Development of a Provisional Core Domain Set for Polymyalgia Rheumatica: Report from the OMERACT 12 Polymyalgia Rheumatica Working Group

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ABSTRACT. ***Objective.*** The Outcome Measures in Rheumatology (OMERACT) polymyalgia rheumatica (PMR) working group aims to develop a core set of outcome measures to be used in clinical trials for PMR. Previous reports from OMERACT 11 included a qualitative study of the patient experience and a preliminary literature review.

Methods. A 3-round Delphi survey of clinicians and patients with PMR was undertaken to identify a candidate core domain set for PMR research. Additionally, a literature review of outcome measures and their respective measurement instruments was undertaken. Meetings of patient research partners and clinicians were convened to review face validity of the provisional core domain set, which was subsequently presented and discussed at the OMERACT 12 congress.

Results. Of the 60 clinicians taking part in round 1, 55 took part in round 2 and 51 in round 3. Of the 55 patients who took part in round 1, 46 and 35 took part in subsequent rounds. In total, 91% of participants in round 3 deemed the resulting draft core domain set reasonable. The literature review identified 28 studies for full review. Measurement instruments for each proposed domain were identified. Clinicians are highly aware of glucocorticoid-related adverse effects, but there is relatively little evidence about their true prevalence and severity, especially in PMR.

Conclusion. A provisional core domain set, presented for clinical trials in PMR, comprises acute phase markers, physical function, death, glucocorticoid-related adverse events, and development of giant cell arteritis. Measurement instruments are suggested that may cover each domain, but these require formal validation for clinical trials in PMR. (J Rheumatol First Release November 15 2015; doi:10.3899/jrheum.141179)

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Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease with the highest incidence in those over 60 years of age, and an estimated prevalence of 711,000 adults in the United States[1]. Its effects can be devastating to patients' lives (Table 1). Glucocorticoids (GC) remain the basis of treatment[2,3]. The OMERACT PMR special interest group (SIG) was set up to identify a set of core outcome measures using the OMERACT Filter 2.0 methodology[4] and builds on work presented at OMERACT 11[5].

Delphi Survey of Clinicians and Patients

A 3-round Delphi survey of 60 international clinicians with an interest in PMR and 55 UK patients with PMR was conducted. In round 1, a list of candidate domains was provided, which had been identified from previous work[5]. Participants were invited to identify their "top 10" domains and to add further domains or comments. Patient and clinician surveys were conducted in parallel for rounds 1 and 2 and combined for round 3. Domains from round 1 placed by > 70% of either group in their top 10 were deemed included. The remaining domains identified by at least 20% of either group were distributed for a second round of voting to determine which were essential additions to those already included. In the final round, an overall opinion on the combined outcome set (Table 2) was sought, and suggestions were invited for potential instruments. Lastly, the survey results were discussed at meetings of patient research partners and clinicians.

Sixty clinicians participated in round 1, 55 in round 2, and 51 in round 3. Of the 55 patients who took part in round 1, 46 and 35 took part in subsequent rounds. Table 2 illustrates the draft core domain set after rounds 1 and 2, which was provided to respondents for round 3, with 91% agreeing that this was a reasonable draft core domain set.

The most common reason given by clinicians for non-agreement (n = 6) was concern about including the domain "muscle weakness" that had been identified by patients, therefore this could not be included in the provisional core domain set but was identified as an item for future research. GC-related adverse effects were identified as important, but there was no consensus on how they should be measured.

Patients requested that "stiffness" be considered instead of "morning stiffness." It was also suggested from the clinician group that development of giant cell arteritis should also be reported in any clinical trial of patients with PMR.

In the past, drug adverse effects have not been included as domains within OMERACT core domain sets, but OMERACT Filter 2.0 makes provision for identifying specific adverse effects of interest[4]. The concerns of both patients and clinicians about potential adverse effects of GC suggested that recording specific GC adverse effects might need to be included in the core set.

Literature Review of Outcome Measures and Measurement Instruments in PMR

A literature search of major medical databases was performed. Relevant PMR terms for both Medline and EMBASE (Table 3) were used, as well as the thesaurus function, which performs searches using all relevant associated terms. Identified titles and the subsequent abstracts were screened. The final full text articles were then reviewed to identify any outcome measures and associated instruments that had been reported.

In total, 562 abstracts were identified, with 28 articles included for full text review. The identified outcome measures and respective instruments relevant to the identified candidate core domains are presented in Table 4.

The instruments found covered all of the candidate domains in the provisional core domain set from the Delphi survey, except for GC-related adverse effects. One study reported poor test-retest reliability for fatigue visual analog scale, morning stiffness duration, and the Medical Outcomes Study Short Form-36 (SF-36) mental component score; however, it was unclear whether this finding reflected variation in the underlying symptoms or was the result of issues with the instruments themselves[6]. The Health Assessment Questionnaire (HAQ) has also been evaluated in

Table 1. A patient's story. From Lorna Neill, OMERACT patient research partner.

"… I started getting fit for a summer hill-walking and after the first long day's walking, came back with soreness and stiffness in the right groin. I thought I had pulled a muscle or damaged a tendon so rested it for a few days. At the point where I could hardly walk as far as the bus stop, had great difficulty getting in or out of a car and could no longer drive because my legs would not do what I wanted them to, I should probably have seen my GP.
Both shoulders became acutely painful and I could not straighten my knees. This was no longer an ache but severe pain which prevented me sleeping at night and forced me to lie flat on my back so that I did not turn over onto sore hips and shoulders.
I could not get out of bed without help, was having night sweats, I had lost my appetite and felt really ill. When I needed to ask for assistance with dressing in the morning, I finally accepted that I was needing more help than my new granddaughter.
The next day I was given a provisional diagnosis of PMR with what I was told were classic symptoms. This was confirmed by my blood tests and I was started on 15 mg of prednisolone. Within 2 weeks I stopped sleeping all day and could move back to my own bedroom, which had been inaccessible as I was quite unable to climb stairs…
Over the 4 years my symptoms have varied in strength around my body, from month to month and over any 24-h period so that if asked to complete any survey question on pain, stiffness, or functioning, it would have to be very clear whether this referred to now, in the last week, or on average since last seen by the doctor."

Table 2. Draft core domain set provided for Dephi exercise round 3.

Core Area	Candidate Domain	Chosen by Clinicians, Round No.	Chosen by Patients, Round No.
Pathophysiological manifestations	Blood tests	1	2
	Morning stiffness (duration, severity)	2	2
	Any glucocorticoid-related adverse effect	2	2
	Physician global	2	2
Life impact	Pain/ache	1	1
	Fatigue	—	1
	Muscle weakness	—	2
	Patient global	1	2
	Ability to do everyday activities	—	2
	Quality of life	—	2

Table 3. Terms used to search Medline and EMBASE.

Database	Term
Medline	Polymyalgia Rheumatica/ polymyalgia.mp. (senile adj2 gout).mp. (rheumatic adj2 gout).mp.
EMBASE	exp rheumatic polymyalgia/ (polymyalgia adj2 rheumatic$).mp. (senile adj2 gout).mp. (rheumatic adj2 gout).mp.

PMR, and was found to be responsive to change and to correlate with other outcome measures[7].

Stiffness

Qualitative work relating to the patient experience of stiffness in rheumatoid arthritis (RA) that allowed a comparison with stiffness in PMR was presented at OMERACT 12 by Serena Halls. Patients with RA reported that their stiffness was highly variable in relation to time, duration, and intensity, and had an effect on many aspects of their daily life. This paralleled our findings regarding stiffness in PMR, in that duration of "morning stiffness" was only 1 aspect: severity and its relationship to physical function were of equal or greater importance to most patients. These findings of our qualitative work on stiffness in PMR were presented in brief at the last OMERACT meeting[5] and have since been submitted for full publication.

GC-related Adverse Events

A large number of adverse events of GC have been described, but extensive review work done by the European League Against Rheumatism Task Force demonstrated that good evidence on their prevalence and severity at different daily and cumulative doses is mostly lacking[7]. This is an important issue because it challenges many of our assumptions about the risks of treatment in PMR (it must be acknowledged that existing data mostly relate to RA, and extrapolation to PMR would require consideration of important confounders such as age, comorbidity, and concomitant medications). The lack of current proven alternatives to GC in PMR is not a reason to ignore their adverse events; indeed a major part of the rationale for potential future clinical trials of disease-modifying therapies, or different doses/tapering rates of GC, is that clinicians and patients wish to reduce the burden of GC-related adverse events in patients with PMR, while maintaining control of disease activity.

According to the OMERACT Filter 2.0, a core adverse event is defined as one that should be measured in every study to which the "parent" core set pertains. Because PMR is currently predominantly treated with GC, and fear of adverse effects is an important factor affecting treatment in routine practice, core set developers might consider designating (some) GC adverse effects as core adverse events. This would allow the collection of high-quality data on the actual incidence of GC-related adverse events. This harmonization of data collection to facilitate data synthesis and metaanalysis

Table 4. Instruments identified for their relevance to identified candidate core domains.

Life Impact		Pathophysiological Manifestations		Rare/Serious or Adverse Events	
Domain	Instrument Used (n)	Domain	Instrument Used (n)	Domain	Instrument Used (n)
Pain/ache	VAS (11)	Blood tests	CRP or ESR (26)	Death	SAE reporting
Fatigue	VAS (2)	Physician global (26)	VAS (3)	Giant cell arteritis	Clinical diagnosis
Patient global	VAS (2)	Stiffness	Duration (min) (7)	Glucocorticoid-related AE	None identified
Quality of life	SF-36 (2)				
ADL	HAQ (4)				

n: no. studies; VAS: visual analog scale; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SAE: serious adverse events; AE: adverse event; SF-36: Medical Outcomes Study Short Form-36; ADL: activities of daily living; HAQ: Health Assessment Questionnaire.

is one of the key arguments for a core outcome set and may also apply equally to core adverse events.

Considerations from the group included the observation that adverse events are always reportable in trials that comply with International Conference on Harmonisation-Good Clinical Practice requirements (www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html), but that naming certain events as core would allow better attention to detail and mandatory reporting, even if zero events occurred in a trial.

Summary OMERACT 12 Special Interest Group

At the OMERACT 12 meeting in Budapest, Hungary, the goal of the PMR special interest group (SIG) was to draft a program for the next 2 years to develop a core outcome measurement set. Each of the core areas within Filter 2.0 was considered in turn.

Pathophysiological manifestations. Although simple measurement of acute phase markers may not be sufficient to identify all aspects of disease activity in PMR, it was felt that acute phase markers (particularly C-reactive protein) are the most useful biomarkers in routine clinical practice. The domain we would ideally like to measure is "disease activity" rather than acute phase markers, which are acknowledged to have limitations as a surrogate for disease activity, at least in clinical practice. Ultimately a biomarker for PMR that reflects disease activity better than the current acute phase markers would be useful; imaging may play a role here. It was concluded that much useful data could be obtained from longitudinal observational studies.

Life impact. Pain and stiffness were also identified as important by the Delphi. Prior work had suggested that, as in RA, for some patients with PMR, pain and stiffness are closely related[5]; hence in the provisional core domain set they are provisionally grouped together. The subjective experience of muscle weakness appeared important to patients, but its cause, whether related to PMR or to its treatment with glucocorticoids, requires further elucidation. Overall, considerations of parsimony and discussions with patients identified physical function as the item that best characterized the effects of PMR on their lives. The HAQ, Modified HAQ, and/or SF-36 may be adequate for identifying at least part of this. However, these generic instruments are unlikely to identify the full extent of the patient experience in PMR, and their content validity may not be optimal. Development of a patient-reported outcome tool for PMR requires a formal, rigorous approach, and this remains part of the agenda for future research.

GC-related adverse effects. Metaanalysis of clinical trial data of the adverse effects of low-dose GC in RA failed to show evidence of substantively elevated risk with GC. This challenges traditional teaching about the risks of GC therapy. However, many clinicians felt that these data may not be applicable to PMR, where patients are older and arguably more vulnerable to adverse effects. Data are lacking to settle this question either way; yet the question is fundamental to arguments for development of new treatments in PMR and to determine whether very slow reduction of GC is very nearly as safe as the usual recommendation of fast reduction.

To perform a metaanalysis in the context of PMR, ideally GC-related adverse effects should be recorded in a consistent way across studies. Feedback from the industry perspective suggested that the standard methods for recording adverse events in clinical trials may not provide the uniformity of data collection that would be needed for this.

Conclusion

The draft core domain set reflecting feedback from the OMERACT 12 PMR SIG is illustrated in Figure 1. The concept of parsimony is particularly relevant to trials of PMR: in many countries including the United Kingdom and The Netherlands, PMR is predominantly managed in primary care by general practitioners, so routine and ongoing data collection may be most appropriately undertaken in this setting. The concept of an "inner core" is thus particularly important for PMR.

Except for GC-related adverse events, within the "inner core" of essential items, candidate instruments that may be adequate for a preliminary outcome set were identified for each domain. The next step will be to begin validating these instruments according to the OMERACT Filter using existing datasets, and where possible, collecting new datasets.

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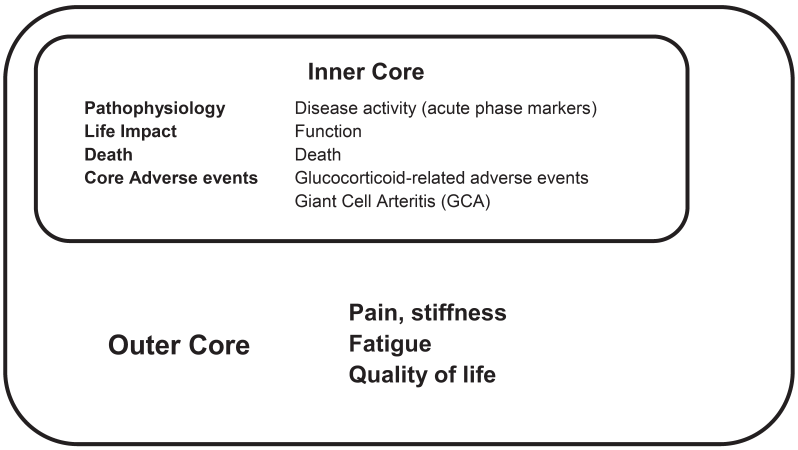

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