Seminars in Arthritis and Rheumatism xxx (xxxx) xxx

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Prioritising domains of glucocorticoid therapy to measure in trials: Results from a modified delphi exercise from the OMERACT glucocorticoid impact working group

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ARTICLE INFO

Keywords:
Delphi
OMERACT
Glucocorticoids
Patient perspective
Adverse effects
Mixed methods

ABSTRACT

Introduction: There is no consensus amongst patients and healthcare professionals about how to measure important adverse effects of glucocorticoids (GCs) that includes the patient's perspective. The OMERACT GC Impact working group sought to identify the domains of greatest importance to both patients and healthcare professionals for use in a proposed core outcome set.

Methods: Patients and healthcare professionals participated in a Delphi consensus exercise to rate the importance of previously identified candidate domains. Those deemed critical to include by at least 70% in both groups, after three rounds of a Delphi exercise were identified as meeting consensus. All participants were asked which additional domains should be measured in all trials in a final survey; those domains selected by more than 70% of all participants were added, resulting in a final list of potential core domains.

Results: In total, 363 people (295 patients and 68 healthcare professionals) participated in the Delphi process. The final list of potential core domains included: bone fragility, diabetes, eye problems and/or changes in vision, high blood pressure, infection, osteonecrosis, mood disturbance, fatigue, sleep disturbance, weight.

Conclusion: The 10 domains identified through this exercise informed the proposed core domain set of GC effects to be considered for use in future clinical trials involving GCs. This core domain set was endorsed at the OMERACT 2020 virtual workshop.

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https://doi.org/10.1016/j.semarthrit.2024.152602
Received 5 August 2024; Received in revised form 26 September 2024; Accepted 16 October 2024
Available online 4 December 2024
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Introduction

Glucocorticoid (GC) therapy is used for many rheumatic and musculoskeletal diseases. GCs have many adverse effects including infection, diabetes and fracture as well as patient reported adverse effects that may be more difficult to measure such as sleep disturbance, thin skin and easy bruising [1]. Clinical trials are investigating ways to reduce the cumulative dose of GCs, and define novel GC dosing regimens, so the need for ways to consistently identify and measure adverse effects of GCs has gained relevance, particularly for GC effects of greatest importance to patients. The Outcome Measures in Rheumatology (OMERACT) GC Impact Working Group (WG) aims to (1) define a research agenda in the context of previous and ongoing work on the medical monitoring and measurement of GC adverse effects and (2) develop a core outcome set of GC effects for the use in future clinical trials involving GCs using OMERACT methodology [2–4].

The GC WG has previously completed systematic literature reviews [2,5] and performed in-depth qualitative analyses [6–8] and survey studies [9,10] with individuals with a range of rheumatic diseases to further understand patient perceptions of GC effects and identified multiple potential domains. The systematic literature review looking into the effect of GC from patients' perspective identified four overarching themes: (1) physical symptoms, (2) psychological symptoms, (3) participation and (4) contextual factors [5]. Domains identified from this and the prior systematic literature review, the qualitative analyses and survey studies were collated, resulting in 63 candidate domains categorized according to these themes for consideration.

A Delphi exercise was conducted to facilitate consensus on the candidate domains for use in a final core domain set that was proposed and endorsed at the OMERACT 2020 virtual workshop [11]. Here, we describe the methodology and results of the Delphi exercise underlying this core domain set.

Methods

The OMERACT GC WG, comprised of clinicians and researchers, a patient research partners (PRPs) and methodologists from the USA, Australia and UK, oversaw the development, management and analysis of the Delphi exercise to build consensus using OMERACT methodology [4,12,13]. Two stakeholder groups were invited to participate: (1) people with rheumatic disease; and (2) healthcare professionals (clinicians and/or researchers). Clinicians and researchers with relevant publications, members of research groups related to rheumatic diseases where GCs are commonly used and professional colleagues of the OMERACT GC Impact working group were also invited to participate. Patients over 18 years of age with experience with glucocorticoids were invited to participate in the Delphi exercise through patient support and advocacy group communications (Creaky Joints, Dragon Claw, the OMERACT Patient Research Partner network, PMRGCAuk, Vasculitis Oz and Vasculitis UK). Clinicians involved in the study were also able to invite patients to participate in the study.

Approval from local ethics committees was obtained both in the United States of America (Hospital for Special Surgery, New York ID 2019-0215) and Australia (Central Adelaide Local Health Network, South Australia HREC/18/CALHN/184). Consent and the three rounds of the Delphi exercise were completed using DelphiManager, hosted and administered via the University of Liverpool, United Kingdom (https://www.comet-initiative.org/delphimanager/).

All survey respondents provided age, sex, and country of residence. Characteristics collected from PRPs included the disease treated with GCs, and glucocorticoid dosing and duration. Clinicians/researchers additionally provided their clinical specialty and professional research field. All participants were asked to rate candidate domains based on importance as a mandatory domain for all future clinical trials involving glucocorticoids on a scale of 1 to 9 (1–3: not important, 4–6: important but not critical, 7–9: critical). At the end of round 1, participants were invited to propose additional candidate domains for consideration.

In rounds 2 and 3, participants were provided both their response to each domain from the previous round and the average score from all other participants. They were then asked to rate the domain again. Following round 3, domains were considered nominated for the core domain set if more than 70% of patients and more than 70% of clinicians/researchers rated the domain as "critical". In contrast, domains could be removed from the subsequent round if more than 70% of participants from each stakeholder group rated it "not important". Results of each round, including summary statistics, were reviewed by the OMERACT GC WG to identify domains that could be added to the core domain set, combined with other similar domains, or removed.

Following review of the third Delphi round results by the WG, it was evident that some aspects of the patient experience that featured prominently in prior qualitative work were not represented in the core domain set. In some cases, a domain was identified as "critical" by more than 70% of one group of collaborators, but not by another.

As noted in the 2018 OMERACT GC workshop [3], novel methodology would be needed to ensure the core domain set reflected observations from the qualitative work and adequately captured the patient's experience and life impact of glucocorticoids. After the third round of the Delphi, the OMERACT GC working group in conjunction with OMERACT leadership and OMERACT methodologist, noting the surprising lack of patient reported and life impact domains in the selected domains, and the participant group differences in the third Delphi round results, chose to pursue a final survey.

A final survey round was conducted using candidate domains from the third Delphi round that had average scores in patient and clinician/researcher groups of 4-6 (important but not critical). The final survey was conducted online via Google Forms. All participants who participated in the original Delphi process were invited to take part in this final survey regardless of participation in rounds 1-3. There were two components to this survey. Firstly, participants were asked whether they agreed that *bone fragility, diabetes, eye problems and/or changes in vision, high blood pressure, infection and osteonecrosis* were "very important to be measured in all future clinical trials involving GCs". These domains had already met the consensus threshold for inclusion as potential core domains after the third round of the original Delphi process. Secondly, participants were asked to select whether each domain should be measured in "every", "some" or "no" future clinical trials involving GCs. If at least 70% of all participants (PRPs and clinician/researchers combined) stated that a domain should be measured in "every" trial, and there was at least 50% agreement within each group, the domain was added to the list of potential core domains.

Results

Demographics

Four hundred and thirteen individuals (339 patients and 74 clinicians/researchers) registered for the first round of the Delphi exercise March 2018 – Feb 2019. Of the 293 patients who completed round 1 of the Delphi exercise, 247 (84%) were female, the majority (89%) were at least 45 years of age and 183 (62%) were taking glucocorticoids at the time of survey completion. The survey was conducted in English; 121 (41%) were residing in the US, 117 (40%) in the UK and 37 (13%) in Australia (Table 1). The patients who participated had lived experience of a broad range of rheumatic diseases, including inflammatory arthritis (29%), vasculitis (40%), and connective tissue disease (23%).

Of the 74 clinicians/researchers, 68 (92%) completed the round 1 survey; 30 (44%) were female, most were rheumatologists (52/68, 76%) (Table 1). Of the 293 PRPs who completed round 1, 140 (48%) completed round 2. Of the 68 clinicians/researchers, 53 (78%) completed round 2. Similar to round 1, PRPs were predominantly female (84%), over 45 years of age (91%) and living in the US (31%), UK (49%) or Australia (12%). There were no substantive differences in

Table 1
Characteristics of those completing round one of the Delphi process.

Patients (n=295)			Healthcare Professionals (n=68)		
Age	- 18	1 (<1%)	Clinical Specialty	Rheumatology	52 (76%)
	18 – 24	3 (1%)		Nephrology	5 (7%)
	25 – 34	12 (4%)		Internal Med	4 (6%)
	35 – 44	19 (6%)		GP/Family	3 (4%)
	45 – 54	66 (23%)		Immunology	2 (3%)
	55 – 64	102 (35%)		Respiratory	2 (3%)
	65+	90 (31%)		Endocrinology	1 (1%)
Country	USA	121 (41%)		Allied Health	1 (1%)
	UK	117 (40%)		Gastroenterology	1 (1%)
	Australia	37 (13%)		Non-clinical	3 (4%)
	New Zealand	4 (1%)	Research field	Outcomes	18 (26%)
	Canada	3 (1%)		Clinical trials	16 (24%)
	Ireland	2 (<1%)		Epidemiology	13 (19%)
	France	2 (<1%)		Qualitative	5 (7%)
	Netherlands	2 (<1%)		Glucocorticoids	2 (3%)
	Bosnia and Herzegovina	1 (<1%)			
	Portugal	1 (<1%)			
	Not specified	6 (2%)			
Disease	Rheumatoid arthritis	61 (21%)			
	ANCA-assoiated vasculitis	50 (17%)			
	Polymyalgia rheumatica	35 (12%)			
	Vasculitis (unspecified)	33 (11%)			
	Myositis	24 (8%)			
	Giant cell arteritis	21 (7%)			
	Spondyloarthritis	14 (5%)			
	Systemic lupus erythematosus	7 (2%)			
	Arthritis (unspecified)	5 (2%)			
	Bechet's disease	4 (1%)			
	Gout	3 (1%)			
	Urticarial Vasculitis	3 (1%)			
	IgA vasculitis	2 (<1%)			
	Polyarteritis nodosa	2 (<1%)			
	Cerebral vasculitis	2 (<1%)			
	Calcium pyrophosphate deposition disease	1 (<1%)			
	Relapsing polychondritis	1 (<1%)			
	Overlap	1 (<1%)			
	Miscellaneous	10 (3%)			
	Unspecified	16 (5%)			

Miscellaneous: asthma, chronic bronchitis, Dressler's syndrome, eosinophilia, fibromyalgia, infection, immune thrombocytopenic purpura, migraine, muscle strain, myasthenia gravis, psoriasis, tendinitis.

demographics of patients and clinicians/researchers identified for those registered for round 1 and 2 (**Supplementary Table 1**). Round 3 was completed by 123 of the 140 (88%) PRPs, and 45 of the 53 (85%) of clinician researchers.

Delphi results

A full list of the candidate domains can be found in **Supplementary Table 2**.

The full list of domains that had met consensus criteria and were rated by collaborators after the third round were bone fragility, diabetes, eye problems and/or changes in vision, high blood pressure, infection, osteonecrosis, and making the condition noticeably better (Table 2). All were mapped to the Pathophysiological Manifestations Core Area of the OMERACT Filter [14]. Notably, a number of patient-reported outcomes prominent in the qualitative work conducted and highly rated in the Delphi exercise, did not meet consensus criteria for inclusion (Table 2). Domains mapping to the Core Area of "Pathophysiological Manifestations" tended to outrank domains mapping to the Core Area of Life Impact for both patients and clinicians. Additionally, there was disparity in ranking of some Life Impact domains. For example, clinicians/researchers highly rated depression and low mood whereas the patient group did not overall, and patients highly rated fatigue whereas the clinician/researcher group did not overall (Table 2).

Final survey

119 patients and 49 clinicians/researchers took part in the final survey. Of the 119 patients participating in the final survey, 101 (85%) were female. Similar to previous rounds, most patients were currently taking glucocorticoids (76/119, 64%) and were from the UK 61/119, 51%), US (34/119, 29%) and Australia (17/119, 14%). Of the 49 clinicians/researchers, 18 (37%) were female and 37 (77%) were Rheumatologists.

There was 100% patient agreement (119/119) and 48/49 (98%) clinicians/researcher agreement on inclusion of the set of domains identified by consensus from Round 3. In the final survey, *weight gain and increase in appetite* now met the consensus threshold; 74% of PRPs and 73% of clinicians/researchers indicated that this domain should be measured in every future clinical trials. *Depression or low mood* met the threshold criteria for patient responses (73%) but was marginally below the threshold in the clinician/researcher stakeholder group (69%). This domain was selected by 127/168 (72%) of all participants and therefore was included in the potential core domain set.

There was discordance between stakeholder groups on some outcomes (table 3); a high proportion of patients voted that *fatigue* (87%) and *sleep disturbance* (81%) should be measured in all future clinical trials compared with 57% of clinicians/researchers for both these domains. *Fatigue* was selected by 127/168 (76%) of all participants and *sleep disturbance* was selected by 124/168 (74%) of all participants, and therefore both these domains were put forward for the potential core domain set. Although 118/168 (70%) of all participants rated *symptoms*

Table 2
Numbers (%) of each group which rated an outcome as critical (score 7/8/9) in round three.

Outcomes	Patients (n=123)	Clinicians/ researchers (n=45)
Domains rated critical to measure by >70% of each group after round 3		
Making the condition noticeably better	102 (89%)	40 (89%)
Bone fragility	106 (86%)	44 (98%)
Eye problems and/or changes in vision	100 (86%)	37 (82%)
Osteonecrosis	82 (85%)	38 (84%)
Infection	98 (83%)	44 (98%)
Diabetes	87 (80%)	43 (96%)
High blood pressure	88 (75%)	38 (84%)
Domains included in round 3 not meeting criteria for inclusion to the core domain set		
Recurrence or worsening of original symptoms on reduction of steroid dosing	92 (80%)	28 (62%)
Muscle and tendon problems	79 (69%)	22 (49%)
Functional independence	78 (67%)	30 (67%)
Being able to resume work	65 (65%)	33 (73%)
Increase in lipids (cholesterol)	74 (64%)	21 (47%)
Fatigue	74 (63%)	17 (38%)
Sleep disturbance	60 (51%)	22 (49%)
Depression or low mood	57 (50%)	35 (78%)
Symptoms related to withdrawal from steroids	58 (50%)	17 (38%)
Changes in appearance of your face	60 (50%)	13 (29%)
Weight gain and increase in appetite	52 (45%)	21 (47%)
Anxiety	49 (44%)	20 (44%)
Problems concentrating	49 (43%)	12 (27%)
Personality change	46 (41%)	21 (47%)
Gut and stomach problems	44 (40%)	4 (9%)
Impact on family and friendships	43 (39%)	7 (16%)
Lack of support of family and friends	44 (39%)	6 (14%)
Changes in appearance of your body	44 (36%)	13 (29%)
Fluid retention and/or ankle swelling	42 (36%)	4 (9%)
Irritability and mood swings	39 (34%)	15 (33%)
Skin changes	34 (29%)	12 (27%)
Impact on sexual relationships	23 (22%)	4 (9%)
Sweating	23 (20%)	1 (2%)
Menstrual problems	5 (7%)	2 (5%)
Thrush (candidiasis)	12 (12%)	2 (4%)

NB: not all 123 patients responded to every item.

Table 3
Final survey response "measure in every clinical trial" for outcomes highly ranked but not meeting consensus criteria in Delphi process.

Outcome	All participants (n = 168)	Patients (n=119)	Clinician/ Researchers (n=49)
Fatigue	127 (76%)	99 (83%)	28 (57%)
Weight gain and increase in appetite	124 (74%)	88 (74%)	36 (73%)
Sleep disturbance	124 (74%)	96 (81%)	28 (57%)
Depression or low mood	121 (72%)	87 (73%)	34 (69%)
Symptoms related to withdrawal from steroids	118 (70%)	95 (80%)	23 (47%)
Muscle and tendon problems	103 (61%)	84 (71%)	19 (39%)
Irritability and mood swings	102 (61%)	76 (64%)	26 (53%)
Increase in lipids	98 (58%)	81 (68%)	17 (35%)
Gut and stomach problems	97 (58%)	82 (69%)	15 (31%)
Anxiety	93 (55%)	77 (65%)	16 (33%)
Changes in appearance of face and/or body	88 (52%)	66 (55%)	22 (45%)
Fluid retention and ankle swelling	85 (51%)	74 (62%)	11 (22%)
Problems concentrating	83 (49%)	76 (64%)	7 (14%)
Personality change	82 (49%)	68 (57%)	14 (29%)
Being able to resume work	68 (40%)	51 (43%)	17(35%)
Sweating	53 (32%)	53 (45%)	0 (0%)
Impact on family and friends	45 (27%)	42 (35%)	3 (6%)
Impact on sexual relationships	39 (23%)	34 (29%)	5 (10%)
Lack of support of family and friends	36 (21%)	34 (29%)	2 (4%)

related to withdrawal from steroids to be measured in all trials, just making it over the threshold, less than 50% (23/49, 47%) of clinician/researchers agreed, therefore this domain was not included in the final set.

Proposed core domain set

The results of the Delphi and the final survey were combined for review. Following review of the proposed core domain set by the OMERACT GC Impact working group, the domain *making the condition noticeably better* was not included in the final core domain set. The Core Domain Set is intended for use in clinical trials in the context of treatment of disease(s), and measurement of disease activity will already be included in these trials. Domain names were additionally refined to reflect shared common terminology amongst patients and clinicians/researchers.

The core domain set that was proposed at the OMERACT 2020 virtual workshop included: bone fragility, diabetes mellitus, eye problems and/or changes in vision, infection, high blood pressure, osteonecrosis, mood disturbance, fatigue, sleep disturbance and weight (Fig. 1) [11]. These were endorsed with working definitions; consensus definitions were subsequently developed in accordance with OMERACT methodology [15].

Discussion

Clinical trials of new therapies and treatment strategies in inflammatory rheumatic diseases often consider the ability to reduce glucocorticoid exposure as glucocorticoid treatment-related toxicity remains a critical clinical issue. Using a Delphi approach to achieve consensus amongst PRPs, clinicians and researchers, we identified a set of candidate core outcomes related to the effects of GC therapy that are of most importance to patients and healthcare professionals. This led to a proposed core domain set including: bone fragility, diabetes, eye problems and/or changes in vision, high blood pressure, infection, osteonecrosis, mood disturbance, fatigue, sleep disturbance, *and* weight.

The OMERACT GC Impact Group has a unique focus within OMERACT, as we examine outcome measurement in relation to a therapeutic agent rather than a specific disease. Although we identified a core set of outcomes which met OMERACT consensus criteria at the end of round three (the original intended end point for the Delphi process), the results incompletely reflected the patient experiences of glucocorticoid that were prominent in the qualitative work, which had informed the selection of candidate domains included in the Delphi exercise.

We observed that in general, domains mapping to the Core Area of "Pathophysiological Manifestations" tended to outrank domains mapping to the Core Area of "Life Impact". This was the case both for patients and clinicians. The difficulty in disentangling the life impact of glucocorticoids versus that of disease may have influenced these rankings. However, in the clinical trial context, for measurement of common outcomes (as opposed to adverse effects in traditional safety reporting),

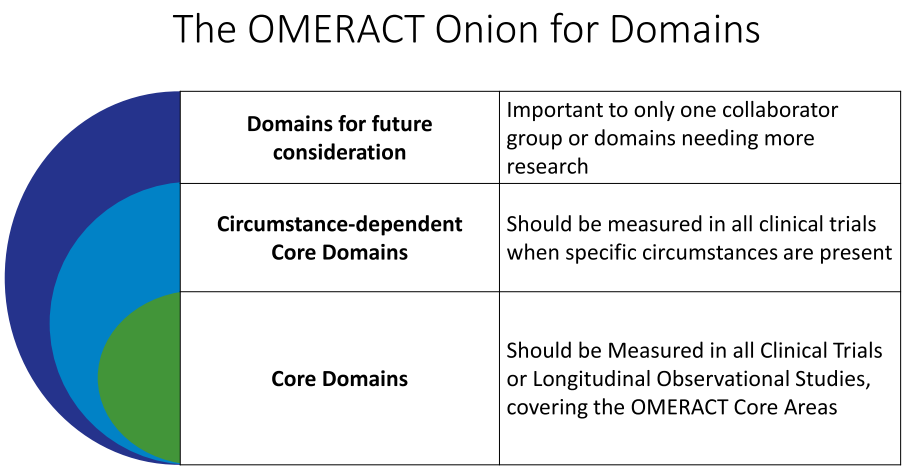

Fig. 1. OMERACT Glucocorticoid impact core domain set.

causal attribution is not necessarily required to make a valid comparison of outcomes between different treatment arms.

In retrospect, we speculate that the Delphi survey methodology, in which a long list of candidate domains is presented, may have contributed to this undervaluing of the life impact of GC therapy. In such a list, if less well-defined domains of patient experience are presented alongside common adverse events such as diabetes and infection, this side-by-side comparison may have inhibited participants from stating that their own lived experience was just as important as the experience of other patients who might have experienced adverse events that they personally had not. The design of the final survey may have helped ensure that the impact of glucocorticoid therapy on quality of life was captured.

It had been noted at the 2018 OMERACT meeting that novel methodology during consensus building would likely be required in order to capture those outcomes that were frequently represented in the qualitative and survey work which have not traditionally been included in clinical trials [3]. Our initial qualitative and survey work along with PRP representation on our working group during the early stages of this project proved crucial for identifying the need for measuring GC-related impacts on patients' lives that clinicians may not fully appreciate, and that a patient reported outcome measure (PROM) that encompasses these effects would need to be identified or developed to adequately measure this in clinical trials. We wished to harness the crucial experience of patients again in prioritizing core domains reflecting the life impact of glucocorticoids. We worked with OMERACT leadership and methodologist to adapt the weighting of responses in the final survey to enable this.

Therefore, we subjected those outcomes to a final survey, which confirmed consensus on the core domains that had emerged from the third round of the Delphi exercise, and in addition, asked all participants to select other domains that should be measured in all trials. By using "one participant, one vote" decision-making in the final survey combined with an online survey method that did not require in-person conference attendance, we were able to ensure that the patient voice was properly acknowledged. Through this additional process, *mood disturbance*, fatigue, sleep disturbance and *weight,* all outcomes frequently described by patients as important in the qualitative work that proceeded the Delphi exercise, were included [6–10].

Strengths of this study include our use of outcomes in the Delphi derived from prior published literature, in addition to qualitative, nominal group and survey data collected for the specific purpose of creating a core domain set of GC effects to be used in future clinical trials. Furthermore, there was broad-based participation. From a PRP standpoint, individuals of different ages, from at least 10 different countries and a spectrum of rheumatic disease were represented. Regarding healthcare professionals, while the majority were practicing rheumatologists, there was representation from clinicians in other medical specialties, including nephrology and respiratory medicine, who also provide clinical care for those with rheumatic diseases. Furthermore, utilizing multiple sources to generate the initial invitation list of both PRPs and clinician-researchers will have reduced any potential response bias.

Limitations of the exercise include that the process was conducted in English and not translated to other languages. While there was some representation from individuals (both PRPs and healthcare professionals) from countries where English is not the official language, there were few, so generalizability to non-English speaking countries is unknown. In addition, the Delphi exercise was conducted exclusively online, thereby excluding individuals without internet access. Nonetheless, those aged 65 years of age and greater comprised 31% of the first round of PRP respondents.

There was a significant attrition amongst participants through the rounds of the modified Delphi exercise, in particular between rounds 1 and 2. There was a time delay of 12 months between these two rounds, which may have contributed. While reasons for drop-out could not be ascertained, the drop-out rate is comparable to other Delphi exercises conducted through OMERACT [16]. The final ranking was inclusive of any participants (i.e., participants did not have to have completed all of round 1-3) in order to maximize participation at this key stage.

As a consequence of our approach, the list of core domains for measurement of glucocorticoid impact was longer than a typical list of core domains for assessment of a disease. This reflects the fact that treatment-related adverse effects are multidimensional whereas the intended effect of most treatments in rheumatology is to reduce disease activity, usually a unidimensional concept that arguably can be captured with fewer outcome measures than the diverse unintended effects of treatments. Use of composite outcome measures spanning multiple domains may be necessary for adequate feasibility within a clinical trial context.

In conclusion, the OMERACT GC-Impact working group performed a Delphi exercise, underpinned by previous systematic literature review and patient qualitative and survey work, to produce a proposal for a final GC Impact OMERACT core domain set with high face validity for patients, clinicians and researchers. This core set was endorsed at the OMERACT GC virtual workshop [11].

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Joanna Tieu reports a relationship with CSL that includes: funding grants. Robin Christensen reports a relationship with Oak Foundation

that includes: funding grants. Joanna C Robson reports a relationship with Vifor Pharma Inc that includes: funding grants and speaking and lecture fees. Joanna C Robson reports a relationship with Sanofi that includes: funding grants. Joanna C Robson reports a relationship with UKIVAS that includes: board membership. Sarah L Mackie reports a relationship with Roche Chugai that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Sarah L Mackie reports a relationship with Sanofi that includes: consulting or advisory and funding grants. Sarah L Mackie reports a relationship with AbbieVie that includes: consulting or advisory. Sarah L Mackie reports a relationship with AstraZeneca that includes: consulting or advisory. Sarah L Mackie reports a relationship with Pfizer that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Sarah L Mackie reports a relationship with GSK that includes: funding grants. Sarah L Mackie reports a relationship with Sparrow that includes: funding grants. Sarah L Mackie reports a relationship with Vifor Pharma Inc that includes: speaking and lecture fees. Sarah L Mackie reports a relationship with UCB that includes: speaking and lecture fees. Sarah L Mackie reports a relationship with Novartis that includes: speaking and lecture fees. Sarah L Mackie reports a relationship with AbbVie that includes: speaking and lecture fees. Susan M Goodman reports a relationship with Novartis that includes: funding grants. Susan M Goodman reports a relationship with Arthritis Foundation that includes: funding grants. Susan M Goodman reports a relationship with Yale that includes: speaking and lecture fees. Susan M Goodman reports a relationship with UCB that includes: consulting or advisory. Susan M Goodman reports a relationship with American College of Rheumatology that includes: board membership. Susan M Goodman reports a relationship with Regenosine that includes: equity or stocks. SLM is the chief investigator on STERLING-PMR trial, funded by NIHR. SLM is supported in part by the NIHR Leeds Biomedical Research Centre. The views expressed in this article are those of the authors and not necessarily those of the NIHR, the NIHR Leeds Biomedical Research Centre, the National Health Service or the UK Department of Health and Social Care. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements/Funding/Disclosures/Conflicts of interest

JT reports: investigator-initiated research support to institution from CSL.

RC reports: Section for Biostatistics and Evidence-Based Research, the Parker Institute is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL).

JCR reports: research support from Sanofi ltd and Vifor Pharma; speaker fees from Vifor Pharma; co-chair UK and Ireland Vasculitis Society (UKIVAS)

SLM reports: Consultancy on behalf of her institution for Roche/Chugai, Sanofi, AbbVie, AstraZeneca, Pfizer; Investigator on clinical trials for Sanofi, GSK, Sparrow; speaking/lecturing on behalf of her institution for Roche/Chugai, Vifor, Pfizer, UCB, Novartis and AbbVie; chief investigator on STERLING-PMR trial, funded by NIHR; patron of the charity PMRGCAuk. No personal remuneration was received for any of the above activities. Support from Roche/Chugai to attend EULAR2019 in person and from Pfizer to attend ACR Convergence 2021 virtually. SLM is supported in part by the NIHR Leeds Biomedical Research Centre. The views expressed in this article are those of the authors and not necessarily those of the NIHR, the NIHR Leeds Biomedical Research Centre, the National Health Service or the UK Department of Health and Social Care.

SG reports: Investigator initiated research support to institution from Novartis and Arthritis Foundation; payment for Yale Symposium lecture; payments for data safety monitoring board from UCB; guideline chair, American College of Rheumatology; ownership interest, Regenosine.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152602.

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