporting document F for example.*

**9. Developing recommendations**

*Describe the process of how the recommendations will be made, e.g. a planned face-to-face/online meeting, pre-defined consensus procedure (e.g. RAND, Delphi etc..), voting. Also, state the criteria that will be used for a recommendation to be accepted (e.g. >80% consensus, all members should agree etc.) See supporting document G for examples.*

**10. Dealing with Conflicts of interest**

*Describe how COIs within the Task Force will be dealt with (e.g. members with COIs may not participate in certain parts of the Guideline development process, or may be excluded altogether). Please adhere to the internal EAN guidelines and rules regarding COIs (see* (https://www.eanpages.org/2020/05/01/update-of-ean-guidance-for-guidelines/)*. All COIs should be included in the relevant forms submitted to the EAN. See supporting document H for example.*

**11. Financial disclosures**

*Please disclose if there will be any funding for the guideline and from which agency.*

*Additionally, please state any compensations made to TF members from: employment by a commercial entity; consultancy fees; royalties from patents, trademark, copyright, or licensing agreements; and industry-sponsored grants (received or pending). See supporting document H.*

**12. Publication of the protocol**

*The EAN encourage publication of the protocol in an open access repository (following approval of the protocol by the EAN) (e.g.* [*https://zenodo.org/*](https://zenodo.org/)*, PROSPERO, on the EAN website).*

**13. Plan for update of the guideline**

*Please consider adding a paragraph describing when, in the opinion of the authors, the guideline should be updated at the latest.*

**14. Dissemination of the guideline**

*Please describe whether there are plans or ideas for dissemination of the knowledge to ensure maximal uptake of the guideline into clinical practice. This may include translation into other languages, presentation at conferences, educational activities, liasing with relevant stakeholders.)*

**15. References**

**Appendix A: Existing guidelines (Suggested appendix)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Ref | Year | Title | Published/endorsed by | Description |
|  |  |  |  |  |

**Appendix B: Time table**

*Provide a realistic estimation of the timeline divided by various stages: protocol development and approval, literature search, data extraction and analysis of the evidence, formulation of the recommendations, writing of the guideline, review by the GPG. Please also consult Leone et al 2015 for deadlines and EAN deliverables*

*Example of graphic depiction of timelines*

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**Appendix C: Search strings**

|  |
| --- |
| PICO |

**Research question 1:**

Database:

Host:

Data parameters:

Date searched:

Search strategy:

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
|  |  |  |

**Supporting document A: Title**

Supporting documents are not meant to be a part of the protocol but to inform or to further explain the content to be included in the final protocol.

**Structure**

|  |  |  |  |
| --- | --- | --- | --- |
| Label | Intervention | Health problem | Participant group /Location |
| *Mandatory* | *Optional* | *Mandatory* | *Optional* |
| EAN[/other scientific societies] guideline … | … on [intervention] | … of [health problem]… on [health problem] | … in [participant group /location] |

**Examples: true or invented titles**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Scope | Label | Intervention | Health problem | Participant group /Location |
| Broad | *EAN guideline* | *-* | *on trigeminal neuralgia* | - |
| Broad intervention, narrow health problem | *EAN guideline* | *on the management* | *of medication-overuse headache* |  |
| Treatment | *ECTRIMS/EAN guideline* | *on the pharmacological treatment* | *of multiple sclerosis* | - |
| Diagnosis | *EAN guideline*  | *on the diagnosis* | *of coma and other disorders of consciousness* |  |
| Narrow intervention, narrow health problem | *EAN guideline*  | *on palliative care* | *of people with severe, progressive multiple sclerosis* |  |
| Narrow intervention, narrow health problem | *EFNS-ENS/EAN guideline*  | *on concomitant use of cholinesterase inhibitors and memantine* |  | *in moderate to severe Alzheimer’s disease* |
| Broad intervention, specific participant group | *EAN guideline*  | *on the management*  | *of narcolepsy* | *in children* |

**Supporting document B: Guideline questions and evidence review questions**

﻿Methods from “*“EAN Medical management issues in dementia”*

Research question 1.1

Should home-living (non-institutionalized) patients with dementia be offered systematic medical follow-up in a memory clinic setting?

PICO question Population: Home living (non-institutionalized) patients with dementia. Intervention: Planned structured follow-up in the

form of consultations offered in a medical dementia specialist team. Comparator: Usual care. Outcome: 1. Institutionalization (Important); 2. Caregiver burden (Important); 3. Acute hospital admissions (Important); 4. Activities of daily living (ADL; Critical).

**Supporting document C*: 8.1 Information sources and search***

***Example 1***

*Methods from: “European Academy of Neurology and European Federation of Neurorehabilitation Societies guideline on pharmacological support in early motor rehabilitation after acute ischaemic stroke”*

*“We will search the following databases: Medline/PubMed, Cochrane Library, Embase). The following characteristics will be carefully detailed by the TF: search terms used; date ranges; inclusion and exclusion criteria. As RCTs are the most appropriate studies to assess the efficacy of an intervention, we will search all randomized clinical trials however we will also include other prospective study designs, such as controlled studies, and observational studies. Whatever evidence will be found, it will be selected and quality assessed using the criteria reported on section 7. No restriction will be made based on European languages, provided the title and abstract of the publication are in English. The complete search strategy for each database will be reported.*

*An example of Medline search string is reported in the Appendix.“*

***Example 2***

*Methods from: “EAN Medical management issues in dementia” guideline protocol (search strategy):*

*• Databases: Six databases are to be searched: MEDLINE and MEDLINE in Process (Ovid Interface); Embase (Ovid Interface); PsycINFO (Ovid Interface); ALIOS (via www.medicine.ox.ac.uk/alois)\*; PubMed (NLM interface)\*\* and The Cochrane Library: CENTRAL database (Wiley Interface).*

*• Search strategy: Sample search strategies for each PICO, formatted for the MEDLINE database (Ovid interface), were included in appendix. Additionally they reported a general search strategy format: ((search terms for dementia) AND (search terms for interventions or PICO topic) and (a study design search filter to identify studies reporting randomized controlled trials OR a study design search filter to identify studies reporting observational studies)). They planned to include RCTs or observational studies and no other limitations were applied to the search.*

*• Supplementary search methods: “Supplementary search methods will be used to identify unpublished studies or studies not indexed in the bibliographic databases identified above. The following search methods are indicated:*

*1. Citation searching studies included at full-text*

*2. Studies will be forwards citation searched in Web of Science (Clarivate Analytic) and backwards searched by task-force members…..*

*3. We will produce a call for evidence from within task force networks and, more broadly, the EAN and wider networks (where links exist). This call for evidence will take the form of a global e-mail asking respondents to identify any potentially relevant studies.*

*4. Resource limits prohibit the searching of trials registers, web-searching and handsearching of conferences.“*

***Example 3***

 *A format that may be used to report the search strategy:*

*We will search the following electronic databases (……). We will contact study authors to identify ongoing unpublished studies. We will search the gray literature, including resources for trial registries (if applicable). We will check the reference lists of eligible studies to identify additional articles.*

*The following eligibility criteria will apply: study design (….), publication date (…), publication status, etc. No language, (….) limitations will be imposed. Studies will be excluded if criteria (….) are not met. The complete search strategy for each database is provided in the Appendix. X.*

**Supporting document D: *8.3 Data collection process***

***Example 1***

*Methods from “European Academy of Neurology and European Federation of Neurorehabilitation Societies guideline on pharmacological support in early motor rehabilitation after acute ischaemic stroke.”*

*“Data from each included article will be extracted by two TF members (reviewers), working independently and using an extraction form which will be devised for the study. Each included study (except for qualitative research reports, see below) will be assessed for selection, performance, detection, attrition and reporting bias, and other bias that might have been detected during the review process [Higgins 2011].*

*Disagreement regarding the extracted elements, classification of evidence, or assessment of effect size will be resolved by consensus; if consensus is not obtained, another TF member will be involved.“*

***Example 2***

*Methods from: „EAN Medical management issues in dementia” guideline protocol:*

* *Data extraction:* “Data on the following items will be extracted from included studies: study design, number of participants, population characteristics (age, gender, baseline MMSE, diagnosis), intervention, comparator, statistical methods, outcome measures”

**Supporting document E: *8.4 Risk of bias assessment of the individual studies***

**Example 1**

*Methods from “EAN Guideline on the Palliative Care of People with Severe MS”*

* *Assessment of risk of bias of individual studies*: “Two TF members assessed the quality of evidence of the included studies using the Cochrane tool for risk of bias (randomized controlled trials, RCTs) and the CASP 10-item tool (qualitative studies, http://www.casp-uk.net/#!casp-tools-checklists/c18f8). Any disagreement was resolved by consensus; if consensus was not obtained, a third TF member was involved.”

**Supporting document F: *8.5 Synthesis of results***

***Example 1***

*Methods from “EAN Guideline on the Classification of Coma and Chronic Disorders of Consciousness: Protocol”*

***“****Depending on the results of the literature search and review, we will propose to conduct a meta-analysis on all available numerical data which report on the utility as well as the sensitivity and specificity of clinical rating scales, as well as active, passive and resting state paradigms of consciousness using neuroimaging and neurophysiology… We will attempt to explore possible sources of heterogeneity. These will likely be related to variances in methods of clinical diagnosis, inclusion criteria and heterogeneity in electrophysiological evaluation and neuroimaging techniques.*

*As to clinical diagnosis, the evaluation of the patient may be performed using unstructured bedside examination, requiring a sound level of neurological expertise (which might not always be the case), or using standardized scales such as the CRS-R33 and accepted consensus-based case definitions such on persistent VS/UWS37 or MCS5”*

**Supporting document G: 9. Developing recommendations**

**Example 1**

*Methods from “European Academy of Neurology and European Federation of Neurorehabilitation Societies guideline on pharmacological support in early motor rehabilitation after acute ischaemic stroke.”*

*Determination of direction and strength of recommendations will be based on TF interpretation of the available evidence: the balance between desirable and undesirable outcomes determines the direction of the recommendation, and this factor, along with the quality of the evidence, determines the strength of the recommendation. Both direction and strength may be modified after taking into account patients’ values and preferences.*

*We will use a two-round approach [Leone 2013]:*

*• Round 1: We will consider the direction of each recommendation first (goal is to achieve the greatest benefit with the lowest harm), which implies a judgment of the balance between desirable and undesirable effects;*

*• Round 2: We will then define the strength of each recommendation, i.e. the degree of confidence that the desirable effects outweigh the undesirable ones (taking into account four determinants: quality of the evidence, balance between desirable and undesirable effects, patient values and preferences). In accordance to GRADE [Guyatt 2008], we will classify the strength of each recommendation as ‘strong’ or ‘weak’ (Table 3).*

*Consensus on each recommendation will be achieved by using Delphi method, in order to minimize biases that can be introduced by group dynamics or dominant personalities [Hsu 2007]. Delphi method involves anonymous voting, facilitated discussions, group feedback, and statistical analysis of the responses. It takes place via email exchanges and teleconferences. TF members will independently answer a questionnaire. At each round, a facilitator will provide an anonymous summary of the TF opinions from the previous round, and areas of disagreement are identified. TF members will be invited to review their earlier answers in light of the replies from other members of the TF. Once consensus is reached (usually in 2-3 rounds), TF members make the assumptions about their decisions explicit. If disagreement still exists, its nature and extent is accounted for and explained in the guideline report.“*

**Example 2**

*Methods from “EAN Guideline on the Classification of Coma and Chronic Disorders of Consciousness: Protocol”*

*“Members of the task force responsible for each topic will send their responses to the PICO questions and of their recommendations to the task force chairperson who will put these drafts together in a document that will be distributed for evaluation to all task force members. The direction of the recommendations will be defined as for or against the intervention and the strength of the recommendations will be graded as strong or weak. In case of uncertainty about a recommendation due to poor evidence the task force members may avoid formulating a recommendation. For the PICO questions where it might be impossible to formulate a recommendation, a consensual remark with additional information expressing a diagnostic or therapeutic option will be written, without grading it.*

*When evaluating the literature and formulating recommendations we will resolve disagreement by consensus in the respective subgroups. If this is not possible, the remaining areas of disagreement will discussed by all task force members who will make the final decision according to a modified Delphi technique.”*

**Supporting document H: 10. Dealing with Conflicts of interest**

***Example 1***

*Methods from “European Academy of Neurology and European Federation of Neurorehabilitation Societies guideline on pharmacological support in early motor rehabilitation after acute ischaemic stroke.”*

*“Each TF member has reported his/her potential conflicts in the EAN Register of Interest form, sent to the TF chair, and copied to the EAN secretariat. The TF chair will also be requested to update on any new conflict of interest by him/her or the TF members at the completion of the guideline [Leone 2015].”*

Furthermore, it is important to plan in advance how to deal with potential COIs when formulating the recommendations:

**Example 2**

Methods from “EAN Guideline on the Classification of Coma and Chronic Disorders of Consciousness: Protocol”

*“Members of the task force having financial or other significant conflicts of interest in a particular recommendation can participate in the discussion but not vote for or against the recommendation.”*