Development of EULAR/ACR guidelines for management of Polymyalgia rheumatica

- Project plan -

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**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
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<tr>
<td>AHRQ</td>
<td>Agency for Health Care Research and Quality</td>
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<tr>
<td>ANCA</td>
<td>Anti-neutrophil cytoplasmic antibodies</td>
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<td>BSR</td>
<td>British Society for Rheumatology</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>EULAR</td>
<td>European League Against Rheumatism</td>
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<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<tr>
<td>GCA</td>
<td>Giant cell arteritis</td>
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<tr>
<td>GP</td>
<td>General practitioner</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations, Assessment, Development, and Evaluation</td>
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<tr>
<td>ISRCTN</td>
<td>International Standard Randomised Controlled Trial Number Register</td>
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<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>NSAIDS</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
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<tr>
<td>PICO</td>
<td>Population, Intervention, Comparator, Outcome</td>
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<td>PMR</td>
<td>Polymyalgia rheumatica</td>
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<tr>
<td>QUIPS</td>
<td>Quality In Prognosis Studies</td>
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<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>SBU</td>
<td>Swedish Council on Technology Assessment in Health Care</td>
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<tr>
<td>TNFi</td>
<td>Tumor necrosis factor-alpha inhibitors</td>
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ORGANIZATIONAL LEADERSHIP AND SUPPORT

This guideline is being developed as a collaborative project of the American College of Rheumatology (ACR), the EUropean League Against Rheumatism (EULAR) and the international Polymyalgia rheumatica (PMR) work group. The ACR and EULAR are funding the project.

PROJECT DEVELOPMENT - RESPONSIBILITIES

The guideline development consists of the core leadership team (B.D and E.M.), a voting panel formed by rheumatologists, specialists in internal medicine, general practitioners (GPs), health care professionals, patients representatives, methodologists and statisticians as well as the literature review team formed by rheumatologists, methodologists and research fellows.

The voting panel is responsible for the formulation of the PICO (=Population, Intervention, Comparator, Outcome) questions, for the rating of the overall quality of evidence and for the formulation of the recommendations. The literature review team is responsible, together with the principal investigator (PI) for the design and conduct of the systematic review as well as for the synthesis of the evidence report.

BACKGROUND

PMR is one of the most common autoimmune inflammatory rheumatic diseases of older people, predominantly occurring in females, and also represents the most common indication for long-term corticosteroid therapy in the community (1). Clinically, PMR is characterized by pain and stiffness in the proximal regions of the extremities and neck with elevated markers of inflammation (2). The prevalence of PMR among persons >50 years of age is estimated at 739 per 100,000, and the prevalence increases up to 4,213 per 100,000 among people of ages 90–95 years (3). PMR was associated with a significant incremental cost compared to the community that were mainly accounted for by co-morbid cardiovascular conditions, hospital stays and imaging (4).

Treatment of PMR is subject to wide variations among clinicians as it may be managed in primary or secondary care by general practitioners, rheumatologists and non-rheumatologists (5). Particularly the initial corticosteroid dose, strategies for tapering, duration of treatment and the use of disease modifying anti-rheumatic drugs significantly differ among physicians caring for PMR patients.
The British Society for Rheumatology (BSR) has recently developed guidelines for diagnosis and management of PMR (5). However there is a need for international guidelines to reduce the variation of practice not only across primary/secondary care but also across different health care systems. Ultimately, in order to be accepted, guidelines will require confirmation of their usefulness in clinical practice. ACR/EULAR endorsed recommendations for PMR will have a significant impact on clinical decision making, reduce practice variations and stimulate further research in areas where there is currently lack of adequate evidence.

**PROJECT OBJECTIVES**

The broad objective of this project is to provide user-friendly, evidence-based recommendations that offer best clinical advice for the short and long term management of patients with a diagnosis of PMR in a primary and secondary care setting. We would also like to develop recommendations on the use of routinely available prognostic factors informing clinical decisions of physicians caring for PMR patients. These recommendations aim at improved outcome of PMR patients and will be based on best clinical evidence, alongside expert consensus. The recommendations will take into account patient choice and informed decision-making.

The specific aims of the guidelines are defined by the key questions outlined below.

**Target population**

The target populations of these guidelines are patients with PMR (meeting the ACR/EULAR provisional classification criteria) (6, 7). Studies of patients with a clinical diagnosis of PMR as well as patients meeting the criteria of Hunder (8), Healey (9), Nobunaga (10) and Bird (11) will be included to the extent that they inform the treatment of PMR. Although PMR patients are usually ≥50 years old, the guidelines are not restricted to any age group, ethnicity or sex.

The guidelines are limited to patients with PMR. Management of PMR patients with concomitant giant cell arteritis (GCA), rheumatoid arthritis (RA) or other conditions that present with PMR features or mimic PMR is not covered by these recommendations.

**Target users of the guideline**

Primary, secondary and tertiary care physicians [i.e. General practitioners (GPs), specialists in general (internal) medicine and rheumatologists].
METHODS

We have been utilizing the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology as a framework to develop the guidelines as described previously (12).

An outline of the project plan is depicted in Figure 1.

PICO questions
The key questions of these guidelines were formulated in the PICO (=Population, Intervention, Comparator, Outcome) format by the voting panel taking patients' experiences and preferences into account. The PICO questions identify the population of interest (=target population), the alternative management strategies (i.e. an intervention and comparator) and all patient-important outcomes (13). Also, key questions on the value of prognostic factors predicting patient-important outcomes were specified in the PICO format considering the presence (I) or absence (C) of the prognostic factors.

The PICO questions were finalized by a two-step process:

I. A preliminary list of PICO questions was identified by a face-to-face discussion at the first guideline development group meeting in November 2012 in Chelmsford, UK, followed by an e-mail based survey among the voting panel.

II: The final PICO questions (with 100% agreement) were generated at the second guideline development group meeting during the EULAR conference in June 2013 in Madrid by discussion, refinement and grouping together of the preliminary PICO questions.

Consideration of patients’ perspectives
We consider the perspectives of the target population in this guideline project by involving patients’ representatives in the guideline development group, by interviewing patients for potential aspects to be covered by the guidelines (particularly by PICO questions) and by a survey among patients (as part of the outcome survey among rheumatologists, GPs and patients) to identify outcome parameters particularly relevant to patients.
Patients’ representatives are involved at all stages of the guideline development process including formulation of the PICO questions, voting on recommendations and presentation of draft guidelines.

**PICO questions on interventions:**

I. Role of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and analgesics
   1. In PMR (P), what is the effect of NSAIDs and/or analgesics (I) on outcome (O) compared with glucocorticoids (C).

II. Duration of glucocorticoid therapy
   2. In PMR (P), what is the effect of short duration of glucocorticoid therapy (I) on outcome (O) compared with long duration of glucocorticoid therapy (C).

III. Initial oral glucocorticoid dose
   3. In PMR (P), what is the effect of low dose oral glucocorticoids (≤ 7.5mg/day of prednisone equivalent) (I) on outcome (O) compared with medium dose of glucocorticoids (> 7.5mg/day but ≤ 30mg/day of prednisone equivalent) (C).
   4. In PMR (P), what is the effect of medium dose oral glucocorticoids (>7.5mg/day but ≤ 30mg/day of prednisone equivalent) (I) on outcome (O) compared with high dose of glucocorticoids (> 30mg/day but ≤ 100mg/day of prednisone equivalent) (C).
   5. In PMR (P), what is the effect of an oral glucocorticoid dose of ≥10mg/day but ≤20mg/day prednisone equivalent (I) on outcome (O) compared with a dose of >20mg but ≤30mg/day of prednisone equivalent (C).

IV. Glucocorticoid schedule
   6. In PMR (P), what is the effect of rapid taper of glucocorticoids (I) on outcome (O) compared with slow taper of glucocorticoids (C).

V. Intramuscular glucocorticoids
7. In PMR (P), what is the effect of intramuscular injection of glucocorticoids (I) on outcome (O) compared with oral glucocorticoids (C).

VI. Divided versus single dosage of oral glucocorticoids

8. In PMR (P), what is the effect of administration of oral glucocorticoid therapy at divided doses (morning plus evening) (I) on outcome (O) compared with single dose (morning only) (C).

VII. Role of non-biologic disease modifying anti-rheumatic drugs

9. In PMR (P), what is the effect of glucocorticoids plus Non-biological disease modifying anti-rheumatic drugs (DMARDs) (I) on outcome (O) compared with glucocorticoids alone (C).

VIII. Role of biological disease modifying anti-rheumatic drugs

10. In PMR (P), what is the effect of glucocorticoids plus biological agents (I) on outcome (O) compared with glucocorticoids alone (C).

11. In PMR (P), what is the effect of biological agents (I) on outcome (O) compared with glucocorticoids alone (C).

IX. Role of non-pharmacological therapy

12. In PMR (P), what is the effect of glucocorticoids plus non-pharmacological interventions (I) on outcome (O) compared with glucocorticoids alone (C).

PICO questions on risk factors:

X. Role of risk factors

13. In PMR (P), what is the effect of older age at diagnosis (I) on outcome (O) compared with younger age (C).

14. In PMR (P), what is the effect of female sex (I) on outcome (O) compared with male sex (C).

15. In PMR (P), what is the effect of high levels of inflammatory markers [i.e. erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP)] at
diagnosis (I) on outcome (O) compared with low levels of inflammatory markers (C).

16. In PMR (P), what is the effect of more active/severe disease at diagnosis (I) on outcome (O) compared with lower disease activity/severity (C).

17. In PMR (P), what is the effect of the presence of peripheral arthritis at diagnosis (I) on outcome (O) compared with absence of peripheral arthritis (C).

18. In PMR (P), what is the effect of longer symptom duration at diagnosis (I) on outcome (O) compared with shorter symptom duration (C).

19. In PMR (P), what is the effect of concomitant conditions at diagnosis that could be exaggerated by PMR and/or glucocorticoid therapy (I) on outcome (O) compared with absence of these conditions (C). (See list of conditions in Appendix B)

20. In PMR (P), what is the effect of rapid response to glucocorticoids (I) on outcome (O) compared with delayed response.

XI. Management of patients in primary vs. secondary/tertiary care:

21. In PMR (P), what is the effect of shared patients' management by primary and secondary care (I) on outcome (O) compared to management in primary care only.

22. In PMR (P), what is the effect of optimal control management of patients (I) on outcome (O) compared to conventional management (C).

At the 2nd guideline development group meeting it was decided not to include PICO questions on the prevention of glucocorticoid induced-osteoporosis and vaccination in PMR for the purpose of the literature review because there are published guidelines by the ACR (14) and EULAR (15), respectively on these issues.

Also, the group decided not to define the following terms at this stage: “short/long duration of glucocorticoid therapy”, “rapid/slow taper of glucocorticoid therapy” “older/younger age”, “high/low levels of inflammatory markers”, “more/less active/severe disease”, longer/shorter symptom duration”, “rapid/delayed response to glucocorticoids”, “optimal/conventional control management”. The group argued that results from literature review will inform the voting panel about the definitions used in clinical studies. Based on these data the voting panel will decide on definitions at the stage of drafting the recommendations.
Figure 1. Flow chart of the project plan for guideline development

1st GDG meeting (Chelmsford 2012)

- Introduction to GRADE
- Discussion on objectives
- Discussion on key questions

Identification of patient's perspectives
Development of PICO questions
Identification of critical and important outcomes

2nd GDG meeting (Madrid 2013)

- Voting panel – voting on objectives
- PICO questions
- Outcomes
- Target user/popul.

- Literature review team
- Presentation search strategies

ACR-review of protocol and publication on website

Sensitive literature search on PMR

MEDLINE, Embase, PubMed, CINAHL, Web of Science, Cochrane, (MESH, text, truncated text), 1970-present

Hand search of homepages to identify guidelines

Trial registries, Conference proceedings

Contact experts
1. Removal of duplicates using reference software
2. Abstract review of identified articles
3. Exclude editorials, commentaries, letters not involving patients
4. Full text review of identified articles
5. Exclude articles not studying PMR, check with PICO questions
6. Data extraction
7. Quality assessment according to AGREE, GRADE, QUIPS

Evidence table PICO 1
Evidence table PICO 2
Evidence table PICO 3
Evidence table PICO n

Level of evidence = study type + quality assessment

Graded recommend.
PICO 1-12

quality, quantity, and consistency assessment recommend.
PICO 13-22

Delphi based approach

3rd GDG meeting (San Diego 2013)
3\textsuperscript{rd} GDG meeting (San Diego 2013)

- Voting panel
- Literature review team
- Presentation of appraised recommendations
- Presentation of evidence tables

\[\text{Drafting guidelines}\]

4\textsuperscript{th} GDG meeting (Southend 2013)

- Voting on draft guidelines

International PMR/GCA symposium (Southend 2013)

- Presentation of draft guidelines
- Feedback target population \rightarrow Feedback target users

- Modification of draft guidelines according to feedback

\[\text{Submission of guidelines to ACR and EULAR for external peer-review}\]

EULAR meeting (Paris 2014)

- Presentation and vote on final guidelines
Importance of outcome parameters

As per GRADE methodology, the lists of outcomes have to be comprehensive and should include potentially patient important outcomes. These outcomes further need to be graded based on relative importance into: critical, important and less important outcomes (12).

The list of outcomes was generated by a three-step process:

I. A list of candidate outcomes was identified after feedback from all the stakeholders of the guidelines panel consisting of rheumatologists, GPs and patients’ representatives. A literature search was also done to look for any additional outcome measures that may have been missed. Subsequently, this revised list of candidate outcome measures was circulated among the members of the guideline development group for their feedback. After receiving the feedback, the final list of candidate outcomes was drafted.

II: In the second step, a survey-based grading of the candidate outcomes was performed. We invited 43 rheumatologists (15 international and 28 practicing in Essex, UK) and 87 GPs (all practicing in Essex, UK) to complete the questionnaire posted on surveymonkey (https://www.surveymonkey.com/). To some of the physicians the questionnaire was emailed and responses were got back be post or fax. Forty-three patients were invited to the survey through PMRGCAuk (www.pmrgcauk.com), a registered charity established to meet the needs of people with PMR and/or GCA, their friends, families and helping professionals. A paper based questionnaire was distributed and was returned post or fax. Each outcome measure was graded based on its relative importance for clinical decisions on a 1 to 9 point scale. Scores from 1-3 indicated limited importance (not important for decision making), 4-6 importance (important, but not critical for decision making) and 7-9 critical (critical for decision making). Fifteen (100%) international rheumatologists, 23 (82%) rheumatologist from Essex, 15 (17%) GPs and 41 (95%) patients responded to the questionnaire. Outcome measures deemed as critical (i.e. score ≥7) by at least 50% of responders in any of the groups (rheumatologists, GPs and/or patient representatives) were included into the preliminary list of outcome parameters presented at the second guideline development group meeting in Madrid.

III: The final list of outcome parameters as depicted in Appendix C was generated at the second guideline development group meeting by discussion, refinement and consensus finding on the preliminary list of outcome parameters.

Systematic Literature Review
The literature search strategies were designed and will be conducted by the literature review team.

The protocol will be submitted to the ACR Guideline Subcommittee for final approval before the systematic review is conducted. In addition, the project protocol will be posted on the ACR web site for public comment. Feedback received will be considered as the systematic review begins. If warranted, the literature review team, PI and ACR may decide to modify the protocol as a result of this evaluation.

Due to the limited literature available in PMR, a sensitive search retrieving all articles on PMR will be conducted. In further steps, articles will be screened whether they fulfill inclusion and exclusion criteria and whether they are applicable to any of the PICO questions.

We will retrieve existing guidelines to determine whether any of the key questions were already addressed. As mentioned above, there are existing ACR (14) and EULAR (15) recommendations on the prevention of glucocorticoid induced-osteoporosis and vaccination, respectively. Therefore, these topics will not be included in the literature search.

The literature searches will be updated in February 2014 to ensure completeness.

**Search strategy: Databases for the identification of relevant articles**

We will search the following electronic databases: Ovid MEDLINE® (1970-present), Embase (1970-present), PubMed (1970 to the present) CINAHL (1970 to the present), Web of Science (1970 to the present) and the Cochrane Library(1970 to the present).

To identify relevant guidelines for the PICO questions the following homepages are searched:

<table>
<thead>
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<th>Websites searched for relevant guidelines:</th>
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<tr>
<td>Agency for Health Care Research and Quality (AHRQ) <a href="http://www.ahcpr.gov/">http://www.ahcpr.gov/</a></td>
</tr>
<tr>
<td>NHS Centre for Reviews and Dissemination <a href="http://www.york.ac.uk/inst/crd/welcome.htm">http://www.york.ac.uk/inst/crd/welcome.htm</a></td>
</tr>
<tr>
<td>NHS Quality Improvement Scotland <a href="http://www.nhshealthquality.org">http://www.nhshealthquality.org</a></td>
</tr>
<tr>
<td>National Institute for Clinical Excellence (NICE) <a href="http://www.nice.org.uk/">http://www.nice.org.uk/</a></td>
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</table>
Search strategy: Search terms

Search strategies were designed using the thesauri for each database, i.e., Medical Subject Headings for OVID Medline, PubMed and Cochrane Library and EMTREE terms for Embase. Text words in title or abstract (e.g. polymyalgia rheumatica) and truncated text words (e.g. polymyalgi*) will also be used in OVID Medline, PubMed, and Embase, and keyword/title/abstract words in the Cochrane Library. “PMR” is also used as a search term; however, articles are excluded if the following terms are also present in the title or abstract: “prenatal mortality rate”, “population mortality rate”, “premature mortality rate”. GCA and temporal arteritis were considered as search terms but not included due to the low expected yield and large volume of non-relevant literature. See Appendix D for the list of search terms used.

Grey literature

The grey literature, such as reports by the Agency for Healthcare Research and Quality will be searched to identify additional peer-reviewed articles not published in journals identified by the above databases. Conference abstracts (particularly including ACR, EULAR, BSR, international PMR/GCA and ANCA meetings) will be reviewed, tracked to determine whether the contents of these abstracts were subsequently published as peer-review articles, and included in the final evidence report in order to ensure the completeness of our literature search. Trial registries, such as ClinicalTrials.gov, ISRCTN and EU Clinical Trials Register, will be searched to identify ongoing and completed trials, and the literature will be tracked to identify published trial results. In the case of ongoing trials, or completed but not yet published trials, every effort will be made to obtain preliminary data for inclusion in the final evidence report. Additional articles will be retrieved searching the reference list of full and review articles and by contacting experts in the field.

Data management
References and abstracts will be imported into bibliographic management software (Reference Manager) and duplicates removed.

Articles will be reviewed by designated members of the literature review team. Titles and abstracts of identified articles will initially be screened to remove editorials, commentaries and letters without inclusion of patients.

The full text of each remaining article will then be additionally screened independently by two members of the literature review team, who will recommend inclusion or exclusion. Results will be compared and discrepancies will be resolved by a third member of the literature review team.

Multiple publications from the same trial will be identified, and additional reports from the same trial will only be considered if separate, pre-specified outcomes are reported.

Inclusion/Exclusion criteria

We will exclude articles that do not study patients with PMR or only include patients who have both PMR and GCA. In the Scandinavian literature, the term GCA/PMR has often been used as a synonym for PMR. Therefore, hand review of articles identified by the literature search will be necessary to decide at an individual basis whether an article meets the inclusion criteria. Symptoms of PMR and rheumatoid arthritis (as well as other conditions) can be overlapping, and some conditions may mimic PMR. Therefore, some studies might have studied a “polymyalgic syndrome” that cannot clearly be recognized as being PMR. These studies are excluded as well.

We exclude editorials, letters not reporting patients’ data and commentaries.

Articles that cannot be assigned to any of the PICO questions are also rejected.

No language restrictions are applied because of the international composition of the guideline development team.

For studies on prognostic factors we exclude studies that do not report a statistical association (or lack of association) with outcome. All factors reported in the study should be in routine clinical use and not require sophisticated equipment or complex analysis. Minimum time for follow-up is set at 6 months. To ensure applicability of findings to routine clinical practice, any study that reports exclusively on imaging or laboratory tests with no reference to patient presentation is excluded.

Data extraction
Study details and results are extracted using a data extraction form from included articles by 2 members of the literature review team according to GRADE methodology. For prognostic factors extracted data include all relevant information to enable quality assessment (see below) as well as odds ratios, relative risks, hazard ratios as well as confounding-adjusted results. The preliminary data extraction form [containing at least the following items: authorship and publication, design, main study population, primary study objective(s), links/overlap with other studies, study inclusion criteria, characteristics of participants, definition of intervention/exposure and control, definition of outcome, method of statistical analysis, length of follow-up, losses to follow-up, missing data, discrete/continuous data (counts, means, SDs etc.), measures of effect and uncertainty, notes] will be piloted in 5 identified articles and evaluated for completeness and handling.

Quality assessment or risk of bias

Identified guidelines will be quality-assessed using the AGREE II tool.

Existing primary interventional studies (related to PICO questions 1-12) about PMR not covered by high quality guidelines will be quality-assessed using GRADE methodology. GRADE is a systematic approach of rating quality of evidence. The use of this system has several advantages; it uses a transparent and explicit approach and is evidence based. GRADE is now the preferred quality of evidence rating system, and has been adopted by over 50 organizations worldwide.

GRADE evaluates the quality of evidence on five specific domains:

1. Study limitations: Confidence in the estimate of the effect decreases if studies have major limitations that may bias their results. The limitations could be:
   a. lack of allocation concealment
   b. lack of blinding
   c. large losses to follow-up
   d. failure to adhere to intention to treat analysis
   e. stopping early for benefit
   f. failure to report outcomes

2. Inconsistency of results: Confidence of the estimate of the effect decreases if there is variability in results (heterogeneity) across studies and investigators fail to identify a plausible explanation.
3. Indirectness of the evidence: Confidence of the estimate of the effect decreases if there are differences between the population, intervention, comparator or outcome of interest, and those included in the systematic review studies.

4. Imprecision: Confidence of the estimate of the effect decreases if the systematic review includes relatively few patients and few events and thus has wide confidence intervals.

5. Publication bias: Confidence of the estimate of the effect decreases if there is evidence that some studies were not reported.

Evidence generated from randomized control trials starts as high quality but can be downgraded if any of the above limitations are present. The quality of the evidence could be rated as high, moderate, low and very low.

After assessing these five domains the overall quality of evidence will be assessed as:

1. High quality evidence (further research is very unlikely to change our confidence in the estimate of effect)

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

3. Low quality (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)

4. Very low quality (Any estimate of effect is very uncertain)

Studies on prognostic factors (any design, PICOs 13-22) are quality assessed using the Quality In Prognosis Studies (QUIPS) tool (12, 16).

During assessment of risk of bias of prognostic factor studies, six important domains will be considered as suggested by this tool: study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting.

**Preparing the evidence report for the voting panel**

Evidence tables are prepared by the literature review team for each PICO question using Review Manager (RevMan) and GRADE profiler (GRADEpro) software. The Summary of Findings table for PICOs 1-12 contains the benefits and harms for each outcome across studies, the assumed and corresponding risk for comparators and interventions [(95% confidence interval (CI)], the absolute risk and relative effect (95% CI), the number of participants/ number of studies, and number needed to treat, and the
quality of evidence for each critical and important outcome (i.e., high, moderate, low or very low).

Evidence tables for PICOs 13-22 report the odds ratios, relative risks or hazard ratios for prognostic factors as well as corresponding p-values. Adjusted results are extracted where possible to address the problem of confounding.

The Evidence Profile documents the quality of the evidence across studies for each outcome, and summarizes the quality factors (i.e., limitations of study design, inconsistency, indirectness, imprecision, and other considerations).

Where possible, meta-analyses using fixed effect methods will be conducted to combine the results of studies for each PICO question.

Statistical heterogeneity will be assessed by considering the chi-squared test for significance at p<0.1 and I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where significant clinical or statistical heterogeneity is considered present, we will carry out sensitivity analyses using random effects methods and excluding studies based on quality issues and clinical characteristics.

**Forming guideline recommendations**

Using the Evidence Profiles, the voting panel will propose recommendations to each key question 1-12 according to the GRADE methodology:

The GRADE system offers two grades of recommendations: “strong” and “weak”.

Four factors affect whether recommendations are strong or weak including. 1) Quality of evidence, 2) balance between desirable and undesirable effects, 3) values and preferences, and 4) use of resources.

Similarly, recommendations on prognostic factors (key questions 13-22) will be graded according to the level of evidence supporting them as being “strong”, “limited” or “conflicting”.

Recommendations on prognostic factors are considered to be supported by strong evidence if consistent findings were reported in multiple (≥2) high-quality cohort studies. Limited evidence requires consistent findings in a single high-quality cohort study. Conflicting evidence results from conflicting findings in high-quality studies (<75% of studies reported consistent findings) (17).

The recommendations process for both, interventional PICOs (1-12) as well as for PICOs on prognostic factors (13-22) will be conducted in two stages:
I) In a Delphi based approach; the voting panel will use the factors mentioned above to make recommendations according to the GRADE methodology and to make recommendations on prognostic factors.

II) At the ACR meeting in October 2013 in San Diego, the panel will present and discuss the overall level of evidence supporting the recommendations and consequently, the guidelines will be drafted. The panel will vote on the guidelines at the international PMR/GCA meeting in November 2013.

Presentation of draft guidelines

The draft guidelines will be presented at the international PMR/GCA meeting in Southend 2013. The international PMR/GCA meeting is open to each physician interested in PMR and/or GCA. PMR patients’ representatives (representing the target population), GPs, specialists in internal medicine and rheumatologists (target users of the guideline) will be invited to the conference and the presentation of the guidelines. Valuable feedback and suggestions for additional evidence or alternative interpretation of that evidence will be considered and incorporated into the guidelines.

External peer review

Draft guidelines will be sent to ACR and EULAR for external peer review to gather feedback on the draft guidelines.

After modification of the guidelines according to the feedback of reviewers the guidelines are submitted for publication to Annals of Rheumatic Diseases and to Arthritis Care and Research.

PRESENTATION AND DISSEMINATION OF FINAL GUIDELINES

The final guidelines are disseminated by publication in the journals Annals of Rheumatic Diseases and Arthritis Care and Research as well as uploading them to the ACR homepage.

UPDATING THE GUIDELINES

An update of the guidelines is intended 3 years upon its publication.
PLANNED APPENDICES OF GUIDELINES (AT MINIMUM)

1. Literature search strategy
2. Evidence Profiles and Summary of Findings Tables for each PICO question

AUTHORSHIP

All members of the guideline development group (i.e. core leadership team, voting panel as well as literature review team) will be included as authors of the guideline.

DISCLOSURES / CONFLICTS OF INTEREST

The ACR’s disclosure and COI policies for guideline development will be followed for this project. These can be found in the ACR Guideline Manual on the ACR web site under Policies & Procedures.
## APPENDICES

### Appendix A. Timelines

<table>
<thead>
<tr>
<th>Time frame</th>
<th>Action to be taken</th>
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| **1 – 5 months** (01/13 – 05/13) | 1. Defining the remit of the guidelines  
2. Consideration of patients’ perspectives  
3. Identification of key questions (PICO format)  
4. Identification and grading potential outcome measures  
5. Literature review plan |
| **Month 6** | 6. Discuss and vote on all the above – remit of the guideline, target population, target users, finalise key questions, outcome grading discussion, discussion of literature review strategy |
| **6 to 10 months** (06/13 – 10/13) | 7. Systematic literature review  
8. Data extraction and evidence table for each of the PICO questions  
9. Grading recommendations, assessing quality, quantity and consistency of studies on prognostic factors |
| **Month 10** (10/13) | 10. Present evidence tables  
11. Present appraised recommendations  
12. discuss the evidence, discuss the judgment forms and wording of recommendation |
| **Month 11** (11/13) | 13. Writing the first guideline draft |
| **Month 11** (11/13) | 14. Discuss and vote on the first draft |
| **Month 11** (11/13) | 15. Presentation first draft of guidelines  
16. Feedback from target population and target users |
<p>| <strong>12 to 14 months</strong> (12/13 – 02/14) | 17. Amend guidelines and finalize draft for submission to ACR for peer review |</p>
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<th>Timeframe</th>
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<tr>
<td>15 to 16 months</td>
<td>18. Send the draft to peer reviewers</td>
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<td>(03/14 – 04/14)</td>
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<tr>
<td>17 to 18 months</td>
<td>19. Discuss peer review comments and finalize draft of guidelines</td>
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<td>(05/14 – 06/14)</td>
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<td>Month 18</td>
<td>20. Presentation and vote on final of guidelines</td>
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<tr>
<td>(06/14)</td>
<td>Meeting – EULAR 2014</td>
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<tr>
<td>19 to 22 months</td>
<td>21. Prepare for submission to journal</td>
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<td>(07/14 – 10/14)</td>
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<td></td>
<td>22. Publish guideline</td>
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Appendix B. List of concomitant conditions that could be exaggerated by PMR and/or glucocorticoid therapy*

- Cardiovascular disease
- Cerebrovascular disease
- Peripheral vascular disease
- Osteoporosis
- Hyperlipidemia
- Diabetes
- Hypertension
- Infection
- Cataract
- Glaucoma
- Peptic ulcer
- Skin disorders
- Adiposity
- Mood disturbances
- Cognitive disorder

*List was generated by the guideline development group by discussion and consensus finding
Appendix C. List of outcome parameters

- Disease remission
- Disease relapse
- Duration of glucocorticoid therapy
- Discontinuation of glucocorticoid therapy
- Development of GCA
- Glucocorticoid side effects (see Appendix E)
- Response to GC therapy
- Cumulative GC dose
- Inflammatory markers (i.e. ESR, CRP)
- Patients assessment of global wellbeing (VAS – Visual analogue score)
- Severity (VAS) / duration (minutes) of morning stiffness
- Lowest possible GC dose (Prednisolone less than 5mg/day)
- Functional status (HAQ or other measures)
- Quality of life (SF-36, EQ5D etc.)
- Mortality
- Hospitalization (due to disease, its complications, co-morbidity and/or treatment related complications)
- Impact on patients’ social environment
- Fatigue
- Imaging of shoulder/hip
- Healthcare resource use (health economics)
- Disease activity score
Appendix D. Proposed search terms used for literature search

*truncation;# Mesh term; $ textword; mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword;

1. Polymyalgia rheumatica #
2. Polymyalgia rheumatica $
3. polymyalgia rheumatica .mp
4. PMR NOT prenatal mortality rate $ .mp
5. PMR NOT premature mortality rate $ .mp
6. PMR NOT population mortality rate $ .mp
7. polymyalgi*
8. polymyalgia $ .mp
9. rheumatic polymyalgia $ .mp
10. polymyalgia arteritica $ .mp
11. forestier certonciny syndrome $ .mp
12. pseudopolyarthitis rhizomelica $ .mp
13. rheumatic myalgia $ .mp
14. rheumatism, inflammatory rhizomelic $ .mp
15. rhizomelic pseudopolyarthritis $ .mp
## Appendix E. Medication Categories

Pharmacological therapy can involve several classes of medications. The table below lists the classes of medication considered, and the constituent medications.

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<td>Glucocorticoids</td>
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<td>Nonsteroidal anti-inflammatory drugs (NSAIDs)</td>
<td>Aspirin, Celecoxib, Diclofenac, Diflunisal, Epirizole, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Ketorolac tromethamine, Meclofenamic acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Salicylate, Sodium salicylate, Sulindac, Tolmetin</td>
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<tr>
<td>Analgesics</td>
<td>Paracetamol, metamizole, tramadol, codeine, dihydrocodeine, morphine, alfentanil, buprenorphine, diamorphine, fentanyl, hydromorphone, methadone and oxycodone</td>
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<td>Tumor necrosis factor-alpha inhibitors (TNFi)</td>
<td>Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab</td>
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<td>Non-TNFi biologicals</td>
<td>Abatacept, Anakinra, Rituximab, Tocilizumab</td>
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<tr>
<td>Non-biological disease modifying anti-rheumatic drugs (DMARDs)</td>
<td>Leflunomide, Methotrexate, Sulfasalazine, Azathioprine, Cyclosporine, Mycophenolate mofetil, Tacrolimus, Cyclophosphamide, chloroquine, hydroxychloroquine, D-penicillamine, gold</td>
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</table>

Medication classes will be considered unless otherwise specified. In cases where individual medications are of interest, these medications will be specifically noted.
Appendix F. Glucocorticoid related side effects*

- Diabetes mellitus/glucose intolerance
- Osteoporosis
- Cardiovascular disease
- Dyslipidemia
- Impaired wound healing
- Infections
- Osteonecrosis
- Myopathy
- Cataract
- Glaucoma
- Atherosclerosis
- Hypertension
- Peptic ulcer
- Weight gain
- Moon face
- Dyspnea
- Palpitations
- Fatigue
- Skin atrophy, bruising
- Mood disorders

*the 15 most worrisome parameters according to patients and physicians (18). Skin atrophy, bruising and mood disorders were added despite a lower rating in (18) because these side effects are particularly relevant for older patients treated with glucocorticoids according to the experience of the guideline development group members.
REFERENCES


of existing approaches The GRADE Working Group. BMC Health Serv Res 2004; Dec 22;4(1):38.


DISCLOSURES OF RELATIONSHIPS

In order for the College to most effectively further its mission and to otherwise maintain its excellent reputation in the medical community and with the public, it is important that confidence in the College’s integrity be maintained. The cornerstone of the ACR’s Disclosure Policy is disclosure of actual and potential conflicts so that they can be evaluated by the College in order to avoid undue influence of potential conflicts.

The purpose of the ACR’s Disclosure Policy is identification of relationships which may pose actual or potential conflicts. These actual or potential conflicts can then be evaluated by the College so that adjustments can be made that will avoid any undue influence. This policy is based on the principle that, in many cases, full disclosure of the actual or potentially conflicting relationship will of itself suffice to protect the integrity of the College and its interests.

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<td>Literature Review Team</td>
<td>London School of Hygiene &amp; Tropical Medicine</td>
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<td>Sources of personal income to include speakers bureau, honoraria, royalties, expert witness fees, advisory boards, or any other sources of income (excludes salary from primary employer)</td>
<td>Intellectual Property to include copyrights, patents, or licenses</td>
<td>Research Grants/Contracts</td>
<td>Investments to include medical industry and non-medical industry</td>
<td>Organizational Benefit</td>
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<td>Yogesh P. Singh</td>
<td>Disclosure forthcoming</td>
<td>Voting Panel/Literature Review Team</td>
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<td>Robert Spiera</td>
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<td>Hospital for Special Surgery</td>
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