The European Stroke Organisation Guidelines: a standard operating procedure

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In 2008, the recently founded European Stroke Organisation published its guidelines for the management of ischemic stroke and transient ischemic attack. This highly cited document was translated in several languages and was updated in 2009. Since then, the European Stroke Organisation has published guidelines for the management of intracranial aneurysms and subarachnoidal hemorrhage, for the establishment of stroke units and stroke centers, and recently for the management of intracerebral hemorrhage. In recent years, the methodology for the development of guidelines has evolved significantly. To keep pace with this progress and driven by the strong determination of the European Stroke Organisation to further promote stroke management, education, and research, the European Stroke Organisation decided to delineate a detailed standard operating procedure for its guidelines. There are two important cornerstones in this standard operating procedure: The first is the implementation of the Grading of Recommendations Assessment, Development, and Evaluation methodology for the development of its Guideline Documents. The second one is the decision of the European Stroke Organisation to move from the classical model of a single Guideline Document about a major topic (e.g. management of ischemic stroke) to focused modules (i.e. subdivisions of a major topic). This will enable the European Stroke Organisation to react faster when new developments in a specific stroke field occur and update its recommendations on the related module rather swiftly; with the previous approach of a single large Guideline Document, its entire revision had to be completed before an updated publication, delaying the production of up-to-date guidelines. After discussion within the European Stroke Organisation Guidelines Committee and significant input from European Stroke Organisation members as well as methodologists and analysts, this document presents the official standard operating procedure for the development of the Guideline Documents of the European Stroke Organisation.

Key words: European Stroke Organisation, guidelines, standard operating procedure

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Introduction

In 2008, the recently founded European Stroke Organisation (ESO) published its guidelines for the management of ischemic stroke and transient ischemic attack (1). This highly cited document was translated in several languages and was updated in 2009. Since then, the ESO has published guidelines for the management of intracranial aneurysms and subarachnoidal hemorrhage (2), for the establishment of stroke units and stroke centers (3), and recently for the management of intracerebral hemorrhage (4).

In recent years, the methodology for the development of guidelines has evolved significantly (5). To keep pace with this progress and driven by the strong determination of the ESO to further promote stroke management, education, and research, the ESO decided to delineate a detailed standard operating procedure (SOP) for its guidelines (6). There are two important cornerstones in this SOP: The first is the implementation of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology for the development of its Guideline Documents (5). The second one is the decision of the ESO to move from the classical model of a single Guideline Document about a major topic (e.g. management of ischemic stroke) to

focused modules (i.e. subdivisions of a major topic). This will enable the ESO to react faster when new developments in a specific stroke field occur and update its recommendations on the related module rather swiftly; with the previous approach of a single large Guideline Document, its entire revision had to be completed before an updated publication, delaying the production of up-to-date guidelines.

After discussion within the ESO Guidelines Committee (GC) and significant input from ESO members as well as methodologists and analysts, this document presents the official SOP for the development of the Guideline Documents of the ESO.

Types of ESO-supported Guideline Documents

The aim of an ESO Guideline Document is to provide recommendations aiming to help stroke care providers reach clinical decisions in their clinical practice based on the best available scientific evidence. They are not expected to cover a certain topic in full extent like a textbook; they rather aim to provide evidence-based answers to focused questions of specific stroke-related topics.

There are three types of Guideline Documents which may be supported by the ESO (Table 1). The first type refers to Guideline Documents which are initiated and prepared by the ESO based on the present SOP; non-ESO specialists from other organizations may be invited to participate.

The second type refers to joint Guideline Documents prepared in collaboration with other scientific organization(s); the issues of the methodological approach, authorship, and publication policies should be agreed between the ESO and the collaborating organization in advance. In general, equal representation of the involved organizations is preferable. The methodological approach of joint Guideline Documents should follow the current SOP for the development of ESO Guidelines.

The third type involves Guideline Documents of another organization(s) which may be endorsed by the ESO after agreement between ESO and the other organization(s) that one or several ESO-members will co-write the manuscript prospectively and will be included in the list of authors.

Table 1 Types of ESO-supported Guideline Documents

Type	Comments
ESO Guideline Document	Launched by the EC and prepared by the ESO according to the SOP. One or several specialists from other organizations may be invited to participate.
Joint Guideline Document between the ESO and other organization(s)	After agreement between the ESO and another organization(s). Equal representation of the involved organizations should be sought.
Endorsement of a Guideline Document of another organization(s) by the ESO	After agreement between the ESO and another organization(s) that one or several ESO members will co-write the manuscript prospectively and will be included in the author list

Structures involved in the development of ESO Guideline Documents

The development of the ESO Guideline Documents is driven by the GC and the Module Working Groups (MWGs). The main characteristics of the GC and the MWG are summarized in Table 2.

The GC consists of a maximum of 10 members, but more nonvoting members may be also included. The chair(s) and new (voting or nonvoting) members of the GC are elected by its current members for a four-year term and approved by the ESO Executive Committee (EC). The tasks of the GC are summarized in Table 2.

The MWG is responsible for developing a Guideline Document for a specific topic or update an existing Guideline Document on regular terms (approximately once every three-years). Each MWG has one leader who is elected by the GC and approved by the EC with a majority vote based on the criteria of scientific integrity, professionalism, self-motivation, clinical expertise, availability, and conflicts of interest (CoI). The module leader is expected to be a physician with experience in the field of stroke. The MWG members are nominated by the MWG leader and approved by the GC and the EC based on the same criteria. Each MWG is expected to have ≤10 members, but this may be higher according to the extent of the topic; as a rule of thumb, one or two members work on one to two PICO questions depending on the range of the PICO questions (please see below for explanation of PICO question). In general, the MWG is expected to be as representative as possible without any barriers on gender, age, nationality, scientific background, specialization, and others. The inclusion of statisticians, analysts, methodologists, or representatives of patients' or caregivers' associations in the MWG is encouraged. Nonphysicians should be included where appropriate. At least one person with previous participation in another MWG is expected to be included in the MWG in order to provide his/her experience with ESO Guidelines. There is no defined duration for the tenure of the MWG given that one of its tasks is to continuously scan major stroke-related journals and inform the GC about new data which may change existing recommendations. The MWG leaders may invite new members if they feel that it is appropriate, or replace existing members (an explanation to the GC is necessary); any such action needs to be approved by the GC and the EC.

For the selection of the MWG members, the GC can publish an open call to ESO members inviting interest for participation in these bodies. Additionally, the GC may contact the national stroke organizations which are ESO organizational members and ask for suggestion of potential nominees. The composition of MWG should be approved by the GC and the EC.

Identification of new topics for an ESO Guideline Document

New topics for ESO Guideline Documents may be identified during ESO-supported Guideline Meetings (GM) like the ESO Karolinska Stroke Update; in addition, they may be directly suggested to the GC by any ESO member (Fig. 1). Input from the

Table 2 Summary of the characteristics of the ESO structures involved in the development of the Guideline Documents

	Guideline Committee	Module Working Group
Acronym	GC	MWG
Number of members	10 (more nonvoting members may be also included)	≤10, but this can be modified.
Elected by	GC chair and new members are elected by current GC members.	MWG leader is elected by the GC; MWG members are elected by the MWG leader.
Duration of terms (years)	Four	Open
Task	• Decision to launch a topic for a Guideline Document • Election of the MWG leader • Critical review and approval of the draft of the Guideline Documents • Decision to update an existing Guideline Document • Organization of Guideline Meetings • Amendment of the SOP • Decision about translation of a Guideline Document and approval of translated Guideline Documents • Decision about parallel publication of a Guideline Document	• Develop or update a Guideline Document based on the SOP • Decide about parallel publication of a Guideline Document • Scan major stroke-related journals and inform the GC about new data which may change existing recommendations

aforementioned sources is transmitted to the GC, which decides with a majority vote for new module topics for a Guideline Document. Given that the resources of the ESO are limited, the GC is expected to prioritize potential topics according to the importance of clinical implications or to the extent of associated controversy. The decision of the GC for a new module topic needs to be approved by the EC.

Update of an existing ESO Guideline Document

Each Guideline Document should be revised approximately every three-years. To be ready on time for publication, the MWG members are expected to start working on a revision approximately 24 months after the publication of the previous Guideline Document.

In the interim, the MWG members are responsible for scanning major journals for new data which may potentially change existing recommendations. If a major development with potentially major impact on patient management and health occurs, this should be discussed within the MWG so that a suggestion can be made to the GC to prematurely update the Guideline Document. The GC is responsible to decide about the need to update an existing Guideline Document based mainly on the suggestion of the MWG members. In the same context, further input is provided by the GM and ESO members who may notify the GC in case that new data which may potentially change existing recommendations are published. The decision of the GC for premature update of a module topic needs to be approved by the EC.

Preparation of the Guideline Document, GRADE methodology, and time frame

The ESO has chosen the GRADE methodology for the preparation of the ESO Guideline Documents. The GRADE methodology will not be discussed in details here as there is extensive related literature available (7–21). Briefly, the GRADE system has a series of advantages over other systems that include clear separation of quality of evidence and strength of recommendation, transparent process of literature search and analysis, explicit comprehensive criteria for downgrading and upgrading quality of evidence ratings, transparent process of moving from evidence to recommendations, explicit evaluation of the importance of outcomes of alternative management strategies, explicit acknowledgment of values and preferences, and clear pragmatic interpretation of strong vs. weak recommendations for clinicians, patients, and policy makers (5).

The GRADE approach starts with the formulation of the PICO questions (the acronym PICO stands for the definition of the Population, Intervention, Comparator, and Outcome). The selected outcomes are given an importance using a nine-degree scale (7–9: critical; 4–6: important; 1–3: of limited importance). Then, a search strategy is formulated, where possible and appropriate in cooperation with the Cochrane Stroke trial registry group. After thorough literature search leading to identification of all available evidence, eligible studies are selected, and their data are extracted and analyzed. The results can be imported into the GRADEProfiler software (22) allowing for the grading of the quality of available evidence for each outcome and each clinical question (Table 3) based on predetermined criteria (Table 4). Quality of evidence is defined as the extent to which one can be confident that an estimate of the effect or association is correct (23). Then, the direction (either 'against' or 'for') and strength of the recommendation (either 'strong' or 'weak') are determined (Table 5), and finally, the recommendation is formulated using a standardized language. It may be possible that a Guideline Document includes a recommendation to use an intervention only in research; this may occur when three conditions are met: (1) there is thus far insufficient evidence to support a decision for or against an intervention, (2) further research has large potential for reducing uncertainty about the effects of the intervention, and (3) further research is thought to be of good value for the anticipated costs (23). Also, it may be possible that a Guideline Document does not include a recommendation; this may occur when at least one of the following three conditions are met: (1) the confidence

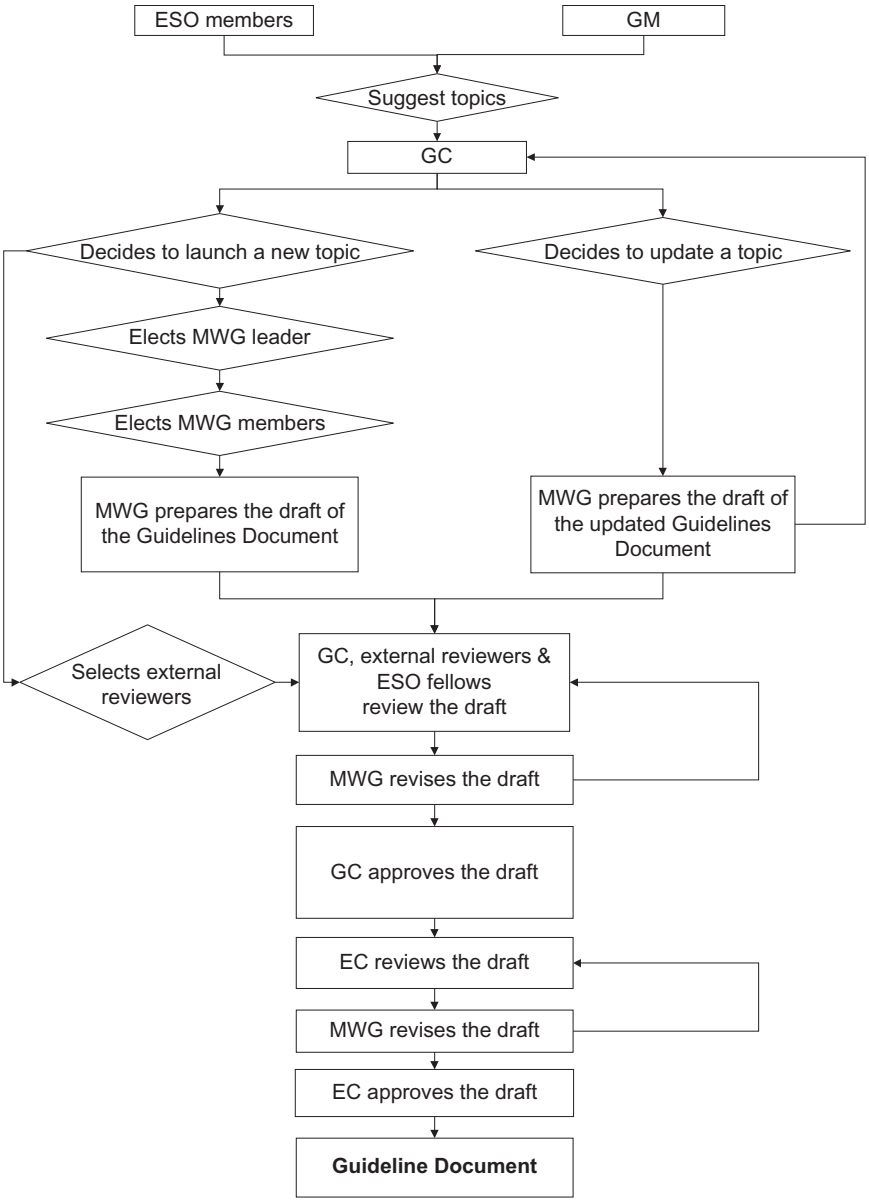

Fig. 1 Scheme of the ESO Guidelines standard operating procedure (SOP). ESO, European Stroke Organisation; GM, Guideline Meetings; GC, Guidelines Committee; MWG, Module Working Group; EC, Executive Committee.

Table 3 Definitions, implications, and symbols of grades of quality of evidence

Grade	Definition	Implication	Symbol
High	We are very confident that the true effect lies close to that of the estimate of the effect.	Further research is very unlikely to change our confidence in the estimate of effect.	⊕⊕⊕⊕
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	⊕⊕⊕
Low	We have limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the true effect.	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	⊕⊕
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.	Any estimate of effect is very uncertain.	⊕

Table 4 Criteria for assigning grade of evidence

Type of evidence
- Randomized trial: high
- Observational study: low
- Any other evidence: very low

Decrease grade if:
- Limitation in study design or execution (risk of bias) (↓1 or ↓2 levels)
- Inconsistency of results (↓1 or ↓2 levels)
- Indirectness of evidence (↓1 or ↓2 levels)
- Imprecise or sparse data ((↓1 or ↓2 levels)
- Publication bias (↓1 or ↓2 levels)

Increase grade if:
- Strong evidence of association: significant relative risk of >2 (<0·5) based on consistent evidence from two or more observational studies, with no plausible confounders (↑1 level)
- Very strong evidence of association: significant relative risk of >5 (<0·2) based on direct evidence with no major threats to validity (↑2 levels)
- Dose response gradient (↑1 level)
- All plausible confounders would have reduced the demonstrated effect or increase the effect if no effect was observed (↑1 level)

Table 5 Definitions and symbols of categories of strength of recommendation

Category	Definition	Symbol
Strong for an intervention	The desirable effects of an intervention outweigh its undesirable effects.	↑↑
Weak for an intervention	The desirable effects probably outweigh the undesirable effects but appreciable uncertainty exists.	↑?
Weak against an intervention	The undesirable effects probably outweigh the desirable effects but appreciable uncertainty exists.	↓?
Strong against an intervention	The undesirable effects of an intervention outweigh its desirable effects	↓↓

in effect estimates is so low that the panels feel a recommendation is too speculative; (2) irrespective of the confidence in effect estimates, the trade-offs are so closely balanced, and the values and preferences and resource implications not known or too variable that the panel has great difficulty deciding on the direction of a recommendation; or (3) two management options have very different undesirable consequences, and individual patients' reactions to these consequences are likely to be so different that it makes little sense to think about typical values and preferences (23). However, it is strongly advisable that the Guideline Documents formulate recommendations even when confidence in effect estimate is low and/or desirable and undesirable consequences are closely balanced.

Principally, we suggest three ways to come to consensus: by the Delphi-method (which is a widely used and accepted method to achieve convergence of opinion by using a series of questionnaires to collect data by participants and allowing for reassessment of initial judgments) (24), through voting in telephone conferences or face-to-face meetings. Though the Delphi-method should be the preferred way of coming to consensus, it might not always be practical and may slow down the guidelines preparation process where it might not be necessary to use it. The MWG should decide which method might be appropriate for different situations in advance. Nevertheless, the final consensus on a recommendation should be made by the Delphi-method.

The members of the MWGs are expected to be trained on the GRADE methodology during special workshops organized by the ESO. Also, publications describing the GRADE methodology will be provided.

The overall process is split into work packages as summarized in Table 6. Each step should be completed within a specific time period in order to complete the development of the Guideline Document in a timely manner (Table 6).

Internal and external review of the Guideline Document

The members of the GC, EC, and two external reviewers are responsible for critically reviewing the Guideline Documents within the prespecified time periods and are expected to disclose their CoIs, which should be published as an appendix along with the Guideline Document. In addition, the GC members are expected to provide feedback about any step during the development of the Guideline Document if required; in particular, they are expected to comment on PICO questions when ready before the procedure moves further.

Initially, the ESO Guideline Document is submitted to the GC and two external reviewers who are expected to provide their comments and/or approval within three-weeks; in addition, ESO fellows are invited to provide their comments. The MWG is responsible to consider and potentially incorporate the comments to the Guideline Document and respond to the reviewers. The members of the GC, the external reviewers, and the ESO fellows review the revised Guideline Document and provide their further comments within two-weeks. In case that a GC member does not respond within the prespecified deadline, an agreement is assumed, and the process moves forward. As soon as consensus approval has been obtained by the GC, the Guideline Document is submitted to the members of the EC who are expected to review the revised Guideline Document and provide their comments within three-weeks. The MWG is responsible to consider and potentially incorporate the comments to the document and

Table 6 Summary of actions toward a Guideline Document

Responsible	Steps for the working group	GRADE steps according to Schünemann *et al.* (23)	Actions	Time schedule (weeks)
Module leader	1		Assemble the working group	4
MWG	2	1	Ask a specific management question to be answered by a recommendation.	4
MWG		2	Identify all important outcomes for every health care question.	
MWG		3	Judge the relative importance of outcomes	
GC; external reviewers			Comment on and approve PICO questions	
MWG; Cochrane Stroke Registry Group	3	4	Perform literature search; identify and summarize all relevant evidence in evidence profiles.	4
PICO group	4	5	Grade the quality of evidence for each outcome.	4
PICO group		6	Decide on the overall quality of evidence across outcomes.	
PICO group		7	Include judgments about the underlying values and preferences related to the management options and outcomes.	
PICO group		8	Decide on the balance of desirable and undesirable effects	
PICO group		9	Decide on the balance of net benefits and cost.	
MWG		10	Grade the strength of recommendation.	
MWG		11	Formulate a recommendation	
MWG	5		Preparation of the Guideline Document	6
GC, external reviewers and ESO fellows	6		Review	12
MWG			Integration of changes	
GC			Review/approval	
EC			Review	
MWG			Integration of changes	
EC			Review/approval	
Module leader			Submission	
Total				34

respond to the EC members. The EC members review the revised Guideline Document and provide their further comments and/or approval within two-weeks. As soon as consensus approval has been obtained by the EC, the Guideline Document is submitted for publication.

Authorship and publication policy

The title of an ESO Guideline Document should have the following format: '*European Stroke Organisation (ESO) Guidelines for . . .*'. For every Guideline Document, a sentence should be included stating that '*the ESO Guidelines Committee and the ESO Executive Committee have approved the current Guideline Document*'. An Executive Summary should be submitted and published as a companion to the main Guideline Document.

It is suggested that the MWG leader is first author, and the other MWG members are listed in alphabetical order; this may change according to the opinions of the MWG if there is full consensus. The list of authors should be approved by the GC and the EC.

An ESO Guideline Document is submitted to the current official journal of the ESO. Parallel publication in more than one journal is possible to allow for wider dissemination. The decision for a parallel publication is based on a majority vote between the members of the MWG, the GC, and the EC. If possible, an open-access policy is sought for the ESO Guideline Documents, in order to make them widely available and increase their dissemination into the scientific community. In the same context, the National Stroke Organisations which are organizational members of the ESO should be asked to circulate the Guideline Documents to their members and post them on the corresponding websites.

CoI

The ESO uses the following definition to describe CoI: *Conflict of Interest is a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest* (25). CoIs are distinguished into 'intellectual CoIs' and 'relationships with industry' (RWI).

Intellectual COI is defined as academic activities that create the potential for an attachment to a specific point of view that could unduly affect an individual's judgment about a specific recommendation (26). Among others, this may refer to relevant personal research and membership of the steering committee of any relevant clinical trial.

RWI is defined as receiving a research grant, being on a speakers' bureau or receiving honoraria, owning stock, or being a consultant or member of an advisory board or any other financial association with industry; this refers both to personal interests as well as interests of the immediate family members. With regard to the development of the Guideline Documents, the ESO does not use a financial threshold to differentiate between minor and major RWI but requires that all persons involved in this process disclose all CoIs in detail. It is the task of the GC and the EC to

evaluate the CoIs of any person involved in the development of the Guideline Documents (including also the members of the MWG and external reviewers) and decide on a case-to-case basis about the suitability of a person to be assigned a role in this process. In addition, the CoIs of the GC members should be disclosed in detail to the EC.

In particular, with regard to the composition of the MWG, the CoIs of the persons who are approached as potential MWG leaders should be disclosed to the GC and the EC, who are responsible for evaluating them. In the final selection of the MWG leader by the GC and the EC, the CoIs should be one of the major criteria based on the ESO's policy that the MWG leader should be free of any major CoI. In addition, the MWG members should disclose their CoIs to the MWG leader, the GC, and the EC in detail before they are assigned this role. It is the responsibility of the GC to evaluate the CoIs of the MWG members. The majority of the MWG members should be free of major CoIs. The MWG members should not be involved in any section of the module for which they have a major CoI, for example, they should abstain from any commenting or drafting or voting, should abstain from discussions about the evaluation of the grade of evidence and the strength or recommendation, should abstain from the discussion about the wording of the recommendations, and should abstain from the writing of the 'additional information' section.

The external reviewers of any Guideline Document should disclose their detailed CoIs to the MWG, GC, and EC, and should be free of any major CoIs.

All GC, MWG, and EC members, as well as the external reviewers involved in a module, should disclaim their CoIs at the publication of the Guideline Document.

If there is a change of CoIs for any of the members of the GC, MWG, and EC during the development of the Guideline Document, this should be disclosed to the GC and re-evaluated; appropriate actions may be taken by the GC if necessary (e.g. substitution of a member).

Translation of an ESO Guideline Document into other languages

The ESO welcomes interest for translating ESO Guideline Documents into other languages. Any individual or organization interested in performing such a translation should discuss this with the GC and the EC. One or two ESO members (whose native language is the requested one) should be assigned by the CG to review and approve the translation before the final approval by the GC and the EC. In general, we recommend that the Guideline Document is translated in its full version, but if necessary, it is possible to translate only the Executive Summary of the Guideline Document as a means for more efficient resource use.

Amendment of the ESO Guidelines standard operating procedure

The SOP may be amended after discussion and majority vote among the members of the GC and approval by the EC.

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