European Society of Human Reproduction and Embryology

External Review report

GUIDELINE: MANAGEMENT OF WOMEN WITH ENDOMETRIOSIS

Review period: 15/02/2013 – 01/04/2013

1. INVITED REVIEWERS

Open invitation:

- Email sent to members of the SIG endometriosis and endometrium (primary or secondary interest)
- Publication in ESHRE update (e-newsletter, March issue)

Personal invitation (relevant stakeholders)

- Coordination of the SIG SQUART and SIG endometriosis and endometrium
- Members of the 2005 guideline development group
- Presidents of relevant International organizations (WES, FIGO, ASRM, ESG, IFFS, WHO)
- 39 European societies on gynecology or fertility
- 27 European patient organizations for women with endometriosis
- 24 colleagues of the GDG members (2 per member)

(reminders were sent 1 week prior to the deadline to invited reviewers that responded on the first invitation)

2. REPORT ON THE REVIEWERS

In total 61 reviewers responded to our invitation and have sent in their comments to the guideline. In the table below, the reviewers are sorted based on the invitation they received and the continent / country they are located in.

Reviewers per method of invitation and response rate

Reviewers	Invited	Responded	%
members of the SIG endometriosis and endometrium	683	22	3,2
ESHRE update	6000	5	0,1
Coordination of the SIG SQUART	4	2	50
Coordination of the SIG endometriosis and endometrium	3	3	100
Members of the 2005 GDG	6	3	50
International organizations	6	4	66,7
European societies	39	11	28,2
European patient organizations	27	0	0
colleagues of the GDG members	24	11	45,8

Number of reviewers per country (World)

USA	4
Australia	3
Brazil	1
Japan	1
Malaysia	1
Thailand	1
EUROPE	50

Number of reviewers per country (specified for Europe)

Norway	2
Finland	1
Iceland	1
Denmark	1
Greece	4
Portugal	4
Italy	3
Spain	2
UK / England	11
The Netherlands	8
Belgium	4
Germany	4
France	2
Scotland	2
Romania	1

3. LIST OF EXTERNAL REVIEWERS

(according to the date comments were received)

Conflicts of Interest	Name	Function	Organisation	Country
/	**Prof. Dr. Petra De Sutter**		SIG SQUART coordinator	**Belgium**
None declared	**Dr. Juan Antonio García Velasco**	Associate Prof - IVI Madrid	IVI Madrid	**Spain**
None declared	**Dr Paul Mills**	Consultant Obstetrician and Gynaecologist	NHS Lothian	**Scotland**
/	**Dr Linda Giudice**		President of ASRM	**US**
YES	**Prof. Dr. Daniela Hornung**	Head of Department Ob & Gyn	Diakonissenkrankenhaus Karlsruhe	**Germany**
None declared	**Jone Trovik**	Scientific secretary	Norwegian Gynecological Association	**Norway**
None declared	**Dr Dominic Byrne**	Consultant Gynaecologist	Royal Cornwall Hospitals Trust	**England**
None declared	**Dr Jan Bosteels**	MD	CEBAM, the Belgian Branch of the Dutch Cochrane Centre	**Belgium**
/	**Ben Cohlen**			**The Netherlands**
None declared	**Martyn Stafford-Bell**	Medical Director	Canberra Fertility Centre, John James	**Australia**
None declared	**Dr Arrianna D'Angelo**	Consultant and Clinical Lecturer	IVF Wales	**UK**
None declared	**Dr Francisco Gonzalez-Gomez**	Professor of Obstetrics and Gynaecology(retired)	Granada University (Dpt.of Obstetrics and Gynaec.)	**Spain**
YES	**Dr. Robert Greb**	Director Kinderwunschzentren Dortmund, Siegen, Dorsten	n.a.	**Germany**
None declared	**Dr. P.G. Crosignani**	Prof of Ob/Gyn. ESHRE Past Chairmen	Scientific direction IRCCS Ca' Granda Foundation Maggiore Policlinico Hospital,Milano	**Italy**
None declared	**Kate Young**	PhD Candidate	The Jean Hailes Research Unit	**Australia**
None declared	**Keiji Kuroda**	Dr.	Juntendo university, Faculty of Medicine, Department of Obstetrics and Gynaecology	**Japan**
/	**Maria Goudakou**			**Greece**
None declared	**Mukhri Hamdan**	Clinical specialist & medical lecturer	University of Malaya	**Malaysia**
YES	**Hilary Critchley**	Professor of Reproductive Medicine	University of Edinburgh	**Scotland**
/	**G. David Adamson**	MD	Committee for Reproductive Medicine of the International Federation of Gynecology and Obstetrics (FIGO)	**USA**
/	**Pr Herve DECHAUD**		CHU Arnaud de Villeneuve	**France**
None declared	**Dr Philip Owen FRCOG**	Chair, Guidelines Committee	RCOG	**UK**
None declared	**M.A. Spath, MD, PhD**	resident OBGYN	n.a.	**The Netherlands**
None declared	**Mr.Luca Fusi, MD FRCOG**	Consultant Gynaecologist & Obstetrician	Ealing Hospital NHS Trust - London	**UK**
/	**Dr JCM van Huisseling**		Groene Hart Ziekenhuis, Gouda	**The Netherlands**
YES	**Dr.Thomas Faustmann**	Senior medical advisor	Bayer Healthcare	**Germany**
YES	**dr. Peter Hompes**	Head of the multidisciplinary Endometriosis Centre, Amsterdam		**The Netherlands**
None declared	**dr. Velja Mijatovic**	Gynaecologist		**The Netherlands**
None declared	**The endopart study team Prof Lorraine Culley**	n.a.	Endopart study	**UK**
None declared	**Ioannis E. Messinis**	Professor/Head	University of Thessalia	**Greece**

None declared	**dr. S.M.Mourad, MD, PhD**	resident OB/GYN, 3rd yea	Radboud University Nijmegen Medical Center	**the Netherlands**
None declared	**Samuel Santos Ribeiro**	Trainee in Gyaenecology/Obstetrics (5th year)	Centro Hospitalar Lisboa Norte	**Portugal**
None declared	**Dr. Ganeshselvi Premkumar**	Fertility trainee Registrar	ABMU Health board NHS Trust, Swansea, UK	**UK**
YES	**PD Dr. Stefan P. Renner**	Assitant Medical Director	Gynecology and Obstetrics Dept., University Hospital Erlangen	**Germany**
/	**Berglind Ósk**			**Iceland**
None declared	**Dr. Kamthorn Pruksananonda**	Associate Professor, Director: Reproductive Medicine Unit, Department of OB/GYN	Chulalongkorn University	**Thailand**
None declared	**Paolo Vercellini**	Associate Professor of Ob/Gyn	Università degli Studi, Milano, Italy	**Italy**
/	**Tommaso Falcone**	M.D.	Endometriosis Special Interest Group of the ASRM	**USA**
None declared	**Harold Verhoeve**	Gynaecologist, Subspecialist in reproductive medicine	OLVG Hospital	**the Netherlands**
YES	**Carla Tomassetti**	Dr	University Hospitals Leuven, Belgium	**Belgium**
/	**George Pados**	MD, PhD, As. Professor OB-GYN	Aristotle University of Thessaloniki	**Greece**
None declared	**Grigoris F. Grimbizis**	Ass Professor, Medical School	Aristotle University of Thessaloniki	**Greece**
YES	**Dr Jacques WM Maas**	Gynaecologist	Maxima Medisch centrum, Veldhoven	**the Netherlands**
None declared	**Hans Kristian Opøien**	MD	Oslo University Hospital Rikshospitalet	**Norway**
None declared	**Paulo C. Serafini**	Associate Professor of gynecology	Huntington Centro de Medicina Reprodutiva; Division Gynecology at University of Sao Paulo	**Brazil**
/	**Dr. Miguel A. Marrero**	M.D., FACOG		**USA**
None declared	**Andreas Stavroulis**	Fellow in MAS	UCLH NHS Foundation Trust	**UK**
None declared	**Ying Cheong**	Senior Lecturer	Complete Fertility Centre Southampton and University of Southampton	**UK**
/	**Florin Stamatian**	Prof	Romanian Society of Obstetrics and Gynecology	**Romania**
None declared	**Fernanda Águas**	MD, Senior graduate assistant of Gynaecology/Obstetrics	Portuguese Gynaecology Society; Coimbra Hospital and Universitary Center	**Portugal**
YES	**Teresa Almeida-Santos**	Head of reproductive medicine service	University Hospital of Coimbra	**Portugal**
None declared	**Michelle Nisolle**	Head of Department of Gynecology-Obstetrics		**Belgium**
Yes	**Päivi Härkki**	Consultant Gynecologist	Helsinki University Central Hospital	**Finland**
Yes	**Lone Hummelshoj**	Publisher/Editor-in-Chief	Endometriosis.org	**England**
None declared	**Bee Kang Tan**	Subspecialty Trainee in Reproductive Medicine and Surgery	Cambridge University Hospitals NHS Foundation Trust	**UK**
YES	**Ana Aguiar**	Hospitalar Assistant	Hospital Santa Maria - Lisboa	**Portugal**
None declared	**Cindy Farquhar**	Postgraduate Professor	Cochrane Menstrual Disorders and Subfertility Group University of Auckland	**UK**
/	**Emile Daraï**	Professor		**France**
Yes	**Luk Rombauts**	Associate Professor	Monash IVF, Monash University	**Australia**
None declared	**Nicola Surico**	Chief of "Department of Obstetrics and Gynecology" University of Eastern Piedmont, "Maggiore della Carità" Hospital, Novara.	Italian Society of Obstetrics and Gynecology (SIGO)	**Italy**
YES	**Axel Forman**	Professor (chair)	The Danish Society of Obstetrics and Gynecology.	**Denmark**

4. METHODOLOGY FOR PROCESSING THE REVIEWERS' COMMENTS

a) All comments were collected in a single file.
b) The chair of the guideline development group (Dr Dunselman) and the research specialist updated the guideline based on the comments and formulated a response to every comment.
c) The reviewers comments report and updated version of the guideline (with track changes) was send to the guideline development group for further remarks. Consensus on the final version was reached during a guideline group meeting.

5. REVIEWER COMMENTS REPORT

All comments of the reviewers are mentioned below with the response of the guideline development group. Although specifically mentioned in the invitation to the reviewers, a number of reviewers did not use the appropriate form to send in their comments and hence did not declare any potential conflicts of interest. However, the GDG feels that these too are valid comments that lead to improvement of the guideline. To distinguish them from the comments from reviewers that have correctly used the form and declared COI, these comments are summarized in a second table starting from page 51.

Biography	chapter	Page & Line numbers	Comments	Consequence
Dr. Juan Antonio García Velasco	4.3b		I know it is not an easy agreeable topic, but I have some comments on Section 4.3b - there are two studies that may add to the Discussion o Garcia-Velasco et al was one of the first studies to challenge the classical dogma of performing surgery prior to ART o Benaglia et al. Fertil Steril 2013 (in press, outcome of ART in women with bilateral endometriomas) - the 2nd recommendation was better phrased in the previous version of the Guidelines, as it seems after reading it that even though pregnancy rates do not improve, surgery should be performed o confirm the diagnosis histologically in women under 40 (as most women undergoing IVF are under 40) may not be that relevant if a good transvaginal scan has been performed o there is no evidence that the risk of infection after oocyte retrieval is reduced if ovarian endometrioma is removed o agree with better accessibility of follicles in selected cases o fully agree with pain - I think this 2nd recommendations needs to be reworded accordingly.	Thank you for your comment. We have taken your comment into account, but as this is a good practice point, the reasons for considering surgery are not necessarily evidence based, but written based on expert opinion and hence not adapted;
Dr Paul Mills	1	32, 112 + 113	Both recommendations are Grade C evidence which is higher than the GPP in recommendations 1.1 + 1.2 Therefore, the use of "may" seems inversely weak when "should" is used in rec 1.1 and 1.2 Therefore suggest changing "may" to "should always" in order to emphasise this.	Thank you for your comment. The phrasing is explained in the table in the section on methodology. Recommendations based on C-level evidence use “may” in their phrasing, while good practice points use “the GDG recommends”, as it has been applied to the recommendations in this section.
	1	34/35, 201 - 203	For the same argument outlines above the evidence level for these is C so using the word "should" instead of "may" emphasises this.	See response above
	2.3b	58, 443	Whilst this recommendation stands well by itself I was really looking for some guidance on whether there is any difference between	Thank you for your comment. The study of Healey 2010 mentions that there is not statistical significant difference between both techniques in reducing pain. They mention that larger studies could show a difference and that individual operator's skill set are important factors in the success of either technique. One point we have added is that with excision, samples for histology can be taken.
	2.3c	59, 475	Should this be clarified and insert " and should be carried out in specialist centres".	Thank you for your comment. We agree with your comment, but since “specialised centres” are not defined, we decided not to add this to the recommendation.

	2.3	67, 750	Whilst I think the aim of this recommendation is to reinforce the advice that there is no advantage in post surgery adjuvant therapy but could be some benefit in secondary prevention this does not communicate well in its current form. Is this necessary as a separate point here as it is covered in later chapters?	We have added a section describing the differences between short- and long-term postoperative hormonal treatment and the different outcomes associated with them.
	2.4	69, 817	Is this recommendation needed as it does not help the clinician in management?	Thank you for your comment; This is a relevant general GDG statement providing the framework for the next recommendations
	2.5	72, 904	If the evidence is unclear then one cannot make a recommendation positive or negative, Therefore the recommendation should just state that evidence is unclear though some people may benefit. (As is worded in RCOG Greentop)	Thank you for your suggestion.
	2.1b	50, 176	Remove Danazol from this recommendation as in the text it clearly states "GDG strongly believe it should not be used if any other medical therapy is available" therefore should not be recommending with equal weight as this would read.	Thank you for your comment. We have considered removing “danazol” from the recommendations, but the GDG group felt they should emphasize the side effects, rather than not mentioning danazol
	3.4	82, 232	Same argument as made for Rec 2.31. If evidence unclear then just state that. Unable to recommend positive or negative if unclear.	Thank you for your comment
	4.1b	87, 161	The word "may" is weak. A clear recommendation should be made. For example if the risk of anaphylaxis is more than risk of abscess then advice should be not to give antibiotics.	Thank you for your comment. The word "may" is in agreement with the strength of the underlying “D-level” evidence. We state in the considerations section that the use of antibiotics seems reasonable, hence we feel not to advise against it.
	4.3b	91+92, 288 + 289	These 2 appear to contradict each other and leave the reader unsure what to do. Should I remove the endometrioma or not ?? If GDG want cysts excised for histology etc then drop Rec 4.9 and state that there is no improvement in Live Birth Rate in 4.10 would be a possible suggestion. Furthermore, given the presence of endometrioma like cysts in a pregnant woman can cause many clinical dilemmas and risk of torsion etc should the advice not be to remove them prior to planned pregnancy as a GPP ?	Based on the available evidence, you should not remove endometrioma with the aim of improving live birth rate, but there may be other indications, as listed, to perform cystectomy. The GDG does not feel that possible complications during pregnancy are an indication for surgery.
	8	102, 43	I agree with this recommendation and it would be great if these actual numbers could be in the supportive text otherwise few clinicians will be able to utilise the recommendation.	Thank you for your suggestion. An example of these absolute numbers is mentioned in the clinical evidence : “The risk of developing cancer in this study (follow-up of 12.7 years) was 0.027% in endometriosis patients and 0.019% in control group, meaning that over 12.7 years, an average of 3 out of 100 endometriosis patients, compared to 2 out of 100 controls developed ovarian cancer (Melin et al., 2006).”
	1.3	36, 239	“Prove “ instead of “proof”.	Thank you for your comment. We have corrected this error in the guideline.
	1.3b	38, 296	Should be rewritten as “ (2) Bowel surgery was not performed in all women.”	Thank you for your suggestion. We have modified this sentence.
	1.3i	43,	Should read “ Since not all patients had a bowel resection, histology was not available in	Thank you for your suggestion. We have modified this sentence.

		462+463	all cases”	
	2.3e	61, 550	“was” instead of “were”	Thank you for your comment. Apparently, “data” can be used both as singular or plural noun. Hence, “date were lacking” is correct.
	5	95, 28	Insert “a” into Authors referred to residual disease as “a” risk factor……	Thank you for your comment. We have corrected this error.
Prof. Dr. Daniela Hornung	Introduction	5,13	direct biopsy of a vaginal localisation … please add: or from a scar (laparoscopy, laparotomy)	Thank you for your suggestion.
	Introduction	5,23	docter .. doctor	Thank you, we have corrected this error
	Chapter 1	9,5	prefer version Rec 1.2. instead of Rec. 1.1.	Thank you for your suggestion.
	Chapter 1	9,6	prefer version Rec 1.4., but exclude postcoital bleeding (mostly sign of ectopia, not endometriosis), exclude menorrhagia (mostly sign of myomas, polyps, not endometriosis)	Thank you for your suggestion. We have revised this section
	Chapter 1	9.10	prefer version Rec. 1.5, but add: although vaginal examination may be inappropriate for adolescents and/or women without previous sexual intercourse. In such cases, rectal examination can be helpful for the diagnosis of endometriosis	Thank you for your suggestion. We have incorporated it in the t ext of the guideline.
	1,3 Medical techn.	10,15	prefer Rec. 1.11	Thank you for your suggestion.
	1,3 Medical techn.	10,19	prefer Rec. 1.14	Thank you for your suggestion.
	Chapter 2	12,37	It is unclear whether the OCP should be taken conventionally, continuously or in a tricycle regimen…. OCP continuously is preferred by most patients and doctors	Thank you for your comment. We have updated the information on this issue.
	Chapter 2	13,51	aromatase inhibitors .. please note "off-label-use"	Thank you for your suggestion. As most medications used in endometriosis are off label. The GDG decided not to add “off label use”
	Chapter 2.5	15,83	Rec 2.28: typo: endometriosis-associateddysmenorrhoea please separate associated and dysmenorrhoea	Thank you for your comment. We have corrected this error.
	Chapter 2.5	15, 84	scip Rec. 2.30	Thank you for your suggestion.
	Chapter 6	20, 148	scip Rec. 6.1	Thank you for your suggestion.
	Chapter 2.3	13,61	Rec 2.14: excision is to prefer in comparison to ablation for two reasons: 1. Histology is possible 2. Complete removal of the implant	Thank you for your comments. We have added the comment on “histology” to the considerations section. The second comment is irrelevant to the point that the outcome discussed is efficacy in reducing pain.
	Chapter 8	101	Please see this paper: Stewart LM, Holman CD, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. Gynecol Oncol. 2013 Feb;128(2):260-4.	Thank you for your suggestion. As this paper was published after the deadline for inclusion of papers, it was not assessed in the guideline. We focused on the risk of cancer specifically due to endometriosis. More information on the influence of parity and IVF treatment is interesting as this could potentially lead to changes in the management of endometriosis to lower the chance of cancer. However, this is something for the future, not for the current guideline.

Jone Trovik		31,76	Dysmenorrhagia?	Thank you for your comment. We have deleted "Dysmenorrhagia".
		43,462	rephrase: there was no histology was not	Thank you for your comment, we have corrected this error in the guideline.
	1.3e	Rec 1.17	But what about MRI and diagnosis of rectovaginal endometriosis? Is there no evidence for that? No trials reporting this?	Thank you for your comment. The usefulness of MRI in rectovaginal endometriosis is included in section 1.3g on "establishing the extent of disease". A sentence was added in section 1.3e (MRI) referring to this section.
	1.3i	461-463	rephrase	Thank you for your suggestion. We have modified this sentence.
	1.3i	Rec 1.20	Merits MRI and sonography to be mentioned as the ones with best evidence?	Thank you for your comment. The GDG feels that there is insufficient evidence to state which is best technique for establishing the extent of the disease.
	2.1b	134	lead? or led?	Thank you for your comment. We have checked this and believe "lead" is correct.
	2.3d		There is currently a rather pressing debate of this risk, leading many infertility directed surgeons to discredit excision. Could this have been discussed more in depth here?	Thank you for your comment. We have added information on the possible consequences of surgery on ovarian reserve to the section on surgery for infertility.
	Rec 3.4		In reality this answers my question about subsequent fertility after excision rather than drainage; still in favour of excision.	OK, see answer previously
	Rec 4.11		This is a good point!	Thank you for your comment
Dr Dominic Byrne	1.1	29-32	Patients with severe endometriosis have deep infiltrating or adhesive disease which may result in symptoms that are not cyclical. It may aid speedier diganosis of severe cases if the recommendations can draw out expert opinion that non cyclical symptoms may indicate more severe disease. Similarly patients with significant deep dyspareunia and dyschezia may indicate deepy infiltrating rectovaginal endometriosis (rAFS III/IV). Again to improve speed of diagnosis the recommendations of the expert panel could draw out these distinctions to aid referring clinicians.	Thank you for your comment. We have combined all comments on recommendations 1.1, 1.2, 1.3 and 1.4 and changed the recommendations accordingly.
	1.3a	36-37	Whilst negative laparoscopy has a high predictive value of not having endometriosis, this is only true if the whole pelvic peritoneum is adequately surveyed. Sometimes in clinical practice diagnostic laparoscopy is cursary and fluid in the pouch of Douglas, or redundant sigmoid/small bowel loops filling the pelvis may obscure significant disease. The guidance could clarify this by making the point that competent laparoscopic survey is required to ensure a neagtive finding; this includes using at least one secondary port for suitable grasper to clear the pelvis of obstruction from bowel loops, or the suction of fluid to ensure the whole pouch of Douglas is inspected. This is in essence a good practice point.	Thank you for your comment. We have added information on a "good" quality laparoscopy in the considerations section.
	2.3	66-67	The evidence to recommend not giving GNRH pre-operatively to improve surgical outcome is weak and limited. This is acknowledged in the text but then the guidance to	Thank you for your suggestion. We have considered it in rewriting/reorganising the sections on pre- and postoperative

			avoid it is given an A rating. This is inappropriate based on the criteria set by the ESHRE guideline scoring system. In our recent survey of UK Endometriosis Centres published in a poster at the Paris ESGE meeting 80% of respondents use pre-operative GNRH analogues before laparoscopic excision of severe endometriosis (Smith-Walker T and Byrne DL. Deep Infiltrating Endometriosis; How do you treat yours? Poster ESGE Paris 2012). The benefit is that surgery is carried out with the endometriosis deactivated. The peritoneum is not inflamed and lesions tend to be firmer and more easy to define, so improving complete excision. Lesser lesions may resolve completely. surgery in non inflammed peritoneum is less vascular and thus vision is improved and likely leads to better quality excision and less risk. The guideline group should include more guidance on pre-op GNRH ananlogues and clarify the limited evidence, indicating that some surgeons will gain qualative benefit. Further research is needed, but the evidence quoted does not support a level A rating for the guidance given in the draft guideline.	medical treatment and secondary prevention. The level A merely reflects that he data came from a systematic review.
	3.3	80	The same clarification as above is needed for GNRH prior to surgery in severe endometriosis for patients with infertility. To recommend not to give pre-op GNRH when there evidence is lacking is too directive as there is insufficent evidence to confirm if it might actually help. Thus the guidance should be less didactic and allow some appreciation of the uncertainty of this decision in cases of severe endometriosis (rAFS III/IV)	Thank you for your comment. The included evidence clearly shows that pre-op medical treatment does not improve pregnancy rate as compared to placebo. Hence, the GDG judged to not prescribe pre-op GnRHa with regard to improving pregnancy rates.
	Intro	5	The ESHRE guidance advises uses of the ASRM scoring system without adequate justification or referral to any of the many other scoring systems; like the recent Enzian scoring system. As the ASRM poorly correlates with symptoms there should be more recognition of its limitations and discussion about the many other scoring systems (maybe even a section on scoring systems and justification why one is preferable to another, rather than just insisting it is preferable to use the ASRM.	Thank you for your comment, we have changed the sentence into "could for example be performed according to the ASRM classification system."
Dr Jan Bosteels			I have a methodological remark concerning the use of the SIGN grades of recommendations. I would strongly recommend using the GRADE approach for future updated versions of the current guideline for the following reasons: 1. Although both systems start from collecting evidence through a systematic review of the literature, SIGN uses multidisciplinary group based judgements whereas GRADE uses methodology based judgements. 2. The level of evidence of a meta-analysis of randomized trials is different from a meta-analysis of observational studies. The level of evidence from a poorly designed RCT is different from a well-designed prospective cohort study. GRADE acknowledges the study limitations whereas SIGN does not. The use of scoring systems to define study	Thank you for your comment. The GDG and methodological expert agree with your comment. We acknowledge the limitations of the used methodology and the benefits of GRADE (although GRADE has its own limitations). The use of GRADE is under consideration for future ESHRE guidelines and updates of guidelines.

			quality does not tell us something about trial validity, the risk of bias, the confidence we may attribute to a particular study for telling us the true treatment effect. 3. To what extent do the SIGN levels of evidence capture quantity, quality, consistency, generalizability, directness of application? 4. What to do when quality of evidence differs across outcomes? SIGN provides no explicit direction whereas GRADE indicates using the lowest quality among crucial outcomes. 5. Strength of recommendations: with SIGN the grades of recommendation relates to the strength of the evidence on which the recommendation is based. GRADE= degree of confidence that desirable effects of adhering to the recommendation outweigh the undesirable effects. A higher quality of evidence does not necessarily lead to stronger recommendations. The determinants of the strength of recommendation are the balance between desirable and undesirable effects, quality of the evidence, values and preferences and costs and affordability. GRADE offers a basis for making methodological judgments between all these determinants. 5. In summary, compared to SIGN, GRADE: *acknowledges limitations of study design as dominating criterion for quality * explicit and transparently addresses quality issues SIGN has labelled important (quantity, consistency, directness, generalizability) * addresses overall quality when different across outcomes * clear separation quality from strength of recommendations * strength of recommendations simple, comprehensive * tied to action by clinicians, policy-makers	
Martyn Stafford-Bell	1	9, Rec 1.3	This is covered on Rec 1.4 and is not necessary	Thank you for your comment. We have combined all comments on recommendations 1.1, 1.2, 1.3 and 1.4 and changed the recommendations accordingly.
	1	9, Rec 1.4	Should we include irregular bleeding, bowel bleeding, dyschezia and haematuria?	Thank you for your comment. This fits the experience of the GDG, but is not mentioned in the referenced papers. We have added these symptoms to the GPP.
	2	12, Rec 2.2, 2.5	The side effects of gestrinone and danazol are such that, even with the advice in 2.3 and 2.6 it is hard to suggest these agents except in patients already established on these treatments, without side effects in whom other treatments have failed. This also applies wherever these agents are mentioned.	Thank you for your suggestion. We have considered eliminating danazol from the recommendations, but have decided to emphasize the side effects of progestagens, and specifically danazol.

	3	16, Rec 3.5	Should we comment here that clear evidence of benefit is lacking?	Thank you for your comment. The grade B of this recommendation reflects the strength of the supporting evidence.
	4	18" Rec 4.2, 4.3	We should advise that all reasonable efforts should be made to avoid multiple pregnancy and that this should be a short- term treatment before moving on to IVF, particularly in patients over the age of 35.	Thank you for your comment. We agree on these points but this guideline focussed on issues specifically on endometriosis. Issues on multiple pregnancy should be included in a guideline on IUI/ IVF.
Dr Arianna D'Angelo	Introduction	23 35 52	doctors typo mistake to improve diagnosis (GDG)	Thank you for your comment, we have adapted the guideline according to your suggestions.
	Recommendation	4.1;4.2;4.3 4.6 4.11	Replace Infertile with subfertile. IUI cannot be recommended if someone is infertile. Also specify that tubal patency must be demonstrated. I am not entirely sure that this is correct. In clinical practice the use of antibiotic MUST be compulsory as the consequences of an infection secondary to endometriosis can be extremely serious and life threatening. I would suggest to be more careful in the recommendation. The only paper to refer to is based on a low number of cases. Possible reduction of ovarian reserve	Thank you for your comment. We have applied the "International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART" According to this glossary infertility is defined as "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse." Hence, IUI can be recommended for infertile patients. We have mentioned in recommendation 4.4 that in case of comprised tubal function, ART should be used, instead of IUI. Regarding recommendation 4.6, we have addressed this below. Regarding the use of antibiotics, the evidence is weak, and hence we do not have a strong recommendation on this. Regarding recommendation 4.11, it was stated "the risk of reduced ovarian function".
	methodology	88	SIG Quality and Safety in ART	Thank you for your comment. We invited all members of the SIG endometriosis and endometrium and we invited the coordinators and deputies of the SIG endometriosis and SQUART, as mentioned in the text
	chapter 1	1.3f	What about the use of biomarker for monitoring the disease? is it useful?	Thank you for your comment. The GDG acknowledge that there may be indications that CA125 is useful in follow up of patients with endometriosis, but there is too little literature to support a recommendation.
	chapter 2	330	Are there any studies on morphin as pain relief? this is very often used in the UK	Thank you for your comment. There are no studies on morphine and endometriosis. Based on your comment, we have specified in the text for which compounds evidence was searched, but not found.
	chapter 2	412	typo mistake	Thank you for your comment, we have corrected this error in the guideline.

	chapter 4	54	Subfertile instead of infertile (see comment above)	See above
	chapter 4	4.6	see comments above. To rephrase or reconsider	See above
	chapter 4	4.11	I would mention the impact of surgery on the AMH Somigliana et al. Fertil Steril 2012 Dec; 98(6):1531-8	Thank you for your comment. The effect on ovarian reserve is mentioned, although the mentioned paper was not, as it was published after the inclusion deadline
Dr Gonzalez-Gomez	1	Page32,line 113	Could be consider level B??	Thank you for your comment. We have combined all comments on recommendations 1.1, 1.2, 1.3 and 1.4 and changed the recommendations accordingly.
	2	Page52,line 247	Depression as collateral effect, should be add?	Thank you for your comment. We have indicated that in deciding on medical treatment, side-effects should be considered. Detailed information on side-effects will be provided as additional information to the guideline
	4	Page85,line 87	If normal tubal permeability	Thank you for your comment. Tubal permeability is mentioned as a reason for moving to ART in the following recommendation:"The GDG recommends the use of assisted reproductive technologies for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed. (GPP)"
	4	Page87,line 159	Any observation about female age?	Thank you for your comment. We agree on these points but this guideline focussed on issues specifically on endometriosis. Issues on female age should be included in a guideline on IUI/ IVF.
	4	Page93,line 316	But improves pain	Thank you for your comment. We have added a sentence to refer to the section on pain.
Dr Robert Greb	1.1.	9, 5	1. "menstrual cycle dependent" instead of "cyclical" 2. specify "symptoms". Meant is mainly pain symptoms (in contrast to other menstrual cycle dependent symptoms such as PMS)? 3. Fatigue is too unspecific and evidence is poor, to associate fatigue with endometriosis. Other reasons for fatigue much more likely than endometriosis	Thank you for your suggestions. We feel "cyclical symptoms" is clear and contains all necessary information, and therefore we did not change it to "menstrual cycle dependent" or "pain symptoms". We have deleted fatigue from recommendation 1.2, as suggested.
	1.1.	9, 6	in infertile women endometriosis may be ALWAYS considered, not only in women with severe dysmenorrhoea. The difference to Box 1.4 is unclear in the condensed version. Meant is: severe dysmenorrhea is an ADDITIONAL risk factor to detect endometriosis in infertile women postcoital bleeding: other reasons much more likely than endometriosis: better delete	Thank you for your comment. We have combined all comments on recommendations 1.1, 1.2, 1.3 and 1.4 and changed the recommendations accordingly.
	1.2	9, 10	induration and / or nodules should not be restricted to uterosacral ligaments. Just delete "of the uterosacral ligaments" ?	Thank you for your comment. We incorporated your suggestion into the recommendation.
	1.3	10, 15	In clinical practise sometimes a negative laparoscopy is described when deeply infiltrating endometriosis outside the peritoneal cavity is overlooked, e.g. if preoperative clinical evaluation was not done properly.	Thank you for your comment. This is in agreement with recommendation 1.20. We have added this information to the considerations section
	1.3	10, 15	"(>3cm in diameter)" is arbitrary and an unnecessary restriction: delete	Thank you for your comment. We agree and have deleted "(>3cm

			in diameter)" in this recommendation.
1.3	10, 23	The evidence in assessing uterine endometriosis (adenomyosis) by MRI, which is associated with endometriosis is missing.	Thank you for your comment. We agree with your comment, but since adenomyosis was not in the scope of the guideline, it is not discussed.
1.3	11, 31/32	kidney sonography can be considered: Pelvic endometriosis and hydroureteronephrosis Luca Carmignani, M.D.,a Paolo Vercellini, M.D.,b Matteo Spinelli, M.D.,c Eleonora Fontana, M.D.,b Giada Frontino, M.D.,b and Luigi Fedele, M.D Fertility and Sterility Vol. 93, No. 6, April 2010	Thank you for your comment. We agree, but feel that the evidence is only based on case reports, and hence there is insufficient strong evidence to support a recommendation.
2.	12, 37	In general throughout guideline: "combined hormonal contraceptives" instead of "combined oral contraceptives" (since oral not the only route anymore)	Thank you for your suggestion. We have incorporated this suggestion in the guideline.
2	12, 37	nutritional therapy does not exist. Meant is probably a certain diet or change in nutrition, but no evidence (see chapter 2.6)	Thank you for your suggestion. We have deleted “nutritional therapy”.
2	12, 37	Many modes of administration exist for hormonal contraceptives (e.g. 21/7, 24/4, phases etc.): better: "should be taken cyclical or continuously"	Thank you for your suggestion. We have incorporated it in the guideline.
2.1	12, 39	"Medical therapies" include all kinds of medication. Here just hormonal therapies suppressing ovarian function are meant. Better "Hormonal therapies" or "Specific medical therapies" or "hormonal therapies affecting ovarian function and/or the endometrium" ? Analgesics is also medical therapy	Thank you for your comment. We changed “medical treatment” into “hormonal treatment”.
2.1	12, 40	see above	
2.1	12, 43	HORMONAL contraceptives	Thank you for your suggestion. We have incorporated your suggestion in the guideline.
2.1	12, 43	"low dose" is arbitrarily and unclear/unprecise: better "prescribing a combined hormonal contraceptive"	Thank you for your suggestion, we have changed the recommendation accordingly.
2.1	12, 46	Only one pilot study available comparing LNG-IUS vs. control. Grade of rec. A seems to me too strong	Thank you for your suggestion. We have checked this and agree that level A is to strong. Thus, the recommendation was downgraded to level B.
2.1	13, 51	oral not appropriate, see above	Thank you for your suggestion. We have incorporated your suggestion in the guideline.
2.3	14, 65	"(> 3cm)" really necessary?	Thank you for your comment. We have added information on the reasoning for the cut off and on the treatment of small endometrioma
2.4	14, 74 and 76	Medical therapy see above	Thank you for your suggestion. We have incorporated it by changing “medical treatment” to “hormonal treatment”
2.4	15, 79	The message is unclear. What is the consequence of distinguishing?	We have added a section describing the differences between short- and long-term postoperative hormonal treatment and the different outcomes associated with them.
2.5	15, 83	"including cystectomy for ovarian endometrioma" (Rec 2.30) redundant and unnecessary	Thank you for your comment, we have updated the recommendation
3.1	16, 92	Medical therapies, meant hormonal therapies? see above	Thank you for your suggestion. We have incorporated it by

				changing “medical treatment” to “hormonal treatment”
	4.3	19, 128	Surgery in women with severe endometriosis? Statement is missing. No evidence available?	Thank you for your comment. A recommendation on severe endometriosis is written in the section: “4.3c Surgery prior to treatment with assisted reproductive technologies in women with deep infiltrating endometriosis”
	5	20, 138-141	The chapter addresses only women with surgical menopause. There exist also women with a history of endometriosis and natural menopause. It should be clarified whether no evidence exists in those women or why the recommendations do not address those patients	Thank you for your comment. We had conducted a literature search on natural menopause, but as this did not result in any useful papers, we had not written any recommendations on this. Based on your comment, we have added a sentence on natural menopause to the considerations section.
	5	20, 141	It seems inappropriate to emphasize explicitly "tibolone" which is just one compound of numerous for HRT	Thank you for your comment. Tibolone is mentioned as stated in the included evidence.
	6	20, 148	The justification or purpose of Rec 6.2 is missing	Thank you for your comment. The general consensus from the guideline group was that clinicians have a duty of care to inform patients about an incidental finding of endometriosis.
Dr. P.G. Crosignani	2	48,100	The practical advantages associated only with OCP use are: I. contraceptive protection 2. long term safety (10-20 years) 3. control of menstrual cycle	Thank you for your comment. We have added this information to the considerations
	3	75,8	In the infertile couples where the female partner is affected by endometriosis. only in very few cases endometriosis is the cause of infertility since the presence of peritoneal or rectovaginal implants. do not reduce fecundability in the vast majority of women. In these couples the reduced fecundability it due to the same causes explaining infertility in the women without endometriosis and identical are the profertility strategies indicated for their treatment. The terms "endometriosis associated infertility" apparently indicates a certain and uniform role of endometriosis in causing infertility. therefore it seems a conceptual mistake. No doubt that severe endometriosis may often induce infertility but severe forms represent only a small proportion of the cases. References ESHRE Capri Workshop Group. Diagnosis and management of the infertile couple: missing information. Hum. Reprod. Update. 10:295-307. 2004. Vercellini P. Somigliana E. Viganà P. Abbiati A. Barbara G. Crosignani PG. Surgery for endometriosis-associated infertility: a pragmatic approach. Hum Reprod. 24(2). 254-269.2009. Vercellini P. CrosignaniPG. Somigliana E. Berlanda N. Barbara G. Fedele l. Medical treatment for rectovaginal endometriosis: what is the evidence? Hum Reprod. 24(10).	Thank you for your comment. Although we agree with your comment, we judged that “endometriosis associated infertility” is clear to the reader and clearly reflects the second major problem for women with endometriosis.

			2504-2514. 2009.	
Kate Young	Intro	15,20	This paragraph is the only mention of the psychosocial impact women face when diagnosed with endometriosis. There is a considerable amount of literature looking at the effect of endometriosis on various aspects of women's lives including their social and work lives; their relationships with significant others, friends and family; and their own emotional health. In failing to adequately detail such issues care providers are poorly equipped to assist women to cope with the documented impact that this enigmatic disease has on its sufferers.	Thank you for your comment. The GDG acknowledge that the psychosocial impact of endometriosis is important and that this topic is not addressed specifically in the guideline. The GDG will consider this topic for inclusion when the guideline will be updated and added a short sentence on it in the introduction.
	2.5	72,904	This recommendation fails to convey that a number of studies (beyond that of RCTs) have found women report significant benefits in adopting lifestyle changes (e.g., healthier diet, increased exercise and sleep) and undergoing alternative therapies on their ability to cope with the symptoms of endometriosis. Such language may discourage care providers from informing women about these options, thus preventing them from making an informed decision with regards to their use.	Thank you for your comment. In the considerations section, we acknowledge the limitations of the guideline development group in assessing and recommending these therapies.
	Appendix 4	109,26	This section fails to mention the significant gap in evidence for the psychosocial aspects of endometriosis, including how women experience the care they receive from health professionals, how they choose from a range of treatments options, and how the experience of endometriosis differs among minority groups (e.g., low socio-economic status, lesbian, and ethnic women).	Thank you for your comment. We have added your suggestion
Keiji Kuroda	Introduction	15, 23	⋯their docters experience⋯ → ⋯their doctors experience⋯	Thank you for your comment, we have corrected this error in the guideline.
	1.3	Page 37	I guess MR imaging is very useful to diagnose ovarian endometrioma and DIE (rectal endometriosis and cul de sac obliteration), but not peritoneal endometriosis. In particular, MRI jelly method is one of the good methods to diagnose DIE (Kikuchi et al 2009). Authors should add MRI for endometrioma and DIE in this chapter. Reference Togashi et al. Endometrial cysts: diagnosis with MR imaging. Radiology. 1991 Jul;180(1):73-8. Kikuchi et al. Diagnosis of complete cul-de-sac obliteration (CCDSO) by the MRI jelly method. J Magn Reson Imaging. 2009: 29(2):365-70.	Thank you for your comment. We have clarified that the indicated section deals on MRI for peritoneal endometriosis. MRI for assessing the extent of DIE is discussed in section 1.3g
	2.3 & 2.5	Page 60 line 508-509 & Page 69 line 818	Guideline said that clinicians should perform ovarian cystectomy for women with endometrioma of 3 cm or more though, in our data, the resection rate of normal ovarian tissue in ovarian cystectomy for small endometriomas was significant higher than large ones (Kuroda et al 2012). Should clinicians perform ovarian cystectomy for endometioma of 3 cm? And authors should add the information of the impact on ovarian reserve in ovarian cystectomy in Chapter 3.2 (Page 7779). Reference Kuroda M et al. Histological assessment of impact of ovarian endometrioma and	Thank you for your comment. We have added information on the reasoning for the cut off and on the treatment of small endometrioma. We have added information on the possible consequences of surgery on ovarian reserve to the section on surgery for infertility.

			laparoscopic cystectomy on ovarian reserve. J Obstet Gynaecol Res. 2012 Sep;38(9):1187-93	
Mukhri Hamdan	1.3	36, 351	It is a good practice to confirm the histology for every endometriosis seen during surgical procedure, even though visual evidence is sufficient. How about a superficial endometriosis? Any recommendation on where the histology to be obtained for superficial cases. Is cytology from aspirated chocolate material a considered diagnostic too (in aspirated cyst cases).	Thank you for your comment. Unfortunately, we did not find sufficient evidence to support recommendation on where the histology to be obtained for superficial cases. Cytology from aspirated chocolate material is not considered a diagnostic tool.
	3.2	77, 101	GDG has given an excellent and very clear evidence on cystectomy for more than 3cm cyst. Any recommendation on closing/stitching back the healthy ovarian tissue after cystectomy done. If we need to close/stitch what is the recommended suture material. What is the recommendation of diathermy usage in case of bleeding Any effect on ovarian reserve if we use suture material? Will it cause adhesion and if we leave it open. Any recommendation on multi-stage surgery. For example treatment of GnRH analogue following first surgery and a second look surgery for completion cystectomy afterwards.	Thank you for your comment. The GDG acknowledges the importance of these questions, but since there is no evidence on these topics, we decided not to elaborate on this.
	4.1b	86, Rec 4.16	Agree with the recommendation of cystectomy if >3cm endometrioma. If endometrioma less than 3cm found at starting of stimulation (newly found or recurrent), what is the recommendation, continue the stimulation, aspirate or cancel the stimulation and pretreament with GnRH analogue.	Thank you for your comment. However, the size of the endometrioma is not well established with regard to pregnancy outcomes.
	4.1b	86, 120	Review by Barnhart 2002 did not include patients who has surgically or medically treated and not clear on the inclusion criteria for the review. Laboratory technique probably have change now and provide better result for embryo obtained from endometriotic patient as more advance on culture technique	Thank you for your suggestion. In the paragraph below, we had already stated that this review is quite “old” and the techniques have improved, which is in agreement with your suggestion.
		18, Rec 4.1	How long should we allow expectant management before perform or advice for IUI. Or should the patient be offered soon after the diagnosis established.	Thank you for your comment. In the mentioned recommendation we advise to use IUI instead of expectant management, since this has a higher chance of pregnancy and live birth.
Hilary Critchley			Thank you very much for the opportunity to provide feedback on this draft. Please see below comments that I hope will be both constructive and helpful. It will be important to ensure consistency with the very recent WES consensus (about to be published in Human Reproduction).	Thank you for your comment.
		15, line 23	typo doctors	Thank you for your comment, we have corrected this error in the guideline.
		19 Summary	I think it important throughout the guideline to use the term heavy menstrual bleeding (HMB) as opposed to "menorrhagia". HMB is now the preferred term. There has been an international agreement to try and move away from confusing terms with different	Thank you for your comment, we have changed “menorrhagia” into “heavy menstrual bleeding” throughout the guideline.

		interpretations across the globe and these are, by example, particularly terms like “menorrhagia” and “dysfunctional uterine bleeding / DUB”(see Munro et al (2011) Int J Gynaecol Obstet 113:3-13). This is particularly important for correct classification and will impact on recruitment into multicentre clinical trials. Note the guideline in UK and New Zealand is about heavy menstrual bleeding (not menorrhagia) – see recommendation 1.4 (page 19).	
	10, rec 1.15	typo: suggest "around ground glass echogenicity".	Thank you for your comment. The paper referred to for this criteria mentioned “the optimal rule to detect endometriomas was 'an adnexal mass in a premenopausal patient with ground glass echogenicity of the cyst fluid, one to four locules and no papillations with detectable blood flow'.” Hence, we did not change the recommendation according to your suggestion.
	13, rec 2.11	Should there be a timeline for use of GnRH analogues?	Thank you for your suggestion. The GDG feels that “evidence is limited regarding dosage or duration of treatment“ and as such this was added to the recommendation on GnRH agonists.
	14, rec 2.22	Should the additional compound for adhesion prevention hyalobarrier be mentioned (see Cochrane review: Cochrane Database Syst Rev. 2006; (2):CD001298. Fluid and pharmacological agents for adhesion prevention after gynaecological surgery. Metwally M, Watson A, Lilford R, Vandekerckhove P. 7. Page 15, recommendation 2.25: Should there be inclusion of timeline, i.e. short term, and that this should have some definition for readers.	Thank you for your suggestion. From the evidence, including the mentioned review, we found that hyalobarrier was not tested specifically for endometriosis. Based on your suggestion, we have added timing (3-6 months) to the text
	Rec 2.28, line 3	typo space.	Thank you for your comment
	Rec 2.30	Should you put in brackets LNG-IUS after levonorgestrel releasing Intrauterine system.	Thank you for your suggestion. It was incorporated in the text.
	20, rec 5.1	Timeline here should be advised.	Age of natural menopause is clarified in the 3rd recommendation of this section.
	21, rec 8.3	Typo are (data are plural)	Thank you for your comment. Apparently, “data” can be used both as singular or plural noun. However, since we have used it as plural throughout the guideline, we have changed it in the recommendation.
	23, line 15	Replace questioning “with questions”.	Thank you for your suggestion. We have adapted this in the guideline.
	Page 25	Has Lone Hummelshoj been invited to comment?	yes
	31	Request replace “menorrhagia” with heavy menstrual bleeding (see earlier comment). Again replace with HMB, lines 69, 79 and line 103. 15. Page 43, lines 462-463: Revise sentence as double negative is confusing for reader. Clarify what is the message here.	Thank you for your comment, we have changed “menorrhagia” into “heavy menstrual bleeding” in the guideline. Thank you for your comment, we have corrected this error in the guideline.
	46, line 61	check use of term “anti- progestagens” for drug gestrinone is accurate. Please confirm gestrinone is in a class of drugs called “anti- progestagens”. This may confuse with	Thank you for your comment. In response to your comment, we have added information on the definition of anti-progestagens.

			agents/ligands that target the progesterone receptor, i.e. progesterone receptor modulators (PRMs).	
		47, line 76	"Anti-progestagens" – see earlier comment.	Thank you for your comment. In response to your comment, we have added information on the definition of anti-progestagens.
	2.1B		Progestogens and "anti-progestagens" again see earlier comment.	Thank you for your comment. In response to your comment, we have added information on the definition of anti-progestagens.
	2.1B	line 124	Typo: Progestagens	Thank you for your comment. We have corrected this error.
			Line 135: I think there is a need to define term and use of term "anti-progestagen" before discussing gestrinone – & confirm gastrinone is still available throughout Europe or where in Europe this is still commonly prescribed.	Thank you for your comment. In response to your comment, we have added information on the definition of anti-progestagens.
		105; lines 26-27	In the glossary may I suggest that you replace "menorrhagia" with "heavy menstrual bleeding" (HMB) and perhaps you can in the text indicate that this is now the preferred term for use rather than "menorrhagia".	Thank you for your comment, we have incorporated it.
		109, line 38	Suggest add "for diagnosis and disease monitoring"	Thank you for your comment. We have added your suggestion
Dr Philip Owen	General		Very thorough and impressive guideline	Thank you for your comment.
	2.1	p 46,47	Suggest inclusion of : Efficacy and tolerability of a contraceptive vaginal ring and transdermal patch in the treatment of endometriosis-associated pain. Reference: Vercellini P et al. Comparison of contraceptive ring and patch for the treatment of symptomatic endometriosis. Fertil Steril 2010 May;93 (7): 2150-2161	Thank you for your comment. The evidence in this section is based on the best available evidence, being the recent systematic review, which did not include the mentioned study. We have updated the information on the different methods for administration.
	4.1 a	84,85 Rec 4.1, 4.2	This is at odds with the NICE guidelines for NHS fertility treatment in UK, 2013 which states: Couples with unexplained infertility, women with mild endometriosis, or men who have 'mild male infertility', should normally attempt to conceive through regular vaginal intercourse for two years rather than receive intrauterine insemination. NICE says this is because new evidence shows that it is no better at achieving a live birth than people attempting to conceive through regular vaginal intercourse.	Thank you for your comment. Firstly, the recommendation states "may" and the evidence is of level C, so this is a weak recommendation, that is open for discussion with the patient. Secondly, the ESHRE and NICE recommendation are based on the same study showing a benefit of IUI in women with endometriosis. The difference in the recommendation can be explained by taken into account cost-effectiveness, which NICE has done. ESHRE does not take costs into account in developing recommendations, however, costs can be taken into account when "translating" the guideline to a national level.
	1.9	1.11	Some uncertainty is being created here. A positive (visual) laparoscopy may be a false positive, this is understood. So, a biopsy is recommended (not a routinely performed procedure by generalist gynaecologists who inevitably perform most laparoscopies). If the biopsy is positive then a diagnosis is made but negative histology 'does not exclude the diagnosis'. So, positive laparoscopy with negative histology result is what diagnosis please? If one is left none the wiser than one must question the value of a biopsy.	Thank you for your comment. We have added additional information on explanations for a false negative histology in the considerations section. Histology is recommended to confirm a positive laparoscopy and ascertain the diagnosis. The value of a negative histology is limited.

	2.2	2.5	Presume Danazol and Gestrinone still widely available?	Thank you for your comment. We have contacted the manufacturer and they have confirmed that danazol is still available in some countries for treatment of endometriosis (France, Greece, Netherlands, Spain, Switzerland and UK). The same accounts for gestrinone.
	2.9	2.10	If add-back HRT prevents bone loss then why is it necessary to approach analogue therapy with add-back with caution in adolescent/young women?	Thank you for your comment. The additional GPP was written to stress the possible complications in young women.
	2.18	2.18	Suggest 'should', not 'can' since it is a grade B recommendation.	Thank you for your comment. However, according to the phrasing applied, level B recommendations should be phrased using “can” rather than “should”
	2.19	2.19	Suggest 'should' not 'can'.	Thank you for your comment. As the evidence supporting this recommendation is level B, “can” is appropriate.
	2.25,2.26	2.25,2.26	Post surgical adjunctive treatment is not recommended so why is it necessary to differentiate between two treatment timings/definitions in 2.26?	We have added a section describing the differences between short- and long-term postoperative hormonal treatment and the different outcomes associated with them.
M.A. Spath	summary of recommendations	9-21	Rather extensive summary, though well legible and applicable thanks to the headings and subdivisions. Therefore very well applicable for clinical practice for general Gynaecologists and residents.	Thank you for your comment.
		29-102	Thorough explanation for each of the recommendations; designating debates and considerations. References easy to consult.	Thank you for your comment.
Mr. Luca Fusi	summary of recommendations	9, rec.1..2	'..fatigue..' This is such an aspecific symptom that should be not included ,as there is no further mention of it in the full guidelines and no reference to it.	Thank you for your comment. We changed “fatigue” into “fatigue in the presence of any of the previous”.
	summary of recommendations	10, rec 1.15 11, line 31	.'.and one to four compartments'. The meaning of this statement is not clear. Perhaps one should add modalities for investigating ureteral / bladder endometriotic involvement such as CT, urogram, cystoscopy etc..	Thank you for your comment. To reduce the confusion, we changed “Criteria” to “ultrasound characteristics”. Investigation of ureteral / bladder endometriotic involvement is discussed in section 1.3g
	summary of recommendations	12,line 37, rec.2.1	..and nutritional therapy..' this should be omitted as it is in contrast with recommendation 2.31 where it says ' it does not recommend the use of nutritional treatment.';.and also is in contradiction with what is written in chapter 3, line 223 : ' we found no evidence of beneficial effect of different types of nutrition''.	Thank you for your suggestion. We have deleted “nutritional therapy”.
	summary of recommendations	14,line 16, rec. 2.17	There is no mention about what to do in the presence of symptomatic endometrioma measuring < 3 cm. .	Thank you for your comment. We have added information on the reasoning for the cut off and on the treatment of small endometrioma
	Chapter 1 1.3f	41, line 413	..diagnosis of endometriosis grade 1-IV is limited, whereas its performance in the diagnosis of endometriosis grade III to IV is better..' perhaps it should read grade I- II is limited ?	Thank you for your comment. This was checked and as it is written exactly matches the referred paper.
	Chapter 1	43, line 452	There is no mention of the possibility of ureteric / bladder endoemtriotic involvement.	Thank you for your suggestion. We have incorporated your

	1.3i		This perhaps should be included with relevant mode of investigation, such as CT urogram, cystoscopy, etc.	suggestion in the text of the guideline.
	Chapter 1 1.3i	43, line 462	'…there was no histology was not available in all cases..' I suggest to rephrase it as it is incorrect.	Thank you for your comment. This was corrected in the guideline.
	Chapter 2, 2.1d	53, line 309	.. due to the severe side effects (vaginal dryness, hot flushes, diminished bone mineral density..'. This statement should perhaps be qualified by the word ' when used alone' as your recommendation 2.11 on page 54 states that they are to be used in combination with oral contraceptive pill, which presumably reduces the incidence of these side effects,	Thank you for your comment. Although the side-effects are due to the aromatase inhibitors, the included papers describe side-effects in women using aromatase inhibitors in combination with progestagens, hence, we did not add "when used alone" to the considerations.
	Chapter 2, 2.3d	59, line 502	There is no mention about the recommended management of endometrioma <3cm in size. perhaps something should be included in the recommendation number 2.17.	Thank you for your comment. We have added information on the reasoning for the cut off and on the treatment of small endometrioma
	Chapter 2, 2.3	67, line 750, rec. 2.26	'..clearly distinguish between short term (<6 month) adjunctive hormonal treatment after surgery as opposed to longer term (>12 -24 months) hormonal treatment aimed at secondary prevention.' This appears somewhat at variance with the evidence presented between line 753 and 734 which does not suggest any demonstrable benefit up to 2 years after surgery.	Thank you for your comment. The GPP to differentiate between short and long term is also valid for studies that are currently performed. The GDG acknowledges the limited evidence on any form of prevention and the unclear differentiation and hopes that the mentioned GPP would clarify the use of postoperative medical treatment for either short or long term in the future.
	Chapter 3, 4.3b	91, line 288.	'In women with endometriomas, clinicians should not perform cystectomy… 'This is a rather prescriptive statement which may need rephrasing. It is highly unlikely that a patient has only endometriomas without evidence of other foci of disease, such as peritoneal disease. As you have indicated that treatment of this type of endometriosis is likely to improve outcome, one would normally also treat the endometriomas at the same time. The statement is also at variance with the systematic review described in line 275 - 277 which states that excision of endometriomas is more favourable with regard to pregnancy. It also contradicts the subsequent statement number 4.10, page 92, which states that '.. recommends clinicians consider cystectomy prior to treatment with assisted technologies, to improve access etc, although it does not seem to improve pregnancy rates.	Thank you for your comment. We acknowledge the coincidence of peritoneal and ovarian endometriosis, but for reasons of clarity they have been discussed separately. Moreover, the evidence on ovarian endometrioma, which is the basis of this recommendation, focuses on surgical treatment of endometrioma specifically, (cystectomy). The review mentioned states that cystectomy is better than drainage, but not that surgery has to be performed. It does not contradict. The GDG group states that surgery can/should be performed for other reasons, but there is no evidence that performing surgery solely to improve the outcomes of ART is beneficial.
	Chapter 6	97, line 13	''Surgical excision / ablation and its inherent risks, of damage to bowel, bladder and blood vessels…' perhaps a mention should be made to ureteric damage as well, both with excision and ablation.'	Thank you for your comment. We have added damage to the ureter.
Dr. Thomas Faustmann	1.1	32, Lines 109-111	Page 32 Conclusions line 109-111: Suggest to expand this statement and emphasize the value and benefit of an early diagnosis AND treatment to prevent symptoms, retard disease progression, decrease the adverse long-term effects of the disease, and improve the quality of life of women. This should be sufficiently addressed in this guideline, as discussed in several publications: Examples: "Early diagnosis and suspicion of	Thank you for your suggestion. The GDG agrees with your statement, but feels that the progression of endometriosis and the natural course of disease is not well studied and has only be described in expert opinions. Therefore, we have decided not to recommend this.

		endometriosis is the key in preventing symptoms" (Ref: Luciano, D.E. and A.A. Luciano, Management of endometriosis-related pain: an update. Womens Health (Lond Engl), 2011. 7(5): p. 585-90.) ; "diagnosis of endometriosis should be confirmed as early as possible in young women with severe dysmenorrhoea to prevent the progression to severe forms of the disease and a subsequent impact on fertility" (Ref: Streuli, I., et al., An update on the pharmacological management of endometriosis. Expert Opin Pharmacother, 2013.) ; "Endometriosis should be considered early in the differential diagnosis of pelvic pain in young women to help avoid the reported delay, often from 7 to 12 years, from onset of symptoms to definitive diagnosis (Ref: Leyland, N., et al., Endometriosis: diagnosis and management. J Obstet Gynaecol Can, 2010. 32(7 Suppl 2): p. S1-32.)	
1.3a	36, Chapter about "laparoscopy in the diagnosis of endometriosis"	"laparoscopy in the diagnosis of endometriosis": Suggest to include a separate statement in this chapter which appreciates the value of a clinical diagnosis which may be sufficient to initiate treatment, as discussed by Vercellini et al: "The common belief that a preliminary laparoscopy must always be performed in order to definitely diagnose the disease should be challenged, as the nonsurgical diagnosis of endometriosis has been demonstrated to be highly reliable" (Vercellini P, et al. Endometriosis: current and future medical therapies. Best Pract Res Clin Obstet Gynaecol 2008;22(2):275–306.)	Thank you for your comment. We have added a sentence and referral to the section of empirical treatment in the section on medical technologies in the diagnosis of endometriosis.
2.1	47, Rec 2.2/2.3 & 2.1a	Danazol and Gestrinone are mentioned and recommended in several parts of this guideline in a not consistent way. In addition the recently published WES consensus statement limits their recommendation for Danazol and gestrinone due to their well known adverse effects. (Johnson N, et al Consensus on current management of endometriosis. Hum. Reprod. (2013) doi: 10.1093/humrep/det050 First published online: March 25, 2013) There is a varying level of evidence in endometriosis for the hormonal options recommended in box 2.2, and as mentioned in chapter 2.1a on page 47 especially COCs have insufficient RCT evidence in Endometriosis (1 study met inclusion criteria in last Cochrane Review). The different degree of clinical evidence for the efficacy in endometriosis of these options should be pointed out in box 2.3 as well.	We have modified the evidence level to A- B, and mentioned the evidence level specifically for all compounds. We added "efficacy" to recommendation 2.3, in response to your comment on the differences in efficacy among the different compounds.
2.1	47, 2.1a and rec 2.4	The benefits of COCs for reducing dysmenorrhea are well described and recognized. But several publications suggest that not all types of pain respond equally to COC use with inconclusive evidence for reductions in dyspareunia and chronic pelvic pain. Examples: (Ref: Seracchioli, R., et al., Post-operative use of oral contraceptive pills for prevention of anatomical relapse or symptom-recurrence after conservative surgery for endometriosis. Hum Reprod, 2009. 24(11): p. 2729-35. ; Vercellini, P., et al., A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril, 1993. 60(1): p. 75-9. ; Zupi, E., et al., Add-back therapy in the treatment of endometriosis-associated pain. Fertil Steril, 2004. 82(5): p. 1303-8. ; Chapron et al discussed that a history of COC use for primary	Thank you for your comment. The evidence in this section is based on the best available evidence, being the recent systematic review. We have taken your comments into account and hope we have included them appropriately.

		dysmenorrhea has been associated with an increased risk of diagnosis of endometriosis (especially deep infiltrating endometriosis) later in life (Ref: Chapron, C., et al., Oral contraceptives and endometriosis: the past use of oral contraceptives for treating severe primary dysmenorrhea is associated with endometriosis, especially deep infiltrating endometriosis. Hum Reprod, 2011. 26(8): p. 2028-35). General remark: When talking about the use of COCs in endometriosis, and knowing it is an estrogen-dependent disease with one of the main principles of hormonal treatments to lower estrogen levels and counteract their stimulating effects on the disease, the ongoing controversial discussion in the medical community about the question whether the inclusion of estrogen in a medication to treat endometriosis may mask the progression of or even result in stimulation of the disease, should at least be captured as one discussion point in this guideline Discussed in: Kappou, D., M. Matalliotakis, and I. Matalliotakis, Medical treatments for endometriosis. Minerva Ginecol, 2010. 62(5): p. 415-32., Crosignani, P., et al., Advances in the management of endometriosis: an update for clinicians. Hum Reprod Update, 2006. 12(2): p. 179-89. Vercellini, P., et al., Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis. Hum Reprod Update, 2011. 17(2): p. 159-70	
2.1	48, 2.1b line 131	The classification of Gestrinone as a anti-progestin has to be challenged; it is a synthetic steroid which binds to androgen receptor, progesterone receptor and estrogen receptor. Furthermore it should be acknowledged that Gestrinone should no longer be used owing to the high-treatment burden of androgenic side effects (Selak V, Farquhar C, Prentice A, Singla A. Danazol for pelvic pain associated with endometriosis. Cochrane Database Syst Rev 2007; 4:CD000068)	Thank you for your comment. In response to your comment, we have added information on the definition of anti-progestagens.
2.1	50, 2.1 rec 2.5 & 2.6	Box 2.5. Danazol (being a synthetic androgen) and Gestrinone are not part of the progestagen class. It seems to be as mistake to mention Danazol here at all, as in lines 173-175 the use was NOT recommended. In box 2.6 clinicians should also take into consideration the different number and level of RCT evidence for progestins when prescribing progestins in endometriosis. The recommendation of gestrinone should also be challenged (also see above) due to their side-effect profile and with available alternatives with better tolerability.	Thank you for your comment. Danazol has several biological effects, including direct binding to progesterone receptors. Progestogens are defined as compounds that interact with progesterone receptors, hence, it is not incorrect to mention danazol in the section on progestogens/progestins. The information on the different progestins is summarized in a systematic review, equalising the differences in evidence level among the different substances. Regarding gestrinone, we have mentioned that clinicians should take side-effects into account.
2.1	Page 48 chapter 2.1b "progestag ens"	Suggest to add a paragraph into the chapter 2.1.b specifically addressing the RCT evidence for those progestagens with an indication and proven effect in Endometriosis (in line with recommendation of WES consensus: Progestins with a proven effect in RCTs and with a specific indication for the treatment of endometriosis such as medroxyprogesterone acetate (Schlaff et al., 2006; Crosignani et al., 2006),	Thank you for your comment. We have taken your comment into consideration, and decided to keep LNG-IUS in a separate recommendation as it is based on different publications.

	& page 50, rec 2.7	norethisterone (Vercellini et al., 2011; Brown et al., 2012), and dienogest (Cosson et al., 2002; Momoeda et al., 2009; Köhler et al., 2010; Harada et al., 2009; Strowitzki et al., 2010a; Strowitzki et al., 2010b; Petraglia et al., 2012; Strowitzki et al., 2012) can be considered as first-line treatments taking into consideration their different side effect profiles. Suggest to delete this dedicated box as LNG IUS could be included in box 2.5 with mentioning of intrauterine administration	
2.3	67, Rec 2.25	This may cause some confusion as medical therapy may not improve the outcome of surgery but is an important adjunct to surgery to prolong the symptom free interval and prevent recurrence of symptoms.	Thank you for your suggestion. We have added this sentence to the text.
2.3	67, Rec 2.26	it is unclear to me what the message of this box is, as it is partially in contradiction to Rec 2.25	Thank you for your suggestion. We have considered it in rewriting/reorganising the sections on pre- and postoperative medical treatment and secondary prevention.
2.4	69, Rec 2.27	Suggest to change wording in the box to give credit to the role of medical therapy post-surgery. Suggested wording"…GDG states that hormonal therapy is effective for prevention of recurrence of disease and painful symptoms in women surgically treated… (discussed in: Falcone, T. and D.ILebovic, Clinical management of endometriosis. Obstet Gynecol, 2011. 118(3): p. 691-705. , Vercellini, P., et al. Surgical versus medical treatment for endometriosis associated severe deep dyspareunia: I. Effect on pain during intercourse and patient satisfaction. Hum Reprod, 2012.	Thank you for your comment. The GDG believes that the proposal is to general. The recommendation we have written is in agreement with the specific data available.
2.4	69, lines 808-812 & Rec 2.30	There is also evidence that Dienogest is effective for consolidation therapy after surgery for the treatment of endometriosis (including reduction of dyspareunia) (Ref: Cosson, M., et al., Dienogest is as effective as triptorelin in the treatment of endometriosis after laparoscopic surgery: results of a prospective, multicenter, randomized study. Fertil Steril, 2002. 77(4): p. 684-92.)	Thank you for your comment. We have investigated it.
2.1B	48, 110	In this chapter about the evidence for progestagens, the available references for Dienogest supporting its efficacy and safety profile as a (long-term) medical treatment option in Endometriosis are missing and should be recognized: Dienogest 2mg was shown to be significantly superior to placebo and when treatment was extended for another 12 months, dienogest showed continued improvements in pain reduction over the long-term. In support of this study from the development programme of Dienogest in Europe, 2 studies (conducted in Japan) demonstrated the efficacy of dienogest in a long-term setting (12 months). Several studies demonstrated equal efficacy of dienogest vs. different GnRH agonists in pain reduction, with clinically relevant advantages over GnRH in the safety and tolerability profile. Supporting references: Petraglia, F., et al., Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment. Arch Gynecol Obstet, 2012. 285(1): p. 167-73. Strowitzki, T., et al., Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet Gynecol	We thank you for your suggestions. Dienogest was mentioned and supported by the guideline. The Cochrane review, which summarises the highest level of evidence, did show that, amongst other drugs, Dienogest is effective in treating endometriosis pain. This, is reflected in the guideline.

		Reprod Biol, 2010a. 151(2): p. 193-8. Strowitzki, T., et al., Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-week, randomized, multicentre, open-label trial. Hum Reprod, 2010b. 25(3): p. 633-41. Strowitzki, T., et al., Detailed analysis of a randomized, multicenter, comparative trial of dienogest versus leuprolide acetate in endometriosis. Int J Gynaecol Obstet, 2012. 117(3): p. 228-33. Harada, T., et al., Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis--a randomized, double-blind, multicenter, controlled trial. Fertil Steril, 2009. 91(3): p. 675-81. Cosson, M., et al., Dienogest is as effective as triptorelin in the treatment of endometriosis after laparoscopic surgery: results of a prospective, multicenter, randomized study. Fertil Steril, 2002. 77(4): p. 684-92. Momoeda, M., et al., Long-term use of dienogest for the treatment of endometriosis. J Obstet Gynaecol Res, 2009.35(6): p. 1069-76. Kitawaki, J., et al., Maintenance therapy with dienogest following gonadotropin-releasing hormone agonist treatment for endometriosis-associated pelvic pain. Eur J Obstet Gynecol Reprod Biol, 2011. Also, the aspect of dose finding in endometriosis is an important additional relevant information and gives reassurance to the clinician when making treatment choices. Dienogest is so far the only oral progestagen for which the optimal dose for endometriosis treatment has been established in a dose finding trial. (Ref: Kohler, G., et al., A dose-ranging study to determine the efficacy and safety of 1, 2, and 4mg of dienogest daily for endometriosis. Int J Gynaecol Obstet, 2010. 108(1): p. 21-5.)	
Dr. P.G.A. Hompes and dr. Velja Mijatovic	Rec: 1.11	We do not feel comfortable with the revised recommendation regarding the need of adding histology to a positive laparoscopy for endometriosis. The recommendation in the 2005 guideline is in our opinion more accurate and practical stating that if peritoneal disease alone is present. the need for histology is controversial Therefore. in these cases visual inspection should be usually adequate. We agree that histology should be obtained in ovarian endometriosis and deep infiltrating disease in order to exclude rare instances of malignancy.	Thank you for your comment. As this has been discussed extensively within the GDG, we have decided not to modify the recommendation.
	Rec: 1.13	We agree with this recommendation and acknowledge that this diagnostic modality is highly operator dependent. As the expertise for performing such sonographic investigations is largely missing in most hospitals, a recommendation should be made to perform a MRI scan. A MRI scan has the advantage. over other methods of investigation, of making a survey of the anterior and posterior compartments of the pelvis at one time, including the retroperitoneal space. Therefore. it may diagnose rectal endometriosis but also endometriosis infiltrating the bladder, ureter as well as sigmoid with an high accuracy.	Thank you for your comment. Your comment on the operator dependency of ultrasound, and the usefulness of MRI to establish the extent of DIE are discussed in the guideline.

		Rec 1.19	To our opinion this issue should be changed. As diagnosis, take laparoscopy, in the fertility work-up is postponed more and more, the routine use of CA125 measurements in patients with infertility might be justified, since it can identify a subgroup of patients who are more likely to benefit from early laparoscopy (Mol et al. 1998)	Thank you for your suggestion. We have mentioned this, as the conclusion of Mol and co-workers in the "clinical evidence on CA-125". However, the potential of CA-125 in this field is not established and hence we feel it should not be the basis of a recommendation for clinical practice
		Rec 1.2	Clinical examination in the diagnosis of endometriosis. To our opinion the following sentence should be added: "Clinicians may consider the diagnosis endometriosis when nodules are seen in the fornix posterior during clinical examination"	Thank you for your comment. We incorporated your suggestion into the recommendation.
		Rec 2.1	It is unclear whether OCp should be taken conventionally, continuously or in a tricycle regimen. This is a GPP formulation. In our opinion, because it is a GPP formulation, it should be changed in: "Treatment with OCP should be advised in a continuous way instead or conventionally or in a tricycle regimen."	Thank you for your comment. The GDG believes that there is insufficient evidence to advise one regimen over another, as is stated in the recommendation. Hence, we have not updated the recommendation to your suggestion.
		Rec 2.5	As a guideline for the endometriosis in the year 2013, and considering side effects and better alternatives for danazol, this medication should be left out, and cypoterone acetate is on discussion	Thank you for your comment. We have considered eliminating danazol from the recommendations, but as danazol is still available for treatment of endometriosis in France, Greece, Netherlands, Spain, Switzerland and UK, we have not deleted it from the guideline but we have added a specific remark on the androgenic side effects associated with its use.
		Rec 2.9	Why is hormonal add-back therapy recommended explicitly at the start of GnRH agonist therapy?	Thank you for your question. As add-back therapy was shown to reduce bone loss without effecting efficacy of GnRHa treatment, the GDG felt there is no harm, with substantial benefit of starting with add-back therapy. Hence the recommendation.
		Rec 3.3	This recommendation is just the other way round. In our opinion it should be: "As laser vaporisation is associated with higher cumulative spontaneous pregnancy rates, clinicians should prefer laser treatment instead of monopolar electrocoagulation".	Thank you for your suggestion. We have adapted the recommendation based on your suggestion to reduce confusion.
The endopart study	Throughout guidance		The guidance appears to lack reference to patients' partners, and how healthcare might be more inclusive of partners and of the couple unit. All chronic illnesses are likely to affect patients' partners to some extent. However, given the absence of an obvious cause or cure, the likelihood of chronic, recurring symptoms, and the potential impact on both sex and fertility, the effect on partners and on the couple unit are especially pronounced. Evidence from the Endopart study(www.endopart.co.uk, publications forthcoming) suggest that endometriosis can have a significant impact not only on women but on their partners, and can cause significant distress and strain for the couple unit. Therefore, we recommend that the guidance takes a more couple-focused approach throughout, and advises healthcare practitioners to: recognise the potential impact of endometriosis on not only female patients, but on those around them especially partners; recognise the support partners may provide to patients; recognise the insight partners might be able to provide into patients' experiences of	Thank you for your suggestion.

		endometriosis (e.g. regarding symptoms, treatment efficacy, treatment side-effects, etc.); and therefore be more inclusive of partners.	
1	29-44	The Endopart study suggests that patients receive insufficient information at the point of diagnosis and as such we recommend that healthcare practitioners signpost ALL patients towards the national charity Endometriosis UK	Thank you for your suggestion. We will produce a patient version of the guideline and notify clinicians on the existence of this. The patient version should contain all necessary information to signpost patients to the national patient organisation.
2	45-73	The Endopart study suggests that patients require more and better realistic information about various aspects of treatment, including detail on procedures, and on the potential effectiveness and side effects of both medical and surgical treatment. In particular, the Endopart study suggests that patients and their partners require honest and realistic information about the likely efficacy and side effects of hysterectomy, to avoid assumptions that this will alleviate all symptoms permanently; and about the recovery process and period following all forms of surgery, to enable better understanding of and planning for the impact this may have on everyday life. Information must be informed by a multidisciplinary perspective. We propose that the guidance could make reference to these suggestions.	Thank you for your comment. We will take your comment into consideration in writing a patient version of this guideline.
3	75-82	The Endopart study suggests that women and their partners may experience considerable uncertainty and anxiety regarding the potential impact of endometriosis on fertility, and that decision making regarding planning for and having children can be significantly affected, whether or not women have been diagnosed as infertile and/or are seeking infertility treatment. Information provided by healthcare practitioners can have a significant impact on concerns ad on decision making. Therefore, healthcare practitioners need to recognise the uncertainty and anxiety that may be experienced by patients and their partners, and provide patients and partners with information and advice that is based on their specific staging and circumstances, as opposed to general or speculative information.	Thank you for your comment. The issue of the psychosocial impact of fertility treatment on couples attending a fertility clinic are discussed in detail in an ESHRE guideline in development. Although not specific for women with endometriosis, the concerns and issues of these women/couples are comparable to other couples starting fertility treatment. One of the points discussed in this guideline is the provision of detailed and specific medical information on the treatment.
Throughout guidance		Considerable guidance is offered relating to endometriosis-associated pain and endometriosis-associated infertility. However, other symptoms, such as fatigue, heavy menstrual bleeding and bowel and bladder irregularities appear to be neglected. The Endopart study and other research (e.g. Jones et al., 2004; Gao et al., 2006) suggests that these symptoms can have a significant impact on quality of life, and as such we propose they are considered more fully within this guideline.	Thank you for your comment. We focused on pain, but we included quality of life, although not many studies were retrieved that report on quality of life. A specific analysis on other symptoms will be explored for the update of the guideline.
Throughout guidance		Linked to the above point, the Endopart study suggests that a number of factors, not only dyspareunia, impact on sex and intimacy for couples, but that couples may not raise such impacts in clinical encounters? We recommend that the guideline advises healthcare practitioners to initiate discussions about the impact of endometriosis on sex, being mindful that these factors other than dyspareunia may have an impact, and to facilitate access to specialist support where necessary (e.g. psycho-sexual or relationship counselling)	Thank you for your comment. We have discussed this issue among the GDG and although they felt a GPP on sexual function would be relevant, it was decided not to incorporate it, as it was not based on a key question, and no literature search was conducted. The issue will be re-investigated in the next version of the guideline.

	App 4	109	The guideline could make reference to recommendations relating to the use of patient-centred interventions. We understand this absence reflects the lack of published reviews of such interventions. However, the guideline also draws attention to the considerable impact of endometriosis on quality of life (e.g. page 5), and the Endopart study and other research suggests that patients report variable, and often negative, experiences with healthcare professionals (e.g. Jones et al., 2004) and limited effectiveness of treatment (e.g. Denny, 2004:; Jones et al., 2004; Denny, 2009). Therefore, we suggest that the research recommendations should highlight the need for the development and testing of patient-centred self-management interventions, with a psychosocial element and a multidisciplinary approach, to enable women with endometriosis to more effectively manage the condition and the impact it has upon their daily lives.	Thank you for your comment. We have added your suggestion
	App 4	109	Furthermore, the guidance lacks recommendations relating to the use of couple-centred interventions throughout. As stated above, evidence from the Endopart study shows that endometriosis can have a significant impact not only on women but on their partners, and can cause significant distress and strain for the couple-unit. Therefore we suggest that the research recommendations should also highlight the need for the development and testing of couple-centred interventions, with a psychosocial element and a multidisciplinary approach.	Thank you for your comment. We have added your suggestion
Ioannis E. Messinis	1	9, rec 1.6	This is true only for women with suspected endometriosis because of the presence of other findings (previous laparoscopy, ovarian endometriomata e.t.c.), otherwise deposits of (ovarian) cancer should be excluded.	Thank you for your comment. A GPP on the exclusion of malignancy is mentioned in the section of laparoscopy.
	1	10, rec 1.17	The cost of MRI is high. This should be emphasized.	Thank you for your suggestion. In the considerations section we have already mentioned that “MRI is not a cost-effective diagnostic tool”.
	1	11, rec 1.19	The statement no to use “CA125” is very strong. It should be written that in CA125 may be helpful to differentiate from ovarian cancer if it is very high (not decreasing). In my view, the use of CA125 should be at doctor’s decision depending also on other findings.	Thank you for your suggestion. We added a sentence in the considerations section that there could be a role for CA-125 in differentiating endometriosis from other ovarian abnormalities and/or disease staging.
	1	11, Rec 1.20	Rectosigmoid endoscopy may be needed	Thank you for your comment. We have decided not to incorporate it.
		60, rec 2.18	Endometrioma >3cm, but on page 69, rec 2.28, size is ≥ 3cm for pain relief	Thank you for your comment. To be consistent, we have adapted it everywhere to ≥3cm.
		70, rec 2.30	Is this for all ages? Also for nulliparous women?	Thank you for your comment. The GDG decided not to specify age in this recommendation, since the available evidence does not allow distinction according to age or parity.
		91, rec 4.9	What should be the size of an endometrioma that needs to be removed before ART in order to improve pregnancy rates? Some studies consider a size of \ 4 cm.	Thank you for your comment. We have stated previously, that endometrioma >3 cm could be removed for reasons of pain, based

				on the review of Hart et al., 2008. In this section we have added a sentence to refer to the section on pain.
dr. S.M.Mourad		Rec 5.3	suggest maximum age instead of mentioning ' age of natural menopause' , e.g. 48-52year conform the WHI studies and 'window of opportunities' theory of beneficial estrogen supplementation	Thank you for your comment. We have decided not to add this, as age of natural menopause differs among populations.
		Rec 4.5	I suggest some mentioning/ comment on poorer embryo quality which seems to be found in endometriosis rather than non-endometriosis ART patients	Thank you for your comment, as there is, to our knowledge, no systematically assessed evidence on this topic, we have not incorporated it.
	In general		although a patient version of the guideline is described to be planned, maybe the recommendations list should comprise an overview of recommendations on patient information	Thank you for your comment. We will, as mentioned make a patient version of the guideline which will include all relevant background information and frequently asked questions by women with endometriosis. We will inform guideline users on the existence of this patient version and hope they will refer to it. We will not elaborate on information that should be provided by doctors to their patients.
	App 4	P 109	suggestion of further research could be focused upon ' implementation of awareness and earlier diagnosis of disease' , i.e. efforts to raise awareness amongst primary care specialists, gastro-enterologists or internal medicine specialists	Thank you for your comment. We have added your suggestion
		page 401	routine ca-125 is recommend against, how about the role of ca125 in discerning endometriosis from e.g. other ovarian abnormalities as dermoid cysts?	Thank you for your suggestion. We have not included studies assessing the use of CA125 for diagnosis of dermoid cysts, as this was outside the scope of the guideline. Hence, we will not add any statements to the guideline, but we included a sentence on potential roles for CA125 outside of the diagnosis of endometriosis
	chapter 5	P 46	I miss a recommendation on the specific items for counselling the patient on the need en (dis-) advantages of using HRT (like vasomotor signs, cardiovascular disease, bone mineral loss and assessment, possible neurocognitive impairment, sexual dysfunction)	Thank you for your comment. We will take this comment into consideration for the update of the guideline.
	Rec 1.6	P 34, l 201	no mentioning of assessment of the rectovaginal septum to diagnose deep infiltrating endometriosis?	Thank you for your suggestion. We incorporated your suggestion into the recommendation.
	Rec 3.6		should here be added :should not be described "to improve spontaneous pregnancy rates. " because suitable evidence is lacking	Thank you for your comment. We have added "to improve spontaneous pregnancy rates" to the recommendation
Samuel Santos Ribeiro	Introduction	5, 5-7	I feel that the phrase "Women with endometriosis can experience painful symptoms and/or infertility, while some women have no symptoms at all" can be confusing; I would rather suggest "While some women with endometriosis can experience painful symptoms and/or infertility, others have no symptoms at all"	Thank you for your suggestion. We have incorporated your suggestion in the guideline.
	Summary	10, Rec 1.12	From a non-specialist in endometriosis' perspective, I was unable to understand why the decided cut-off was of >3 cm and not any other. Could a single sentence and reference of the rationale behind this decision be added to the chapter from where this recommendation originated from?	Thank you for your suggestion. We have removed the cut-off from the mentioned recommendation, as it is not relevant at this point..
	Summary	12-13, Rec	Chapter 2 is flawless in its explanation and extremely clear! Nonetheless, after reading	Thank you for your comments.

		2.2-2.12	the recommendations that derive from it, I didn't find it to be as clear. First of all, I believe rec 2.3 applies to both subsection 2.1 and 2.2, and not only to subsection 2.1. So, I would suggest that it comes just before subsection 2.1. Furthermore, I believe the subsection's title should have the word "hormonal" instead of "medical", since analgesics are also medical treatments and have their own sub-section. Finally, I feel that the GDG's concern on the use of danazol is strongly expressed in page 49 and then left out in these recommendations. Reading recommendation 2.5 (from a non-specialist's point of view) I wrongfully understood that the GDG considered all hormonal treatments to be equally valid options, without the strong concerns on danazol stated in page 49.	Recommendation 2.1 is mentioned in the beginning of the chapter. We changed "medical treatment" into "hormonal treatment" and emphasized the androgenic side effects of danazol in the recommendations.
	Summary	15, rec. 2.26	The explanation of this recommendation is clear in the chapter from where it originates from. Nonetheless, I feel that the recommendation is a bit confusing and does not summarise what was said. That said, I would suggest "The GDG recommends that clinicians clearly distinguish adjunctive short-term (<6 months) hormonal treatment after surgery from long-term (>6 months) hormonal treatment, since the latter is aimed at secondary prevention." Was this the intended conclusion or did I understand it wrong?	Thank you for your suggestion. We have changed the recommendation accordingly.
	Diagnosis	42, 429	Replace "100" with "200" and remove the word "immunological" (in May et al 2011 they tested over 200 biomarkers also)	Thank you for your comment. As the paper states that "These studies assess over 200 potential biomarkers" we have replaced "100" with "200" in the guideline
	Treatment of pain	51-52, all	I feel that the lack of evidence in the use of antagonists is stressed at least twice in this chapter, but then did not originate a GDG recommendation. Do you think it would be relevant to have an extra recommendation on this?	Thank you for your comment. As there is no evidence on the use of antagonists, and these are not in clinical use, we did not find it necessary to recommend against the use of these substances.
	Treatment of pain	64, section 2.3g	I failed to see many other products being referred, namely Hyalobarrier® and Intercoat®. I understand that mentioning all available methods could be too much, but from a non-specialist's point of view, I feel that 1) in Europe, Hyalobarrier® in becoming more and more well-known/used and 2) Intercoat® should deserve a reference since it also has been studied in endometriosis (Anja Hirschelmann et al. A review of the problematic adhesion prophylaxis in gynaecological surgery. Arch Gynecol Obstet 2012:1089–97).	Thank you for your suggestion. We have updated the section to include all common products and added a GPP.
			OTHER GENERAL REMARKS (PLEASE IGNORE THIS SECTION IF THE TEXT IS STILL TO BE PROOFREAD – IT CONTAINS SMALL REMARKS THAT DO NOT RELATE TO THE CLARITY AND CONTENT)	Thank you for your comments and thorough proofreading. Although not answering all these comments individually, we have corrected the mentioned errors and adapted the text based on your remarks.
	Table of contents	13-14, all	Recheck the tabulation, as it skips or repeats numbers/letters (i.e. from 1.3f to 1.3i; 2.3 repeated twice)	
	Introduction	5, 11-19	I suggest a full review of this paragraph, as follows "Endometriosis is diagnosed based on the women's history, signs and symptoms; the diagnosis is corroborated by physical examination and imaging techniques and finally proven by histology of either a directly	

		biopsied vaginal lesion or of tissue collected during laparoscopy. The visual recognition of endometriosis alone during laparoscopy is of limited value since it has a high false positive rate. Laparoscopy also allows direct surgical treatment and disease staging, which should preferably be performed according to the ASRM classification system (American Society for Reproductive Medicine, 1997). This classification system assigns points to the different locations of the disease resulting in four stages: minimal, mild, moderate and severe. These stages, however, reflect poorly the severity of endometriosis-related pain and infertility."	
Introduction	5, 22-26	Although I understand what is said, I feel that the compounding of many ideas make these sentences harder to read. Hence, I would suggest "Furthermore, due to the wide variety of clinical practice in the management of women with this disease, doctors frequently experience difficulties in establishing a final diagnosis of endometriosis. This results in many women receiving either delayed or suboptimal care (Kennedy et al., 2005)". If you opt to keep this paragraph as it originally is, please do change "docters" to "doctors".	
Introduction	5, 27-29	Missing the reference for WERF EndoCost (Nnoaham et al, 2011)	
Whole document	All	Suggestions in terms of consistency between chapters: 1) I would suggest adopting the same rule for all verbs ending with "-ize" or "-ise". For instance, in page 5 line 34, "optimize" is written with "-ize", but further ahead in the text most verbs are written with "-ise" 2) . I would suggest consistency in the spelling of words with double vowels like "dysmenorrhea"/"dysmenorrhoea" (written differently according to the section where it is used) 3) One rule for the use of abbreviations (in some chapters the only extended versions are always used, while others always use both the short and long versions and finally others show both the first time and then only the abbreviation) 4) Adopt one rule of use of capital letters in the table on page 27 5) Consistency using the terms “IC 95%”, “IC (95%)” and “95% IC” (written differently in the whole guideline) 6) Consistency in presenting percentages (mostly presented as i.e. 35 %, but in page 37/lines 282-289 they are presented between brackets and in page 41/lines 406-409 they are presented in units) 7) Consistency in the use of numbers (i.e. in page 49, lines 149-150 numbers are sometimes spelled-out and other times not “…6 months.”…“six and 12 months”) 8) Consistency in the use of compound words (i.e. “down regulation” and	

		"downregulation" are both used in the guideline) 9) Consistency in referring to some journals (i.e. in page 56, line 374 "Obstet Gynecol"; in page 90, line 226 "Fertil Steril") 10) Consistency in article page reference (i.e. in page 62, line 585 "1598-92"; in page 83, line 33 "2683-7")	
Whole document	All	Similar phrases are used twice, making the text confusing in the following sections: - Diagnosis of endometriosis, page 38, lines 311-314; Diagnosis of endometriosis, page 39, lines 341-344	
Summary	15 and 17, rec 2.31 and 3.8	I suggest replacing "nutrition" with "nutritional supplements"	
Summary	16 and 19, rec 3.4 and 4.8	I suggest replacing "rate" with "rates"	
Summary	9-21, all	Suggest joining the following recommendations: - Recs 1.18 and 1.19 - Recs 7.1 and 7.2	
Guideline scope	23, 4	I suggest replacing "laparoscopy" with "laparoscopy/laparotomy"	
Methodology	26, 63	I suggest replacing "meeting" with "meetings"	
Diagnosis	31, 98	I suggest replacing "was" with "were"	
Diagnosis	33, 161	…endometriosis includes not only a physical examination of the pelvic but also…	
Diagnosis	38, 296	I suggest replacing "not in all women bowel surgery was performed" with "bowel surgery was not performed in all women"	
Diagnosis	43, 462	I suggest removing "there was no"	
Treatment of pain	48, 120	I suggest replacing "(200 mg three times daily) for six months)" with "(200 mg three times daily, for six months)"	
Treatment of pain	48, 124	I suggest replacing "pragestagens" with "progestagens"	
Treatment of pain	48, 131-132	The lack of commas in each side of "in a total of twelve patients" makes the phrase difficult to comprehend	
Treatment of pain	49, 160	I suggest removing "However"	
Treatment of pain	58, 459	Using the expression LUNA twice can make the sentence confusing	
Treatment of pain	58, 461	Using the verb "to include" twice can make the phrase confusing	

	Treatment of pain	68, 779	Correct brackets	
	MAR	83, 34-37	Duplicate reference	
	MAR	89, 211	Using the derivatives of the word “study” twice can make the phrase confusing	
	MAR	89, 218	I suggest replacing “is” with “are”	
	Menopause	95, 28	I suggest adding “a” between “residual disease as” and “risk factor”	
	Endometriosis and cancer	102, 50	I suggest replacing this reference for the printed version of the reference: “Munksgaard PS, Blaakaer J. The association between endometriosis and gynecological cancers and breast cancer: a review of epidemiological data. Gynecol Oncol. 2011 Oct;123(1):157-63”	
	Appendix 1:abbreviations	103	I suggest adding GDG and also GIN (used in page 26, line 58)	
Dr. Ganeshselvi Premkumar	Introduction	5, 23	Doctors (spelling “o” instead of “e”)	Thank you for your comment, we have corrected this error in the guideline.
	Introduction	5,30	Social (spelling - delete “et”)	Thank you for your comment. We have not changed “societal” into “social”, since we mention costs for society, which is societal costs, rather than social costs.
	Summary	12,41, rec 2.2	Prescribe (spelling - include “r” next to “c”)	Thank you for your comment, we have corrected this error in the guideline.
	Summary	13,58	“pain” instead of “painful”	Pain or painful symptoms? Ask NE SPEAKER
	Summary	15,83, rec 2.28	Space between “associated / dysmenorrhea”	Thank you for your comment, we have corrected this error in the guideline.
PD Dr. Stefan P. Renner	Introd.	3, 27	WERF - please explain abbreviation	Thank you for your suggestion. We have incorporated your suggestion in the guideline.
	Introd.	6, 38	The German Society for Gynecology and Obstetrics ("Deutsche Gesellschaft für Gynäkologie und Geburtshilfe") has an endometriosis guideline since 2006. You can find this under: "http://www.awmf.org/leitlinien/detail/ll/015-045.html". Alternatively I would suggest (as all mentioned guidelines are in English) to state, that previous ENGLISH guidelines are....	Thank you for your suggestion. We have incorporated your suggestion in the guideline.
	chap 1	9, 6	although obvious that the letters A-D means level of evidence (LOE) the guidelines are being read from the start and it should be described earlier (including the abbrev. "GDG" for guidelines discussion group)	Thank you for your comment. A short table on necessary information to understand the recommendations will be added.
	1.3a	11,15 36, 248	Disagree with the statement Rec. 1.10, as this is a major problem in women who just suffer from deep infiltrating, i.e. vaginal endometriosis. Of course you cannot find a publication in this field, because patients are not diagnosed and thus not included as "false negative"	Thank you for your suggestion. We have added information based on this comment to the text.

		12,41	Danazol is not available any more in Germany since 2005 (!) Does this really has to be included (side effects!) The German recommendations are NOT to use it any more although it could be purchased in other countries. I would eliminate this from recommendation	Thank you for your comment. Danazol is still available in several European countries. We have emphasised the androgenic side effects of this drug and would recommend to eliminate danazol from the guideline in a German version adapted to the local context.
	2.4	68 ff	Talking about secondary prevention there is a paragraph missing about "risk factors for relapse" - because only for women at high risk secondary prevention should be discussed (as chemotherapy in oncology). Unfortunately there is a lack of literature concerning this point. Some paper address age, stage of endometriosis (no effect) and other anamnestic points. Another paper found out the pain level preoperative as being main risk factor: Gynecol Endocrinol. 2010 Mar;26(3):230-5. doi: 10.1080/09513590903159623. Preoperative pain and recurrence risk in patients with peritoneal endometriosis. Renner SP, Rix S, Boosz A, Lermann JH, Strissel PL, Thiel FC, Oppelt P, Beckmann MW, Fasching PA.	Thank you for your comment. Risk factors are another topic, and are related to risk factors for endometriosis development and recurrence, and not within the scope of this guideline.
	2.3g	14, 72 64, 649 ff	Why are special substances for adhesion prophylaxis mentioned? of course there are some out there without effect (or very small study numbers) Others, that are widely used should be mentioned (or discussed) as well, i.e. Hyalobarrier. See Cochrane Review Barrier agents for adhesion prevention after gynaecological surgery Ahmad G, Duffy JMN, Farquhar C, Vail A, Vanderkerchove P, Watson A, Wiseman D 2010 or other literature as: Pellicano M et al., Reproductive outcome after autocrosslinked hyaluronic acid gel application in infertile patients who underwent laparoscopic myomectomy. Fertil Steril 2005 Feb; 83[2]: 498-500	Thank you for your suggestion. We have updated the section to include all common products. Hyalobarrier was not tested for endometriosis, the Pellicano trial was for myomectomy. We have added a GPP that some barrier agents have been established in gynecological surgery, but have not been established in endometriosis, which was the focus of the key question.
		48,124	Spelling mistake "pragestagens" should be "progstagens"	Thank you for your comment. We have corrected this error.
	2.1b	48, 111 ff	This is a nice review of progestagens - although it is mentioned in the recommendations the studies from Köhler et al. are not mentioned in the text. Is there a special reason for this especially because Dienogest is the only substance for which INSURANCES pay in Germany and other European countries apart from GnRH..	We thank you for your suggestion. We have included dienogest in the review and it is recommended as treatment for endometriosis.
	2.1 c	51, 208	again (see above point) the comparison to Dienogest is missing (see Köhler et al. Int J Gynaecol Obstet. 2010 Jan;108(1):21-5. doi: 10.1016/j.ijgo.2009.08.020. A dose-ranging study to determine the efficacy and safety of 1, 2, and 4mg of dienogest daily for endometriosis. Köhler G, Faustmann TA, Gerlinger C, Seitz C, Mueck AO. ALSO: There is no recommendation for add-back therapy. There are several options but shouldn't EHSRE give a recommendation concerning patients characteristics and substances? This would be great for basic clinical work.	Thank you for your suggestion. Add back therapy is mentioned as part of a recommendation for GnRHa. No specific add back therapy can currently be recommended. We have included this in the guideline.
Dr. Kamthorn Pruksananonda	1, 1.1	9, Rec1.2	Add: nonmenstrual pelvic pain that failed conventional medical treatment	Thank you for your comment. As stated in the introduction of chapter 2, it has been shown that “the response to hormonal therapy does not always predict the presence or absence of

				endometriosis". Therefore, the GDG decided not to add "nonmenstrual pelvic pain that failed conventional medical treatment" to the recommendation.
	1, 1.2	9, Rec1.5	Add: with respect to social believe and culture	Thank you for your suggestion. This is already mentioned in the considerations section.
	1, 1.3	10, Rec1.9	except young adolescent	Thank you for your comment. We have added a section referring to empirical treatment before this statement.
	1, 1.3	10, Rec1.11	should not apply to stage I & II endometriosis	Thank you for your comment. The GDG does not agree with this comment and hence did not change the recommendation in the guideline.
	1, 1.3	10, Rec1.14	Transabdominal ultrasound should be use in young adolescent who never had sexual intercourse	Thank you for your comment. We already mentioned that adolescents should be evaluated by other techniques in the section on clinical examination.
	2,	12, Rec2.1	acupuncture is widely use in Asia	Thank you for your comment. As this is a European guideline and acupuncture is not widely used or well described, we did not include it in the recommendation
	2, 2.1	12, Rec2.4	Add: women in reproductive age group	Thank you for your comment, but we feel that combined oral contraceptives should not be limited to women in reproductive age group.
	4, 4.1	18, Rec4.4	Add: women age more than 35 should also been considered	Thank you for your suggestion. However, we have not added this to the recommendation.
Paolo Vercellini	2.5	50,176	The progestogens are indicated (MAP, cyproterone acetate and dienogest), but nor-ethisterone acetate (NEA) is not included. There are several published studies, including RCTs, demonstrating the efficacy and tolerability of this extremely cheap medication also in women with deep lesions. In the experience of this reviewer, NEA is the best progestin for patients with endometriosis, and control of symptoms and lesions can be achieved in about three quarter of cases at ridiculous costs. Which are the major reasons to exclude only one compound when evidence is available supporting its use?	Thank you for your comment. We have added NEA to the recommendation. We added and deleted danazol from the recommendation, as suggested.
	2.15	59,474	Although enough data are available demonstrating that LUNA in not effective in the reduction of dysmenorrhoea, the evidence on the impact on deep dyspareunia is less clear. Banning tout court LUNA also for deep dyspareunia, at present seems not completely justified. Moreover, such a definitive statement might expose surgeons to medico-legal problems in case of transection of uterosacral ligament also for treatment of endometriotic foci. Limiting the recommendation to LUNA for dysmenorrhoea, and adding that more data on the effect on deep dyspareunia are needed, could be wiser.	Thank you for your comment. We went back to the review and the included studies to check this. The review only mentions pain, and does not specify dyspareunia. The included study of Johnson et al 2004, has investigated 3 types of pain, including dyspareunia, but concludes "LUNA is effective for dysmenorrhoea in the absence of endometriosis, although there is no evidence of effectiveness of LUNA for non-dysmenorrhoeic chronic pelvic pain or for any type of chronic pelvic pain related to endometriosis." Hence, we feel that it is not justified to advise LUNA for dyspareunia.
	3		This reviewer could not find a recommendation on surgery for rectovaginal	Thank you for your comment. The paper or Vercellini 2006 was

		endometriosis as a fertility-enhancing procedure. There is evidence that this type of surgery, although effective on pain, may not be effective on infertility. Indeed, a reference is included (vercellini et al., 2006) regarding the only available comparative study on surgery versus observation for rectovaginal endometriosis (no between-group difference in cumulative pregnancy rate), but there do not seem to be comments on this in the text	added, although it did not change the recommendations.
3.2	78,124	There is no mention on the NNT in case a laparoscopy is indicated in women with otherwise unexplained infertility in search of stage I/II endometriosis that cannot be reliably anticipated clinically. Although treatment of minimal-mild lesions is associated with a (marginally) significant effect, no more than 50% of the above women will arbour this type of endometriosis. This translates in a number needed to treat of 25! This reviewer strongly believes that medicine based on a national health system, as in Europe, cannot afford surgical procedures with such a low performance, and that women must be informed in detail on the very limited increase in the chances of pregnancy before deciding on whether to undergo laparoscopy for infertility. At the end, we are spending citizens' taxes. It seems that even ASRM has recently issued recommendations against indicating a laparoscopy in women with unexplained infertility in search for peritoneal endometriosis.	Thank you for your comment. The GDG believes that there are believers and non-believers with regard to this topic. We will take your comment into consideration.
3.3	78,125	The suggestion of using CO2 laser instead of unipolar electricity is based on a single, non-randomised study, demonstrating post-operative pregnancy rates in the order of 80%, when formal RCTs demonstrated results between 20% and 30%. This should raise concern on the existence of biases. Moreover, unipolar electricity is available everywhere and costs almost nothing, whereas CO2 laser equipments are very costly and delicate. In the absence of robust evidence in favour of lasers (RCTs), this reviewer would highlight the need for further data before conclusions are drawn.	Thank you for your comment. The recommendation is based on the referenced paper. We have commented on a need for further data on this topic.
4.8	91,261	This recommendation is unclear. Does the GDG recommends performing an operative laparoscopy before ART performance? In this case, please see point 3.2, otherwise it should be stated clearly that a laparoscopy before ART in women without ovarian endometriomas is not indicated. In addition, this recommendation seems based on a single, retrospective study.	Thank you for your comment. We have updated the recommendations.
4.9,4.10	91, 288; 92,289	Recommendations 4.9 and 4.10 seems contradictory, as the former suggests avoiding endometrioma excision, whereas the latter appears to favour it. A modification in wording may help avoid confusion.	Thank you for your comment. We have updated the recommendations
2	45,21-28	The text seems to suggest that performance of a laparoscopy is recommended anyway. However, when ovarian endometriomas are not present, this seems questionable as there is no demonstration that physical destruction of peritoneal endometriosis in adolescent women modifies the natural history of the disease. Adolescents are psychologically particularly fragile. In case OCPs are effective in relieving pain and	Thank you for your comment. Information on adolescents was already mentioned in the text section of empirical treatment, but was extended based on the comment.

			transvaginal US does not identify ovarian cysts, why should a young girl undergo a laparoscopy?	
	Entire text		This reviewer suggest avoiding the definition "deep infiltrating endometriosis" (as well as the acronym DIE) in favour of, simply, "deep endometriosis".	Thank you for your suggestion. We have adopted the suggestion in the guideline.
	2.3	65,531	The definition of deep endometriosis (that extends more than 5 mm beneath the peritoneum) is arbitrary, not consistently reproducible, and not based on a demonstrated pathophysiology of the lesion. This reviewer feels that it should be definitively abandoned.	Thank you for your comment. We have deleted “more than 5mm” from the sentence.
Harold Verhoeve	2, Rec 2.31	70, 883	I would leave out the sentence : " However, the GDG acknowledges that some women who seek complementary and alternative medicine may benefit from this." In my opinion this contains a double message which suggest controversy (obviously debated within the GDG) and is put in as a politically correct statement. the paragraph above the recommendation is clear enough.	Thank you for your suggestion. This sentence is indeed the result of the debate within the GDG and within the literature and therefore, we have removed the second sentence to the considerations.;
	3, Rec 3.8	82, 232	See my remark above	We have commented on this remark above
	1, 1,.3i	43, 463	there was no histology was not available in all cases. in this sentence ' was not' should be deleted	Thank you for your comment. This was corrected in the guideline
	2, 1b	48, 124	pragestagens should be progestagens	Thank you for your comment. We have corrected this error
	2, 2.5	72, 884	I would change the word/phrase limited evidence with no evidence	Thank you for your comment. Stating that there is no evidence is not correct as there is evidence, for instance papers written in Chinese, which we did not include in this analysis
	4, 4.7	89, 223	In my opinion the recommendation and grade B is too strong. It is a high quality review but contains poor studies, because good studies are not available. So in order to be as consequent as in my remark about complementary medicine I would say there is no evidence that pre-treatment is beneficial or cost-effective. The forest-plot may point towards a beneficial effect, but this is no proof (no RCT's performed, biased and confounding studies)	Thank you for your comment. Based on the limitations of the studies included in the review, the evidence level was downgraded from A to B. Cost-effectiveness in not taken into account, but can be considered when “translating” this European guideline in a “national” context.
	4		Maybe I missed it, but I didn't find a recommendation as to adjunctive medical treatment (down regulation) after surgery and before the start of ART.	Thank you for your comment. This is indeed mentioned in the guideline in section 4.2
Carla Tomassetti	meth	p26, table	current layout not fully legible, confusing	Thank you for your comment. The table was updated to improve clarity.
	ch 1.3a	p36, l 242+	it would be very useful for clinical practice to describe what a 'good quality diagn laparoscopy' is, e.g. systematically checking: -uterus and adnexae -peritoneum of ovarian fossae, vesico-uterine fold, douglas, pararectal spaces -rectum, sigmoid (!isolated sigmoid nodules) -appendix, caecum -diaphragm -perform a speculum examination and palpation of the vagina and cervix under laparoscopic control to check for 'buried' nodules	Thank you for your suggestion. We have included this in the guideline.

			Because only when checking all these areas thorougly, one could conclude whether a lapsc is negative or not (looking at the internal genitalia alone is not enough)	
	rec 1.13	p38 l 302	add phrase 'by adequately experienced clinicians'	Thank you for your comment. This is mentioned in the considerations section.
	ch 1.3f	p 41 l 415-417	as this sentence is not supported by literature evidence, by personal experience in clin practice or by the actual rec 1.19, in my opinion it is does not have a place in this guideline	Thank you for your comment. We have clarified that this is the conclusion of the authors (Mol and co-workers) of the cited review, not of the GDG.
	ch 1.3i	p 43 l 462-3	typing error in 'Since…studies': delete 'was not'	Thank you for your comment. This was corrected in the guideline.
	ch 1.3i	p 43 l 481-483	'Since…endometriosis.': end of the sentence difficult to understand, might benefit from rephrasing	Thank you for your comment. This was amended in the guideline.
	rec 2.1	p45 line 29	as further in the guideline, nutritional therapy is mentioned as being unsuitable for treating endometriosis symptoms, I doubt it has a place in this recommendation	Thank you for your suggestion. We have deleted “nutritional therapy”.
	ch 2.3f	p63 l 606-612	for diaphragmatic endometriosis, pleurodesis/pleural abrasion or pleurectomy might not be sufficient: excision of a diaphragmatic nodular lesion (either via thoracoscopy/tomy or laparoscopy or combined procedure) should be considered in case of important clinical symptoms	Thank you for your suggestion. We adapted the guideline based on your comment.
	ch 3	p 75 etc	an important issue has not been mentioned in this chapter: what is the approach towards fertility management in women with endometriosis who underwent surgery? This is an important clinical question but not adequately addressed in this chapter. Mentioning the EFI (Endometriosis fertility index, as published by Adamson and Pasta in 2010 in Fertil Steril; and recently validated and published by our group although I acknowledge the time limits of literature review for this guideline) could give clinicians a very valuable tool to counsel patients on their fertility options after surgery. Added advantage of the EFI is that it is not restrictive to the lower AFS stages (for which most of the evidence is applicable), and could even for DIE and higher stages give reliable information as to whether the start of an ART treatment should be sooner rather than later (before other non-ART options have been tried). I would strongly advise to incorporate the EFI in the guideline.	Thank you for your comment. This important question was not included in the scope of the guideline and hence not addressed. We will incorporate this in the update of the guideline
Grigoris F. Grimbizis	Chap 1	Page 10 / Rec 1.9	Comment 1. Hydrolaparoscopy represents another minimally invasive endoscopic technique, which could potentially be applied for the diagnosis of endometriosis. Its diagnostic accuracy is not yet known. Comment 2: What are the indications for performing laparoscopy to diagnose endometriosis?	Thank you for comments. Regarding hydrolapaproscopy, in the guideline we focussed on established techniques, but we may include this in the update of the guideline. Regarding indications for performing laparoscopy, we have added the information.
	Chap 1	Page 10 / Rec 1.16	Comment 1. "The usefulness of 3D ultrasound to diagnose rectovaginal endometriosis is not well established" but it seems to be at least helpful See Guerriero et al, J Ultrasound Med 2009; 28:1061–1066 Grasso et al, Abdom Imaging (2010) 35:716–725	Thank you for your comment. We already stated in the considerations that the limitations are due to operator dependency, not excluding any potential helpfulness.

	Chap 2	Page 14 / Rec 2.19	Clinicians should consider surgical removal of Deep Infiltrating Endometriosis associated with pain in young patients as their last therapeutic option due to the higher complications rates and post-operative adhesion formation (GPP)	Thank you for your suggestion. The GDG did not adopt the proposed GPP
	Chap 3	Page 16 / Rec 3.5a	In infertile patients with Deep infiltrating Endometriosis not associated with pain the value of Surgical treatment is not yet proven. Due to the high complications rate it is not recommended (GPP)	Thank you for your comment. We agree that the use of surgical treatment is not yet proven, hence we mentioned "can consider". Additional information on the complication rate is added.
	Chap 3	Page 17 / Rec 3.7a	In infertile women with endometriosis prescription of post-surgical adjunctive hormonal treatment is not indicated to improve spontaneous pregnancy rates but it could be given because it is probably associated with lower recurrence rates (important clinical parameter / see Cochrane review of Furness et al, 2012)	Thank you for your comment. We agree with your comment, but this section focussed specifically on pregnancy, while recurrence is discussed in chapter 2.
	Chap 6	Page 20 and 97 / Rec 6.1&2	Asymptomatic endometriosis could also be considered an incidental finding of an endometrioma during TVS routine examination in patients not wishing pregnancy at that period of their life. In those cases, there is a potential for endometrioma to have an adverse effect on their future fertility since there is a proven association between endometriosis and woman's fertility. Although the natural history of endometriosis is not yet fully known, endometriosis seems to be a chronic inflammatory disease and restoration of normal anatomy together with histological confirmation of the disease seems to be mandatory (see chapter on diagnosis). Furthermore, laparoscopy is indicated for diagnosis of the disease. In those cases, it seems reasonable to recommend removal of the cyst (see and treat strategy or only see strategy?) Recommendation: In women with asymptomatic ovarian endometriosis laparoscopic surgical treatment of the disease could be applied as a therapeutic option to confirm diagnosis and to avoid potential adverse effect on fertility potential (GPP)	Thank you for your comment. The recommendation has been altered to specify an incidental finding 'at time of surgery'. The GDG recommends that clinicians follow their own national guidelines for the management of ovarian cysts detected incidentally on ultrasound scan.
Dr Jacques WM Maas	introduction	5, 11-19	maybe something should be added on the incompleteness of the classification system, it does not score deep infiltrating endometriosis	Thank you for your suggestion. We have incorporated your suggestion in the guideline.
		15, rec2.28	typo endometriosis-associateddysmenorrhea	Thank you for your comment. This was corrected in the guideline
	1.3b	38, 298	what is meant with observation. How do we know whether clinicians are experienced in performing tvs.	Thank you for your comment. We have replaced "observation" with "notion". This statement is based on the experience of the guideline group, hence it is not based on definite criteria for "highly experienced clinicians in TVS"
	1.3i	43, 462	typo there was no histology was	Thank you for your comment. This was corrected in the guideline
	2.1b	50, rec 2.5	dienogest was not earlier mentioned, what is evidence on dienogest	We thank you for your suggestions. Dienogest was mentioned and supported by the guideline. The Cochrane review, which summarises the highest level of evidence, did show that, amongst other drugs, Dienogest is effective in treating endometriosis pain. This is reflected in the guideline.
	2	45, rec 2.1	what is nutritional therapy (not explained)	Thank you for your suggestion. We have deleted "nutritional therapy".

Hans Kristian Opøien	"Methodology"	p 26, l 48	"The literature searches included studies published before January 2012", but at least 2 of the references used are published after that date, which seems inconsistent –see under.	Thank you for your comment. The literature searches also included papers "entered in PUBMED before January 1, 2012" A sentence was added to clarify this point
	2.1b	p 50, l 182	Reference: Brown J et al. Cochrane Database of Systematic Reviews 2012	Thank you for your comment. In the first paragraph of the clinical evidence, it is explained why we included this updated review.
	6	P 98, l 36-44	Pearce CL et al…Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol 2012 Apr;13(4):385-94.	Thank you for your comment. The literature searches also included papers "entered in PUBMED before January 1, 2012" A sentence was added to clarify this point.
	6	p97, l 16	"…the fact that it is likely that there is little risk that asymptomatic minimal disease will become symptomatic." This is a study with 39 women with endometriosis referred for sterilization asked if they had any PAIN symptoms some years later: Do you really mean that this say ANYTHING about INFERTILITY and whether endometriosis found in a young woman (that have not tried to conceive) may or may not contribute to a later condition of infertility???	Thank you for your comment. We have amended the sentence that follows p97 line 16 as follows: 'However, in view of possible other negative effects of endometriosis e.g. effects on fertility, increased risk of ovarian carcinoma, there is a need…'
	4.1a	P84, l55-62	In Werbrouck`s study; all the patients had the endometriosis surgically removed before IUI in contrary to Omland study. This should be mentioned in the text as well, when comparing the studies.	Thank you for your comment. For clarity we added "diagnostic laparoscopy only" to the evidence on the Omland study .
	4.1b	P86, 128-133	This was a long awaited critically analysis of Barnards review; but addition to what is written on different drug use, some of the studies included in the review did not state whether the patients were operated or not before IVF. But why is the review later used as "Clinical evidence" at page 89, 196-198?	Thank you for your comment. We have added a sentence on the treatment before IVF. In the next section, we referred to the paper as an introduction to the relevance of the question on "medical therapy before IVF".
Paulo C. Serafini	1, 1-3	29, 268-269 44, 485-486	Like ultrasound examination, laparoscopy is operator-dependent (knowledge, skills, experience and so on); therefore, I believe that rec 1.10 should be downgraded to B. Based on several well-known ultrasonographers who utilize transvaginal sonography after bowel preparation/cleansing - it should be incorporated on the work-up since facilitate the recognition of the ureter, bladder and bowel involvement as well as the overall pelvic DIE mapping since it also reduces "gas" content.	Thank you for your suggestion. We have added a paragraph ion operator dependency in the considerations section, but we feel this should not be the reason to downgrade the evidence level of the recommendation. Regarding the second suggestion, the GDG decided not to elaborate on this in the text of the guideline
	2	45-73	Outstanding	Thank you for this compliment
	3	75-82	Excellent	Thank you for this compliment
	4	83-93	Excellent	Thank you for this compliment
	5	95-96	Excellent	Thank you for this compliment
	6	97	Requires further research	Thank you for your comment. We agree that this topic requires further research, but the setup of such studies is challenging, mainly recruitment of (non-endometriosis) patients, numbers of patients (low prevalence) and long-term follow up.
	7	99	Very wise, concur	Thank you for this compliment
	8	101	Excellent, concur	Thank you for this compliment

Andreas Stavroulis	4.3b	288	Rec 4.9: The recommendation reads as if it is for endometrioma of any size and site (uni-, bilateral). I would consider to specify in the recommendation the 'unilateral 3-6cm endometrioma' as stated in the text.	Thank you for your comment. We have updated the recommendations
Ying Cheong Cindy Farquhar	1.3f		Regarding biomarkers and endometriosis, reference to the newest review is worthwhile, as it has included more up to date studies in this area and also some recommendations on future study design (Fassbender et al 2013).	Thank you for your comment. This review was not included since it was published after the deadline for inclusion of papers. We feel this review does not oppose, nor confirms our recommendations, hence we did not add it to the current version of the guideline. We will include it in the update of the guideline.
	2.3g		Ahmad et al 2008 has been updated and this may change the recommendations. I have emailed the authors to check the progress of the editorial process for this review.	Thank you for your comment. The most recent update (2011) mentions that there have been no changes. .
	4.3b		In section 4.3b, the recommendations on the management of endometriomas do not reflect the clinical evidence, conclusions and considerations stated in the sections above. The recommendation Rec 4.9 (B) was that 'clinicians should not perform cystectomy…improve pregnancy rates' followed by the next recommendation Rec 4.10 (GPP) 'in women with an ovarian endometrioma…. The GDG recommends clinicians to consider cystectomy…improve pregnancy rates' is confusing. Should rec 4.9 not just read 'there is no evidence to support performing cystectomies on women undergoing ART improve pregnancy rates' rather than 'clinicians should not perform..'?	Thank you for your comment. We have updated the recommendations
	4.3c		In section 4.3c, there should be some guidance on management of women with DIE with pain and subfertility requiring ART or at least reference to section 2.3e.	Thank you for your comment. We have added a sentence to refer to the section on pain.
	3.2		Page 77 'Acosta staged endometriosis' please reference	Thank you for your comment. We have added the reference.
	3.2		In practice, women with infertility not infrequently proceed to ART, this is particularly true for older patients with lower ovarian reserve. Sections 3.2 Surgery for treatment of endometriosis-associated infertility and sections 4.1b Assisted reproductive technology in women with endometriosis and their respective recommendations has not highlighted this possible overlap. More cross-referencing between these chapters may be useful. Some advice on the impact of surgery on ovarian reserve should be stated in section 3.2 as well.	Thank you for your suggestion. We have incorporated them in the guideline.
	2.3e		Cross-referencing complications rates of DIE surgery as stated in section 2.3e in section 4.3c will be useful for readers.	Thank you for your suggestion. We have added a sentence referring to section 2.3e in section 4.3c
			Overall excellent work.	Thank you
	1.3a	35	In the GPP 1.12 I would suggest that this recommendation has the potential for harm - especially taking the biopsy for deep infiltrating disease….and as it is not based in evidence it is not really worth recommending.	Thank you for your comment. We have added in the considerations section that laparoscopy should be performed by skilled clinicians
			Section 2.1 page 12 -13 It would be useful to add the length of treatment to all the recommendations in this section - for example for danazol and GnRH agonists it is generally not recommended to continue therapy for more than 6-9 months but for the combined oral contraceptive pill it can we used indefinitely.	Thank you for your comment. In the recommendations, we have mentioned that "evidence is limited regarding dosage and duration of treatment", hence, we decided not to put details on this in the guideline

			Section 2.3 page 66 and 67 I found that re 2.25 and 2.26 were not entirely consistent and perhaps even confusing. Is the distinction between short adjunctive therapy and longer term treatment for prevention that important? I think that the recommendation is quite strong ("should not prescribe…" when in fact there was some reduction in pain at 12 months and more studies might come to a different conclusion. If patients need contraception does the "should not" still appl. They should suggests some sort of harm but your GPP suggests some sort of secondary prevention … Also the 2.25 isn't consistent with 2.29 and 2.30	A sentence was added to the considerations section stating that there is no benefit for improving the outcome of surgery, but it could be prescribed for other indications, for instance contraception.
			Section 3.2 page 77. You describe Nowrooozi as a well designed RCT. If it was well designed then they wouldn't have used a SSN as way of allocating the randomisation. The method generating the randomisation sequence and concealing allocation are two of the most important features of study design. Perhaps you could say in a quasi-RCT similar results were reported.	Thank you for your comment. The GDG decides that the allocation based on SSN is not a reason to downgrade this RCT, especially since the limitations of the paper are discussed explicitly.
			Rec 3.3 page 78 do you need a recommendation on this point as it based on low quality evidence and is only a C. it is an old study and most surgeons do not use laser anymore. Is there any recommendation about measuring AMH levels before or after surgery to see if there has been a impact on ovarian reserve?	Thank you for your comment. The GDG decided to incorporate the recommendation, although it is of low quality (C). AMH level and ovarian reserve were not included in the scope of the guideline, but will be considered in an update of the guideline
			Section 4.3b rec 4.9 and page 91. is there any guidance about the size of the endometrioma….The SR by Hart suggests benefit so this recommendation is a bit confusing. and it is not consistent with rec 4.10 on page 92.	Thank you for your comment. We have stated previously, that endometrioma >3 cm could be removed for reasons of pain, based on the review of Hart et al., 2008. In this section we have added a sentence to refer to the section on pain.
Fernanda Águas			After reviewing the guidelines on "Management of women with endometriosis" I hereby notify my agreement with the recommendations. I also declare that I do not have any comments to add to the consensus text.	Thank you for your comment.
Teresa Almeida-Santos		P5 L23	doctors instead of docters	Thank you for your comment, we have corrected this error in the guideline.
	1.2	rec 1.6	"must" or "are recommended to" instead of "may"	Thank you for your comment. The level of evidence is "C" and "may" is the appropriate phrasing for "C level" evidence. "Must" or "are recommended" reflect stronger supporting evidence.
Michelle Nisolle	1	36, 247-9	It could be mentioned that retroperitoneal lesion could be underdiagnosed. Fibrosis could be the only sign of DIE, non visible	Thank you for your comment. We have added this to the guideline.
	1	39, 327	Small endometrioma could be missed by transvaginal sonography	Thank you for your comment. We have added a sentence on this to the considerations section.
	2	53, 297	The presence of aromatase in endometriosis is controversial in the literature . It could be mentioned.	Thank you for your comment. We have added a sentence on this in the introduction of the section.
	2	59,493,495	It should be precised if the recurrence concerns the presence of ovarian endometrioma or the pain	Thank you for your suggestion. Your suggestion was incorporated in the recommendation.
	2	61	In this important section , the recurrence rate after surgery should be precised as it has	Thank you for your suggestion. The recurrence rate is added to the

			been done about the comparison of ovarian endometrioma technical surgeries.	text.
	3	77	For this important question, there are 2 other manuscripts in the literature, one RCT from Maheux et al and another one from an Italian team.	Thank you for your suggestion. The mentioned studies are summarized in the review by Jacobson 2010.
	4	92,305	In order to know if surgery of DIE is needed before IVF, there is a retrospective study published in Fertil Steril by Matthieu d'Argent et al and another one by Ballester M et al in Human Reprod	Thank you for your comment. The study by Ballester (Mattieu d'Argent as second author), although not included due to the inclusion deadline, does not confirm, nor contradict the recommendation on surgery prior to IVF in DIE patients. They conclude that "surgery should be considered after failure of two ICSI–IVF cycles for patients younger than 35 years with poor ovarian reserve before opting for an oocyte donation program." I could not retrieve a recent paper in Fertil Steril. from Mattieu d'Argent as first author.
Päivi Härkki	1		Good recommendations	Thank you for your comment
	2		Good recommendations	Thank you for your comment
	3.2	77, 81-85	Is there enough evidence about superiority of CO2 laser vaporisation over monopolar electrocoagulation? There is only one article about this subject and patients had moderate to severe endometriosis, not minimal to mild endometriosis. I suppose monopolar electrocoagulation is more commonly used than laser vaporisation. Rec 3.3	Thank you for your comment. The GDG decided to incorporate the recommendation, although it is of low quality (C).
	3.2	77, 102-104	Should there be some comment about preoperative AMH. If it is already low, excision of endometrioma may be not recommended for infertility treatment and IVF should be recommended without surgery. Compare recommendations 3.4 and 4.11.	Thank you for your comment. AMH level and ovarian reserve were not included in the scope of the guideline, but will be added in an update of the guideline.
	4		Good recommendations, especially Rec 4.9 and 4.11.	Thank you for your comment
	5		It was nice to see your recommendations for combined estrogen/progestin therapy after radial surgery (Rec 5.1) because it has been a controversial subject.	Thank you for your comment
	6		Good recommendations	Thank you for your comment
	7		Good recommendations	Thank you for your comment.
	8		Good recommendations	Thank you for your comment
Lone Hummelshoj	Introduction	p5, 14-15	It is of concern that only "false positives" are mentioned in connection with visual diagnosis of endometriosis; false negatives are very real if women are laparoscoped by surgeons who are not familiar with all the different appearances of endometriosis, or if s/he does not look hard enough. You see only what you recognise, and a diagnosis of endometriosis is very dependent on the curiosity of both the surgeon and the pathologist -- that goes for a "clinical" diagnosis as well...	Thank you for your suggestion. We have incorporated your suggestion in the guideline.
	Introduction	p5, 21-22	Simoens et al 2007 did not investigate quality of life in this paper and this is therefore an inappropriate reference in this context.	Thank you for your suggestion. We have deleted the reference.
	1	p29, 9-10	Is it being suggested that "early onset of symptoms" is a "cause of diagnostic delay"? Really? Also, the "normalisation of symptoms" is not just by "family doctors" but by women (girls) themselves, as well as their mothers (Ballard et al, Fertil Steril 2006), and -	Thank you for your comments. We have updated the text based on your comments.

		in some cases - even gynaecologists and other "specialists" (Nnoaham et al, Fertil Steril 2011).	
1	p29, 24-28 and 62-63 and p32, 112-113	A prospective study has been done to investigate symptoms associated with endometriosis versus symptoms in a population not diagnosed with endometriosis (Nnoaham et al, Fertil Steril 2012). This study also showed that menstrual dyschezia strongly predicted some stages of endometriosis, so it is of concern that this symptom is not listed. Dysreuria is also missing from the symptoms listed.	Thank you for your suggestion. As this paper was published after the deadline of included papers, we did not add it to the clinical evidence, but mentioned it in the considerations section. The mentioned symptoms were added to the recommendation.
1	p37, 268-269	It is of grave concern to women with (un-diagnosed) endometriosis everywhere that ESHRE will recommend, based on one systematic review (Wykes et al, BJOG 2004), that if any surgeon does not visually recognise endometriosis at laparoscopy, his/her findings are accurate to the extent that endometriosis has been ruled out as a cause of that woman's symptoms! See additional comments above to the Introductory section. This statement alone will contribute to the "diagnostic delay", and the woman may go on for years to suffer from symptoms until she is brave enough to seek a second opinion -- and we all know of many thousands of women, who had a first negative laparoscopy, who have subsequently gone on to be diagnosed by someone who recognises the disease. The statement is also in direct contradiction with the GPP right below it. Furthermore, please don't dismiss the "clinical diagnosis" to move women to treatment …we must never lose sight of the objective: to get women treated so that they are symptom free.	Thank you for your comment. We have added a section in response to your comment.
1	p38, 309-319	Reference to Nnoaham et al, Fertil Steril 2012 should be included in the section on ultrasound for ovarian endometrioma, as this was a significant finding of this prospective study.	Thank you for your comment. Since this papers was published after the deadline for inclusion of papers, we will not include it in the clinical evidence section.
2	p45, 29 and p56, 358-366	A blanket statement lumping analgesics on par with hormonal treatments does not serve the individualisation of treatment for women with endometriosis well. Furthermore, "pointing out some side effects" is not sufficient of a statement. The significant side effects associated with long-term use of NSAIDs (and other analgesics) are important to list, not least in the infertile population since NSAIDs inhibit ovulation (Duffy and Stouffer, Hum Reprod 2002). Furthermore, women need to be counselled on the risk of gastric ulceration and cardiovascluar disease with regular use of NSAIDs, the latter varying significantly between different types of NSAIDs (McGettigan and Henry, PLoS Med 2013) .	Thank you for your suggestion. Based on your suggestion, we have specified the side-effects of NSAIDs.
2	p45, 29 and p47, 68 and p50, 176	A blanket statement recommending hormonal treatments, without acknowledging the difference in severity of side effects, is a dis-service to women with endometriosis (the GPP below it, does not make up for the blanket statement). Furthermore, how can it be justified to include danazol in such a blanket statement without an appropriate caveat (see Johnson et al, Hum Reprod 2013 on the patient population who should be subjected to danazol) and a recommendation on gestrinone based on a 12 patient study	We have added the specific side effects of danazol to the recommendations. As not to emphasize Danazol, we have discussed it in the section on progestagens, as it also has properties similar to progestagens. Regarding gestrinone, we added an definition of anti-progestagens, and gestrinone fits this definition.

		conducted 23 years ago (Hornstein et al, Fertil Steril 1990)? Also, danazol is not a progestagen (Rec 2.5), and is gestrinone really an "anti-progestin"? Isn't it a synthetic steroid?	
2	p50, 178	Brave to proactively encourage clinicians to prescribe a medical treatment, which doesn't have an FDA approved indication for the treatment of endometriosis.	Thank you for your comment. Mirena is approved as contraceptive, for the treatment of idiopathic menorrhagia (heavy menstrual bleeding, HMB) and for protection from endometrial hyperplasia during estrogen replacement therapy for climacteric symptoms. We thought about adding "off-label use" to the recommendation, but the group felt that as this is the case for most of the medical treatments used in endometriosis, it would be redundant and incorrect to only mention it for LNG-IUS.
2.3	p56, 391 and p62, 569	In this day and age, should "laparotomy" be used in a heading? Propose that either the word "Laparotomy" is removed, or that "Laparotomy-laparoscopy" is replaced with the word "surgery". No woman with endometriosis should be subjected to a laparotomy unless absolutely necessary (ie. the surgeon having to revert) - those unable to perform laparoscopies, should be encouraged to refer.	Thank you for your comment. We have changed the title based on your comment
2.3	p58, 443	"endometriotic spots" -- seriously??	Thank you for your comment. We adapted this based on your comment to "peritoneal endometriosis"
2.3	p63, 606-621	For pneumothorax medical treatment is mentioned in the narrative, but only surgical intervention is recommended (Rec 2.21) -- is this not an oversight?	Thank you for your suggestion. We have adapted this in the guideline and the recommendation
2.3	p65, 677	Rec 2.22: Really? Whatever happened to outcome of relevance to women?	Thank you for your suggestion. Fertility and pain outcome has now been included
2.3	p67, 749-751 and p69, 820-821	Rec 2.25, 2.26, and 2.30 appear to be in direct conflict with each other.	Thank you for your comment. We have rewritten the sections on postoperative medical therapy and secondary prevention as to clarify the difference.
3	Section 3 and 4	The r-ASRM, without a reference, is referred throughout these sections as the AFS/ASRM stage -- consistency?	Thank you for your comment. We acknowledge the confusion that the different classification systems may cause. However, in the section on the clinical evidence, we have consistently referred to the classification system mentioned in the paper. In all recommendations, we have mentioned AFS/ASRM, as they are similar although the supporting evidence used different classification over time.
3	p78, 125	Rec 3.3: might this reference not be associated with the fact that those surgeons able to use CO2 lasers may be better surgeons and consequently remove endometriosis more thoroughly resulting in improved fertility rates? In other words: do consider surgical skills rather than the tools they use in making recommendations.	Thank you for your comment. The GDG agrees, but believes that they cannot recommend on "surgical skills"

	3	p80, 188-190	Rec 3.6 and 3.7 are in agreement (ie. the same statement). Is a GPP then necessary when the evidence speaks for itself?	Thank you for your comment. Recommendation 3.6 deals on pre-operative medical treatment, while recommendation 3.7 deals on post-operative medical treatment. Hence the 2 separate recommendations.
	5	p95, 11-13	This statement is left hanging without any given reason, why it is there (ie., a "because….." is missing)	Thank you for your comment. This is just an introductory statement, explaining the issues discussed in detail below.
	2 and 3	Rec 2.31 and Rec 3.8	It is interesting that the GDG is not prepared to recommend nutritional and other complementary therapies because "potential benefits/harms are unclear", yet it is happy to recommend analgesics and hormonal drugs where the harms are clear. Do consider evidence from two RCTs, which showed that dietary intervention following endometriosis surgery in the form of vitamins, minerals, salts, lactic ferments and fish oil appeared to be an effective alternative to hormonal treatment, that is associated with similar pelvic pain reduction and quality of life improvement (Sesti et al, Fertil Steril 2007; Sesti et al, Gynecol Reprod Biol 2009).	Thank you for your comment. The RCT of Sesti et al 2007 is included and described in the evidence section. However, the GDG judged that the evidence was too weak to base a recommendation on. Furthermore, we only state that these therapies are not well established and the GDG could not write recommendation (as they did for analgesics) supported by expert opinion for these alternative therapies. The outcome of the second study of Sesti et al 2009, was recurrence rate, which was not discussed in this section. This is in agreement with the statement on complementary therapy in the Montpellier consensus statement.
	Overall		The lay-out was difficult to follow, ie. all the statements appear in the first section (Summary of Recommendations), but are not referenced, so one has to move to a section further down the document, with the narrative, in order to look for references. In the Summary of Recommendations, these statements should mirror the boxes of recommendations in the main (chaptered) section (ie. with references included), and it would be helpful, from a readability point of view, to have the statements precede the narrative so that one can link the statement with the subsequent justification. Some references mentioned in the narrative, are not listed in the reference lists…	Thank you for your comments. The summary of recommendations in the first section had the purpose of giving an overview of all recommendations, which are later explained in the guideline text. Since this seems confusing, we will consider transforming the “summary of recommendations” into an appendix. Although we accept your comment on the order of mentioning the evidence and recommendation, we feel that the recommendation derived from the evidence should be mentioned after the recommendation.
	Overall		I found the document focused more on methodology than on key messages about how to treat/manage endometriosis, and that whereas a rigorous methodology and process is needed in guideline development, one must be careful it doesn't become so cumbersome that important issues are not addressed simply because the process and an unyielding format doesn't allow for them so be so.	Thank you for your comment. We acknowledge that the rigour of the methodology limits the freedom, but we feel this contributes to the quality of the guideline and the trustworthiness. We do not agree on the statement that the methodology limits the issues discussed. We would like to ask the reviewer to elaborate on “important issues that are not addressed”
	Overall		There are several paragraphs - both within the introduction and in the document itself - that simply don't make sense from a grammatical/syntax point of view, nor is the language of the recommendations and their associated references consistent. I suggest a careful review, and re-write where needed, by someone with English as their native written language.	Thank you for your comment. We will take this comment into consideration and act accordingly.
Bee Kang Tan	2.5		There is no mention on the role of GnRH analogue in this section i.e. to use or not to	Thank you for your comment. We have searched for papers

			use.	addressing secondary prevention without focussing on a certain intervention and we did not find any studies on GnRH analogues.
	3.2		I would have thought that Rec. 4.11 would be applicable to this section as well and given its importance, should be reiterated here.	Thank you for your comment. We have copied the recommendation.
	General		To the lay person, it may not be clear that an increase in pregnancy rate does not necessarily translate to an increase in live birth rate. I feel that it is very important to clarify this point in the guideline.	Thank you for your comment. Although this was already mentioned, we added a sentence in the introduction of chapter 3 on this topic.
Ana Aguiar	Introduction	5,13	… vaginal lesion localisation….	Thank you for your comment. We have reviewed and updated the language of the introduction, taking into account your comment.
	Introduction	5,23	doctors instead of docters	Thank you for your comment, we have corrected this error in the guideline.
	Introduction	5,27	put WERF in Appendix 1: Abbreviations	Thank you for your suggestion. We have put "WERF" in the list of abbreviations in the guideline.
	Introduction	6,65	Saridogan E. instead of Saridogan E;	Thank you for your comment. Since the "ESHRE Special interest group" is part of the author section of this reference, we did not change Saridogan E; into Saridogan E. As proposed
	Introduction	6, 68	put together without the paragraph	Thank you for your comment, we have corrected this in the guideline.
	Introduction	6,73	D'Hooghe T instead of d`Hooghe T	Thank you for your comment, we have corrected this error in the guideline.
	Introduction	6,77	366-73.e8 instead of 366-373.e8 (to follow the same in all references)	Thank you for your comment, we have corrected this and we will review the style of all references in the guideline.
	1,1.1	Rec 1.1	put GDG in Appendix 1: Abbreviations	Thank you for your suggestion. We have added "GDG" to the list of abbreviations.
	1,1.1	Rec 1.2	suggestion: not to put fatigue alone as it can mean any disease context, my proposal: …and fatigue in the presence of any of the previous.	Thank you for your comment. We changed "fatigue" into "fatigue in the presence of any of the previous".
	1,1.1	Rec 1.4	"… previous diagnosis of ovarian cyst, irritable bowel syndrome or pelvic inflammatory disease." can´t be considered symptoms and put all together like that, referral to line 6	Thank you for your comment. We agree but have not updated the recommendation accordingly.
	1,1.3	10, Rec 1.17	I suggest to put as the previous Rec starting by: The usefulness…	Thank you for your comment. We have added "clinicians should be aware that.." to the recommendation.
	2,	12,Rec 2.1	Can´t the final part "It is unclear whether the OCP should be taken conventionally, continuously or in a tricycle regimen." be put on the Rec 2.4?	Thank you for your comment. We have updated this section.
	2,2.1	13, Rec 2.11	Put all in the plural form: 2… progestagens, oral contraceptive pills or GnRH analogues…"	Thank you for notifying us on this error.
	2	12, Rec 2.5	It´s unclear the correspondence of oral or depot to which medication	Thank you for notifying us on this error.
	2,2.2	13, Rec 2.12	"… other analgesics…" should be specified which other class of analgesics besides NSAID or not said at all	Thank you for your comment. Based on your comment, we have specified in the text for which compounds evidence was searched, but not found.
	2, 2.4	15, Rec	…endometriosis-associated dysmenorrhea instead of "endometriosis-	Thank you for notifying us on this error.

		2.28	associateddysmenorrhea”	
2, 2.4	15, 2.29	Rec	What is meant is secondary prevention of endometrioma, why not to take off “…ultrasound diagnosed…”?	Thank you for your comment. We have removed “ultrasound diagnosed”.
2, 2.31	15, 2.31	Rec	The second part of the recommendation - “However the GDG acknowledges that some women who seek complementary and alternative medicine may benefit from this” – this is not a recommendation, is a finding, maybe superfluous to be put	Thank you for your comment. This recommendation was the result of extensive debate within the guideline group. Although the second part of the recommendation would seem redundant to some, the GDG judged that it supports women that have seeked alternative treatment and feel they have benefited from it.
3, 3,2	16, Rec 3.4		I suggest an standardization of designations between recommendations and so “perform excision of the endometrioma capsule” should be named cystectomy; As endometrioma is designed endometriomata in other several rec	Thank you for your suggestion, but to clarify the surgical technique we decided to mention “excision of the endometrioma capsule” instead of cystectomy
3,3.3	17, Rec 3.8		The same as comment to rec 2.31	See above
1, 1.1	29, 34		Not necessary to put part of the definition of dyschezia as it is already in the Appendix 2: Glossary	Thank you for your comment. We have removed the definition of dychezia in the text.
1, 1.1	30,43		Can uterine cramping be considered a symptoms or is the cause of a or several of symptoms?	Thank you for your comment. The GDG considers “Uterine cramping” as a symptom, and therefore did not change the text.
1,1.1	32,121		Its incomplete. … Hum Reprod. 2012 Dec;27(12):3412-6.	Thank you for your comment. We have updated all references.
1,1.1	32, 126		366-73	Thank you for your comment. We have updated all references.
1,1.1	34, 197		I propose substitute “…clinical examination” by “…vaginal examination should be omitted…”	Thank you for your suggestion. We have incorporated your suggestion in the guideline.
1, 1.3b	39, 355		To general, I suggest: “… highly ultrasound skilled clinicians.”	Thank you for your suggestion. We have added this to the guideline
1,1.3f	41, 425-6		This sentence is contradictory. I suggest to take off the last not and remains: “…were mentioned.”	Thank you for your comment. We have corrected this error
1,1.3i	43, 462		I suggest: … bowel resection, histology was not available…”	Thank you for your comment. This was corrected in the guideline.
	43, 469		Miss final point	Thank you for notifying us on this error.
2,2.1b	48, 124		progestagens	Thank you for notifying us on this error.
2, 2.1b	50, 181		…Cochrane Database Syst Rev. 2012 Mar 14;3:CD002122. Standardize all the Cochrane references through all the document references	Thank you for notifying us on this error.
2,2.2	56, 374		Obstet Gynecol. 1985 Mar;65(3):379-83	Thank you for notifying us on this error.
2,2.3e	62, 585		1598-9	Thank you for notifying us on this error.
3,	75, 10		I suggest to put all in singular: “… pregnancy rate, miscarriage rate, ectopic pregnancy…”	Thank you for notifying us on this error.
4	83, 33		2683-7	Thank you for notifying us on this error.
4	83, 33		Is the same reference as de previous in line 29?	Thank you for your comment. This publication was simultaneously published in Human Reproduction and Fertility and Sterility.

				However, due to the apparent confusion, we have deleted one of the 2 references.
	6	98,33	43	Thank you for notifying us on this error.
	6	98, 45-46	…1991;36:513-5	Thank you for notifying us on this error.
	8	102,50	Is complete : Gynecol Oncol. 2011 Oct;123(1):157-63.	Thank you for notifying us on this error.
Luk Rombauts	1.3b	298-301	Due to the operator dependency and the observation that in several European institutions clinicians are not experienced in performing TVS for the diagnosis of rectal endometriosis, the GDG feels that they cannot recommend TVS to be used for diagnosis of rectal endometriosis, except if performed by clinicians highly experienced in TVS. --> Should this not really need a recommendation for better training or scanning by sonologists in expert centres (see also top 5 recommendations below)	Thank you for your suggestion. We will take your suggestion into account in the implementation of the guideline.
	3.2	Rec 3.3	The recommendation to prefer CO2 laser over other surgical approaches is based on a low quality study and seems so archaic that I can't see it deserves a mention.	The GDG decided to keep the recommendation, but accepts your opinion on this.
	4.3b	4.10	This recommendation conflicts with the one in 4.9. The evidence is to recommend cystectomy to confirm the diagnosis histologically (presumably for the very low risk of cancer), or to reduce the (very low) risk of infection after oocyte retrieval is just not strong enough to make it into a recommendation, especially as the risks of lower ovarian reserve and potentially premature ovarian failure override the other concerns.	Thank you for your opinion. The GDG has taken it into account, but decided not to change the recommendation accordingly.
	2.3d	502-507	I think it would be appropriate here to refer to the potential risk of excision to ovarian reserve. I know that pain and fertility have been addressed in separate sections, but busy clinicians that will use these guidelines could certainly use the prompt here, as many of their patient will have pain and infertility or at least the desire to have further children.	Thank you for your suggestion. We have added an indication of the risk for ovarian reserve to section 3.2. implementation tools will be developed to aid in crosslinking sections to make it easier for busy clinicians to find the relevant information fast and easy
Nicola Surico	1	31, line 101-104	Each symptom is not predictive of endometriosis. the association between two or more symptoms seems to be suspicious for endometriosis (not predictive).	Thank you for your comment. We changed “predictive of” into “risk factors for” as stated in the papers supporting this statement.
	1	37, line 26	Statement not clear and confusable. what does it means “a positive laparoscopy”?	Thank you for your comment. This is mentioned in the text above the recommendations
	1.3	37, 281-282	Transvaginal ultrasound with saline contrast sonovaginography (Dessole et al. 2003), transvaginal "tenderness-guided" ultrasonography (Guerriero et al. 2008) and transvaginal ultrasound with water-contrast in the rectum (Valenzano Menada et al, 2008) could represent an advance in the diagnosis of deep endometriosis	Thank you for your comment. We feel these techniques are not “established” techniques and hence they are not discussed in detail in the guideline.
	1.3 e	40, line 364	In the title it must be added: peritoneal endometriosis.	Thank you for your suggestion. We have incorporated your suggestion in the guideline.
	1.3 f	42, line 435	Replace “not to use” with “critical use.	Thank you for your comment, but the GDG strongly believes that we “not to use” is correct, with the outcome of diagnosing endometriosis.
	1.3 i	43, line 463	Histology of endometriosis can be proven even after partial dissection or shaving	Thank you for your suggestion. We have incorporated your

			without total bowel resection.	suggestion in the guideline.
	2.1 a	47, line 96	Recent papers demonstrated that continuous use of the OCP is more effective than the cyclic use. Delay of menstruation by continuous instead of cyclic OC administration statistically significantly reduced the frequency and severity of dysmenorrhea. (Vercellini et al. 2003).	We appreciate your comment and have included it into the guideline.
	2.1 a	52, line 246	Rec . 2.9: addback therapy is recommended especially in long GnRH analog therapy.	Thank you for your comment. In the recommendation, we advise add back therapy from the start of treatment, independent of short or long therapy.
	2.3 e		No detail or recommendation on urological deep endometriosis: why bladder or ureteral endometriosis are cited in extragenital endometriosis? (and not the bowel)	Thank you for your comment. We have copied the information on surgery for bladder and ureteral endometriosis to the section on DIE.
	3.2	78, line 125	.....CO2 laser vaporization or in alternative bipolar coagulation.....	Thank you for your comment. We have mentioned it as it was in the referenced paper.
Axel Forman	--	--	Overall, these guidelines represent a tremendous work and a huge step forward for endometriosis treatment. The authors are to be commended for their great efforts	Thank you for your comment.
	1.3e	p 40 line 364 ff	I can agree that in experienced hands, ultrasound is a reliable method for assessment of infiltration of the bowel wall. For the less experienced , MRI represents a more reliable alternative which offers a better assessment of high lesions and the relation to the ureter	Thank you for your comment.
	2.3d, e	p 59, line 484 ff	I think it should be specified that no studies have focused specifically on surgery for peritoneal endometriosis in pain patients, in contrast to endometriomas and deeply infiltrating lesions	Thank you for your comment. Peritoneal disease is described in section 2.3a. As a lot of patients have not only peritoneal disease, hence this was not labelled as “peritoneal disease only”.
	2.3g	page 64 line 666 ff	I have difficulties about the statement that use of icodextrine is "probably not effective". Both trials cited showed significant effects at the posterior side of the uterus. Moreover, control patients were treated with lactated Ringer's solution, which has anti-adhesion effects by itself, which strengthens the conclusions related to no treatment at all. None of the site-specific methods cited in the review have been tested against this standard, and the evidence for these methods seems comparably weak.	Thank you for your opinion.

Comments from reviewers that did not use the reviewer comments form

Biography	Comment	Consequence
Prof. Dr. Petra De Sutter	I have read the guideline with pleasure and much interest, since we have already done some research on guideline development with the group of Jan en Willianne before, and thus this guideline is very familiar to me. I checked in detail the actual guideline part (I did not read the whole second part following that due to lack of time, and because I know how they developed this guideline) and found no content mistakes, only two minor typo's (docters instead of doctors on page 5, line 23 and two words written together on page 15, line 83).	Thank you for your comment, we have corrected these errors in the guideline.
Dr Linda Giudice	I have reviewed the guidelines – excellent monograph. 2 items in the summary up front – I suggest you define "GDG" and also label the grade of recommendations in the boxes on the right in the Summary recommendations as one doesn't find its definition until going further into the document. Thank you for the opportunity to review this document.	Thank you for your suggestion. We have incorporated your suggestion in the guideline
Ben Cohlen	1. Rec 1.1 and 1.2 can be combined into 1 recommendation 2. Your recommendations suggest to perform laparoscopy in all patients suspected to have endometriosis; what is wrong in treating women with mild symptoms and no active wish to become pregnant WITHOUT performing a lap first (for instance oral contraceptives) 3. Rec 4.9, 4.10 and 4.11 are much too vague… How about size of the endometrioma's? small endometrioma's can be left alone before starting IVF, but what if they are larger than say 7 cm? Leaving it up to the patient is not fair, we should come with an (evidence based) treatment suggestion. 4. Please give a bit more detailed advice on the use of MRI. Based on a very small study of 44 patients only evidence level D you suggest NOT to use MRI to diagnose endometriosis whereas MRI DOES play a role in the diagnosis of deep infiltrating endometriosis. This seems contra-dictionary. Furthermore the radiologist should have special interest and expertise in endometriosis. 5. CA 125 should not be used to DIAGNOSE endometriosis, I agree, but what about follow-up and recurrence? 6. You focus on treating associated PAIN only; why not focus on improving Quality of Life? What about sexual functions? What validated questionnaires were used? How was pain determined in these trials? 7. Is there any role for SERMs or SPERMS? (selective receptor modulators) 8. Rec 2.19 should include something of the high risks of major	Thank you for your comments. - 1. We have combined all comments on recommendations 1.1, 1.2, 1.3 and 1.4 and changed the recommendations accordingly. - 2. We agree with your opinion, hence a GPP on empirical treatment in the section on medical treatment. We added a sentence referring to the section on empirical treatment in the introduction of the current chapter. - 3. We agree that we should come with an "evidence-based" comment on the size of the endometrioma, but since there is no evidence, we have not elaborated on this. In the studies included in the Benschop review, the size of the endometrioma ranged between =1.28 cm and < 6 cm. But this was not taken into account in the meta-analysis. - 4. Based on the evidence, we recommend not to use MRI for peritoneal disease. There is is too little evidence to advice it as diagnostic tool for DIE, but MRI is mentioned as a tool to establish the extent of DIE. In the considerations, it is mentioned that MRI is very operator dependent. - 5. The GDG acknowledge that there may be indications that CA125 is useful in follow up of patients with endometriosis, but there is too little literature to support a recommendation. - 6. We acknowledge that for women with endometriosis QoL is more important than reduction of pain. We also included QoL as an outcome in the literature searches (mentioned in the introduction of chapter 2), but as most studies measure pain, and not QoL, we ended up with recommendations on pain, rather than QoL. - 7. These compounds were included in the searches, but not discussed or recommended, since insufficient data. We added a sentence on these in the

	complications 9. Rec 3.5 based on 2 cohort studies: what is the risk of publication bias regarding this subject (negative trials will probably not be published) 10. There is no mention of sexual functioning and improvement of this after for instance surgery. Should an expert on sexual functioning be a member of your team? (you can contact Dr Dijkstra, Isala Clinics Zwolle on this subject) 11. Your suggestions on future research are too many, dealing with every issue, but should be prioritized ! and a bit more detailed: what is the world waiting for? 12. Please ask Dr W.K.H. Kuchenbecker, endometrioses expert, as a reviewer as well, I will copy him in in this mail Thank you and your team for all the effort!!! Although depressing to see the levels of evidence regarding a world-wide disease of great impact, you did a wonderful job	introduction of the hormonal therapies. - 8. This is specified in the text (clinical evidence section 2.3e) - 9. Based on the cohort studies, we have graded the level of evidence "B" and hence the recommendations is weak, reflecting the possibility of larger bias (including publication bias) - 10. Sexual function: We acknowledge that this could have been added to the guideline, but in defining the key questions, we focussed on the major problems of women with endometriosis. We also acknowledge that having a monodisciplinar GDG is one of the limitations of the guideline. We will keep this in mind when the guideline will be updated. - 11. We have added your suggestion. - 12. As you had forwarded your reply to him, he was invited as reviewer, but unfortunately he did not comment on the guideline
G. David Adamson	- Rec 2.1: usually termed "tricyclic"	Thank you for your comment. We have rewritten this section in the guideline.
	- Rec 2.8: I think the evidence is reasonable that 3 months works as well as 6 months. There are many studies on 3 and 6 months of treatment. Longer duration with add-back is also acceptable. recurrences occur but then retreatment is possible. I would be a little more subtle in this statement.	Thank you for your comment. The GDG feels that the evidence on duration is to limited to include this into a recommendation
	- Rec 2.11: I might put the oral contraceptive pill first because it is likely cheapest and safest, the GnRh analogues second since they are approved for this but expensive and possibly progestins second or third because of side effects overall, with aromatase inhibitors last.	Thank you for your suggestion. We have incorporated your suggestion.
	- Rec 2.22: I am not convinced there is not literature bias on this issue, and I would point out that no studies have shown less pain or higher fertility rates as a result of use of oxidized regenerated cellulose.	Thank you for your suggestion. A comment on fertility and pain has been included
	- Rec 2.28: I think it should be added that if the cystectomy is technically difficult it is acceptable to coagulate or otherwise ablate the cyst wall in order to minimize damage to the ovary.	Thank you for your suggestion. The surgical challenges are discussed in the text, but it is not necessary to mention it in the recommendation.
	- Rec 3.2 - 3.3: It is acceptable as an alternative, especially in young women who just have suspected or possible endometriosis, to treat with Controlled ovarian stimulation with clomiphene and/or intrauterine insemination for up to 3-4 cycles before laparoscopy.	Thank you for your suggestion. Based on your suggestion, we have added a paragraph in the considerations section on IUI as an alternative to surgery.
	- Rec 3.4: Again, if the cystectomy becomes technically difficult it is acceptable to ablate the cyst wall in order to minimize ovarian damage.	Thank you for your comment
	- Rec .1 -4.2: Okay--consistent with my comment above.	Thank you for your comment
	- Rec 4.8: I think the opoien study is the only one showing this, and it is	Thank you for your comment. We acknowledge your comment, but the GDG has decided

	inconsistent with the studies on more severe disease. Therefore, I would probably lighten this statement up so that a lot of unnecessary surgery does not get done. Note that in the US only IVF and ICSI are "assisted reproductive technologies", not IUI.	not to change the recommendation. In the guideline it is clearly stated that we use the ICMART technology.
	- Rec 4.8-4.9: Recommendation 4.8 and 4.9 don't make sense. Why would removing lesser disease help with IVF but not more disease? It also does not square with the literature. (4.9 there are essentially no data to support this statement, or to state that it should be done. We don't know the answer. WERF is trying to do a study to find the answer.	Thank you for your comment. These recommendations are directly based on the existing evidence on this topic. There is evidence of a beneficial effect in peritoneal disease, but there is no "good" evidence for DIE, hence we state that the effectiveness of surgery before ART in DIE is not well established. We hope the WERF study will bring some much needed input on this topic.
	- Rec 4.10: See comment above. it is not known if pregnancy rates are improved or not. that is why the EndoART trial is being attempted by WERF.	Thank you for your comment. We look forward to including good quality evidence on this topic to the update of this guideline.
	- Rec 6.1: risky procedures should be avoided, but not necessarily all procedures.	Thank you for your suggestion. Based on our extensive literature search it was not possible to categorise procedures according to risk. There was no published evidence that any intervention should be carried out for incidental disease.
	- Rec 8.1: Check recent data. Clear cell and endometrioid cancer might be slightly increased from a very low background rate.	Thank you for your comment. In the clinical evidence, we have stated "The association is strongest in cases of endometrioid and clear-cell ovarian cancer histologies (RR approx. 3) (Sayasneh et al., 2011, Munksgaard & Blaakaer, 2011)", which is consistent with your comment.
	- Rec 2.19: it should be noted that extensive bowel surgery is often not needed or indicated, especially in younger patients, and treatment should be based on patient age, symptoms, and the ability to remove at least some of the disease without having serious surgical complications and/or postoperative sequelae.	Thank you for your comment. As we found no evidence specifically on young patients, we have not focussed on them in the current guideline.
	Section 3.2, p77, line 100: Please find attached additional data in a prospective cohort study published in AJOG 1994 by Adamson and Pasta. These data confirm the findings in the studies you have published.	Thank you for your comment. The mentioned paper was included in the evidence table, but the GDG member commented that "SR of operative laparoscopy versus no treatment or medical treatment: impossible to assess the effect of surgery alone."
Maria Goudakou	Thank you for asking our opinion about the guidelines for endometriosis. The endometriosis group has done an excellent work. I just have some points to comment that I hope will be useful for the final version. 1. Considering the diagnosis of endometriosis, the low percentage of endometriosis appearance or reappearance in menopausal women should be mentioned (summary of recommendations page 11). 2. The evidence that any additive for adhesion prevention after operative laparoscopy for endometriosis might be helpful, is low (management of women with endometriosis, page 14, Rec 2.22). So, it should be mentioned. 3. After burning or traumatizing of a tissue a considerable amount of healing substances are produced (TGF-β, growth factors e.t.c) that might have influenced the ovarian response or the fertility parameters. For this reason no	Thank you for your comments: 1. The experts of the GDG have the opinion that endometriosis has a very low prevalence in postmenopausal women. As such, this was not added to the guideline 2. We have checked and this is mentioned in the text. 3. The GDG decided not to elaborate on this topic 4. The GDG believes that this recommendation could be helpful in reducing anxiety among women with endometriosis, as you state.

	one is convinced that the power used to coagulate or vaporize the endometriosis might have influenced the pregnancy rate (management of women with endometriosis, page 16, Rec 3.3). 4. I think that the Rec 8.3 statement should be the best practice point since any reference about higher percentage of some cancers in endometriosis women could get the women anxious and insecure about their future (summary of recommendations, page 21)without any real reason. Our warmest wishes	
Pr Herve DECHAUD	- for the remmendation rec 4.6, we have to hightlight the increased risk of ovarian abscess following oocyte retrieval. there are papers concerning this point. - We have to explain clinical symptoms related to these kind of abscesses. - We have to make remmendations about treatments (try to not touch endometriomas during oocytes pick-up, antibiotics, ovarain drainage (surgical or ultrasound). Thank you again for your work.	Thank you for your suggestion. Preventing and treating ovarian abscesses was not the scope of this guideline, hence we have limited our recommendation on this in women with endometriosis by pointing out the use of antibiotic prophylaxis..
Dr JCM van Huisseling	I have a few comments: In general I would prefer to unifie the formulation of some recommendations in order to avoid medico-legal problems. e.g. terms as "should" could in my opinion better be replaced by "it is recommended" (there is a difference in formulation in the different chapters)	Thank you for your comments. We agree with this proposal, but the differences in “should” and “recommended” or “should consider” are based on the discussion of the GDG. We have looked at all recommendations, and unified where possible.
	Chapter 1 Diagnosis: FDG-PET or other PET is not mentioned? Probably this is still in a research phase. Maybe a remark concerning this field can be added.	Thank you for your comment. The GDG acknowledge that FDG-PET or other PET could have potential in the diagnosis of endometriosis, but there is no evidence to support a recommendation.
	Chapter 2 Treatment: It is not clear to me how to start medical treatment , maybe a recommendation can be given in which order medical treatment can be started: Is it better to start with a GnRh agonist and continue with OAC or progestagens? Or doesn’t this make any difference or has never been investigated?	Thank you for your comment. The order of given medical treatment is unclear from the literature and hence the GDG states that the decision depends on patient preferences, side effects, costs and availability.
	Recommendations2.24 and 25 are somewhat confusing. However level A the studies are rather weak and are in my opinion not strongly clinically relevant. Is it an option to leave these out since rec 2.26 and 2.27 cover the matter?	Thank you for your suggestion. We have considered it in rewriting/reorganising the sections on pre- and postoperative medical treatment and secondary prevention. The level A reflects that there is a systematic review summarising the evidence on this topic.
	The same can be applied to Rec 4.9: Cystectomy prior to etc. etc. does not improve pregnancy rates, HOWEVER one can have good reasons to perform a cystectomy: see REC 4.10	Thank you for your comment. We agree that these recommendations cannot be read independently, but since the first is evidence based, and the second in a good practice point, we had to separate them.
	Personally I would not recommend REC 6.2: the word incidental is confusing. Does it also means accidental? In the Netherlands we have an expression:	Thank you for your comment. The general consensus from the guideline group was that clinicians have a duty of care to inform patients about an incidental finding of

	"Don't wake up sleeping dogs". I know it is a medico-legal slippery path but some patients can take all info and counseling and some can't. So for psychological reasons it can be wise not to fully inform all patients about an accidental/incidental finding if there is no clinical relevance to it. To put this in a guideline makes it susceptible for medico-legal trouble. I hope my remarks are clear to you and I am willing to elucidate if necessary.	endometriosis. However, this is a recommendation only, and clinicians are advised to tailor their care to the individual patient.
Berglind Ósk	I really liked reading the ESHRE Endometriosis guideline. I when i read the infertility part saw that there was no mention of the immunological factors that can cause for example implantation failure and miscarriages in women with endometriosis. I would have loved to see a chapter on that subject. Immunological treatments with IVF are getting more and more popular and are increasing the success rate for women with endometriosis. - Many doctors say that up to 30% of endometriosis women have some sort of immunological problems. (http://www.babyfriendlybook.com/)	Thank you for your comment. Immunological factors are not included in the current guideline, but we will consider adding a section on immunological factors when the guideline will be updated.
Tommaso Falcone	Hi- the guidelines were reviewed by the Endometriosis Special Interest Group of the ASRM there was only one comment - see below. "In women with an ovarian endometrioma, the GDG recommends clinicians to consider cystectomy prior to treatment with assisted reproductive technologies to confirm the diagnosis histologically, reduce the risk of infection after oocyte retrieval, improve accessibility of follicles or improve endometriosis-associated pain, although it does not improve pregnancy rates. It might be worthwhile to denote a size recommendation for the endometrioma that they recommend clinicians remove prior to ART."	Thank you for your comment. We agree that we should come with an “evidence-based” comment on the size of the endometrioma, but since there is no evidence, we have not elaborated on this. In the studies included in the Benschop review, the size of the endometrioma ranged between =1.28 cm and < 6 cm. But this was not taken into account in the meta-analysis.
George Pados	Herein, please find my comments on the ESHRE guideline: Management of women with endometriosis. Congratulations to all the contributors for their fantastic and highly scientific work. Introduction: line 27 It has been focused mainly on cost parameters and not optimization of management.	Thank you for your comment. We have reviewed and updated the language of the introduction.
	Rec 1.1 is more appropriate than rec 1.2 Rec 1.3 is more appropriate than rec 1.4	Thank you for your comment. We have combined all comments on recommendations 1.1, 1.2, 1.3 and 1.4 and changed the recommendations accordingly.
	Rec 1.7 should be omitted	Thank you for your comment. The GDG feels this is a valid recommendation and therefore it will not be deleted.
	Rec 1.10 It should be added: ...given that the Gynecologist is an accredited endoscopist or has adequate training	Thank you for your comment. We have added information on a “good” laparoscopy and the characteristics of the clinician performing the surgery.

	Rec 1.13 TVS is indicative but not conclusive for rectal endometriosis. On the contrary, ultrasonography with rectal probe, although not associated with high patients' compliance, has higher sensitivity.	Thank you for your suggestion. The GDG has decided not to change the current recommendation based on your suggestion, as the recommendation is based on the referenced evidence.
	Rec 1.17 ...but it has a high sensitivity rate for deep infiltrating endometriosis	Thank you for your comment. There is too little evidence to advice MRI as diagnostic tool for DIE, but it is mentioned as a tool to establish the extent of DIE.
	Rec 2.3 is more preferable than 2.2. It should be, also, added: ... taking into account side effects and restricted efficacy.	Thank you for your comment. We have taken this into consideration, but decided not to update the recommendation based on it.
	Rec 2.4: Oral contraceptives reduce mainly dysmenorrhea and non-menstrual pain but not dyspareunia.	Thank you for your comment. We have again checked the referenced paper which states “at the end of treatment, a significant reduction in deep dyspareunia was observed in both groups,...” Hence, we did not modify the recommendation as suggested.
	Rec 2.22 and 2.23: Both should be omitted and instead to add: Clinicians should administer barrier agents for de novo adhesion formation, although there is limited evidence from randomized clinical trials to support their beneficial effect.	Thank you for your suggestion. The GDG believes that a balanced representation of the literature is given in the text. The formulation of the recommendation was extensively discussed within the GDG and reflects the strength of the evidence, hence we did not change it.
	Rec 3.3 It should be change to: In infertile women with stage I/II endometriosis, clinicians may consider the use of bipolar instead of monopolar electrocuagulation. If CO2 laser is available in the operation theatre, it should be preferred, since it has been shown, but not definitely proven that its use is associated with less adhesion formation and higher cumulative spontaneous pregnancy rates.	Thank you for your suggestion. The GDG decided not to incorporate it in the guideline.
	Rec 3.4. It should be added: In patients with previous operations for endometriotic cysts, the "three-step" technique or the "combined" technique (excision of the cyst wall and CO2 laser ablation of the hilus) should be an alternative approach, since it has been clearly shown that these approaches have less impact on ovarian reserve.	Thank you for your comment. To our knowledge, this technique is mentioned only in observational studies and not well established for supporting a recommendation on this.
	Rec 4.2 is more accurate than 4.1/4.3	Thank you for your comment
	Rec 4.5/ rec 4.6 should be omitted, since they are lacking scientific evidence.	Thank you for your comment. We agree, and acknowledge (Hence the level C and D) that the evidence behind these recommendations is of limited quality/quantity. However, we believe that they have an important message that fits within the scope of this guideline.
	Rec 4.10 is more accurate than 4.9/ 4.11 Rec 5.3 is more accurate than 5.1/ 5.2 Rec 8.1 is more accurate than 8.2/ 8.3	Thank you for your comment
Dr. Miguel A. Marrero	I have reviewed the entire draft version of "The ESHRE guideline: Management of women with endometriosis" and I have the following comments: CONTENTS, page 4, after 2.3g Adhesion prevention after endometriosis surgery .....page 64; it should follow, 2.3h Medical therapies adjunct to ... CONTENTS, page 4, 4.1a Intrauterine insemination with controlled ovarian	Thank you for your comment, we have corrected this error in the guideline.

	stimulation in women with endometriosis ...84	
	INTRODUCTION, page 5, Clinical need for the guideline, line 9, the general female population of reproductive age to 50% in infertile ...	Thank you for your comment. We have added “female” in this sentence.
	INTRODUCTION, page 5, Clinical need for the guideline, line 12, corroborated by physical examination and imaging techniques (transvaginal sonography for ovarian endometriomas and pelvic magnetic resonance imaging (MRI) for adenomyosis) and finally proven ...	Thank you for your suggestion. We have not changed the guideline based on your suggestion, since we believe this information is not necessary in a concise introduction and it is explained in detail in the first chapter of the guideline.
	INTRODUCTION, page 5, Clinical need for the guideline, line 19, severe. These stages however poorly reflect pain symptoms, but correlate better with infertility.	Thank you for your comment, but the GDG does not agree and therefore did not change the sentence.
	INTRODUCTION, page 5, Clinical need for the guideline, line 23, endometriosis and their doctors experience difficulties in diagnosing the disease and with the wide variety of clinical practice management of women with this disease. INTRODUCTION, page 5, Clinical need for the guideline, line 35, endometriosis to improve their care and ...	Thank you for your comments. We have reviewed and updated the language of the introduction, taking into account your comments.
	1.3 Medical Technologies in the diagnosis of endometriosis, page 10, Rec 1.10, A negative diagnostic laparoscopy in women with symptoms and signs of the disease is highly accurate for the exclusion of the diagnosis of endometriosis, but it does not exclude the diagnosis of adenomyosis.	Thank you for your comment. However, adenomyosis is not the topic of the guideline and hence its diagnosis is not discussed.
	1.3 Medical Technologies in the diagnosis of endometriosis, page 10, Rec 1.17, Clinicians should be aware that the usefulness of magnetic resonance imaging (MRI) to diagnose peritoneal endometriosis is not well established, but it may help to diagnose adenomyosis.	Thank you for your comment. However, adenomyosis is not the topic of the guideline and hence its diagnosis is not discussed.
Prof Florin Stamatian	Firstly, I want to congratulate you and your staff for your exquisite work.	Thank you for your comments and suggestions:
	I think that perhaps in the introduction the definition may require a little more insight, by stressing the importance of the particularities of the ectopic endometrial tissue: modified architecture, a different metabolic behaviour or a modified receptors pattern. (introduction pg 5 line 5)	Thank you for your comment. The guideline development group focused on the clinical questions on endometriosis.
	Although, add back therapy has been discussed in the chapter related to pain associated endometriosis, I consider it important to be mentioned again when discussing Ag GnRh treatment prior to IVF. (pg 223).	Thank you for your comment. However, as the GDG recommends not to prescribe hormonal treatment, including GnRHa, there seems to be no relevance of repeating the information on add-back therapy
	Perhaps the most challenging subject, according to my personal interest is represented by the strategy that one should follow regarding a 3-6 cm endometrioma prior to IVF. I believe that today we do posses evidence enough (see bibliography) to recommend against surgery in particular in some categories (AMH < 1; prior surgery for endometriosis, or bilateral endometrioma). (pag 289 – 290)	Thank you for your comment. However, this section deals on surgery for improving spontaneous pregnancy rates, while the review of Sallam is included in the evidence for surgery before ART.

	Gupta S, Agarwal A, Agarwal R, Loret de Mola JR. Impact of ovarian endometrioma on assisted reproduction outcomes. Reprod Biomed Online 2006;13:349–360. Sallam H, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. Cochrane Database Syst Rev 2006; CD004635.	
Emile Daraï	Comment on the guidelines for endometriosis 1. line 49 : Guidelines from France are available from the Collège National des Gynécologues et Obstétriciens Français (CNGOF) published in a special issue of the Journal de Gynécologie, Obstétrique et biologie de la reproduction 2007 2. Rec 1.2 : the last symptom concerning fatique is not specific and can be source of misdiagnosis and should be deleted. 3. Rec.1.6 : I think i twill be interesting to add vaginal nodule visible in the posterior vaginal fornix. 4. Rec 1.13 : I think that the accuracy of TVS is not so high to rule out the diagnosis of rectal endometriosis. Hence I suggest to delete « or ruling out ». 5. Concerning DIE, the authors did not note, as in the review from Meuleman et al, that a randomized study is available comparing laparoscopy to open surgery for colorectal resection (Daraï et al Ann Surg 2010) showing that laparoscopy should be first recommended thank to a lower complication rate. Hence for R 2.20, we think that it is now necessary to state that laparoscopy should be recommended for DIE treatment associated with colorectal involvement. In REC 2.20, we think that the terms »or laparotomy » should be deleted. LEVEL A ; Moreover, it is maybe times to reinforce in this specific setting the importance of specialized or referent centres. In addition a sub-analysis of this randomized trial (Fertil Steril 2011) demonstrated that spontaneous pregnancy rate was significantly higher after colorectal resection by laparoscopy compared to open surgery. It is quite strange that the sole randomized study on this subject is never cited as reference. (Professor Emile Daraï) 6. Line 665, I think that it is important to clarify that Trew et al trial demonstrated the absence of efficacy on de novo adhesion as adhesion prevention may included adhesion reformation. It is maybe necessary to underline the absence of data on the relevance of other products available to prevent adhesion in the specific setting of endometriosis. 7. As mentioned previously, a sub-analysis of a randomized trial comparing laparoscopy to open surgery for colorectal endometriosis has demonstrated (Fertil Steril 2011) that spontaneous pregnancy rate was	Thank you for your comments and suggestions - 1. We have incorporated your suggestion in the guideline. - 2. We changed “fatigue” into “fatigue in the presence of any of the previous”. - 3. The sentence “or visible vaginal nodules in the posterior vaginal fornix” was added to the recommendation. - 4. This recommendation is based on the paper of Hudelist 2011, that states “the results of our meta-analysis suggests that TVS is indeed very useful for sonographic diagnosis but also presurgical exclusion of bowel endometriosis.” Therefore, the recommendation was not changed according to your suggestion. - 5. We have added the references to the clinical evidence, but the GDG decided not to add a recommendation on this topic. - 6. This issue was extensively discussed and the GDG agreed on the content on Icodextrin. Regarding the second comment, the text has now been added. - 7. We have added information from your papers to the section of surgery for pain, with mentioning the data on surgery. - 8. We have incorporated this paper in the evidence, although it did not change our recommendations.

	significantly higher after colorectal resection by laparoscopy compared to open surgery. Moreover, this trial evaluated pregnancy rate according to proved infertility. At least, this randomized trial has to be referenced. In addition, there is no data on pregnancy rate after surgery of DIE. The authors assimilated advanced stages of the disease according to ASRM classification to disease with DIE. I think that it is important to distinguish fertility outcomes of patients with stage III-IV ASRM from patients with DIE (Stepniewska, Chapron Hum Reprod 1999,, Daraï) even the authors cannot conclude . Hence, we can imagine a REC 3.6: in infertile women with DIE, data are insufficient to recommend surgical removal to enhance fertility. 8. Finally, in REC 3.5, you give the reference of Vercellini 2006 demonstrating that expectant management gave similar results that surgery for rectovaginal septum endometriosis while the recommendation is “to consider surgery”.	