Additional guidance on the methodology for the development/update of EULAR recommendations

The '2014 update of the EULAR standardised operating procedures for EULAR-endorse recommendations' (van der Heijde et al, ARD 2015;74:8-13) describe the methodology pertaining to the development or update of EULAR recommendations. However, there has been some misunderstanding regarding the evaluation of the strength of the recommendations. The template that should be used is the Oxford level of evidence and strength of recommendations (Oxford Centre for Evidence-based Medicine Levels of Evidence) as detailed in Tables 1 and 2 in the SOP. The most recent and up-to-date levels of evidence that should be applied are as follows:

Level	Therapy/prevention/aetiology/harm
1a	Systematic review with homogeneity of RCTs
1b	Individual RCT (with narrow confidence interval)
1c	All or none
2a	Systematic review with homogeneity of cohort studies
2b	Individual cohort study (including low quality RCT; e.g. <80% follow-up)
2c	'Outcomes' research; ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Grades of recommendation	
A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or troublingly inconsistent or inconclusive studies of any level

EULAR Secretariat | Seestrasse 240 | 8802 Kilchberg | Switzerland
T: +41 44 716 30 37 | F: +41 44 716 30 39
taskforces@eular.org | www.eular.org

In the SOP is mentioned that the GRADE-system should be used for guidance. The aim of this statement is to take the quality of research into account, not the GRADE system itself. Assessment of risk of bias is an important aspect of grading. When the risk of bias is judged as 'high', the contribution of the study to the overall level of evidence should be downgraded. This is also in agreement with the recommendations by the OCEBM: '*Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size*'. This will be taken into account when formulating the recommendations and applying the level of evidence and strength of recommendation. Another difference between the SLRs used by EULAR and by GRADE is that EULAR applies a more general SLR, including for instance 'all DMARDs' vs. 'all comparators' rather than a separate SLR for each formulated (detailed) sub-question. GRADE should not be applied in the formulation of the recommendations. In addition, EULAR is not using the terms 'strong' or 'conditional' recommendation, but rather provides general recommendations. However, the various parts of a recommendation can be supported by different levels of evidence.

Example from the RA recommendations:

If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD* or a tsDMARD*should be considered; current practice would be to start a bDMARD[§]
*level of evidence 1a, strength of recommendation A; [§]level of evidence 5, strength of recommendation D

For further guidance review recent the following recommendation papers with the accompanying SLRs:

RA management recommendations

Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R, Aletaha D, Aringer M, Boers M, Buckley CD, Buttgereit F, Bykerk V, Cardiel M, Combe B, Cutolo M, van Eijk-Hustings Y, Emery P, Finckh A, Gabay C, Gomez-Reino J, Gossec L, Gottenberg J-E, Hazes JMW, Huizinga T, Jani M, Karateev D, Kouloumas M, Kvien TK, Li Z, Mariette X, McInnes I, Mysler E, Nash P, Pavelka K, Poór G, Richez C, van Riel P, Rubbert-Roth A, Saag K, da Silva J, Stamm T, Takeuchi T, Westhovens R, de Wit M, van der Heijde D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update.
Ann Rheum Dis 2017;76:960-77

Nam JL, Takase-Minegishi K, Ramiro S, Chatzidionysiou K, Smolen JS, van der Heijde D, Bijlsma JW, Burmester GR, Dougados M, Scholte-Voshaar M, van Vollenhoven R, Landewé R. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis.
Ann Rheum Dis 2017;76:1113-36

Ramiro S, Sepriano A, Chatzidionysiou K, Nam JL, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, Bijlsma JW, Burmester GR, Scholte-Voshaar M, Falzon L, Landewé RBM. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis.
Ann Rheum Dis 2017;76:1101-36

EULAR Secretariat | Seestrasse 240 | 8802 Kilchberg | Switzerland
T: +41 44 716 30 37 | F: +41 44 716 30 39
taskforces@eular.org | www.eular.org

Chatzidionysiou K, Emamikia S, Nam J, Ramiro S, Smolen J, van der Heijde D, Dougados M, Bijlsma J, Burmester G, Scholte M, van Vollenhoven R, Landewé R. Efficacy of glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis.
Ann Rheum Dis 2017;76:1102-07

axSpA management recommendations

van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, Regel A, Ciurea A, Dagfinrud H, Dougados M, van Gaalen F, Géher P, van der Horst-Bruinsma I, Inman RD, Jongkees M, Kiltz U, Kvien TK, Machado PM, Marzo-Ortega H, Molto A, Navarro-Compàn V, Ozgocmen S, Pimentel-Santos FM, Reveille J, Rudwaleit M, Sieper J, Sampaio-Barros P, Wiek D, Braun J. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis.
Ann Rheum Dis 2017;76:978-91

Regel A, Sepriano A, Baraliakos X, van der Heijde D, Braun J, Landewé, R, Van den Bosch F, Falzon L, Ramiro S. Efficacy and safety of non-pharmacological and non-biological pharmacological treatment: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis.
RMD Open 2017;3:e000397

Sepriano A, Regel A, van der Heijde D, Braun J, Baraliakos X, Landewé R, Van den Bosch F, Falzon L, Ramiro S. Efficacy and safety of biological and targeted-synthetic DMARDs: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis.
RMD Open 2017;3;e000396-e000396

Désirée van der Heijde, June 2017

Additional guidance on the use of systematic reviews and meta-analysis as the basis of a systematic literature review

In the systematic literature reviews (SLR's), secondary literature (e.g. existing systematic reviews and meta-analyses) can be used as a starting point. In order to ensure a uniform selection and quality assessment of these systematic reviews and meta-analyses the following procedure regarding the use of secondary literature has been decided:

- Cochrane reviews can be included without further critical appraisal.
- All other systematic reviews or meta-analyses must undergo a critical appraisal by the use of the AMSTAR 2 tool [1]

The AMSTAR 2 consists of 16 items and is not intended to generate an overall score. However, seven domains can critically affect the validity of a review and conclusion and must gain special attention:

- Protocol registration before commencement of the review (item 2).
- Adequacy of the literature search (item 4).
- Justification for excluding individual studies (item 7).
- Risk of bias from individual studies being included in the review (item 9).
- Appropriateness of meta-analytical methods (item 11).
- Consideration of risk of bias when interpreting the results of the review (item 13).
- Assessment of presence and likely impact of publication bias (item 15).

1. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. 2017;358:j4008.

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EULAR Secretariat | Seestrasse 240 | 8802 Kilchberg | Switzerland
T: +41 44 716 30 37 | F: +41 44 716 30 39
taskforces@eular.org | www.eular.org