

Towards a Core Outcome Measurement Set for Polymyalgia Rheumatica: Report from the OMERACT 2018 Special

Interest Group

Claire E Owen^{1,2}

Max Yates^{3,4}

Helen Twohig⁵

Sara Muller⁵

Beverley Shea^{6,7}

Lee S Simon⁸

Catherine L Hill^{9,10}

Sarah L Mackie¹¹

Key words: polymyalgia rheumatica; outcomes; OMERACT.

Conflict of interest: none.

Correspondence and requests for reprints to:

Dr Claire Owen

Rheumatology Department

Austin Health – Repatriation Campus

Level 1, North Wing

300 Waterdale Road,

Heidelberg West VIC

Australia 3081.

Email: claire.owen@austin.org.au

Telephone: +613 9496 4013

¹ Department of Rheumatology, Austin Health, Heidelberg VIC, Australia.

² Department of Medicine, University of Melbourne, Parkville VIC, Australia.

³ Department of Rheumatology, Addenbrooke's Hospital, Cambridge, United Kingdom.

⁴ Norwich Medical School, University of East Anglia, Norwich, United Kingdom.

⁵ Arthritis Research UK Primary Care Centre, Primary Care Sciences, Keele University, Keele, Staffordshire, United Kingdom.

⁶ Ottawa Hospital Research Institute, Ottawa, Ontario, Canada.

⁷ School of Epidemiology, Public Health and Preventative Medicine, University of Ottawa, Ottawa, Ontario, Canada.

⁸ SDG LLC, Cambridge, Massachusetts, United States of America.

⁹ Rheumatology Unit, Royal Adelaide Hospital, Adelaide, SA, Australia.

¹⁰ Discipline of Medicine, The University of Adelaide, Adelaide, SA, Australia.

¹¹ Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom and NIHR-Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Towards a Core Outcome Measurement Set for Polymyalgia Rheumatica: Report from the OMERACT 2018 Special Interest Group

CE Owen MBBS(Hons) Consultant Rheumatologist, M Yates PhD Clinical Research Fellow, H Twohig MBChB General Practitioner, S Muller PhD Senior Research Fellow, B Shea PhD Senior Methodologist and Adjunct Professor, LS Simon MD Principal, CL Hill MD Clinical Professor and Consultant Rheumatologist and SL Mackie PhD Associate Clinical Professor and Consultant Rheumatologist.

Abstract

Objective: To report the progress of the OMERACT Polymyalgia Rheumatica (PMR) Working Group in selecting candidate instruments for a core outcome measurement set.

Methods: A systematic literature review identified outcomes measured and instruments used in PMR studies, and a respondent survey and raw data analysis assessed their domain match and feasibility.

Results: Candidate instruments were identified for pain (VAS/NRS), stiffness (VAS/NRS and duration) and physical function (HAQ-DI/MHAQ). Domain match and feasibility assessments were favourable, however validation in PMR was lacking.

Conclusion: Further assessment of candidate instruments is required prior to recommending a PMR core outcome measurement set.

Polymyalgia rheumatica (PMR) is an inflammatory disease characterised by sub-acute onset pain and stiffness in the shoulders and hips. Oral glucocorticoids represent the mainstay of treatment and whilst cessation of therapy is the ultimate goal, up to 50% of PMR patients continue to require prednisolone 2-3 years after diagnosis.(1) It is unclear what starting dose or tapering schedule achieves the best outcome, nor what benefit may be offered by putative glucocorticoid-sparing agents. Significant morbidity from glucocorticoid-induced complications is recognised and likely surpasses that seen in comparable rheumatic conditions.(2)

There is currently no agreed core outcome measurement set for PMR clinical trials. A lack of consistency in definitions for domains or instruments used to assess patients with PMR is characteristic of the existing literature.(3) A core outcome measurement set for universal use in studies of PMR would improve the quality of future research.

In 2016, OMERACT (Outcome Measures in Rheumatology) endorsed a core domain set for PMR. The inner core of the “onion”, signifying items to be measured in all PMR clinical trials, comprised four domains: pain, stiffness, physical function and systemic inflammation.(4) Here we report the progress of the PMR Working Group in identifying and evaluating suitable instruments mapping to these core domains. This work includes an updated systematic literature review, online respondent survey and raw data analysis evaluating the domain match and feasibility of selected instruments in line with the first two signalling questions of the OMERACT Filter 2.1: Instrument Selection Algorithm.(5-7) The proceedings of the OMERACT 2018 PMR Special Interest Group (SIG) are also detailed, in particular the major points discussed, and consensus reached regarding which candidate instruments should continue through the Filter.

Systematic literature review

To obtain all published articles reporting outcome measures mapping to the OMERACT endorsed PMR core domain set, five databases [MEDLINE, CINAHL, Embase, Web of Science, Cochrane Library] were searched from inception to 30/9/2017. This yielded 16222 references, which was reduced to 90 full-text studies following removal of duplicates and screening abstracts. Forty-six studies were included in the review. Risk of bias was assessed using a modified Quality in Prognosis Studies (QUIPS) tool.(8) The systematic review protocol was registered with PROSPERO – CRD42017080058.

Two/ten randomised controlled trials and 12/23 prospective cohort studies measured outcomes in each of the four core domains. The most commonly assessed domain was systemic inflammation (43/46 studies), usually by erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP). Pain was measured in 32/46 studies, most often using a visual analogue scale (VAS). Stiffness was measured in 28/46 studies, typically as duration of morning stiffness. Physical function was assessed in 22/46 of studies, most frequently using the elevation of upper limb (EUL) score as part of the PMR-AS(9), or the health assessment questionnaire (HAQ). There was no association between higher-quality clinical research trials (assessed by QUIPS tool) and the number of outcomes measured from the core domain set.

Online respondent survey

The patient perspective on candidate instruments for pain (VAS/numeric rating scale [NRS]), stiffness (VAS/NRS, and duration of morning stiffness), physical function (health assessment questionnaire-disability index [HAQ-DI]/modified health assessment questionnaire [MHAQ]) and systemic inflammation (ESR/CRP) was evaluated using a web-based survey. Google Docs links were created [for each instrument](#) and included in the *Newswire* newsletter of the charity PMRGCAuk that is distributed to 1800 readers and the *Health-Unlocked* web forum comprising 6986 members, [yielding between 28 and 73 responses for each of the instruments examined](#). Patients were asked a series of questions addressing face validity and feasibility that had been developed by consensus of the PMR Working Group. Ethical approval was received from the University of East Anglia Research Ethics Committee (2017/18 – 81) and all respondents provided written informed consent to publish the results prior to survey completion.

Participants from three continents (Europe, North America, Australia/New Zealand) contributed 51 responses for pain VAS/NRS, 51 for stiffness VAS/NRS, 51 for duration of morning stiffness, 73 for HAQ-DI, 28 for MHAQ and 62 for ESR/CRP. Disease duration ranged from new diagnosis to 17 years; current prednisolone dose was 0-50mg daily. Most respondents agreed candidate instruments were both a suitable match for the target domain and feasible to complete: approval for pain VAS was 68.6%/NRS 60.8%; stiffness VAS 62.8%/NRS 58.8%; duration of morning stiffness 58.8%; HAQ-DI 70%; MHAQ 53.6%; and ESR/CRP 54.8%. The free text responses further contextualised the numerical scores and will be the subject of a separate publication arising from this work.

Raw data analysis

Two prospective observational cohort studies contributed raw data to further assess the domain match and feasibility of candidate instruments for pain, stiffness and physical function: the Melbourne Predictors of Relapse in PMR (MPR-PMR) study; and The PMR Cohort.(10) Specifics pertaining to each of these studies' designs and baseline patient demographics are outlined in Table 1. Ethical approval was received from the Austin Health Research Ethics Committee for the MPR-PMR study (HREC/14/Austin/158) and the Staffordshire Research Ethics Committee for The PMR Cohort

(12/WM/0021v), with written informed consent including publication of results provided by all participants in both instances prior to study enrolment.

Statistical analysis was conducted using Stata.(11, 12) A data completion rate >80% was ensured for each instrument, prior to generating a frequency distribution histogram. The proportion (percentage) of participants with the lowest (“floor”) and highest (“ceiling”) values was recorded, and the normality of each distribution assessed (based upon the coefficient of skewness where 0 = normal and -0.5 to 0.5 is approximately symmetric).

The data completion rate ($\geq 96.3\%$) and time taken was deemed acceptable for all of the candidate instruments examined. Pain VAS/NRS and stiffness NRS were both associated with >15% of respondents scoring the highest possible value (VAS/NRS = 10) at baseline, and the lowest value (VAS/NRS = 0) at multiple timepoints during treatment and follow-up. Both versions of the HAQ, but especially the MHAQ, were similarly characterized by floor effects (lowest value = 0) throughout but did not show the same ceiling problems (highest value = 3). The floor and ceiling patterns observed appeared consistent with the expected clinical course for patients with newly-diagnosed PMR.

At baseline in both studies, pain levels were at the higher end of the scale (VAS/NRS) then appropriately trended to lower values following treatment (Figure 1). Whilst the MPR-PMR study measured duration of morning stiffness, as compared with stiffness NRS in The PMR Cohort, the pattern of distribution was similar for both instruments and mirrored that seen for pain VAS/NRS. MHAQ results at baseline in The PMR Cohort were typically lower than those recorded using HAQ-DI, which might be explained by the shorter format of this instrument. During follow-up, no major differences were noted in the performance of the HAQ-DI compared with MHAQ (Figure 2).

Summary of the OMERACT 2018 PMR SIG

Participants including clinicians, researchers and patient partners discussed the results of the three workstreams in detail at the OMERACT 2018 PMR SIG. The purpose of the SIG was to establish whether instruments mapping to the four core domains had satisfied tests for domain match and feasibility, and if they should continue through the OMERACT 2.1 Filter.(5-7)

The interchangeability of VAS and NRS for the measurement of pain, the most suitable instrument to measure stiffness (VAS/NRS versus duration of morning stiffness) and the appropriateness of HAQ as a patient-reported outcome measure (PROM) across different age groups and in the modern day represented the major points of discussion. Although the raw data analysis revealed no major differences in the performance of pain VAS and NRS in the two PMR populations studied, no head-to-head comparison was available, and this may require additional study. VAS/NRS and duration of morning stiffness were both acknowledged to possess limitations in their respective abilities to measure the patient experience of stiffness (particularly when eliciting responses from non-English speaking patients); this issue is common to many rheumatic diseases and no better alternative for measuring stiffness in PMR is currently described. Whilst some HAQ questions may be less relevant to older persons (eg. “do chores such as vacuuming or yard work?”) or contextually out of date (eg. “run errands?”), it is otherwise a well-validated instrument that in other diseases has been shown to be responsive to change over time and capable of discriminating between groups of interest. The development of an entirely new instrument for the domain of physical function was therefore deemed unnecessary. However, it is recognised that

the overall life impact of PMR reaches beyond the four core domains and there remains an unmet need for a disease-specific PROM for PMR.

Future research agenda

At the end of the SIG, consensus was reached amongst the participants that candidate instruments for pain (VAS/NRS), stiffness (VAS/NRS and duration of morning stiffness) and physical function (HAQ-DI/MHAQ) were either green (“good to go”) or amber (“more work needed or a concern, but go”) for domain match and feasibility. Moving forward, the PMR Working Group will focus upon appraising the existing evidence for each instrument’s measurement properties before addressing any identified gaps by undertaking focused analysis of relevant datasets. Our objective is to generate a PMR core outcome measurement set for future endorsement by OMERACT.

References

1. Kremers HM, Reinalda MS, Crowson CS, Zinsmeister AR, Hunder GG, Gabriel SE. Relapse in a population based cohort of patients with polymyalgia rheumatica. *J Rheumatol* 2005;32:65-73.
2. Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van der Heijden GJ. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: A meta-analysis. *Annals of the Rheumatic Diseases* 2009;68:1833-8.
3. Duarte C, Ferreira RJ, Mackie SL, Kirwan JR, Pereira da Silva JA, Group OPRSI. Outcome measures in polymyalgia rheumatica. A systematic review. *J Rheumatol* 2015;42:2503-11.
4. Mackie SL, Twohig H, Neill LM, Harrison E, Shea B, Black RJ, et al. The omeract core domain set for outcome measures for clinical trials in polymyalgia rheumatica. *J Rheumatol* 2017;44:1515-21.
5. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: Omeract filter 2.0. *J Clin Epidemiol* 2014;67:745-53.
6. Boers M KJ, Tugwell P, Beaton D, Bingham CO III, Conaghan PG, et al. The omeract handbook. Internet; [cited May 17, 2017]; Available from: <https://omeract.org/resources>.
7. Beaton DE, Maxwell LJ, Shea B, Wells GA, Boers M, Grosskleg S et al. Instrument selection using the omeract filter 2.1: The omeract methodology. *J Rheumatol* 2018;(submitted).
8. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280-6.
9. Leeb B, Bird H. A disease activity score for polymyalgia rheumatica. *Ann Rheum Dis* 2004;63:1279-83.
10. Muller S, Hider S, Helliwell T, Bailey J, Barraclough K, Cope L, et al. The epidemiology of polymyalgia rheumatica in primary care: A research protocol. *BMC Musculoskeletal Disorders* 13:102.
11. StataCorp. Stata statistical software: Release 13. College Station, TX: StataCorp LP; 2013.
12. StataCorp. Stata statistical software: Release 15. College Station, TX: StataCorp LLC; 2017.