

METHODS

For this project, we followed the policy and procedure manual for clinical practice guidelines by the American College of Rheumatology (ACR).[1] Accordingly, we used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology as a framework to develop these recommendations involving 2 expert panels:[2–5] a) a Core Expert Panel (CEP) of clinicians and methodologists (BD, ELM, CD, YS, AH, PP, DC, SM) who drafted the protocol, coordinated the survey on outcome parameters, conducted the systematic literature review (SLR) and the evidence synthesis; and b) a voting panel consisting of 42 members, including rheumatologists ($n=25$), specialists in internal medicine ($n=2$), general practitioners ($n=4$), allied health care professionals ($n=4$) and patient representatives ($n=7$) from Europe, USA, South America, Africa, India, Japan, Australia and New Zealand. The voting panel formulated the PICO (=Population, Intervention, Comparator, Outcome) questions, interpreted the evidence and drafted the final recommendations.

Involvement of patients in the development of the recommendations

GRADE encourages the involvement of patients in the development of management recommendations and supports a shared clinical decision of treatment between physicians and patients.[3,4] For this project, patients' representatives were involved in each step, from the formulation of the key questions and outcomes, to the formulation and approval of the final recommendations. A challenge in this regard is the selection of adequate patients' representatives given that thoughts, values and preferences should be considered from as many patients' subgroups as possible. We invited the chairs and other members of Polymyalgia rheumatic giant cell arteritis UK (PMRGCAuk) as well as patient's representatives from USA to participate in this

exercise. PMRGCAuk is a patient charity for people with Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) and has recently conducted a survey within UK to identify the thoughts and concerns of people living with PMR.[6,7] We recognized that these people (and their experience from the survey) may not reflect the feelings of all PMR patients; however, their close contact with other PMR patients, their interest in patients' values and preference as well as their experience with research studies qualified them as representative members of the recommendation development group. For other, non-English patients, language restrictions were an insuperable barrier to participate in this project.

Formulation of the key questions and outcomes

The key questions were framed in the PICO format, taking patient experiences and preferences into account.[8] We formulated 12 PICO questions on therapeutic interventions and 10 questions on prognostic factors as detailed in the Supplementary Box S1 (a+b) below.

Supplementary Box S1a. PICO questions on interventions

1. In Polymyalgia rheumatica (PMR) (P), what is the effect of Non-steroidal Anti-inflammatory drugs (NSAIDs) and/or analgesics (I) on outcome (O) compared with glucocorticoids (C).
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).
3. In PMR (P), what is the effect of low dose oral glucocorticoids ($\leq 7.5\text{mg/day}$ of prednisone equivalent) (I) on outcome (O) compared with medium dose of glucocorticoids ($> 7.5\text{mg/day}$ but $\leq 30\text{mg/day}$ of prednisone equivalent) (C).
4. In PMR (P), what is the effect of medium dose oral glucocorticoids ($>7.5\text{mg/day}$ but $\leq 30\text{mg/day}$ of prednisone equivalent) (I) on outcome (O) compared with high dose of glucocorticoids ($> 30\text{mg/day}$ but $\leq 100\text{mg/day}$ of prednisone equivalent) (C).
5. In PMR (P), what is the effect of an oral glucocorticoid dose of $\geq 10\text{mg/day}$ but $\leq 20\text{mg/day}$ prednisone equivalent (I) on outcome (O) compared with a dose of $>20\text{mg}$ but $\leq 30\text{mg/day}$ of prednisone equivalent (C).
6. In PMR (P), what is the effect of rapid taper of glucocorticoids (I) on outcome (O) compared with slow taper of glucocorticoids (C).
7. In PMR (P), what is the effect of intramuscular injection of glucocorticoids (I) on outcome (O) compared with oral glucocorticoids (C).
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).
9. In PMR (P), what is the effect of glucocorticoids plus Non-biological disease modifying anti-rheumatic drugs (I) on outcome (O) compared with glucocorticoids alone (C).
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).
12. In PMR (P), what is the effect of glucocorticoids plus non-pharmacological interventions (I) on outcome (O) compared with glucocorticoids alone (C).

Supplementary Box S1b. PICO questions on prognostic 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 (including cardiovascular disease, cerebrovascular disease, peripheral vascular disease, osteoporosis, hyperlipidaemia, diabetes, hypertension, infection, cataract, glaucoma, peptic ulcer, skin disorders, adiposity, mood disturbances, cognitive disorder) at diagnosis that could be exaggerated by PMR and/or glucocorticoid therapy (I) on outcome (O) compared with absence of these conditions (C).
20. In PMR (P), what is the effect of rapid response to glucocorticoids (I) on outcome (O) compared with delayed response.
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).

All questions were framed in the PICO (=Population, Intervention, Comparator, Outcome) format

As per GRADE methodology, the list of outcomes was supposed to be comprehensive including all parameters potentially relevant to patients. We, therefore, conducted a survey among 43 rheumatologists (most of them were members of the voting panel), 87 General Practitioners (GP, all from UK) and 43 patients (all from PMRGCAuk).[6] An international survey was unfortunately not feasible within the short time-period available given the necessity for translation of the questionnaire for non-English countries and the lack of a pre-existing research network between GPs, patients and rheumatologists in non-UK countries.

A candidate item list was generated by literature review and additional input from the voting panel (including contribution from patients), containing 119 outcome measures including symptoms, physical examination findings, laboratory parameters, imaging, composite outcome measures, drug related adverse effects, functional status, quality of life and PMR-related complications. Survey participants were asked to rate each parameter based on its relative importance for clinical decision-making according to a 1-9 point scale (1-3 not important, 4-6 important, but not critical and 7-9 critical). All parameters with a grading of ≥ 7 by $\geq 50\%$ of responders in at least 1 of the 3 groups (i.e., rheumatologists, GPs or patients) were presented to the voting panel, which refined and agreed upon the final list of critical outcome measures as detailed in Supplementary Box S2.

Supplementary Box S2. Outcome parameters used for the systematic literature review

- Disease remission
- Disease relapse
- Duration of glucocorticoid therapy
- Discontinuation of glucocorticoid therapy
- Development of giant cell arteritis
- Glucocorticoid 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)
- Response to glucocorticoid therapy
- Cumulative glucocorticoid dose
- Acute phase reactants
- Patients assessment of global wellbeing
- Severity / duration of morning stiffness
- Lowest possible glucocorticoid dose (prednisone equivalent less than 5mg/day)
- Functional status (Health Assessment Questionnaire or other measures)
- Quality of life (Short Form-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

The panel decided not to include PICO questions on the prevention of GC-induced osteoporosis and immunization in PMR because there are published recommendations by the ACR [9] and European League Against Rheumatism (EULAR) [10], respectively on these issues. Also, the group decided not to specify cut-offs for most PICO items (such as long and short duration of GC therapy, rapid and slow taper of GCs, older and younger age, high and low levels of inflammatory markers, more and less active/severe disease, longer and shorter symptom duration, rapid and delayed response to GCs, optimal and conventional control management) because there are no uniformly accepted definitions for these parameters. The group further argued that literature review might reveal relevant cut-offs (i.e. the cut-offs that were used to segregate groups in clinical studies) for these items.

Systematic Literature Review

Details concerning the SLR are presented in a separate manuscript.[Dejaco et al., ARD 2015 (in press)] In brief, 2 members of the CEP (CD, Rheumatologist, Graz, Austria and YS, Rheumatologist, Southend, UK, counselled by PP, clinical epidemiologist, London, UK) performed a literature search aimed at retrieval of all published articles in PMR, without limitation on the languages of the publications. We used Ovid MEDLINE®, Embase, PubMed, CINAHL, Web of Science and the Cochrane Library databases and applied the thesauri of PMR for each database, text words in title or abstract, abbreviations and truncated text words as key words. The grey literature (e.g., reports by the Agency for Healthcare Research and Quality, conference abstracts) was reviewed to identify additional peer-reviewed articles not tracked by the search described above. We reviewed trial registries to identify ongoing and completed trials and contacted sponsors/investigators to request any

available results. Additional papers were retrieved by searching the reference list of full and review articles and by contacting experts in the field. The literature search was limited to articles published from January 1970 through June 2013. An update search was performed in April 2014. New data were presented to the voting panel in order to discuss a possible modification of the recommendations based on this new information.

We excluded all articles that did not report original data, did not study patients with PMR, or that considered PMR and GCA patients as a single group. For PICO on prognostic factors, we excluded all studies investigating factors that were not routinely available [e.g. cytokines other than interleukin (IL)-6, adhesion molecules ect. [11,12]] and/or trials with a follow-up of fewer than 6 months. The panel argued that studies with a shorter time frame were not helpful to predict outcomes of PMR patients given the usual duration of PMR of >6-12 months.[13,14]

Two members of the CEP (CD, YS) independently reviewed all articles identified by the literature search, performed data extraction and quality appraisal. Two additional members of the CEP (SM, Rheumatologist, Leeds, UK and DC, Rheumatologist, Genova, Italy) helped with review and data extraction of non-English articles. References and abstracts identified by the search were imported into bibliographic management software (Zotero Version 4.0.20, Fairfax, VA, USA) and duplicates were removed. Titles and abstracts were screened to remove editorials, commentaries and letters without patient data. The full text of each remaining article was then tested against the inclusion and exclusion criteria. The CEP also made every effort to identify multiple publications from a single trial. Study details and results were extracted using a pre-specified data extraction sheet. Appraisal of studies was

performed according to GRADE methodology and using the Quality in Prognostic Studies (QUIPS) tool as detailed below.

Any disagreement was resolved by discussion. In case a consensus was not achieved (15.6% of articles), a third member of the CEP (AH, clinical epidemiologist, London, UK) was consulted and made the final decision.

External evidence: After the results of the SLR became available, the panel recognized that there is a paucity of data regarding safety aspects of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) (no prospective data), GCs (39 prospectively studied patients) and methotrexate (MTX, 97 prospectively investigated patients) in PMR. The panel found it difficult to balance benefits versus harms of these substances in PMR, given that the available studies had an insufficient sensitivity to detect rare and long-term side effects. On the other hand, all these drugs have been the standard of care for other conditions such as RA or osteoarthritis (OA) and thousands of patients have been followed-up in (non PMR) clinical studies already.[15–17] In order to inform the voting panel about important safety aspects, the panel decided to revise the protocol toward the presentation of other ACR and EULAR recommendations related to the use of NSAIDs, GCs and MTX in populations with a similar demography [i.e. RA, OA, gout, calcium pyrophosphate disease (CPPD) and giant cell arteritis] to the guideline group. The panel strongly felt that it would be unethical not to take such information into account. The information retrieved from these papers was ultimately used as indirect, supporting evidence. Supplementary Table S1 details the recommendations and the information that was presented to the panel in addition to the data from the SLR in PMR. The rationale for the consideration of ACR and EULAR recommendations (and supporting references) rather than any other source of data was the assumption that ACR and EULAR

recommendations are supported by high-quality SLRs and that the recommendations made in these papers can be accepted as the current standard of clinical care. We retrieved the recommendation papers from ACR and EULAR homepages and focused on recommendations published after January 1st, 2000.

Supplementary Table S1. ACR and/or EULAR recommendations used to inform the voting panel about safety aspects of Non-Steroidal Anti-inflammatory Drugs (NSAIDs), Glucocorticoids (GCs) and methotrexate (MTX)

Recommendation	Year	Substances	Statements presented to the guideline panel*
EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee For International Clinical Studies Including Therapeutics (ESCSIT) [18]	2006	NSAIDs	<ul style="list-style-type: none"> In acute gout, NSAID use is associated with an increased risk of gastrointestinal bleeding and may have cardiovascular toxicity.
EULAR evidence based recommendations for the management of hand osteoarthritis: Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT) [19]	2007	NSAIDs	<ul style="list-style-type: none"> Major concern over NSAIDs is GI toxicity (dose dependent and increases with age) Concern exist that cardiorenal toxicity may be a class related side effect of NSAIDs rather than a specific side-effect of coxibs <u>Note:</u> EULAR recommendations on hip [20] and knee [21] osteoarthritis raise the same concerns and are therefore not separately reported
Recommendations for Use of Selective and Nonselective Nonsteroidal Anti-inflammatory Drugs: An American College of Rheumatology White Paper [17]	2008	NSAIDs	<ul style="list-style-type: none"> If a patient and provider agree to utilize an NSAID for arthritis pain relief, then the patient should be advised of the potential toxicities and relevant monitoring should be pursued. If a patient is taking aspirin for cardioprotective benefit, then selective and nonselective NSAIDs should be avoided. This combination is associated with an elevated risk of GI bleeding. However, if a patient is educated about this risk and wants to take the drugs concomitantly, then a PPI or misoprostol should be added to the regimen. If a patient and provider agree to utilize an NSAID for arthritis pain relief, and the patient has risk factors for GI bleeding, then the patient should be treated concomitantly with either misoprostol or a PPI. If a patient has compromised liver function, then the risks of selective and nonselective NSAID use should be carefully considered. Diclofenac should be avoided in patients with liver disease. If a patient is fully anticoagulated with warfarin, heparin, or other anticoagulants or is thrombocytopenic, then use of nonselective NSAIDs should be avoided because they can increase the risk of bleeding.
EULAR recommendations for calcium pyrophosphate deposition. Part II: Management [22]	2011	NSAIDs	<ul style="list-style-type: none"> Because CPPD predominates in the older patient, the use of NSAIDs should be carefully considered according to the benefit and relative risk
American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand,	2012	NSAIDs	<ul style="list-style-type: none"> Health care providers should not use oral NSAIDs in patients with contraindications to these agents and should be aware of the warnings and precautions associated with the use of these agents. For persons age ≥ 75 years, the TEP strongly recommends the use of topical rather than oral

<p>Hip, and Knee [23]</p>			<p>NSAIDs in patients with knee osteoarthritis who do not have a satisfactory clinical response to full-dose acetaminophen</p> <ul style="list-style-type: none"> • Based on good clinical practice, oral NSAIDs should not be used in patients with chronic kidney disease stage IV or V • The decision to use an oral NSAID in patients with chronic kidney disease stage III should be made by the practitioner on an individual basis after consideration of the benefits and risks.
<p>2012 American College of Rheumatology Guidelines for Management of Gout. Part 2: Therapy and Anti-inflammatory Prophylaxis of Acute Gouty Arthritis [24]</p>	<p>2012</p>	<p>NSAIDs</p>	<ul style="list-style-type: none"> • The potential drug toxicities due to comorbidities and drug–drug interactions are considerable in treatment of acute gout. Examples include underlying moderate and severe chronic kidney disease, congestive heart failure, peptic ulcer disease, diabetes mellitus, ongoing infection or high risk of infection, anticoagulation or antiplatelet aggregation therapy and hepatic disease
<p>EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT) [25]</p>	<p>2007</p>	<p>NSAIDs, GCs</p>	<ul style="list-style-type: none"> • There are concerns over the gastrointestinal, renal and cardiovascular side effects of NSAIDs. • Replacement of NSAIDs by COX-2 selective drugs, or the addition of gastroprotective agents can reduce gastrointestinal complications • the long term use of COX-2 selective drugs has been associated with increased cardiovascular risk • the long term safety of low dose GCs is largely unknown
<p>EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases [16]</p>	<p>2007</p>	<p>GCs</p>	<ul style="list-style-type: none"> • Comorbidities and risk factors for adverse effects should be evaluated and treated where indicated. These include hypertension, diabetes, peptic ulcer, recent fractures, presence of cataract or glaucoma, presence of (chronic) infections, dyslipidemia and co-medication with NSAIDs • The occurrence of GC-related AEs, osteoporosis in particular, is dependent on dose and duration.
<p>American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis [9]</p>	<p>2010</p>	<p>GCs</p>	<ul style="list-style-type: none"> • Using the smallest dose of GCs for the shortest duration possible is recommended as an important strategy to minimize osteoporosis risk.
<p>Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice [26]</p>	<p>2010</p>	<p>GCs</p>	<ul style="list-style-type: none"> • no definite conclusions can be drawn on the occurrence of most AEs, because there often is a lack of good quality evidence • Possibly increased risk for infections, peptic ulcer, mood disturbances, diabetes, Body weight and fat redistribution, osteoporosis. Increased risk for interference with hormone secretion and glaucoma
<p>EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases [27]</p>	<p>2013</p>	<p>GCs</p>	<ul style="list-style-type: none"> • Before starting medium/high-dose GC treatment, consider comorbidities predisposing to AEs. These include diabetes, glucose intolerance, cardiovascular disease, peptic ulcer disease, recurrent infections, immunosuppression, (risk factors of) glaucoma and osteoporosis. Patients with these comorbidities require tight control to manage the risk/ benefit ratio • Keep the requirement for continuing GC treatment under constant review, and titrate the dose against therapeutic response, risk of under treatment and development of AE • All patients should have appropriate monitoring for clinically significant AEs. The treating physician should be aware of the possible occurrence of diabetes, hypertension, weight gain, infections, osteoporotic fractures, osteonecrosis, myopathy, eye problems, skin problems and neuropsychological AEs • For several AEs it has been proven that the occurrence depends on dose and duration of GC treatment

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs [28]	2010	GCs, MTX	<ul style="list-style-type: none"> • Long-term use of GCs can lead to adverse events, but there may also be safety concerns in the intermediate term, although most studies on the toxicity of GCs are of low quality and short duration. • MTX is considered the anchor drug in RA both on the basis of its efficacy as well as the beneficial long-term safety profile • <u>References to a metaanalysis from 2009</u> summarizing the occurrence of AEs in 3463 patients with a mean MTX dose of 8.8mg/week and therapy duration of 36.5 months [15]: GI AE 30.8%, liver enzymes >2x upper limit of normal 12.9%; 3.7% stopped for liver toxicity; conflicting data regarding risk of liver fibrosis, cytopenia of 1 cell line 5.2% (up to 1.4% pan-cytopenia), AE concerning skin/hair 8.9%, AE regarding CNS 5.5%, AE of the lung 2.4% (pulmonary dysfunction, cough, unspecified pulmonary adverse drug reactions), MTX pneumonitis 0.4%, no increased risk for serious infections, insufficient data regarding risk of lymphoma and malignancies
American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis[29]	2008/ 2012	NSAIDs, GCs, MTX	<p><u>Reference the Guidelines for monitoring drug therapy in rheumatoid arthritis</u> of the American College of Rheumatology Ad Hoc Committee on Clinical Guidelines [31]:</p> <ul style="list-style-type: none"> • The toxicities of NSAIDs include dyspepsia (common), gastric or small bowel bleeding or ulceration (uncommon), renal insufficiency (rare), confusion, depression, rash, headache (rare), and hepatic toxicity (rare). NSAIDs may also reversibly inhibit platelet function and prolong bleeding time. • The toxicities of low-dose systemic glucocorticoids (≤10 mg prednisone daily or equivalent) include increased appetite, weight gain, fluid retention, acne, development of cushingoid facies, hypertension, diabetes, atherosclerosis, glaucoma and cataract formation, osteoporosis, a vascular necrosis, increased susceptibility to infection, and impaired wound healing • The most serious toxicities of MTX include hepatic fibrosis (rare) and cirrhosis (rare), pneumonitis (uncommon), and myelosuppression

*References and individual studies supporting the statements in the recommendations were presented to the guideline panel on request

AE, adverse event; CNS, central nervous system; COX; cyclooxygenase; CPPD, calcium pyrophosphate disease; GCs, Glucocorticoids; GI, gastrointestinal; MTX, methotrexate; NSAID, Non-Steroidal Anti-inflammatory Drugs; PPI, proton pump inhibitor; RA, Rheumatoid Arthritis; TEP, total endoprosthesis;

Literature appraisal and evidence report

We used the GRADE methodology for appraisal of primary interventional studies [32,33] and the QUIPS tool for studies on prognostic factors.[34] According to GRADE, the quality of evidence is graded from high, moderate, low to very low based on the evaluation of the following 5 domains: (1) Study limitations (limitations related to randomization, lack of allocation concealment, lack of blinding, large losses to follow-up, failure to adhere to intention to treat analysis, early termination and failure to report outcomes); (2) Inconsistency of results; (3) Indirectness of evidence; (4) Imprecision; and (5) Publication bias. Randomized control trials are initially presumed to be high level evidence, whereas observational studies are initially presumed to be low quality. Studies may be downgraded by 1-2 levels if any of the limitations mentioned above are present. Under certain circumstances upgrading is possible, as well.[32]

Forming recommendations

According to GRADE methodology, the voting panel should consider the following aspects when formulating the recommendations: 1) Overall quality of evidence; 2) balance between desirable and undesirable effects; 3) patients' and clinicians' values and preferences; and 4) resource use. External evidence on safety aspects was taken into account (as indirect evidence) in this project in order to identify the optimal trade-off between benefit and harm of interventions (see also above). Prognostic factors were used to build subgroups and to adapt the recommendations based on the presence or absence of unfavorable prognostic factors. Final recommendations were either "in favor" or "against" an intervention, and were graded with "conditional" or "strong". A strong recommendation in favor (against) was considered when the

panel was very certain that benefits did (did not) outweigh risks and burdens, preferences/values of patients were met (not met) and resource use was reasonable (unreasonable high). In case some uncertainty existed, a conditional recommendation was made.

Discussions about the evidence and the possible wording of the recommendations were conducted at the Annual Meeting of the ACR in October 2013, where the group also decided to create a flow chart supporting clinical decision pathways. Further, the group discussed and finally consented about the principal direction and strength of the recommendations. Thereafter, 3 members of the voting panel (CD, BD, ELM) drafted the preliminary recommendations/flow chart that was subject to further discussion and refinement at another face-to-face meeting (before the International conference for PMR and GCA 11/2013 in Southend, UK), four online conferences and e-mail-based communications. At each of these meetings/online conferences/e-mail contacts, the project leaders summarized the comments of the participants and asked for any dissent. The final recommendations were then circulated by e-mail for formal acceptance. At this stage, we set the dateline for a response at 21st April 2014, and assumed a consent to the final paper in case no further clarifications were requested. Since no dissent was reported until this dateline, a consensus was assumed for all points. Voting and grading of the level of agreement as performed in earlier recommendations was not necessary for this project.[35]

In addition to the individual treatment recommendations based on PICO questions and supporting evidence from the SLR, the panel formulated several principles that were uniformly considered important to be conveyed to those with PMR or involved with the management of PMR. These principles were formulated with understanding that they reflect current standards of clinical care, values and preferences of

clinicians and patients and were of such a generic nature that they were considered to be 'overarching'. [28,35]

The first draft recommendations were publicly presented at the International conference for PMR and GCA 11/2013 in Southend, UK. This conference was open to all physicians and allied health care professionals interested in PMR and/or GCA, as well as to patients. Feedback and suggestions obtained at this meeting were recorded, summarized and presented to the voting panel by the project leaders in an online conference for further discussion and incorporation into the recommendations.

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