Methods Report on the Development of the European Evidence-based (S3) Guideline for the Treatment of Acne – Update 2016

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1 Introduction

A comprehensive description of the updating process of the European evidence-based S3 Guideline for the Treatment of Acne 2016 (hereafter referred to as EU Acne Guideline 2016 or the Guideline) is provided. The Guideline was developed in accordance with the standard operating procedures of the European Dermatology Forum (EDF) (see Appendix A). The underlying methodology incorporated the quality criteria of the Appraisal of Guidelines Research & Evaluation II (AGREE II) Instrument [1], as well as the recommendations of the Cochrane Collaboration, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group [2], and the German Association of Scientific Medical Societies (AWMF) [3].

The update of the EU Acne Guideline is based on systematic literature searches, systematic evaluations of the search results, and a consensus conference based on formal consensus methodology (nominal group technique).

2 Participation of relevant interest groups

2.1 Nomination of experts

In January 2015, the expert panel of the 2011 version of the Guideline was contacted to request their participation in updating the Guideline. All experts, except for Niels K. Veien (Denmark) and Ruta Ganceviciene (Lithuania), agreed to participate again.

Additionally, as suggested by the expert panel, three new members were accepted, namely Hans Bredsted Lomholt (Denmark), Zrinka Bukvic Mokos, MD (Croatia) and Julien Lambert, MD (Belgium).

Nominations were confirmed by the EDF. To qualify as an expert, an individual had to satisfy at least some of the following criteria:

- extensive clinical experience in the treatment of acne,
- relevant publications in the field of acne,
- relevant experience in evidence-based medicine.

Emphasis was placed on selecting a representative panel of experts from across Europe who are still actively involved in patient treatment.

2.2 Expert methods group

The Division of Evidence Based Medicine (dEBM) at Charité – Universitätsmedizin Berlin was chosen as the methodological centre due to the experience and expertise in the development of guidelines in dermatology. The first European S3 Guideline for the Treatment of Acne was also developed by the dEBM team.

2.3 Participation of patient representatives

Although extensive efforts were made to find patient representatives, these were unsuccessful due to the current lack of patient organisations in this area. Patients were, however, invited to join the external review.

For a detailed overview of all participating experts, see Appendix B.

3 Kick-off Meeting

Two online (screen-sharing) - telephone conferences took place on 27th February and 2nd March 2015 as kick-off meetings. Conflicts of interests were presented, discussed, assessed and judged by the group to be acceptable for participation in the guideline work (see Appendix F). At the time, the declarations of conflicts of interests by Vincenzo Bettoli, Julien Lambert, and Maja Vurnek Zivkovic were not yet available. COI declarations of all members were later re-discussed at the beginning of the online consensus conferences with confirmation of acceptability of the members.

A discussion of the methodological approach used for the EU Acne Guideline 2016 took place. Consensus was reached to adopt the same methods as for the 2011 version, with a few amendments, as listed below.

During the kick-off meeting, the expert group discussed and confirmed the interventions and the questions that were to be considered and subsequently reached a consensus regarding the main focus of the Guideline. The expert group decided that suitable treatment options were to be presented in a clinical treatment algorithm, taking into account the type of acne and the severity of the disease.

As a result of the kick-off meeting, the inclusion criteria of the previous EU Acne Guideline (version 2011) were modified for the assessment of induction therapy to include:

- only randomized controlled trials (RCT),
- only studies that report lesion count (mean or median change) as outcome,
- as a new fixed combination, the treatment option tretinoin plus clindamycin.

Furthermore, it was decided to:

- include two Cochrane reviews: one on light therapies and one on combined oral contraceptives pills,
- conduct a systematic evaluation of the available literature on maintenance treatment,

4 Methods

The methods of this evidence and consensus-based Guideline follow a systematic review approach including systematic literature searches, a two-step screening approach using pre-defined exclusion/inclusion criteria as well as a risk of bias assessment.

The nominal group process for consensus based decisions is described in Chapter 7.

4.1 Literature search

MEDLINE, MEDLINE In-Process and EMBASE (via OvidSP) were systematically searched (for a sample search strategy, see Appendix C). For topical and systemic treatments, the search covered 2010 to 5th July 2015. The inception dates were determined by the literature search periods covered in the previous EU Acne Guideline.

4.2 Standardized inclusion/exclusion criteria

The included interventions are listed in Table 1. Only randomized controlled trials evaluating the below-listed anti-acne treatments including patients with acne were eligible for inclusion. Studies had to report lesion count at baseline and follow-up, or a mean/median change in lesion count as an outcome.

Table 1: Interventions included in the guideline

Systemic treatments	Topical treatments	Light therapies
Antibiotics • Erythromycin • Clindamycin • Tetracycline • Doxycycline • Minocycline • Lymecycline	Antibiotics • Erythromycin • Clindamycin • Tetracycline • Nadifloxacin	Intense pulsed light
Isotretinoin	Azelaic acid	Photodynamic therapy
Combined oral contraceptives pills	Benzoyl peroxide	Blue light, red light, visible light
Zinc	Retinoids • Adapalene • Isotretinoin • Tretinoin	Laser
	Fixed combinations: Adapalene/BPO BPO/clindamycin Erythromycin/tretinoin Erythromycin/isotretinoin Erythromycin/zinc Clindamycin/tretinoin Clindaymcin/zinc	

Exclusion criteria (adapted from previous EU Acne Guideline 2011) were as follows:

- Study does not address management of active acne,
- more than 20% of the patients have chloracne, acne venenata, acne fulminans, acne necroticans, acne agminata, or rosacea,
- occupational acne,
- fewer than 12 patients randomized per study arm.

4.3 Data Screening and extraction

All identified records were screened for inclusion/exclusion by two independent assessors (SR, CD). Each selected abstract was included in the full text screening. Two assessors (SR, UA) screened all full texts for inclusion using the pre-defined inclusion/exclusion criteria. For included studies, data was extracted independently by two assessors (SR, UA) using a standardized data extraction form (MS Excel sheet) containing the following items:

- Author, year
- Intervention, control intervention(s)
- Number of randomized participants
- Severity of acne
- Study duration

- Percentage reduction in lesion count from baseline to time point of evaluation
- Other outcomes/statistics
- Comments
- Safety
- Number of drop outs due to adverse events

The forms were compared and any discrepancies were reviewed by a third assessor (RE) and resolved through discussion. The final evidence tables are described in detail in Chapter 6.

4.4 Methodological evaluation

A basic methodological evaluation took place. An assessment of study conduct in regards to blinding (evaluator, assessor, investigator and/or patient), the generation of the randomization list and in regards to the statistical analyses took place. These were the basic criteria for the assignment of the grade of evidence, see explanations for ‘Grade of evidence’ in Section 6.2.1.

4.5 Results

The update search generated 990 hits. After de-duplication 806 records were screened. The two independent assessors (SR, CD) determined that 87 publications were eligible for full-text evaluation. Two of these 87 publications had been identified through reference list screening and packaging inserts. Data was extracted from 47 articles (including one article reporting data for two studies).

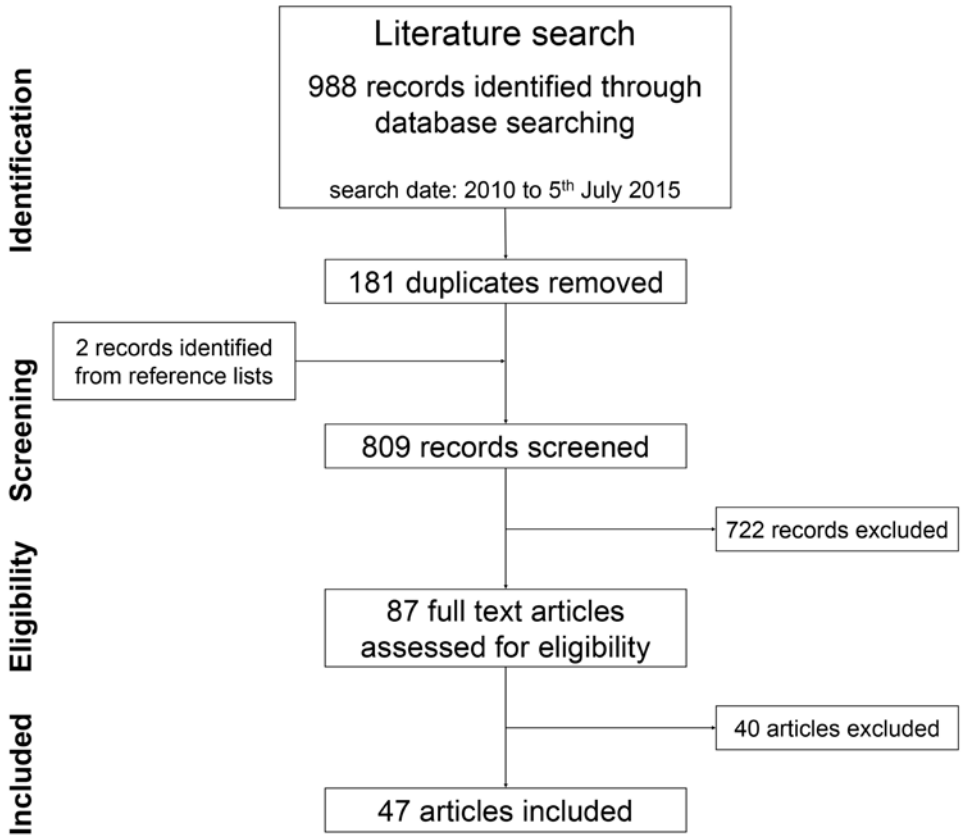

Figure 1: Flow of information – update search for induction treatment of acne

As this is an update of the EU Acne Guideline 2011, altogether, data from 210 records (222 RCTs) was extracted, see evidence tables, Chapter 6.

Included in the EU Acne Guideline 2016 - as tabular summaries - are the results of 154 studies (126 from previous guideline version, 28 from update search) as decided by the experts with regards to clinical relevance.

5 Reviews

During the kick-off meeting it was decided to use Cochrane reviews for the areas of ‚laser and light therapy' and 'hormone therapy'. Furthermore, the dEBM team conducted two systematic reviews independently, one for maintenance therapy and one for patient preferences; the results of which were also used as evidence base.

5.1 Laser and light treatment

For reasons of feasibility the group decided to use the Cochrane Review currently being developed by Barbaric et al. The authors contacted and provided the

guidelines group with a preliminary draft. However, unfortunately, the final version of the Cochrane review was not finished by the time the guideline was finalised. The guidelines group did take the results of the systematic review of the 2011 version of the guideline together with the preliminary results of the Cochrane review into account to phrase the current recommendations of the update. The preliminary version of the Cochrane systematic review “Light therapies for acne” by Barbaric et al. [4] was checked for sufficient methodological quality (see Appendix D, checklist by Scottish Intercollegiate Guidelines Network [SIGN]). Detailed results from the Cochrane review could unfortunately not be displayed in the guidelines as it was still preliminary.

5.2 Combined oral contraceptives pills

The Cochrane review “Combined oral contraceptive pills for treatment of acne” by Arowojolu et al. (2012) [5] served as a base for the induction treatment with hormonal agents. Author conclusions were included in the Guideline. The reviews had been assessed and an acceptable methodological quality was determined using the “Methodology Checklist 1: Systematic Reviews and Meta-analyses” by SIGN (see Appendix E).

5.3 Patient preferences

The dEBM team conducted a separate systematic review on the available evidence of patient preferences in acne treatment. The results were published separately [6] and taken into consideration for the guideline.

5.4 Maintenance treatment

The dEBM team conducted an independent systematic review on acne maintenance treatment defined as ‘maintenance is the treatment period that follows a successful induction therapy at the end of which patients had achieved a pre-defined treatment goal’. The results were published separately [7] and taken into consideration for the guideline.

6 Evidence tables

Three evidence tables (MS Excel) for the induction treatment of acne are appended to the EU Acne Guideline 2016; the first two tables (comedonal and papulopustular acne) contain multiple sheets, separated by treatment. The last table, conglobate acne, contains only one sheet due to scarce evidence.

6.1 Categorising available evidence

Only RCTs reporting lesion counts were included and systematically assessed. Studies highlighted in green have been added as a result of the update literature search.

Attempts were made to match the study populations in the included trials to the different acne types as defined by the expert group (comedonal/ papulopustular/ conglobate). Attempts were also made to identify sources of indirect evidence to serve as a base for the assessment of efficacy in the given acne types. Certain studies provided evidence applicable to different acne types (e.g. inflammatory lesion counts applicable to papulopustular acne and non-inflammatory lesion counts applicable as indirect evidence for comedonal acne) and hence were included in both evidence tables.

1) Comedonal acne: A trial on comedonal acne was categorized as such if (a) this had been clearly stated by the authors and/or (b) this designation could be confirmed by patient baseline data provided (comedo count provided, few or no inflammatory lesions). Due to the paucity of studies on comedonal acne, indirect evidence was generated by means of looking at the percentage decrease in non-inflammatory lesions (NIL) in trials on patients with other acne types.

2) Papulopustular acne: A trial on papulopustular acne was categorized as such if (a) this had been clearly stated by the authors of the trial and/or if (b) this designation could be confirmed by patient baseline data. For papulopustular acne, the EU Guideline group had agreed that inflammatory lesions (IL) count as outcome measure would provide the best evidence.

3) Nodular/conglobate acne: A trial on nodular/conglobate acne was categorized as such if (a) this was clearly stated by the authors and/or (b) the study reported a respective nodule and/or cyst count at the beginning of the trial. The percentage reduction in nodules (NO) or cysts (CY) served as the main outcome measure.

6.2 Presentation of data in evidence tables

On each sheet, headings and subheadings name the comparisons and then list the included studies. Underneath all of the studies within one comparison, summaries of efficacy and safety/ tolerability are provided taking all studies into account (some exceptions apply, see corresponding details below).

6.2.1 Individual summary of efficacy, safety and grade of evidence

Extracted items (Figure 2) are explained below:

Author(s)	Interven-tions	N	S	D	B	% ↓IL	Other Outcomes / statistics	Comments	Summary of efficacy	Safety	Drop outs	Summary of safety	Grade of evidence

Figure 2: Heading of evidence tables – example: papulopustular acne

“Author(s)”: States the name of the first author and the year of publication; in case of data from the same study group being published in separate publications, the first author of each publication is listed. The reference number of the study corresponds to the number in the reference list (provided in parentheses).

“Interventions”: Lists the investigated medications with concentration, application regime.

“N = number”: Total number of patients randomized is provided; for studies identified in the current literature search numbers were extracted for each treatment arm separately.

“S = severity”: Grade of severity (1 - mild, 2 - moderate or 3 - severe) as defined by authors of the study or if no such categorization was provided, as assessed by the guideline group taking into consideration the lesion count at baseline or the scale/score given at baseline (for example, Burke-Cunliffe/Leeds score). See chapter 2.1.1 Acne grading system of guideline text.

“D = duration”: Duration of study in weeks stated; in cases where a study lasted longer than 12 weeks, the methodologists attempted to extract outcome data for week 12 (or as close to this point as possible); in this case, two information are provided the first number gives the overall length of the study in weeks, whereas the second number gives the time point at which outcome data were extracted.

“B = Blinding”: Data was extracted as provided by the authors (I - investigator-blinded; P - patient-blinded; E - evaluator-blinded; A - assessor-blinded; 1x - single-blinded; 2x - double-blinded).

“% ↓ NIL/IL = Percentage reduction in lesion count”: Percentage reduction in lesion count from baseline to time point of evaluation.

Table ‘Comedonal acne’: The mean percentage reduction in non-inflammatory lesions is stated. Where this was not available, the percentage reduction in comedones (open and/or closed) is listed. In absence of the mean percentage reduction of lesion count, the median percentage reduction was extracted.

Table ‘Papulopustular acne’: The mean percentage reduction in inflammatory lesions is stated. Where this was not available or calculable, the median percentage reduction in IL is stated. The reporting of papules and pustules was seen as equivalent to IL. If studies reported mean percentage reduction in papules and pustules separately, we calculated the mean percentage reduction in IL (adding papules [PA] count and pustules [PU] count, divided by 2). If none of the above mentioned lesion counts were available, we reported the mean percentage reduction in total lesion count (total lesion count = NIL + IL count).

Table ‘Conglobate acne’: The mean percentage reduction in nodules and cysts is provided. If this was not available or calculable, the mean percentage reduction in nodules or cysts separately, or in IL was extracted.

“Other statistics”: Any other statistical information provided in the paper and considered relevant.

“Comments”: Summary of additional information about the methods such as randomization, data analyses (ITT), other relevant information (e. g. split-face, age if study on children, only abstract available, etc.).

“**Summary of efficacy”:** NIL, IL, NO, CY or their components (papules, pustules, open or closed comedones) were taken into account. We defined a treatment to be superior to another treatment if there is a difference ≥ 10% in efficacy outcome (see chapter 3).

“Safety”: The number of patients with at least one adverse event and the three most common adverse events as stated by the author(s).

“Drop-outs”: Number of drop-outs due to adverse events.

“Summary of safety”: A global comparison of safety data was done taking into consideration the number of patients with at least one adverse event, the three most common adverse events and drop-out rates due to adverse events. If no such data was available the authors’ conclusion was added. If studies failed to report safety/ tolerability aspects no summary of safety/ tolerability was drawn (reported as ‘insufficient data’).

Summary of safety was not done for studies comparing verum versus vehicle/placebo. Direct comparisons of active treatments are the main focus of the guideline in terms of safety.

“Grade of evidence”: Each trial included in the Guideline was evaluated with regard to its methodology and assigned a grade of evidence according to a modified grading system used in previous guidelines [8, 9].

A Randomized, double-blind clinical trial of high quality (for example, sample-size calculation, flow chart of patient inclusion, intention-to-treat [ITT] analysis, sufficient sample size)

B Randomized clinical trial of lesser quality (for example, only single-blind, no ITT)

C Comparative trial with severe methodological limitations (for example, not blinded, very small sample size)

6.2.2 Overall summary of efficacy, safety and level of evidence

For each comparison the overall evidence was assessed, a ‘level of evidence’ assigned and a summary for efficacy and safety/ tolerability given (Figure 3).

Summary efficacy: comparable efficacy azelaic acid = BPO (range reduction IL: azelaic acid: 45 - 84%, BPO: 44 - 84%) (LE 2) Azelaic acid = BPO: 1 A study, 1 B study, 1 C study
Summary safety / tolerability: superior safety/tolerability azelaic acid > BPO (LE 4) Azelaic acid > BPO: 1 A study, 1 C study

Figure 3: Summary efficacy and safety – example: papulopustular acne

Level of evidence (LE): In addition to assigning a grade of evidence to individual trials, the methodologists assigned levels of evidence to the various treatment options. The levels of evidence, which can be regarded as an overall rating of the available efficacy and safety/ tolerability data for each treatment option, were defined as follows:

1 ***Further research is very unlikely to change our confidence in the estimate of effect.***

At least two trials are available that were assigned a grade of evidence A and the results are predominantly consistent with the results of additional grade B or C studies.

2 ***Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.***

At least three trials are available that were assigned a grade of evidence B and the results are predominantly consistent with respect to additional grade C trials.

3 ***Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.***

Conflicting evidence or limited amount of trials, mostly with a grade of evidence of B or C.

4 ***Any estimate of effect is very uncertain.***

Little or no systematic empirical evidence; included trials are extremely limited in number and/ or quality.

The assignment of the different grades of evidence to a resulting level of evidence is shown in Table 2.

One trial with a grade of evidence A is equivalent with respect to its impact on the level of evidence to two trials with a grade of evidence B.

One study with a grade of evidence A is equivalent with respect to its impact on the level of evidence to four trials with an evidence grade of C.

Table 2: Generation of level of evidence

Level of evidence	**Number of studies with specific grade of evidence**
Summary of efficacy:	
1	At least 2 A studies
2	At least 1 A study and 1 B study
3	At least 1 A study
4	Less than 1 A study
Summary of safety/ tolerability:	
1	At least 3 A studies
2	At least 2 A studies and 1 B study
3	At least 2 A studies
4	Less than 2 A studies

Summary efficacy: Within each comparison, each study was assigned a grade of evidence. If the studies came to the same conclusion, they were grouped together/added, and then compared to studies/grouped studies with other conclusions. Hereby the grades of evidence were added/subtracted, as appropriate, the result was than transformed to a final level of evidence (see Table 2).

Summary safety/ tolerability: Results of studies within a comparison were grouped in the same manner as was done for summary of efficacy. Grades of evidence of the studies were transformed into a level of evidence for the safety/ tolerability conclusion.

Safety and tolerability criteria to achieve a higher level of evidence were stricter than for the efficacy assessment (see Table 2).

6.2.3 Summary tables of the EU Acne Guideline 2016

Due to the large amount of available treatment options with a multitude of possible comparisons, only selected comparisons on efficacy and safety/ tolerability were transferred into the summary tables.

Selection of presented comparisons:

Monotherapy with topical antibiotics was not considered due to the risk of the development of antibiotic resistance. Different dosages and frequencies of

application were pooled whenever possible. For combination treatments, only marketed fixed combinations were included.

For comedonal acne, only topical treatments were selected as appropriate.

There is only one study investigating patients with comedonal acne therefore no summary of direct evidence for safety/ tolerability could be included. Summary of efficacy for comedonal acne is based on indirect evidence from NIL counts in trials on papulopustular acne.

7 Development of recommendations/ consensus process

7.1 Relating severity and type of acne to clinically relevant patient groups / summary of recommendations

To reflect frequent clinical situations for which guidance is needed, a fourth group summarizing severe papulopustular acne/moderate nodular acne was introduced. With this, four relevant clinical patient populations where defined: a) comedonal acne; b) mild to moderate papulopustular acne; c) severe papulopustular acne/moderate nodular acne, and d) conglobate acne.

Since evidence for severe papulopustular acne could not be directly extracted from clinical trials, attempts were made to differentiate studies on mild to moderate papulopustular acne versus moderate to severe papulopustular acne.

7.2 Consensus conference

All recommendations were discussed and voted on via an online-telephone consensus conference using formal consensus methodology. The consensus conferences took place on 30th September 2015 and 2nd October 2015. The conference was chaired by PD Dr. med. Alexander Nast, who is an AWMF-certified moderator for consensus conferences.

First, the existing evidence was presented to the group and discussed with regard to efficacy, safety, patient preference and other relevant factors, for example, antibiotic resistance or pathophysiological reasoning.

Recommendations from the EU Acne Guideline 2011 were re-evaluated taking the available evidence into account. Then, voting took place sentence-by-sentence. All experts were entitled to vote in the consensus conference.

For each recommendation, the number of supporting experts was documented. Three levels of consensus were defined and distinguished: ‘strong consensus’ (agreement of ≥ 90 % of the members of the expert group) – this was generally aimed at, ‘consensus’ (75 to 89 % agreement) or ‘weak consensus’ (50 to 74 % agreement). All consented text passages are presented in boxes highlighted in grey throughout the EU Acne Guideline 2016.

7.3 Strength of recommendation

To make the recommendations precise, a, standardized language was used to express the strength of recommendation throughout the EU Acne Guideline:

1) **is strongly recommended**
   Good efficacy data, reasonable safety profile, good balance of possible benefits and harms, patient preference for the medication, high level of evidence and directness of available evidence.

2) **can be recommended**
   Good efficacy data, good balance of possible benefits and harms, good patient acceptance, limitations with respect to the level of evidence and the directness of the evidence.

3) **can be considered**
   Limitations with respect to efficacy and/ or limitations with respect to safety and or very relevant limitations with respect to available evidence (very little or no trials available while strong expert opinion is in favour).

4) **is not recommended**
   Insufficient efficacy or less favourable balance of possible benefits and harms

5) **may not be used under any circumstances**
   Harmful intervention with very unfavourable balance of possible benefits and harms

6) **a recommendation for or against treatment X cannot be made at the present time (open recommendation)**
   Due to a lack of evidence, it is impossible to make a recommendation for or against treatment X at the present time. Insufficient data from clinical trials; promising case reports or expert opinions may exist.

7.4 Results of consensus conference

The first consensus conference took place on September 30th, 2015 with the following experts participating (in alphabetical order): Z. Bukvic Mokos, K. Degitz, B. Dréno, A. Finlay, H. Gollnick, M. Haedersdal, J. Lambert, A. Layton, H. Lomholt, F. Ochsendorf, C. Oprica. The second consensus conference took place on October 2nd with the following experts participating (in alphabetical order): Z. Bukvic Mokos, K. Degitz, A. Finlay, H. Gollnick, J. Lambert, A. Layton, J. López Estebaranz, H. Lomholt, F. Ochsendorf, C. Oprica, T. Simonart

All votes passed with a strong consensus (>75% agreement) except for the first column in the summary of recommendations for induction therapy of comedonal acne. The voting results are shown in the following two tables (equivalent to the treatment algorithm):

Results of the consensus conference voting for therapeutic recommendations for induction therapy acne:

	Comedonal acne	**Mild-to-moderate papulopustular acne**	**Severe papulopustular/ moderate nodular acne**	**Severe nodular/ conglobate acne**
High strength of recommendation	6 of 10 in favour	9 of 11 in favour	10 of 10 in favour	10 of 10 in favour
Medium strength of recommen-dation				
Low strength of recommendation				
Alternatives for females				

Results of the consensus conference voting for therapeutic recommendations for maintenance therapy acne:

<table>
<tr><th></th><th>Comedonal acne</th><th>Mild-to-moderate papulopustular acne</th><th>Severe papulopustular/ moderate nodular acne</th><th>Severe nodular/ conglobate acne</th></tr>
<tr><td>High strength of recommendation</td><td rowspan="4">11 of 11 in favour</td><td rowspan="4">11 of 11 in favour</td><td rowspan="2">11 of 11 in favour</td><td rowspan="2">11 of 11 in favour</td></tr>
<tr><td>Medium strength of recommen-dation</td></tr>
<tr><td>Low strength of recommendation</td></tr>
<tr><td>Alternatives for females</td><td colspan="2">11 of 11 in favour</td></tr>
</table>

A majority voting on authorship took place considering in the following criteria: “An author is defined as an expert who contributed at least in 1 of the following 4 activities: kick-off conference, active writing, first consensus conference, second consensus conference.” The criteria passed with 10 of 10 in favour of the criteria.

8 Limitations

8.1 Evidence

The evaluation of available evidence was based on 10% difference. We were unable to conduct a more elaborate analysis (e.g. risk ratio calculation) due to suboptimal reporting in many publications such as missing measures of statistical dispersion.

An extensive search for newly developed guidelines published since 2011 was not performed because the dEBM team produced the first version and this is an update. The group was aware of the Canadian Acne Guideline published in 2015, which in itself was based on the 2011 EU Acne Guideline and of the Malaysian Acne Guideline 2012.

8.2 Cost considerations

No economic aspects were evaluated. It would have gone beyond the scope of this Guideline to consider the pricing and reimbursement regimes in every single

European country. The differences throughout Europe are too large, as are those in patients' willingness and ability to pay for medication, and in the availability of generics. European guidelines are always meant to be used as a source for national and local adaptation, and pharmaco-economic considerations should be taken into account at these levels.

9 External review

The Guideline underwent an extensive external review. From November 16th through December 13th 2015 the Guideline was available online for comments and amendments. This period of online availability was announced using the following mailing lists: EDF Board, EDF Guideline Committee, EDF Members, EADV Board, Union Européenne des Médecins Spécialistes (UEMS).

Additionally, every participant was encouraged to invite all potentially interested parties to review and comment on the guideline.

The EU Guidelines Group received and evaluated 74 comments. A document summarizing all comment, management and responses is available at the dEBM.

10 Dissemination and implementation

The Guideline will be published online on the EDF website (www.euroderm.org). Additionally, a short version of the Guideline alongside with this methods report (online only) will be published in the Journal of the European Academy of Dermatology and Venereology.

Furthermore, all involved experts are invited to give talks and present the results and recommendations of the Guideline at conferences.

Implementation will be pursued at a national level by local medical societies. Materials such as an online version, a short version (see above) and a therapeutic algorithm will be supplied. The EDF is planning to include the Guideline in the EDF Guidelines App.

11 Evaluation

Because no further funding for this Guideline is available, no formal Europe wide evaluation program has been planned at this point. Strategies for evaluating the impact on a national level (e.g. assessment of awareness, treatment adhesion and patient changes) are in preparation.

12 Funding and editorial independence

The European S3 Guideline for the Treatment of Acne was funded by the EDF. At the beginning of the project, cooperate partners of the EDF with an interest in the field of acne were contacted and invited to provided funding for an update of the EU Guideline. The group itself was not informed about declarations of interest for support and final contributions for the cooperate partners. For means of transparency, the sources of support are declared after the finalisation of the guidelines. Contribution was given as an unrestricted educational grant to the EDF. Supporting bodies and the EDF treasurer had no influence on the guidelines contents at any stage of the guidelines development.

13 Future updates of the Guideline

In accordance with the standard operating procedures of the EDF, the European S3 Guideline for the Treatment of Acne will need to be updated after 31. December 2020. In case of new interventions being licensed or relevant new studies or reports are being published (e.g. new occurrence of highly relevant adverse events) the EDF subcommittee on acne will evaluate the need for an earlier update.

14 Declaration and management of conflicts of interest

Prior to the kick-off meeting all authors and methodologists were asked to complete an adapted “Form for Disclosure of Potential Conflicts of Interest” of the International Committee of Medical Journal Editors (ICMJE). All declarations were continuously updated (see Appendix F) and classified as none (with respect to acne), mild/moderate [institutional or personal] (e. g. grants for research, consultancy for scientific programs, CME talks, professional societies; received by the institution or as personal honoraria with respect to acne) or severe (e. g. employee, shareholder, patents, royalties, speakers bureaus, investor talks) conflicts of interest (see Table

3). At the beginning of the consensus conference the declarations were discussed by the expert panel with respect to possible bias. No conflicts of interest leading to the exclusion of an expert were identified.

Table 3: Classification of conflicts of interests of expert panel and methodologists

Category	**Names**
none	Bettoli, Lomholt, Simonart, Zivkovic
mild/moderate institutional	Alsharif, Dressler, Erdmann, Haedersdal, Rosumeck, Werner
mild/moderate personal	Bukvic Mokos, Degitz, Dréno, Finlay, Gollnick, Lambert, Layton, López Estebaranz, Nast, Ochsendorf, Oprica, Zouboulis
severe	*none*

15 References

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Appendices

Appendix A European Dermatology Forum – SOP, Version 35, March 2015

SOP for creation of European Dermatology Guidelines

Step	Responsible	Task	Months duration
1	EDF Guidelines Committee (EDF-GC) *	Decision of topic of specific guideline Identification of potential chairperson and subcommittee members.	At EDF meeting
2	EDF Board	Discussion and approval of the choice, and level of guideline (S1, S2 or S3) as well as chairperson	Via round email
3	Chairperson guideline subcomittee	Formation of guideline subcommittee: Nomination of EDF members (50 %) Identification of possible EADV members (25 % of members for the subcommittee) who could work within the subcommittee. Chairman of EDF guideline subcommittee asks EADV president for approval. Finally approval of the chairperson of the subcommittee by the group.	
4	EDF Guidelines Subcommittee (EDF-GSubC)	Development of a business plan (information available at B Schulze, EDF guideline secretariat) Organization of Corporate support for full coverage of planned costs. Corporate support to be transferred by companies to EDF Guidelines Bank account.	
5	EDF Board	Confirmation of business plan and signature of the contract for financial support of guideline	Via round email
6	Chairperson of EDF-GC	Send information on the intended guideline to national dermatological societies	
7	EDF-GSubC	**Start of work on the guideline content** Identify all existing guidelines for the specific guideline (active process: literature survey plus contact to Dermatological Societies) Select the guidelines with highest quality. Criteria for selection: 1. Availability of strength of evidence 2. Availability of strength of recommendation Evidence of mechanics of literature review (adhere to the recommendations of the Cochrane collaboration. These standards should assure high quality for the systematic literature search as well as for the critical appraisal of the papers. For further information see http://www.cochrane.org/crgprocedures/chapter4/1.htm Identification/nomination of additional EDF members for the EDF-GSubC from amongst the authors of the best guidelines	1
8	EDF-GSubC	Start with literature survey	0,5
9	Chairperson of EDF-GSubC	Consider involvement of other disciplines and patients´ organisations	1
10	EDF-GSubC	Meeting 1. to decide the author of the first draft (normally the chairperson of the subcommittee) and to discuss the present guidelines, their strengths and weaknesses 2. Discuss responsibility for chapters of the guideline 3. 6 months later to discuss the draft (consensus conference)	6
11	EDF-GSubC	Circulate draft version for approval among members of the guideline subcommittee	1
12	EDF-GSubC Chairperson EDF guideline committee	Deliver draft version including completed list of conflicts of interests (using the standard form) to EDF guideline committee chairperson, who forwards it to 1. EDF board 2. EDF guideline committee 3. EDF membership including corporate members 4. Board of EADV 5. UEMS dermatology guideline group (President UEMS dermatology and head of guideline committee UEMS)	1
13	Chairperson of EDF-GC	Send guideline for official approval to UEMS (formal approval)	3 weeks
14	Chairperson of EDF-GSubC EDF-GC	Consider proposals concerning the guideline and finalize text. Send final version of EDF board for approval	0,25 (round email)
15	EDF guideline secretariat	Distribute guideline for in advance information to EDF members and National Dermatological Societies	1
16	1. EDF GC/EDF 2. Chairperson of EDF GSubC 3. EDF GC	**Publication** 1. on the EDF website 2. Chairperson of EDF GSubC suggests a journal for publication to the Chairperson of EDF GC / EDF board which approves the decision. Publication of additional short versions / translations possible after approval by Chairperson of EDF GC 3. EDF Guidelines book	6

The normal expiry date of a guideline is 3 years after finishing point 16. In well defined exceptions the expiry date may be prolonged up to 5 years.

**** The Guideline Committee consists of the founding members of the EDF guideline work as well as of chairpersons of guidelines subcommittees.***

Appendix B Members of the EU Guideline Group

Each member of the EU Guideline Group has specific responsibilities. At all stages of the guideline process, these responsibilities need to be defined.

Project leader and coordinator	Alexander Nast, MD Division of Evidence Based Medicine (dEBM) Klinik für Dermatologie Charité – Universitätsmedizin Berlin Charitéplatz 1 10117 Berlin Germany Tel.: +49 30 450518 313 Fax: +49 30 450518 977 E-mail: alexander.nast@charite.de http://www.debm.de http://www.derma.charite.de
Project office (methods group)	Stefanie Rosumeck, M.A. Corinna Dressler, M.Sc., Ph. D. Ricardo Niklas Werner, MD Ricardo Erdmann Ubai Alsharif Division of Evidence Based Medicine (dEBM)
Expert group	Vincenzo Bettoli, MD (Italy) Hans Bredsted Lomholt (Denmark) Zrinka Bukvic Mokos, MD (Croatia) Klaus Degitz, MD (Germany) Brigitte Dréno, MD (France) Andrew Finlay, MD (United Kingdom) Ruta Ganceviciene, MD (Lithuania) Harald Gollnick, MD (Germany) Merete Haedersdal, MD (Denmark) Julien Lambert, MD (Belgium) Alison Layton, MD (United Kingdom) Jose Luis Lopez Estebaranz, MD (Spain) Falk Ochsendorf, MD (Germany) Cristina Oprica, MD (Sweden) Thierry Simonart, MD (Belgium) Maja Vurnek-Živković (Croatia)
Moderation of the consensus conferences	Alexander Nast, MD

Appendix C Search strategy

Search strategy for topical and systemic treatments:
Databases: Ovid MEDLINE®

#	Search Statement
1.	exp acne/
2.	"acne*".ab,ti.
3.	1 or 2
4.	exp benzoyl peroxide/
5.	"benzoyl peroxid*".ab,ti.
6.	exp Retinoids/
7.	"retinoid*".ab,ti.
8.	exp Naphthalenes/
9.	"adapalene".ab,ti.
10.	exp isotretinoin/
11.	"isotretinoin".ab,ti.
12.	exp retinoic acid/
13.	"tretinoin".ab,ti.
14.	exp dicarboxylic acids/
15.	"azelaic acid".ab,ti.
16.	exp zinc/
17.	"zinc".ab,ti.
18.	exp Antibiotics, Antitubercular/
19.	exp clindamycin/
20.	"clindamycin*".ab,ti.
21.	exp doxycycline/
22.	"doxycyclin*".ab,ti.
23.	exp erythromycin/
24.	"erythromycin*".ab,ti.
25.	exp lymecycline/
26.	"lymecyclin*".ab,ti.
27.	exp minocycline/
28.	"minocyclin*".ab,ti.
29.	"nadifloxacin".ab,ti.
30.	exp tetracycline/
31.	"tetracyclin*".ab,ti.
32.	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33.	Randomized Controlled Trials as Topic/
34.	randomized controlled trial/
35.	Random Allocation/
36.	Double-Blind Method/
37.	Single Blind Method/
38.	clinical trial/
39.	clinical trial, phase I.pt.
40.	clinical trial, phase II.pt.
41.	clinical trial, phase III.pt.
42.	clinical trial, phase IV.pt.
43.	controlled clinical trial.pt.
44.	randomized controlled trial.pt.
45.	multicenter study.pt.

46.	clinical trial.pt.
47.	exp Clinical Trials as topic/
48.	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49.	(clinical adj trial$).tw.
50.	((singl$ or doubl$ or treb$ or tribl$) adj (blind$3 or mask$3)).tw.
51.	Placebos/
52.	placebo$.tw.
53.	randomly allocated.tw.
54.	(allocated adj2 random$).tw.
55.	49 or 50 or 51 or 52 or 53 or 54
56.	48 or 55
57.	case report.tw.
58.	letter/
59.	historical article/
60.	57 or 58 or 59
61.	56 not 60
62.	3 and 32 and 61
63.	limit 62 to yr="2010 -Current"

Appendix D Methodology checklist – Barbaric et al. (Preview, date: 16. May 2015)

S I G N	**Methodology Checklist 1: Systematic Reviews and Meta-analyses** SIGN gratefully acknowledges the permission received from the authors of the AMSTAR tool to base this checklist on their work: *Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C,. et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology 2007, **7**:10 doi:10.1186/1471-2288-7-10. Available from http://www.biomedcentral.com/1471-2288/7/10 [cited 10 Sep 2012]*

Study identification (*Include author, title, year of publication, journal title, pages*)

Barbaric J, Abbott R, Car M, Gunn LH, Layton AM, Majeed A, Car J. Light therapies for acne. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD007917. DOI: 10.1002/14651858.CD007917.pub2 (Preview, date: 16. May 2015)

Guideline topic: European Evidence-based (S3) Guideline for the treatment of acne (ICD L70.0) Update 2016	Key Question No: Which kind of light therapies is effective to treat acne patients?

Before completing this checklist, consider:

Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO reject. IF YES complete the checklist.

Checklist completed by: Stefanie Rosumeck, M.A. and Corinna Dressler, M.Sc., Ph.D.

SECTION 1: INTERNAL VALIDITY

	In a well conducted systematic review:	**Does this study do it?**	
1.1	The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper.	Yes X **If no reject**	No □
1.2	A comprehensive literature search is carried out.	Yes X Not applicable □ **If no reject**	No □
1.3	At least two people should have selected studies.	Yes X	No □ Can't say □
1.4	At least two people should have extracted data.	Yes X	No □ Can't say □
1.5	The status of publication was not used as an inclusion criterion.	Yes X	No □
1.6	The excluded studies are listed.	Yes X	No □
1.7	The relevant characteristics of the included studies are provided.	Yes X	No □
1.8	The scientific quality of the included studies was assessed and reported.	Yes X	No □
1.9	Was the scientific quality of the included studies used appropriately?	Yes X	No □
1.10	Appropriate methods are used to combine the individual study findings.	Yes X Can't say □	No □ Not applicable □
1.11	The likelihood of publication bias was assessed appropriately.	Yes □ Not applicable	No □ X
1.12	Conflicts of interest are declared.	Yes X	No □

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1	What is your overall assessment of the methodological quality of this review?	High quality (++) X Acceptable (+) □

		Low quality (-)□ Unacceptable – reject 0 □
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes X No □
2.3	**Notes:** 1.10. Only 3 RCT could be combined for a meta-analysis. Other included studies were reported narratively 1.11. Authors planned to test for publication bias, but the number of included trials was too low for a funnel plot.	

Appendix E Methodology checklist – Arowojolu et al. (2012)

SIGN	**Methodology Checklist 1: Systematic Reviews and Meta-analyses** SIGN gratefully acknowledges the permission received from the authors of the AMSTAR tool to base this checklist on their work: *Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C,. et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology 2007, **7**:10 doi:10.1186/1471-2288-7-10. Available from http://www.biomedcentral.com/1471-2288/7/10 [cited 10 Sep 2012]*
Study identification (*Include author, title, year of publication, journal title, pages*) Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. *Cochrane Database of Systematic Reviews* 2012, Issue 7. Art. No.: CD004425. DOI: 10.1002/14651858.CD004425.pub6.	
Guideline topic: European Evidence-based (S3) Guideline for the treatment of acne (ICD L70.0) Update 2016	Key Question No: Should combined oral contraceptive pills be used to treat acne in female patients?
Before completing this checklist, consider: Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO reject. IF YES complete the checklist.	
Checklist completed by: Stefanie Rosumeck, M.A. and Corinna Dressler, M.Sc., Ph.D.	

SECTION 1: INTERNAL VALIDITY			
In a well conducted systematic review:		**Does this study do it?**	
1.1	The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper.	Yes X **If no reject**	No □
1.2	A comprehensive literature search is carried out.	Yes X Not applicable **If no reject**	No □ □
1.3	At least two people should have selected studies.	Yes □	No X Can't say □
1.4	At least two people should have extracted data.	Yes X	No □ Can't say □
1.5	The status of publication was not used as an inclusion criterion.	Yes X	No □
1.6	The excluded studies are listed.	Yes X	No □
1.7	The relevant characteristics of the included studies are provided.	Yes X	No □
1.8	The scientific quality of the included studies was assessed and reported.	Yes X	No □
1.9	Was the scientific quality of the included studies used appropriately?	Yes X	No □
1.10	Appropriate methods are used to combine the individual study findings.	Yes X Can't say □	No □ Not applicable □
1.11	The likelihood of publication bias was assessed appropriately.	Yes □ Not applicable	No □ X
1.12	Conflicts of interest are declared.	Yes X	No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	What is your overall assessment of the methodological quality of this review?	High quality (++) □ Acceptable (+) X Low quality (-)□ Unacceptable – reject 0 □	

2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes X No □
2.3	**Notes:** 1.3: only one author assessed identified title and abstracts 1.8: Assessment was done according to Higgins 2011 ("adequacy of sample size, randomization protocol, allocation concealment, inclusion and exclusion criteria, blinding, the extent of premature withdrawals and loss to follow up and method of analysis"); only 'allocation concealment' was noted for each study in 'Characteristics of included studies' section; an overall summary stated in the 'Risk of bias in included studies' paragraph somewhat allows for a judgement of the separate studies if desired 1.9.: No specific sensitivity analysis were performed but statement in paragraph 'Quality of the evidence' 1.10.: Very few studies were combined in meta-analyses. Some of these were pooled in spite of statistical heterogeneity (e.g. Analysis 3.3. I^2=79%, Analysis 13.1. I^2=71%, Analysis 13.2 I^2=68%); no explanation for heterogeneity, sensitivity analysis or meta-regression was provided – unclear why no random-effects models were chosen 1.11.: less than 10 publication per comparison 1.12.: Authors attempted to extract financial support of each included study; only one author of the systematic review declared conflicts of interest; no funding for preparation of the systematic review	

Appendix F Conflicts of interests of the members of the experts and methods group

		Ubai Alsharif	Vincenzo Bettoli	Zrinka Bukvic Mokos	Klaus Degitz
1	**Work Under Consideration for these Guidelines**				
1.1	Grant	European Dermatology Forum for evidence generation and project coordination	No	No	No
1.2	Consulting fee or honorarium	No	No	No	No
1.3	Support for travel to meetings for the study or other purposes	No	No	No	No
1.4	Fees for participation in review activities such as data-monitoring boards, statistical analysis, end-point committees, and the like	European Dermatology Forum for evidence generation and project coordination	No	No	No
1.5	Payment for writing or reviewing the manuscript	European Dermatology Forum for evidence generation and project coordination	No	No	No
1.6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
1.7	Other	No	No	No	No
2	**Relevant Financial Activities Outside Submitted Work**				
2.1	Board membership	No	No	No	STIEFEL in 2012
2.2	Consultancy	No	No	No	No
2.3	Employment	No	No	No	No
2.4	Expert testimony	No	No	No	No
2.5	Grants/grants pending	dEBM has received research grants from Pfizer (systematic review on psoriasis maintenance therapy) and GlaxoSmithKline (systematic review on time until onset of action of treatments for acne vulgaris). GlaxoSmithKline is a manufacturer of anti-acne treatments (BPO/clindamycin); dEBM has received compensation for participation in a clinical trial on scar treatment from MERZ; dEBM has a pending grant from MEDA for a systematic review outside of the field of acne	No	No	No

2.6	Payment for lectures including service on speakers bureaus	No	No	GlaxoSmithKline for lecture titled 'Current Concepts on the Pathogenesis of Acne' (lecture in Croatian language) in Zagreb on February 14, 2014 for Croatian dermatologists	Stiefel, MEDA Pharma
2.7	Payment for manuscript preparation	No	No	No	Stiefel for an interview
2.8	Patents (planned, pending, or issued)	No	No	No	No
2.9	Royalties	No	No	No	No
2.10	Payment for development of educational presentations	No	No	No	No
2.11	Stock/stock options	No	No	No	No
2.12	Travel, accommodations, and meeting expenses unrelated to activities listed	No	No	No	No
2.13	Other (err on the side of full disclosure)	No	No	No	No
3	**Other relationships**	No	No	No	No

		Brigitte Dréno	**Corinna Dressler**	**Ricardo Erdmann**
1	**Work Under Consideration for these Guidelines**			
1.1	Grant	No	European Dermatology Forum for evidence generation and project coordination	European Dermatology Forum for evidence generation and project coordination
1.2	Consulting fee or honorarium	No	No	No
1.3	Support for travel to meetings for the study or other purposes	No	No	No
1.4	Fees for participation in review activities such as data-monitoring boards, statistical analysis, end-point committees, and the like	No	European Dermatology Forum for evidence generation and project coordination	European Dermatology Forum for evidence generation and project coordination
1.5	Payment for writing or reviewing the manuscript	No	European Dermatology Forum for evidence generation and project coordination	European Dermatology Forum for evidence generation and project coordination
1.6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No
1.7	Other	No	No	No
2	**Relevant Financial Activities Outside Submitted Work**			

2.1	Board membership	Galderma, MEDA Pharma, Pierre Fabre Pharma, La Roche-Posay	No	No
2.2	Consultancy	No	No	No
2.3	Employment	No	No	No
2.4	Expert testimony	No	No	No
2.5	Grants/grants pending	Galderma, Pierre Fabre Pharma	dEBM has received research grants from Pfizer (systematic review on psoriasis maintenance therapy) and GlaxoSmithKline (systematic review on time until onset of action of treatments for acne vulgaris). GlaxoSmithKline is a manufacturer of anti-acne treatments (BPO/clindamycin); dEBM has received compensation for participation in a clinical trial on scar treatment from MERZ; dEBM has a pending grant from MEDA for a systematic review outside of the field of acne	dEBM has received research grants from Pfizer (systematic review on psoriasis maintenance therapy) and GlaxoSmithKline (systematic review on time until onset of action of treatments for acne vulgaris). GlaxoSmithKline is a manufacturer of anti-acne treatments (BPO/clindamycin); dEBM has received compensation for participation in a clinical trial on scar treatment from MERZ; dEBM has a pending grant from MEDA for a systematic review outside of the field of acne
2.6	Payment for lectures including service on speakers bureaus	Galderma, MEDA Pharma, Pierre Fabre Pharma, La Roche-Posay	No	No
2.7	Payment for manuscript preparation	No	No	No
2.8	Patents (planned, pending, or issued)	No	No	No
2.9	Royalties	No	No	No
2.10	Payment for development of educational presentations	Galderma, Pierre Fabre Pharma, La Roche-Posay	No	No
2.11	Stock/stock options	No	No	No
2.12	Travel, accommodations,	No	No	No

	and meeting expenses unrelated to activities listed				
2.13	Other (err on the side of full disclosure)	No	No	No	
3	**Other relationships**	No	No	No	

		Andrew Y. Finlay	**Harald Gollnick**	**Merete Hædersdal**	**Julien Lambert**	**Alison Layton**
1	**Work Under Consideration for these Guidelines**					
1.1	Grant	No	No	No	No	No
1.2	Consulting fee or honorarium	No	No	No	No	No
1.3	Support for travel to meetings for the study or other purposes	No	No	No	No	No
1.4	Fees for participation in review activities such as data-monitoring boards, statistical analysis, end-point committees, and the like	No	No	No	No	No
1.5	Payment for writing or reviewing the manuscript	No	No	No	No	No
1.6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No	No
1.7	Other	No	No	No	No	No
2	**Relevant Financial Activities Outside Submitted Work**					
2.1	Board membership	No	European Dermatology Forum, German Dermatological Society	No	MEDA, Galderma, Pierre Fabre	No
2.2	Consultancy	Galderma Global Alliance (World and European), Novartis Advisory Board meetings, Napp Advisory Board, Archimedes Advisory Board, Amgen Advisory Board	No	No	MEDA	GlaxoSmithKline, MEDA Pharma, Galderma, L'Oréal on an ad hoc basis
2.3	Employment	No	No	No	No	Harrogate and District NHS Foundation Trust, Consultant Dermatologist, self employed

						private practitioner as Consultant Dermatologist, working at BMI Duchy Hospital, Harrogate
2.4	Expert testimony	No	No	No	No	No
2.5	Grants/grants pending	No	No	Almirall, Galderma, Leo Pharma, Lumenis, Lutronic, Procter & Gamble	No	GlaxoSmithKline, Galderma
2.6	Payment for lectures including service on speakers bureaus	No	GlaxoSmithKline, Galderma, Intendis, Novartis, IMTM	Galderma	MEDA	Galderma, GlaxoSmithKline, MEDA Pharma
2.7	Payment for manuscript preparation	No	No	No	No	No
2.8	Patents (planned, pending, or issued)	No	No	Leo Pharma	No	No
2.9	Royalties	Joint copyright owner of the DLQI, CDLQI and FDLQI. Royalties go to Cardiff University	No	No	No	No
2.10	Payment for development of educational presentations	No	No	No	No	GlaxoSmithKline, MEDA Pharma, Galderma
2.11	Stock/stock options	No	No	No	No	No
2.12	Travel, accommodations, and meeting expenses unrelated to activities listed	No	No	No	No	No
2.13	Other (err on the side of full disclosure)	Joint copyright owner of the Cardiff Acne Disability Index. This is freely available with no charge.	No	Loan of laser devices from Candela/ Syneron and Palomarc/ Cynosure	No	Act as CI/PI for a number of NIHR clinical trials some of wich are sponsored by pharmaceutical companies (Galderma, Leo Pharma, Intendis, Wyeth, Novartis). Resource supporting

						these studies is provided to the NHS Organisation l work for
3	**Other relationships**	No	No	No	No	Member of the Global Alliance and European Acne Panel. This is supported by unrestricted educational grants from Galderma. The groups embrace many international dermatologis ts who work to improve outcomes for acne and report on recent clinical trials.

		Hans Bredsted Lomholt	**Jose Luis López Estebaranz**	**Alexander Nast**	**Falk Ochsendorf**
1	**Work Under Consideration for these Guidelines**				
1.1	Grant	No	No	European Dermatology Forum for evidence generation and project coordination	No
1.2	Consulting fee or honorarium	No	No	No	No
1.3	Support for travel to meetings for the study or other purposes	No	No	No	No
1.4	Fees for participation in review activities such as data-monitoring boards, statistical analysis, end-point committees, and the like	No	No	European Dermatology Forum for evidence generation and project coordination	No
1.5	Payment for writing or reviewing the manuscript	No	No	European Dermatology Forum for evidence generation and project coordination	No
1.6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
1.7	Other	No	No	No	No
2	**Relevant Financial Activities Outside Submitted Work**				
2.1	Board membership	No	No	No	No

2.2	Consultancy	No	Galderma, MEDA Pharma	No	Expert meetings: Vichy Laboratories, MEDA Pharma, GlaxoSmithKline Stiefel Pharma, Galderma Laboratories
2.3	Employment	No	No	No	No
2.4	Expert testimony	No	No	No	No
2.5	Grants/grants pending	No	No	dEBM has received research grants from Pfizer (systematic review on psoriasis maintenance therapy) and GlaxoSmithKline (systematic review on time until onset of action of treatments for acne vulgaris). GlaxoSmithKline is a manufacturer of anti-acne treatments (BPO/clindamycin); dEBM has received compensation for participation in a clinical trial on scar treatment from MERZ; dEBM has a pending grant from MEDA for a systematic review outside of the field of acne	No
2.6	Payment for lectures including service on speakers bureaus	No	MEDA Pharma, Bayer, GlaxoSmithKline	Intendis/Bayer Healthcare, Pfizer, Boehringer Ingelheim, Novartis, MEDA, Biogen Idec, Abbott (now Abbvie)	Lectures during congresses/ CME activities: MEDA Pharma, GlaxoSmithKline Stiefel Pharma, Galderma Laboratories
2.7	Payment for manuscript preparation	No	No	No	No
2.8	Patents (planned, pending, or issued)	No	No	No	No
2.9	Royalties	No	No	No	No
2.10	Payment for development of educational presentations	No	No	No	No
2.11	Stock/stock options	No	No	No	No
2.12	Travel, accommodations, and meeting expenses unrelated to activities listed	No	No	No	No
2.13	Other (err on the side of full disclosure)	No	No	No	No
3	**Other relationships**	No	No	No	No

		Christina Oprica	Stefanie Rosumeck	Thierry Simonart
1	**Work Under Consideration for these Guidelines**			
1.1	Grant	No	European Dermatology Forum for evidence generation and project coordination	No
1.2	Consulting fee or honorarium	No	No	No
1.3	Support for travel to meetings for the study or other purposes	No	No	No
1.4	Fees for participation in review activities such as data-monitoring boards, statistical analysis, end-point committees, and the like	No	European Dermatology Forum for evidence generation and project coordination	No
1.5	Payment for writing or reviewing the manuscript	No	European Dermatology Forum for evidence generation and project coordination	No
1.6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No
1.7	Other	No	No	No
2	**Relevant Financial Activities Outside Submitted Work**			
2.1	Board membership	No	No	No
2.2	Consultancy	No	No	No
2.3	Employment	No	No	No
2.4	Expert testimony	No	No	No
2.5	Grants/grants pending	No	dEBM has received research grants from Pfizer (systematic review on psoriasis maintenance therapy) and GlaxoSmithKline (systematic review on time until onset of action of treatments for acne vulgaris). GlaxoSmithKline is a manufacturer of anti-acne treatments (BPO/clindamycin); dEBM has received compensation for participation in a clinical trial on scar treatment from MERZ; dEBM has a pending grant from MEDA for a systematic review outside of the field of acne	No
2.6	Payment for lectures including service on speakers bureaus	Galderma symposium in Stockholm and Oslo	No	No
2.7	Payment for manuscript preparation	No	No	No

2.8	Patents (planned, pending, or issued)	No	No	No
2.9	Royalties	No	No	No
2.10	Payment for development of educational presentations	No	No	No
2.11	Stock/stock options	No	No	No
2.12	Travel, accommodations, and meeting expenses unrelated to activities listed	No	No	No
2.13	Other (err on the side of full disclosure)	No	No	No
3	**Other relationships**	No	No	No

		Ricardo N. Werner
1	**Work Under Consideration for these Guidelines**	
1.1	Grant	European Dermatology Forum for evidence generation and project coordination
1.2	Consulting fee or honorarium	No
1.3	Support for travel to meetings for the study or other purposes	No
1.4	Fees for participation in review activities such as data-monitoring boards, statistical analysis, end-point committees, and the like	European Dermatology Forum for evidence generation and project coordination
1.5	Payment for writing or reviewing the manuscript	European Dermatology Forum for evidence generation and project coordination
1.6	Provision of writing assistance, medicines, equipment, or administrative support	No
1.7	Other	No
2	**Relevant Financial Activities Outside Submitted Work**	
2.1	Board membership	No
2.2	Consultancy	No
2.3	Employment	No
2.4	Expert testimony	No
2.5	Grants/grants pending	dEBM has received research grants from Pfizer (systematic review on psoriasis maintenance therapy) and GlaxoSmithKline (systematic review on time until onset of action of treatments for acne vulgaris). GlaxoSmithKline is a manufacturer of anti-acne treatments (BPO/clindamycin); dEBM has received compensation for participation in a clinical trial on scar treatment from MERZ; dEBM has a pending grant from MEDA for a systematic review outside of the field of acne
2.6	Payment for lectures including service on speakers bureaus	No
2.7	Payment for manuscript preparation	No
2.8	Patents (planned, pending, or issued)	No
2.9	Royalties	No
2.10	Payment for development of educational presentations	No
2.11	Stock/stock options	No
2.12	Travel, accommodations, and meeting expenses unrelated to activities listed	No

2.13	Other (err on the side of full disclosure)	No
3	**Other relationships**	No