The development of the European Society of Coloproctology (ESCP) Guideline for Haemorrhoidal Disease

R.R. van Tol[1], S.Z. Kuiper[1], A.J.M Watson[2], J. Jongen[3], D.F Altomare[4], N. Qvist[5], T. Higuero[6], J. Muris[7], S.O. Breukink[1], J. Kleijnen[7]

1. Department of Surgery, Maastricht University Medical Centre +, 6202 AZ, Maastricht, the Netherlands
2. Department of Surgery, Raigmore Hospital, Iverness IV2 3UJ, Scotland, UK
3. Park Klinik, Goethestraße 11, 24116, Germany
4. Department of Surgery, University of Aldo Moro of Bari, Piazza G. Cesare, 11 - Policlinico 70124 Bari, Italy
5. Department of Surgery, University of Southern Denmark, Campusvej 55, 5230 Odense M, Danmark
6. Clinique Saint Antoine, 11 boulevard du général Leclerc, Beausoleil, France
7. Department of Family Medicine/General Practice, Maastricht University Medical Centre, 6202 AZ Maastricht, the Netherlands

Correspondence to: J. Kleijnen, Department of Family Medicine, Maastricht University Medical Centre, PO Box 5800, 6202 AZ Maastricht, the Netherlands (e-mail: jos@systematic-reviews.com)

1. Introduction

The European Society of Coloproctology (ESCP) aims to establish international guidelines for the treatment of grade I-IV haemorrhoidal disease (HD), using the best available evidence. The guidelines provide guidance on the most effective (surgical) treatment and management of patients with HD. By providing this information, the ESCP hopes to improve outcomes after treatment such as, recurrence of disease, complications, symptoms and patient satisfaction.

This article explains the processes and methods used to develop and update guidelines for HD. These processes and methods are based on internationally recognized guideline development methodology. These include criteria of quality, as detailed in the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (https://www.agreetrust.org/agree-ii/) [1], primary methodological research and evaluation undertaken by the guideline development group (GDG).

The goal of this paper is to achieve a consistency of approach in other areas of coloproctology.

2. Development process

2.1. Phase I: setting the scope

After invitation by the European Society of Coloproctology (ESCP), one of the colorectal surgeons (SB) of the guideline development group (GDG) was asked to establish an international guideline for HD.

The ESCP functioned as the stakeholder with an interest in the guideline topic. During the guideline development, the ESCP was informed of progress by email. These guidelines were supported by a small grant from the ESCP enabling GDG members to meet and a surgical resident to work with the methodologist (JK). The GDG had full control over the wording of the guideline and there was no influence from the funding body.

We first considered the aim of the guidelines, taking into account the health problems to be addressed, the patient group and the target audience.

It was decided that the guidance would apply to patients with all stages of haemorrhoids in whom (surgical) interventions are being considered. Haemorrhoidal disease is mostly classified according to the grading system developed by Goligher et al. [2-4] and therapeutic options are generally based on the haemorrhoid grade.

This guideline needed to address both the diagnostic and therapeutic modalities for use in the management of haemorrhoidal disease and included the following sections: symptoms, diagnosis & classification, basic treatment, outpatient procedures, surgical interventions and special situations (i.e. thrombosed haemorrhoids, coagulation defect, immunodeficiency and pregnant women). The guideline is intended for use by all practitioners treating patients with haemorrhoids (e.g. general practitioners, surgeons, gastroenterologists, dermatologists), healthcare workers and patients who desire information about the management of haemorrhoidal disease.

The process of considering the aim of the guideline, defining the target group and describing the users, was compacted into a guideline scope. In the scope, we also enlisted key issues to be addressed in the guidelines. The key issues function as the foundation for which possible recommendations are made, which in turn allowed the creation of the review questions.

2.2. Phase 2: invitation guideline development group (GDG)

The guideline was prepared by a guideline development group (GDG) which included members from six European countries (i.e. Denmark, Italy, France, Germany, the Netherlands and the UK). First we contacted the international representatives of the European Society of Coloproctology (ESCP). On the recommendation of these representatives (i.e. snow ball method) healthcare professionals with an in-depth understanding of outcomes relevant for treatment of haemorrhoids and experience with the development of a COS were invited. The aim was to include as many panel members as possible (18, 20), to increase the reliability of the group judgment [5, 6].

In composing the GDG, we considered several factors. First, all clinical members had to have an affinity with the diagnosis and treatment of haemorrhoids, considering that clinical knowledge on the subject is key. Second, distribution of geographical differences between surgeons was wished for, as the guideline is aimed at an international audience.

The GDG consisted of five colorectal surgeons (SB, DA, JJ, NQ, AW), one gastroenterologist (TH), one general practitioner (JM) who specializes in the treatment of haemorrhoidal disease, one surgical resident (RT) and one methodologist (JK) with extensive experience of guideline development [table 1]. One dermatologist (CH) commented on the guideline drafts, but was not a member of the GDG. Each GDG member identified at least one patient in their country who could read English to comment on the draft guideline.

The GDG members were assisted by a team of methodologists (staff at Kleijnen Systematic Reviews Ltd) whose work covered input from information specialists, quality assurance, and evidence review and support.

Table 1: Guideline Development Group (GDG)

Guideline member	Institution	Country
Angus Watson, Colorectal surgeon	Raigmore Hospital	Scotland
Johannes Jongen, Colorectal surgeon	Park Klinik Kiel	Germany
Donato Altomare, Colorectal surgeon	University Aldo Moro of Bari	Italy
Niels Qvist, Colorectal surgeon	University of Southern Denmark	Denmark
Stephanie Breukink, Colorectal surgeon	Maastricht University Medical Center (MUMC+)	The Netherlands
Thierry Higuero, Gastroenterologist	Clinique a Beausoleil	France
Jean Muris, General practitioner	Maastricht University Medical Center (MUMC+)	The Netherlands
Charles Henquet, Dermatologist	Maastricht University Medical Center (MUMC+)	The Netherlands
Jos Kleijnen, Methodologist	Maastricht University Medical Center (MUMC+) & Kleijnen Systematic Reviews Ltd	The Netherlands & UK
Robin van Tol, Surgical resident	Maastricht University Medical Center (MUMC+)	The Netherlands

2.3. Phase 3: formulating review questions

Two researchers (RT and JK) developed a set of review questions assessing the key issues listed in the scope. The review questions were built up using a reverse process, starting with possible recommendations based on the GDG's knowledge of practice shortcomings and practice variations. Budgetary constraints necessitated an efficient and pragmatic process.
The review questions were formulated using the PICO (population, intervention, comparator and outcome) framework to assess the effectiveness of an intervention and similar frameworks for other types of questions e.g. about diagnosis. The PICO framework is a helpful structured approach for developing questions about interventions (**table 2**).

Table 2: Formulating a review question on the effectiveness of an intervention using the PICO framework.

Population	Which population are we interested in? How best can it be described? Are there subgroups that need to be considered?
Intervention	Which intervention, treatment or approach should be used?

Comparators	Are there alternative(s) to the intervention being considered? If so, what are these (for example, other interventions, standard active comparators, usual care or placebo)?
Outcome	Which outcomes should be considered to assess how well the intervention is working? What is really important for people using services? Core outcome sets may be used where appropriate; one source is the COMET database.

A draft scope, including the review questions, was distributed by email to the GDG for their input. Review questions were altered and clustered into chapters (i.e. basic treatment; outpatient procedures; surgical treatment) according to the comments and feedback of the GDG, creating major premises and subjects for the guideline. Further, the GDG discussed and agreed on a set of outcomes critical and important for making decisions in clinical settings, including operational procedures and recommendations for diagnostic assessment [**table 3**]. These are crucial for application of GRADE for assessment of the strength of the evidence, which in turn leads to appropriate wording of the recommendations.

Table 3: set of outcomes critical and important for making decisions

Outcome measures
Symptoms (e.g. pain, blood loss etc)
Patient satisfaction
Recurrence
Complications
Quality of life
Re-operation
Time to return to normal
Costs of operation
Duration of operation
Duration of hospitalization

2.4. Phase 4: literature search

The review questions functioned as a framework for the design of the literature searches, informed the planning and process of the evidence review, and acted as a guide for the development of recommendations by the GDG. The GDG provided expertise (for example, when a condition is described in many different ways in the literature).

A literature search was performed in MEDLINE (Ovid), PubMed, EMBASE (Ovid), and the Cochrane Database of Systematic Reviews through August 2017. Key word combinations included haemorrhoid, haemorrhoidal disease, interventions, techniques (rubber band ligation, h(a)emorrhoidopexy, h(a)emorrhoidectomy, Procedure for Prolapse and Haemorrhoids (PPH), Milligan-Morgan, Ferguson, Doppler guided, and stapled haemorrhoidopexy). There were no restrictions concerning publication format or language. The search was not limited by date and good-quality published reviews followed by controlled trials followed by observational studies.

The searches in databases were supplemented by checking references in the reviews and primary studies that we found. In addition, the GDG identified relevant studies from their collections. The search strategy was designed and implemented by the surgical resident (RT) with help from an information specialist (JK and SK). The full search is available in appendix X.

Inclusion focused on available systematic reviews addressing each question, supplemented by further studies published after the time frame covered by the systematic reviews. We used a hierarchy of best available evidence for study selection, i.e. well performed systematic reviews, meta-analyses, randomized trials, controlled observational studies, case series and expert opinion (figure 1). If evidence of a higher level was available, no lower level of evidence was sought or included.

Figure 1: The pyramid of evidence

2.5. Phase 5: Reviewing research evidence

Data were extracted by the surgical resident (RT) and checked by the methodologist (JK) and the Guideline Development Group (GDG). Inclusion focused on available meta-analyses, systematic reviews addressing each question, supplemented by further studies published after the time frame covered by the systematic reviews.

Quality assessment was a critical stage in reviewing the evidence. It required a systematic process of assessing bias through considering the appropriateness of the study design and the methods of the study. We used the ROBIS tool to assess the risk of bias in systematic reviews [7] [table 4]. The full ROBIS tool and guidance documents are available from the ROBIS Web site (www.robis-tool.info) and as Appendices at www.jclinepi.com. We used the Cochrane checklist for assessing risk of bias of randomized trials [8].

Table 4: ROBIS Domains and signaling questions [7]

	Phase 2				Phase 3
	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	Risk of bias in the review
Signaling questions	1.1 Did the review adhere to predefined objectives and eligibility criteria?	2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	3.1. Were efforts made to minimize error in data collection?	4.1. Did the synthesis include all studies that it should?	A. Did the interpretation of findings address all of the concerns identified in domains 1 to 4?
	1.2 Were the eligibility criteria appropriate for the review question?	2.2 Were methods additional to database searching used to identify relevant reports?	3.2. Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	4.2. Were all predefined analyses reported or departures explained?	B. Was the relevance of identified studies to the review's research question appropriately considered?
	1.3 Were eligibility criteria unambiguous?	2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	3.3. Were all relevant study results collected for use in the synthesis?	4.3. Was the synthesis appropriate given the nature and similarity in the research questions, study designs, and outcomes across included studies?	C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?
	1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	2.4 Were restrictions based on date, publication format, or language appropriate?	3.4. Was risk of bias (or methodologic quality) formally assessed using appropriate criteria?	4.4. Was between-study variation minimal or addressed in the synthesis?	
	1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	2.5 Were efforts made to minimize error in selection of studies?	3.5. Were efforts made to minimize error in risk of bias assessment?	4.5. Were the findings robust, for example, as demonstrated through funnel plot or sensitivity analyses?	
				4.6. Were biases in primary studies minimal or addressed in the synthesis?	
Judgment	Concerns regarding specification of study eligibility criteria	Concerns regarding methods used to identify and/or select studies	Concerns regarding methods used to collect data and appraise studies	Concerns regarding the synthesis	Risk of bias in the review

2.6. Phase 6: Developing and wording recommendations

The quality of the evidence was summarized using the GRADE approach, by outcome across all relevant studies [table 5] [9, 10].

The GRADE system assesses the quality of the evidence for intervention studies by looking at features of the evidence found for each 'critical' and 'important' outcome.

We aimed to only do the GRADE assessments once the recommendations were at an advanced stage, so that this laborious process was kept as efficient as possible,

If needed, we updated high-quality systematic reviews, or their primary studies used, as evidence for informing a new review. Meta-analysis from the systematic reviews were updated by the surgical resident and the methodologist using ReviewManager version 5.3 software.

The quality of evidence is classified as high, moderate, low or very low.

Table 5: quality of the evidence according to GRADE [10]

High	Further research is very unlikely to change our confidence in the estimate of effect. GRADE ++++
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. GRADE +++
Low	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. GRADE ++
Very low	Any estimate of effect is very uncertain. GRADE +

According to the classification mentioned above, the specific wording of ‘must’, ‘should’, ‘could’, ‘may’, or ‘may not’, has been used for the recommendations. In case of high evidence, the term ‘must’, was implemented in the guideline. Concerning moderate evidence, this was recommended using ‘should or could’. The low graded evidence was interpreted as ‘could or may’, and very low evidence was implemented in the recommendations as ‘can be considered’.

The following sections were included in the evidence review [table 6]:

- summary of the evidence, including the 'summary of findings' table from the GRADE profile (if this improves readability and the GRADE system has been used)
- evidence statements
- full GRADE profiles
- evidence tables

Table 6: Example of a GRADE table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	phlebotonics	no phlebotonics	Relative (95% CI)	Absolute (95% CI)		
Remaining symptoms (bleeding)												
2	randomised trials	not serious a	serious b	not serious	not serious	publication bias strongly suspected c	4/99 (4.0%)	23/91 (25.3%)	RR 0.15 (0.05 to 0.44)	215 fewer per 1,000 (from 142 fewer to 240 fewer)	⊕⊕◯◯ LOW	CRITICAL
Remaining symptoms (overall symptom improvement)												
5	randomised trials	not serious d	serious e	not serious	not serious	publication bias strongly suspected c	181/193 (93.8%)	99/175 (56.6%)	RR 1.69 (1.57 to 1.74)	390 more per 1,000 (from 322 more to 419 more)	⊕⊕◯◯ LOW	CRITICAL
Remaining symptoms (pain assessed with: dosis analgesics)												
2	randomised trials	not serious f	serious b	not serious	not serious	publication bias strongly suspected c	11/99 (11.1%)	48/91 (52.7%)	RR 0.21 (0.02 to 1.05)	417 fewer per 1,000 (from 26 more to 517 fewer)	⊕⊕◯◯ LOW	CRITICAL
Complications												
7	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected c	10/246 (4.1%)	10/265 (3.8%)	RR 0.00 (-0.04 to 0.04)	-- per 1,000 (from 36 fewer to 39 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Prior to the first face-to-face meeting of the GDG, all members were sent an overview of the review questions with applied evidence from the literature search. This gave all members the opportunity to assess the evidence and review questions before meeting up. The first face-to-face meeting was carried out at the twelfth ESCP conference in Berlin in September 2017.

During this meeting, review questions were altered and optimized according to the experts’ interpretations of the evidence found in the literature search [table 7].

Both the surgical resident (RT) and the methodologist (JK) adjusted the review questions and by email permission was obtained from the GDG.

Table 7: Final set of review questions for the guideline of HD

Pre-operative phase	• Which factors should be assessed during history taking? • In which position should we do physical examination? (knee-chest-, lithotomy- or left lateral position) • How should haemorrhoidal disease be classified?
Basic treatment	• What are the effects of toilet training versus no toilet training on occurrence and symptoms in patients with haemorrhoidal disease? • What are the effects of laxatives versus no laxatives on occurrence and symptoms in patients with haemorrhoidal disease? • What are the effects of local treatments versus no local treatments on occurrence and symptoms in patients with haemorrhoidal disease? • What are the effects of phlebotonics versus no phlebotonics on occurrence and symptoms in patients with haemorrhoidal disease?
Outpatient procedures	• What are the effects of rubber band ligation versus sclerotherapy versus infrared coagulation on symptoms, recurrence and complications in patients with haemorrhoids which are suitable outpatient treatment options? • What are the effects of rubber band ligation versus DG-HAL versus stapled haemorrhoidopexy versus traditional haemorrhoidectomy on symptoms, recurrence and complications in patients with haemorrhoids which are suitable outpatient treatment options?
Surgical procedures	• What are the effects of DG-HAL + mucopexy versus muxopexy alone on symptoms, recurrence and complications in patients with haemorrhoidal disease which are suitable for surgical treatment options? • What are the effects of DG-HAL + mucopexy versus stapled haemorrhoidopexy on symptoms, recurrence and complications in patients with haemorrhoidal disease which are suitable for surgical treatment options? • What are the effects of DG-HAL + mucopexy versus traditional haemorrhoidectomy on symptoms, recurrence and complications in patients with haemorrhoidal disease which are suitable for surgical treatment options? • What are the effects of stapled haemorrhoidopexy versus traditional haemorrhoidectomy on symptoms, recurrence and complications in patients with haemorrhoidal disease which are suitable for surgical treatment options?
Special situations	• How could we define and treat thrombosed haemorrhoids in a primary care setting? ○ What are the effects and side effects of basic treatment (i.e. analgesics, flavonoids, heparin and nifedipin) versus surgical treatment (i.e. stapler and traditional haemorrhoidectomy)?

	○ What are the effects and side effects of stapled haemorrhoidopexy versus the traditional haemorrhoidectomy? • How should we treat haemorrhoids in patients with coagulation defects? ○ What are the effects and side effects of RBL in patients with coagulation defects compared to patients who underwent RBL without coagulation defect? → no literature found ○ What are the effects and side effects of sclerotherapy in patients with coagulation defects compared to patients who underwent sclerotherapy without coagulation defect? ○ What are the effects and side effects of stapled haemorrhoidopexy in patients with coagulation defects compared to patients who underwent stapled haemorrhoidopexy without coagulation defect? • How should haemorrhoids be treated in patients with immune deficiencies? ○ What are the effects and side effects of RBL in patients with immune deficiencies compared to patients who underwent RBL with no immune deficiencies? • How should we treat pregnant women with internal and/or external haemorrhoids? ○ What are the effects and side effects of basic treatment (i.e. sit bath and flavonoids) versus the traditional haemorrhoidectomy?

During a second face-to-face meeting in Amsterdam, in January 2018, the GDG members used their judgment to decide what the evidence meant in the context of the guideline referral and decided what recommendations could be made to practitioners, commissioners of services and others. No Delphi process was conducted, GDG reached consensus on all recommendations. In case of minority dissent, we planned to explicitly report this, however, full consensus was reached on all recommendations.

Some recommendations are 'strong' in that the GDG believe that the vast majority of practitioners or commissioners and people using services would choose a particular intervention if they considered the evidence in the same way as the GDG. Similarly, if the GDG believed that the vast majority of practitioners or commissioners and people using services would not choose a particular intervention, if they considered the evidence in the same way as the GDG, a negative recommendation was made ('Do not offer').

If evidence of effectiveness for an intervention was either lacking or too weak for firm conclusions to be reached, the GDG used expert opinion; or it made no recommendation.

3. The validation process for draft guidelines

The draft version of the guideline will be posted on the ESCP website for consultation with registered stakeholders and respondents. The ESCP informs registered stakeholders and respondents that the draft is available and invites them to comment by the deadline. Questions for stakeholders are posted with the draft guideline. The ESCP will also ask stakeholders to comment on recommendations identified as likely to substantially increase costs, and their justification, and to consider whether any other draft recommendations are expected to add substantial costs.

A 4-week consultation will be used.

3.1. Finalizing and publishing the guideline

The development time for guideline is between 12 and 27 months (from the start of scoping to publication). We plan to update the guideline on an annual basis. This will involve update searches and assessment of any relevant research found in relation to the current recommendations and consideration whether recommendations need to be adapted or changed.

Program	**Period**
Development guideline protocol	March 2017
Establishing the Guideline Development Group	April 2017
First skype meeting Introduction and explanation of the process	May 2017
Development of review questions	June 2017
First face-to-face meeting Altering the review questions	September 2017 during the ESCP Berlin
Literature searches ROBIS assessment	October-December 2017
Second face-to-face meeting Development of recommendations	January 2018 in Amsterdam
Grade process	January-August 2018
Consultation open Stakeholders submit comments	September 2018
Validation and checking	October- November 2018

4. Conflict of interest

Jos Kleijnen (Kleijnen Systematic Reviews Ltd) has cooperated in the development and is co-author of the ROBIS, PRISMA, QUADAS, STARD and PROBAST tools.

5. References

1. Dans, A.L. and L.F. Dans, Appraising a tool for guideline appraisal (the AGREE II instrument). J Clin Epidemiol, 2010. **63**(12): p. 1281-2.
2. Banov, L., Jr., et al., *Management of haemorrhoidal disease.* J S C Med Assoc, 1985. **81**(7): p. 398-401.
3. Gaj, F., et al., *The new classification of haemorrhoids: PATE 2000-Sorrento. History of the scientific debate.* Minerva Chir, 2002. **57**(3): p. 331-9.
4. Elbetti, C., et al., *The single pile classification: a new tool for the classification of haemorrhoidal disease and the comparison of treatment results.* Updates Surg, 2015. **67**(4): p. 421-6.
5. Boers, M., et al., *Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0.* J Clin Epidemiol, 2014. **67**(7): p. 745-53.
6. Sinha, I.P., R.L. Smyth, and P.R. Williamson, *Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies.* PLoS Med, 2011. **8**(1): p. e1000393.
7. Whiting, P., et al., *ROBIS: A new tool to assess risk of bias in systematic reviews was developed.* J Clin Epidemiol, 2016. **69**: p. 225-34.
8. Savovic, J., et al., *Evaluation of the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials: focus groups, online survey, proposed recommendations and their implementation.* Syst Rev, 2014. **3**: p. 37.
9. Kong, Y., et al., *Rating the quality of evidence: the GRADE system in systematic reviews/meta-analyses of AKI.* Ren Fail, 2015. **37**(7): p. 1089-93.
10. Neumann, I., et al., *[The GRADE system: a change in the way of assessing the quality of evidence and the strength of recommendations].* Rev Med Chil, 2014. **142**(5): p. 630-5.