The old, the new and the ever-changing view of haemorrhoidal disease research

SUMMARY

This thesis consisted of two aims. The first aim of this thesis was to address heterogeneity in study outcomes in haemorrhoidal disease (HD) research and find solutions to improve homogeneity in outcome reporting. The second aim was to prepare and develop an international, high quality, multidisciplinary guideline for HD.

Systematic reviews of the effectiveness of HD treatments highlighted the lack of uniform outcome definition, -measurement and -reporting in research data, hindering optimal evidence synthesis (1-3). A solution to improve homogeneity in outcome reporting was the development of a Core Outcome Set (COS). A COS represents a consensus-derived minimum set of outcome parameters that should be reported in all studies that report on a particular condition (4). Since no COS for HD existed yet, a logical next step was the development of such a COS for HD.
A detailed protocol (**chapter 2**) described the development process of the COS consisting of two main phases: 1) a literature review to ascertain which outcomes are commonly used in clinical trials for HD and 2) a consensus study according to the Delphi methodology. Additionally, qualitative interviews (**chapter 5**) were conducted to gain a deeper understanding and obtain information directly from the patients about their experiences with HD and treatment preferences (5, 6).
For the literature review (**chapter 3**) Medline (Pubmed), Embase (OVID) and Cochrane were searched for interventional studies for adult patients with HD. Two authors independently identified and reviewed eligible studies and finally 34 studies were included. The outcomes used in the studies were categorized according to the framework of OMERACT 2.0 filter (7, 8) a practical framework to develop and validate domains and outcomes for any health condition (9). This resulted in three Core Areas, 10 Domains and 59 different types of outcomes. Core Areas included Life impact, Pathophysiological manifestations, Resource use/economic impact and Death. No outcome could be placed into the Core Area Death. Apparently, death was not an outcome of interest in HD studies.
The Core Area Life impact included the following three Domains: patient satisfaction, time to return to normal and quality of life. The Core Area Pathophysiological manifestations consisted of three Domains: symptoms, complications and recurrence. The Core Area Resource use/ economical impact included four Domains: duration of operation, duration of hospitalization, re-operation and costs.
The most reported Domains were symptoms (100%), complications (91%), recurrence (59%) and patient satisfaction (41%) [table 1,2 and 3].

Table 1: Outcome Domains in 42 studies included according to OMERACT 2.0 filter Core "Life impact"

Domain	Number of outcomes reported within Domain	Number of studies reporting outcomes in Domain (%)
Patient satisfaction	1	14 (41)
Time to return to normal	6	12 (35)
Quality of life	2	8 (24)

Table 2: Outcome Domains in 42 studies included according to OMERACT 2.0 filter Core "Pathophysiological manifestations"

Domain	Number of outcomes reported within domain	Number of studies reporting outcomes in Domain (%)
Symptoms	22	34 (100)
Complications	18	31 (91)
Recurrence	2	20 (59)

Table 3: Outcome Domains in 42 studies included according to OMERACT 2.0 filter Core "Resource use/ economical impact"

Domain	Number of outcomes reported within domain	Number of studies reporting outcomes in Domain (%)
Duration of operation	3	10 (29)
Duration of hospitalization	2	13 (38)
Re-operation	2	13 (38)
Costs	1	5 (15)

Twenty-two different outcomes were used in the Domain 'symptoms'. Most reported outcomes were pain (91%), blood loss (94%) and prolapse (71%). Eighteen different outcomes were used in the Domain 'complications'. Recurrence was used in 20 studies (59%). Patient satisfaction was used in 14 studies (41%) using non-validated questionnaires. On average, 5.8 different outcomes (2-8) were assessed per study. With this review, we derived potentially relevant Domains and Outcomes for the development of a COS for HD (47).

For the COS development, the Delphi methodology was followed (**chapter 4**). In collaboration with the European Society of Coloproctology (ESCP) 43 national representatives were invited to participate in the study. Besides, Dutch-speaking male

and female participants (>18 years) (n=30) having HD were asked to participate in the study. The Delphi process consisted of four phases.

In *phase one*, the outcomes, which were identified in the literature review (10), were operationalized into a questionnaire for healthcare professionals and a separate questionnaire for patients.

Phase two involved two sequential rounds of the questionnaire for healthcare professionals and one patient round, aiming to prioritize the different outcomes (11). Participants were asked to rate the appropriateness of each Domain and Outcome on a 9-point Likert scale. In round one, the first part of the questionnaire regarding the question 'What domains should we use as primary and secondary end-points in the COS for HD?', the domains (in order of level of appropriateness) 'symptoms', 'patient satisfaction', 'recurrence', 'complications', 'prolapse' and 'pain' were rated appropriate as primary end-point options. In the same round, the domains 'patient satisfaction', 'complications' and 'recurrence' were rated as appropriate as secondary end-points and 'symptoms', 'prolapse' and 'pain' were rated as unsure. In the second part of questionnaire, regarding the question 'Which outcomes should be included in the domains?', most outcomes (i.e. 'pain', 'prolapse', 'itching', 'soiling', 'blood loss', 'abscess', 'incontinence', 'anal stenosis', 'stricture', 'fistula', 'severe bleeding', 'severe pain', 'urinary retention', 'thrombosis') were rated as appropriate. The Outcomes 'urgency' and 'constipation' were rated as unsure. The Outcomes 'edema' and 'nodule' were rated as inappropriate and were omitted.

The following definitions of recurrence were rated as appropriate: 'recurrent prolapse after a symptom free period', 'reappearance of initial symptoms' and 'further intervention necessary'. The definition 'residual symptoms in relation to degree of satisfaction' was rated as unsure and 'histological proved recurrence' was rated as inappropriate. In round two, healthcare professionals rated the Domains 'symptoms', 'patient satisfaction', 'recurrence' and 'complications' as primary endpoints. As secondary endpoints, all Domains (i.e. 'patient satisfaction', 'recurrence', 'prolapse', 'complications', 'symptoms' and 'pain') were rated as appropriate. Regarding the question: "Which Outcomes should be included in the Domains", 'constipation', 'urgency', 'urinary retention' and 'thrombosis' were rated as unsure. 'Pain', 'prolapse', 'itching', 'soiling', 'blood loss', 'abscess', 'incontinence', 'anal stenosis', 'fistula', 'stricture', 'severe pain' and 'severe bleeding' were rated as appropriate outcomes.

To define recurrence the following options were rated as appropriate: 'further intervention necessary', 'recurrent prolapse after symptom free period', 'reappearance of initial symptoms', and 'residual symptoms in relation to degree of satisfaction'. In conclusion, the questionnaire rounds did not result in a clear-cut selection of primary and secondary endpoints for HD. Most Domains and Outcomes were considered important and only three Outcomes were excluded. Patients rated 'symptoms' as most important to discuss during the outpatient clinic. They reported the following complaints: 'pain', 'prolapse', 'itching', 'soiling' and 'blood loss'.

In *phase three* a face-to-face consensus meeting was conducted with 16 healthcare professionals in order to get consensus on the final endpoints of the COS [table 4]. Healthcare professionals rated the Domain 'symptoms' as the most appropriate primary endpoint in the COS. Further, healthcare professionals reached consensus that the Domains 'complications', 'recurrence' and 'patient satisfaction' should all be used as secondary endpoints in the COS for HD.

Besides uniformity in reporting, this Delphi study underlined the need to integrate Patient Reported Outcome Measures (PROMs) next to traditional clinical outcomes. PROMs have become an increasingly important component of assessing treatment response. Healthcare professionals agreed that the Domain 'symptoms' should be a Patient Reported Outcome Measure (PROM) and include the Outcomes 'pain', 'prolapse', 'itching', 'soiling' and 'blood loss'.

In *phase four* a short survey was sent to the healthcare professionals in order to reach consensus on 'how' the selected endpoints should be assessed and at which time points pre- and post-procedure. 'Incontinence' should be assessed by the Wexner Fecal Incontinence Score, 'abscess' by physical examination, 'urinary retention' by ultrasonography, 'anal stenosis' by physical examination, and 'fistula' by MR-imaging if physical examination is inconclusive [table 4]. During follow-up, the Outcome 'symptoms' should be assessed at baseline (i.e. before the procedure) and at 7 days, 6 weeks (arguably by telephone) and one-year post-procedure. The Outcomes 'abscess' and 'urinary retention' should be assessed 7 days' post-procedure, and 'rectal stenosis', 'incontinence' and 'fistula' one year post-procedure [table 5].

This resulted in the first international COS for HD based on an international Delphi study. Use of this COS will improve the quality and uniformity of future research and enhance evidence synthesis for meta-analyses and guidelines.

Table 4: Summary of the core Domains for haemorrhoidal disease

Core Outcome Set	
PRIMARY OUTCOME	
• Patient reported symptoms • Blood loss • Pain • Prolapse • Itching • Soiling	Patient Reported Outcome Measure (PROM)
SECONDARY OUTCOME	
• Complications • Incontinence • Abscess • Fistula • Urinary retention • Anal stenosis	 Wexner Fecal Incontinence Score Physical examination MR imaging after inconclusive physical examination Ultrasonography Physical examination
Recurrence	The reappearance of initial symptoms
Patient satisfaction	This endpoint will be included in the PROM.

Table 5: Follow-up scheme.

	Outcomes	Baseline	7 days	6 weeks	1 year
Primary endpoint	Symptoms (PROM)	X	X	X	X
Secondary endpoints	Abscess		X		
	Urinary retention		X		
	Anal stenosis				X
	Incontinence				X
	Fistula				X

Since these traditional clinical outcomes – mostly selected by healthcare professionals - may not include all relevant benefits and harms as experienced by patients. However, differences in such preferences are difficult to predict and may vary between conditions (21-25).

During individual interviews (n=15), patients were encouraged to describe their experiences and symptoms they encounter having HD. Blood loss and anal pain were the most commonly reported symptoms. Participants indicated that these symptoms were directly associated with emotional burden, daily adjustments, and social impact. For example, in patients having blood loss before the diagnosis was known, this symptom resulted in feelings of fear. Besides, blood loss resulted in embarrassment and

avoidance of social activities. Participants were not always completely satisfied with the process and outcomes of treatment. They expected greater openness and exchange of information regarding the different treatment options and the expected outcomes from their healthcare professionals.
This was the first study that showed that certain aspects relevant to the patient were overlooked when HD-treatment effectiveness was assessed by only traditional endpoints such as prolapse, recurrence and complications. Furthermore, this study showed that patients had different preferences regarding the treatment options compared to the preferences of the clinician.

In the **second part** of the thesis the development of the first international guideline for HD in collaboration with the European Society of Coloproctology (ESCP) is described. Up till now, only country-specific guidelines have been published, including the American Society of Colon and Rectal Surgeons guideline (12), the Italian (13)- and the French HD guideline (14). The methodological quality of these guidelines could be improved by being much more specific regarding the methods used to formulate the recommendations.
To see how the current Dutch situation was before the introduction of the new guideline, a nationwide survey (**chapter 6**) was conducted using a validated web based program. The survey was distributed among 619 officially registered Dutch colorectal consultants, fellows and residents and contained questions regarding the treatment options for each grade of HD.
Grade I and II HD were most often treated conservatively or with Rubber Band Ligation (RBL). Respondents chose for more invasive treatment options like Doppler-Guided Haemorrhoidal Artery Ligation (DG-HAL), stapled haemorrhoidopexy and haemorrhoidectomy in case of grade III and IV HD. In case of recurrent HD, they often preferred basic treatment and RBL. This study showed that there is considerable variability in treatment of HD in the Netherlands.
In a protocol (**addendum**) the seven steps of the guideline development were described using the AGREE II instrument [21]. We started with defining the scope of the guideline in *phase one*. The target group of the guideline consisted of all physicians treating patients with HD, healthcare workers and patients who desire information regarding the treatment management of HD. The patient population included patients with all stages of HD. The guideline needed to address both the diagnostic and therapeutic modalities for HD management.
In *phase two* the guideline development group (GDG) was composed and consisted of five colorectal surgeons, one gastroenterologist and proctologist (TH), one general practitioner (JM) specializing in the treatment of HD, one surgical resident (RT) and one methodologist (JK) with extensive experience in guideline development.

In *phase three* the first set of review questions were developed. The review questions were built up using a reversed process, starting with possible recommendations based on the GDG's knowledge.
In *phase four* a literature search was performed in MEDLINE (Ovid), PubMed, EMBASE (Ovid), and the Cochrane Database of Systematic Reviews. The search was focused on existing systematic reviews addressing each review question, supplemented by other studies published after the time frame covered by the systematic reviews.
In *phase five* data of the included papers were extracted by the surgical resident (RT) and checked by the methodologist (JK) and the GDG.
In *phase six* the GDG decided what recommendations could be made based on the evidence found in literature. GRADE was used to indicate the quality of the evidence (15).
This resulted in the first international guideline for HD (**chapter 7**) including 34 recommendations covering six sections: 1) evaluation: symptoms, diagnosis & classification, 2) basic treatment, 3) outpatient procedures, 4) surgical interventions, 5) special situations and 6) other surgical techniques [figure 1].
For grade I and II HD, RBL appears to be the treatment of choice, because patients who undergo RBL showed a significantly better response compared to patients treated with sclerotherapy (SCL) and/or infrared coagulation (IRC). Besides patients treated by RBL have significantly less recurrence compared to patients treated with SCL or IRC. IRC may be the first treatment option in bleeding grade I HD because it causes less pain and complications (16). However, complication rates were similar in higher grade HD between RBL, IRC and SCL (17-19).
For grade III and IV HD, haemorrhoidectomy remains the treatment of choice. Comparing stapled haemorrhoidopexy (SH) and haemorrhoidectomy, the efficacy of SH is generally lower than haemorrhoidectomy (20), especially in grade IV HD (20). The DG-HAL + mucopexy may be considered in patients with grade II-III HD. However, more research regarding this technique is necessary. The additional effect of the Doppler is currently being questioned since two studies showed that significantly more complications and unscheduled postoperative events were reported in the DG-HAL + mucopexy group compared to the mucopexy alone group (21, 22).
The flow diagram for all degrees of haemorrhoids is shown below (figure 1).
This international multidisciplinary guideline provides an up to date and evidence based summary and may serve as a useful guidance for patients and clinicians.

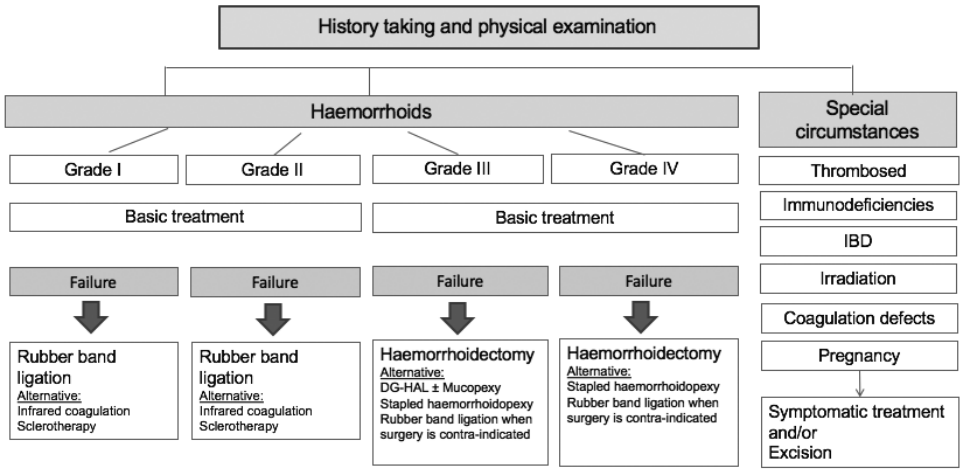

Figure 1: flow diagram grade I-IV HD.

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SAMENVATTING

Dit proefschrift is geschreven met twee doelen:

1. Het eerste doel van het proefschrift was om de heterogeniteit in onderzoeksuitkomsten aan te pakken in hemorrhoiden onderzoek en om oplossingen te vinden om de homogeniteit in de rapportage van de resultaten te verbeteren.
2. Het tweede doel was het opstellen en ontwikkelen van een internationale multidisciplinaire richtlijn voor de behandeling van hemorrhoiden.

Hemorrhoiden is een van de meest voorkomende anorectale aandoeningen. De werkelijke prevalentie van aambeien is echter niet bekend; ziekenhuisstudies zijn niet representatief voor de totale populatie met hemorrhoiden en community-gebaseerde studies hebben alleen op zelfrapportage vertrouwd. Dit heeft geleid tot gerapporteerde prevalentie percentages variërend van 4,4-45% (1-4). In Nederland wordt de prevalentie geschat op ongeveer 8,6 per 1000 personen. De piek incidentie lijkt tussen de leeftijd van 45-65 jaar te liggen (5, 6). In de algemene bevolking is de prevalentie vergelijkbaar bij mannen en vrouwen (2, 7). Hoge oestrogeenreceptorniveaus zijn geïdentificeerd in aambeien, wat hemorroïdale symptomen tijdens de zwangerschap kan verklaren (8). Er is een verhoogde prevalentie onder hogere sociaaleconomische groepen, maar dit kan gezondheidsgerelateerd gedrag weerspiegelen (9).

Met de voortdurende evolutie van verschillende behandelingen voor de zorg van hemorrhoiden is het belangrijk dat de effectiviteit van (chirurgische) behandelingen op een systematische manier wordt geanalyseerd. Klinische onderzoeken naar de effectiviteit van interventies voor hemorrhoiden hebben een breed scala aan uitkomsten en uitkomstmaten gebruikt. Verschillende richtlijnen wezen op het gebrek aan uniformiteit van de definitie, meting en rapportage van uitkomsten. Hierdoor wordt optimale bewijssynthese belemmerd en ontbreken richtlijnen van hoge kwaliteit (10-12).

Een oplossing om de homogeniteit in de resultaat rapportage over hemorrhoiden te verbeteren, is het ontwikkelen en gebruiken van een gestandardiseerde uitkomstenset. Een uitkomstenset vertegenwoordigt een uit consensus verkregen minimale set uitkomstparameters die moet worden gerapporteerd in alle studies die over een bepaalde aandoening rapporteren (13). Een overeengekomen uitkomstenset zal het vermogen verbeteren om toekomstige studies te vergelijken en om een optimaal behandelingsalgoritme voor hemorrhoiden te ontwikkelen. Aangezien er nog geen

uitkomstenset voor hemorrhoiden bestaat, is een belangrijke stap voor het verbeteren van hemorrhoiden onderzoek de ontwikkeling van een gestandardiseerde uitkomstenset voor dergelijk onderzoek.
De afgelopen tien jaar zijn verschillende nationale richtlijnen voor de behandeling van hemorrhoiden gepubliceerd (35-37). De meest recent bijgewerkte richtlijn is van de Amerikaanse colorectale chirurgen (14). De methodologische kwaliteit van deze richtlijnen kan worden verbeterd door veel specifieker te zijn over de methoden die worden gebruikt om hun aanbevelingen te formuleren. Daarom willen we een internationale, multidisciplinaire, hoogwaardige richtlijn ontwikkelen in samenwerking met de European Society of Coloproctology (ESCP) die zowel diagnostische als therapeutische modaliteiten voor het beheer van hemorrhoiden aanpakt.

Doel 1

Hoofdstuk 2: een protocol voor het ontwikkelen van een gestandardiseerde uitkomstenset voor hemorrhoiden.
Hoofdstuk 3: literatuuroverzich van de verschillende uitkomsten in hemorrhoiden studies
Hoofdstuk 4: een Delphi proces om een internationale uitkomstenset te ontwikkelen voor hemorrhoiden.
Hoofdstuk 5: een kwalitatieve studie naar de ervaringen van patienten met hemorrhoiden.

Doel 2

Hoofdstuk 6: een nationale enquete naar het behandelalgortime onder de Nederlandse chirurgen.
Hoofdstuk 7: de richtlijn van hemorrhoiden.
Bijlage: de methodiek achter de richtlijn.

Voor de ontwikkeling van een gestandaardiseerde uitkomstenset moet een stapsgewijze aanpak worden gevolgd die in een protocol wordt beschreven (**hoofdstuk 2**). Een van de eerste pogingen om de resultaten te standardiseren werd in de jaren zeventig door de Wereldgezondheidsorganisatie uitgevoerd met betrekking tot kankeronderzoeken. Dit resulteerde in een WHO-handboek met richtlijnen die de minimumvereisten voor gegevensverzameling in kankeronderzoek aanbevelen (15). Het meest opmerkelijke werk tot nu toe met betrekking tot standaardisatie van resultaten sindsdien is uitgevoerd door de OMERACT-samenwerking (Outcome Measures in Rheumatology) (16). Sinds OMERACT zijn er andere voorbeelden (d.w.z. HOME, IMMPACT) van

vergelijkbare initiatieven om aanbevelingen te ontwikkelen over de resultaten die in klinische onderzoeken moeten worden gemeten (17, 18). De OMERACT-gemeenschap heeft echter onlangs de OMERACT-filter 2.0 gepubliceerd, die een zorgvuldige uitleg geeft over hoe deze in andere subspecialiteiten kan worden geïmplementeerd (19). In dit proefschrift hebben we besloten deze methode te volgen. In navolging van het OMERACT-initiatief is de eerste fase bij het ontwikkelen van een uitkomstenset een literatuuronderzoek naar de soorten uitkomsten en uitkomstmaten die zijn gebruikt in eerder gepubliceerd onderzoek naar hemorrhoiden (**hoofdstuk 3**). In hemorrhoiden onderzoek worden verschillende uitkomsten (bijvoorbeeld verzakking, recidief, complicaties en duur van de operatie) gebruikt als primaire en secundaire uitkomsten. Deze heterogeniteit in de rapportage van uitkomsten bemoeilijkt de juiste vergelijking tussen onderzoeken. Zelfs twee recent uitgevoerde gerandomiseerde gecontroleerde studies van een onderzoeksgroep uit Engeland gebruiken verschillende primaire uitkomsten. In de eerste studie, de HubBLe-studie, wordt rubber band ligatie (RBL) vergeleken met de doppler (DG-HAL). De auteurs gebruiken 'herhaling na één jaar na de procedure' als primaire uitkomst. De tweede studie, de eTHoS-studie, waarbij geniete hemorroïdopexy wordt vergeleken met de traditionele hemorroïdectomie, wordt 'een gebied onder de curve van de kwaliteit van leven' gemeten als primaire uitkomst met behulp van het beschrijvende systeem EQ-5D-3L (20-22).
De tweede fase bij het ontwikkelen van een uitkomstenset is een Delphi proces. Eerst zullen de resultaten die in de literatuurstudie zijn geïdentificeerd, worden geoperationaliseerd in een vragenlijst voor artsen en een afzonderlijke vragenlijst voor patiënten. Daarna volgen twee opeenvolgende rondes van de vragenlijst om deze uitkomsten te prioriteren. Fase drie bestaat uit een vergadering met artsen om overeenstemming te bereiken over de eindpunten van de uitkomstenset. Dit wordt beschreven in **hoofdstuk 4**.
Door een uitkomstenset voor hemorrhoiden te ontwikkelen, moeten we echter voorzichtig zijn dat behandelvoorkeuren en -uitkomsten aanzienlijk kunnen verschillen tussen patiënten met hemorrhoiden (23). Kwalitatieve interviews bij patiënten met hemorrhoiden kunnen worden uitgevoerd om een dieper inzicht te krijgen en rechtstreeks van de patiënten informatie te verkrijgen over hun ervaringen met hemorrhoiden en behandelingsvoorkeuren (**hoofdstuk 5**) (24, 25).

Richtlijnen dienen het doel om klinische (gedeelde) besluitvorming met betrekking tot behandelingskeuzes te ondersteunen, volgens het beste beschikbare bewijs. Verschillende nationale HD-richtlijnen zijn gepubliceerd (14, 26, 27). De Nederlandse richtlijn is in 2015 gepubliceerd.
Om de huidige praktijk in de behandeling van hemorrhoiden in Nederland te verkennen voordat een internationale richtlijn wordt geïntroduceerd, zullen we een nationale enquête onder Nederlandse colorectale consultants, fellows en arts-assistenten

uitvoeren (**hoofdstuk 6**). Deze resultaten dienen als richting voor de volgende fase van het ontwikkelen van een internationale richtlijn voor hemorrhoiden.
Verschillende initiatieven (d.w.z. NICE, GIN-McMaster) ontwikkelden checklists voor de ontwikkeling van richtlijnen en beschreven dat een richtlijn moet worden ontwikkeld volgens een proces dat begint bij het gekozen onderwerp en zich uitstrekt tot toekomstige updates van richtlijnen. De AGREE Enterprise ontwikkelde het AGREE-instrument, een online tool om de kwaliteit en rapportage van praktijkrichtlijnen te beoordelen (28). Bestaande hemorrhoiden richtlijnen beschrijven geen duidelijke ontwikkelingsmethode zoals voorgesteld door de AGREE-checklist. Ze rapporteren vaak hun beoordelingsvragen en methoden voor het formuleren van hun aanbevelingen niet. In samenwerking met de European Society of Coloproctology (ESCP) zal een internationale kwaliteitsrichtlijn voor hemorrhoiden worden ontworpen. In **hoofdstuk 7** worden de resultaten van de definitieve ESCP richtlijn voor de behandeling van hemorrhoiden gepresenteerd. In **de bijlage** worden de ontwikkelingsprocessen en -methoden volgens het AGREE II-instrument beschreven.

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