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## Improving benefit-harm assessment of glucocorticoid therapy incorporating the patient perspective: The OMERACT glucocorticoid core domain set

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## ABSTRACT

**Objective:** Our primary objective was to develop an Outcome Measures in Rheumatology (OMERACT) core domain set to capture the impact of glucocorticoids (GC), both positive and negative, on patients with Rheumatic conditions.

**Methods:** The OMERACT Filter 2.1 was used to guide core domain selection. Systematic literature reviews, qualitative studies and quantitative surveys were conducted by the OMERACT GC Impact working group to identify candidate domains for a core domain set. A summary of prior work and Delphi exercise were presented at the OMERACT 2020 virtual GC workshop. A proposed GC Impact core domain set derived from this work was presented for discussion in facilitated breakout groups. Participants voted on the proposed GC Impact core domain set.

**Results:** 113 people, including 23 patient research partners, participated in two virtual workshops conducted at different times on the same day. The proposed mandatory domains to be evaluated in clinical trials involving GCs were: infection, bone fragility, hypertension, diabetes, weight, fatigue, mood disturbance and death. In addition, collection of disease specific outcomes was included in the core domain set as “mandatory in specific circumstances”. The proposed core domain set was endorsed by 100% (23/23) of the patient research partners and 92% (83/90) of the remaining participants, including clinicians, researchers and industry stakeholders.

**Conclusion:** A GC Impact core domain set was endorsed at the OMERACT 2020 virtual workshop. The OMERACT GC Impact working group will now progress to identify, develop and validate measurement tools to best address these domains in clinical trials.

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## Background

Glucocorticoids (GCs) have been widely used for the treatment of patients with inflammatory disorders since 1948 [1]. Despite the recognized benefits and well-documented GC-related adverse effects that are delineated in the Glucocorticoid Toxicity Index (GTI) [2], there has been no standardized method to measure the impact of systemic GC use from the patient perspective in rheumatic diseases.

The Outcome Measures in Rheumatology (OMERACT) GC Impact Working Group was established to develop a core set of outcomes that reflect the impact of GC treatment to be measured in future clinical trials. Central to this process has been patient engagement, following the OMERACT filter 2.1 for core domain selection, using the OMERACT handbook [3–6]. In prior OMERACT GC Impact special interest group meetings, we presented preliminary work to review existing outcome measures for GCs and identify GC-related outcomes important to patients [7, 8]. This work included an initial and an updated systematic literature review of validated GC patient reported outcome measures [9]. Additionally, qualitative studies [10, 11] and surveys [12] involving patients with a range of rheumatic conditions were carried out by the working group.

In this paper, we report on the OMERACT 2020 GC virtual workshop, where we presented the additional qualitative and quantitative work conducted since the OMERACT 2018 GC Special Interest Group meeting in 2018, the development process of the core domain set including the Delphi process, and ultimately voted on the mandatory outcomes in this core domain set.

## Methods and results

*Nominal groups involving patients with systemic lupus erythematosus (SLE) and idiopathic inflammatory myositis (IIM)*

The original qualitative and quantitative work included patients with rheumatoid arthritis (RA), polymyalgia rheumatica/giant cell arteritis and anti-neutrophil cytoplasm antibody (ANCA)- associated vasculitis (AAV) [10–12]. Following an interim review of patient disease subgroups from the first Delphi round, the working group recognized the need to increase representation from patients with SLE and IIM, who typically receive high doses of GCs and/or require long-term GC. Patients with SLE and IIM who were current or previous GC users were invited to participate in discussion groups using Nominal Group Technique [13], a highly structured method that involves

reaching consensus by generation and sharing of ideas, clarification of ideas, and ranking of results. Groups of 5–10 participants were asked two open-ended questions about their experience of the positive benefits and adverse effects of GC use.

This study was conducted in the USA and involved 21 patients (17 with SLE, 4 with IIM), and 57% had experience taking GC for greater than 10 years. The domains identified were:

- Benefits: controls disease and symptoms, works fast, increases energy, relieves pain
- Adverse effects: bone loss, weight gain, psychological effects, damaged internal organs

#### RA online survey

A survey of Australian RA patients participating in a prospective biologics registry was conducted to supplement the previous studies, specifically evaluating reasons for stopping prednisolone (prednisone equivalent; most common form of oral GC in Australia) cessation [14]. This study used the Beliefs in Medicines Questionnaire (BMQ), which employs a five-point Likert scale to assess the level of agreement to statements on the necessity and concerns of prednisolone and medicines in general. A qualitative analysis of respondents' free-text comments on reasons for stopping prednisolone was performed.

Of the 1010 patients invited to participate in this online survey, 804 (80%) patients responded, of which 432 had stopped prednisolone, 251 (31%) were currently taking prednisolone, 18 (2%) declined prednisolone and 103 (13%) had not been offered prednisolone. Current prednisolone users had greater prednisolone specific necessity scores (3.6 [3.5–3.7] vs 1.7 [1.6 – 2.7],  $p < 0.001$ ) indicating that, on average, they had stronger agreement on the necessity of prednisolone. The main reasons for stopping prednisolone were adequate disease control (131/432, 30%) and adverse effects (109/432, 25%). The most common adverse effects cited in patients who had ceased prednisolone were weight gain, osteoporosis and neuropsychiatric effects.

#### Delphi exercise and developing a core domain set

A Delphi exercise was carried out to identify domains important to patients, researchers and clinicians. An extended report of the Delphi process and results are available in a separate publication [parallel publication in preparation]. Patients from several patient organizations and registries were invited to participate to enable diversity amongst participants, inclusion of a broad range of disease groups and GC doses and durations. Most patients were from the United States (41%), United Kingdom (40%) and Australia (13%). Whilst patients with RA (21%) represented the largest disease group, patients who responded also self-reported diagnoses of other inflammatory arthritis, vasculitis and connective tissue disease. Clinicians and researchers who have contributed to GC literature or members in Rheumatology and musculoskeletal disease research groups were invited to participate. Most clinicians and researchers were from the United States (26%), Australia (26%) and United Kingdom (19%).

Delphi items were informed by the results of the systematic reviews, patient surveys and qualitative work previously reported, with 63 candidate outcomes to be prioritized to a core set [7, 8]. Three rounds of the Delphi were completed (Round 1: 295 patients/68 clinician-researchers, Round 2: 137 patient/53 clinician-researchers, Round 3: 123 patients/45 clinician researchers). Results and feedback from Delphi participants were reviewed by the OMERACT GC Impact working group after each round.

Based upon the initial three rounds of the Delphi, the outcomes which met OMERACT definitions for inclusion in the core domain set (reaching agreement of critical to measure in clinical trials by  $\geq 70\%$  of all stakeholder groups) were:

1. Bone fragility
2. Diabetes Mellitus
3. Eye problems and/or changes in vision
4. Infection
5. High blood pressure
6. Osteonecrosis
7. Making the condition noticeably better

Discordance between patients and clinicians/researchers in prioritizing outcomes and the need to explore novel ways of incorporating patient perspectives in determining the relative importance of GC effects have been recognized as key challenges in developing the GC core domain set in prior OMERACT meetings. The working group identified outcomes that did not meet strict OMERACT definitions for inclusion but had featured prominently in the prior work. A final survey asked respondents to consider whether these outcomes should be measured in “every”, “some” or “never” in clinical trials.

The final survey was analyzed using proportional weighting based upon stakeholder group and number of participants. The following additional domains were included into the core domain set:

1. Mood disturbance
2. Fatigue
3. Sleep disturbance
4. Weight

The domain names were refined to reflect shared common terminology among patients, clinicians, and researchers. The combined group of domains were reviewed by the OMERACT GC Impact working group. To refine the core outcome set further, the working group acknowledged that the outcome “making the condition noticeably better” would already be measured in the context of a clinical trial as disease-specific outcomes. Disease-specific outcomes will vary by clinical trial and are included as “mandatory in specific circumstances” in the GC core domain set. In OMERACT GC working group discussions, it was agreed that outcomes deemed rare, typically occurring with high doses or long-term follow-up (osteonecrosis, eye problems and sleep disturbance), would be better included as optional domains. During these discussions, the working group also reflected on patients' views in the qualitative work linking weight and appearance. Appearance was therefore included in the core domain set as an optional domain. Death is included as a mandatory domain for all OMERACT core domain sets. The final core domain set is depicted in Fig. 1.

#### Virtual workshop

OMERACT 2020 was conducted virtually due to the COVID-19 pandemic. Participation was invited through the OMERACT patient research partners network, OMERACT working groups, the Australia and New Zealand Vasculitis group (ANZVASC) and all patient, research and clinician participants of the Delphi process.

Prior to the workshop, a lay summary and video summarizing the work was made available to participants [15]. Additional detailed written reports and a pre-recorded presentation of the qualitative and quantitative work, and core domain selection, were provided online. Registered workshop participants were able to comment or post questions related to the reading material or core domain set on the OMERACT GC discussion board.

Two identical 90-minute workshops comprised a short plenary session prior to simultaneous breakout group sessions, led by an OMERACT facilitator with the assistance of a content expert and reporter. Each group was asked to discuss the proposed core domain set (Fig. 1) and provide feedback. Finally, all participants were invited to vote on whether to endorse the mandatory domains of the core domain set.

# Core outcome domain set for glucocorticoid impact

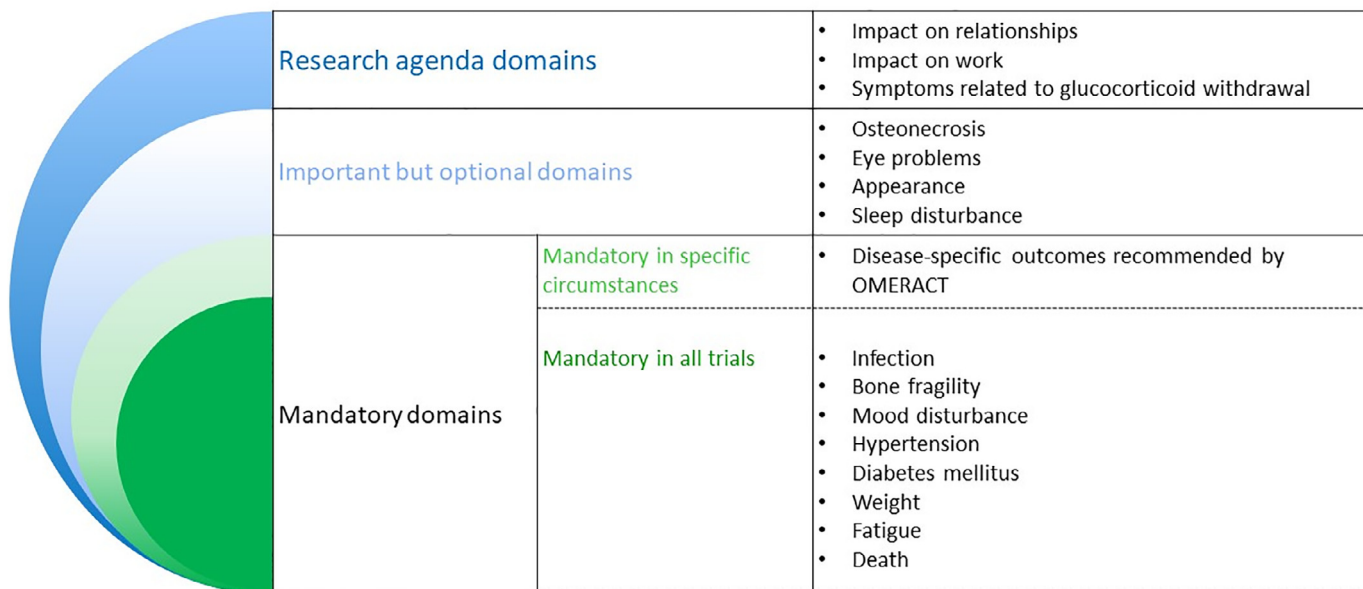


Fig. 1. OMERACT Glucocorticoid impact core domain set.

A total of 113 people participated in the two workshops, including 23 patient research partners. The proposed mandatory domains of the core domain set were endorsed, with 100% (23/23) of the patient research partners voting to ratify and 92% (83/90) of the remaining participants, including clinicians, researchers and industry stakeholders.

Overall, feedback from the breakout groups was positive. Key issues highlighted by the breakout groups could be summarised in the following themes:

## a) Domain definitions

For the workshop, working definitions of each domain were provided to facilitate discussion during breakout sessions based on original descriptions from the Delphi exercise and preliminary work identifying candidate outcomes. It was clear from the workshop summaries that opinions on the breadth of domains differed. The preliminary working definitions were refined after reviewing this feedback (Table 1). Breakout groups facilitated insightful discussion on how the interpretation and measurement of each domain is influenced by several factors including: GC dose, trial design, and feasibility of measurement.

## b) Attribution

Although there was general agreement on the proposed mandatory domains of the core domain set, participants recognized the overlap with other effects from other medications and rheumatic conditions.

## c) Contextual factors

Breakout groups noted the dependence of the GC Impact domains on patient and disease related factors. The development of the core domain set was informed from work involving patients from different countries and living with a wide range of rheumatic conditions. However, it was acknowledged that clinical trials will focus on select patient and clinical factors, which may influence the impact of GCs.

Table 1.

Mandatory domains and working definitions.

Domain	Working definition
Diabetes Mellitus	blood glucose (sugar), high blood glucose, development of diabetes mellitus and/or worsening control
Hypertension	blood pressure, development of hypertension (high blood pressure), and worsening hypertension
Bone Fragility	bone density, report of fractures, and osteoporosis or osteopenia
Fatigue	tiredness or feeling wiped out
Infection	recurrent, atypical and serious infections
Mood disturbance	changes in mood including depression, irritability, mood swings, euphoria and anxiety
Weight	weight, appetite, and weight gain
Death	*mandatory OMERACT domain

## d) Patterns of GC use

The breakout groups discussed potential differences in how GC related effects are experienced based on the dose range, dosing pattern and duration. These are likely to impact the way each domain is measured.

## Discussion

We present the endorsed OMERACT core domain set for clinical trials involving GCs, developed by a multi-national group of stakeholders, including patients, clinicians, and researchers. The core domain set received strong support by both patient and clinician/researcher/industry stakeholder groups, who endorsed the proposed domains at the OMERACT 2020 virtual workshop. This OMERACT GC core domain set enables the validation of existing instruments and the development and validation of new instruments incorporating these domains to measure the effects of GCs in clinical trials.

The domains and definitions are not prescriptive of how each will be measured. The terminology used in the core domain set have been determined according to shared terminology and to enable sufficient



flexibility to adapt to specific contextual factors, including varied trial designs, GC dose and duration, and disease related factors. Working domain definitions were informed by the prior work and we have incorporated feedback from the OMERACT 2020 GC workshop. It is anticipated that outcome measurement instruments, both clinician-assessed and patient-reported, will be sought to address the mandatory items in the core domain set. In the context of a clinical trial, GC-specific tools will be used in conjunction with the relevant disease-specific measurement instruments. Discussion at the virtual workshop reiterated the need for instruments to be adaptable to the context of different trial conditions. Moreover, the attribution of a domain to GC, disease or other medication(s) remains a challenge that will be faced in instrument selection.

The qualitative and quantitative work consistently emphasized the positive impact of GCs, particularly in treating the underlying disease and the effects on fatigue [11, 12]. These positive effects were reiterated in the results of the Delphi process. The outcome “making the condition noticeably better” met OMERACT definitions for inclusion into the core domain set. In practical terms, the impact of GCs on the underlying disease in the clinical trial setting will be varied and disease specific and was therefore included as “mandatory in specific circumstances”. This means the positive benefits of GCs in each disease condition will be quantified in clinical trials using disease specific outcome measures. In future work on instrument selection, the positive and negative impacts of GCs will remain important considerations to reflect the balance that both patients and clinicians have emphasized.

The OMERACT GC workshop aimed to discuss and vote on the proposed OMERACT GC core domain set; instrument selection, including considering the GTI, forms a later stage of the OMERACT framework. A number of breakout groups raised the GTI as a potential measurement tool, which the working group acknowledged the need to consider as a measurement tool in subsequent stages. In the words of its authors, the GTI was developed as an instrument for the assessment of GC toxicity. It was developed by an expert panel of clinicians and researchers without patient input, who sought to create an instrument to assess the impact of GC-associated morbidity. Notably, the objectives and item selection process for the GTI differ from the OMERACT process in several key areas. GTI items were identified from literature review and items were selected for inclusion by nominal group technique amongst an expert panel of clinicians [2]. Moreover, the focus was on items that could be attributable to GC rather than disease, and unlikely related to GC therapy prior to trial entry. The OMERACT GC core domain set has been developed using a patient-centered approach to qualitative and quantitative studies to supplement literature reviews, incorporating both positive and negative impacts of GC into a core domain set after the Delphi process described, and did not exclude domains influenced by both disease and GC. Patients, clinicians, and researchers were invited to participate in the Delphi exercise. At this stage, the GTI has not undergone extensive validation despite its inclusion in RCTs and will be considered within the instrument selection stage of the OMERACT process for GC.

Since inception, the OMERACT GC group has recognized that the experience of inflammatory conditions and of GCs allows patients a unique perspective on the impact of GCs that overlaps but remains distinct from the perspective that clinicians have observing patients with different conditions and GC regimens. The difficulty in capturing both perspectives to achieve a representative domain set has been a challenge throughout the domain selection process including the Delphi exercise. The initial three rounds of the Delphi demonstrated that both groups prioritize pathophysiological domains commonly ascribed to GCs, and which are typically easier to define and measure in the context of a clinical trial. A bias to these domains had been considered possible in light of the methodology used to develop consensus.

The approach to the final survey including proportional weighting of responses was developed in OMERACT GC working group

meetings. The proportional weighting of patient and clinician/researcher responses from the final survey recognized the imbalance in group sizes and the exclusion of domains that featured prominently in the patient-centered qualitative work used to derive the candidate domains for the Delphi. The final survey sought to identify whether there were additional domains important to both patient and clinicians/researcher groups after acknowledging the effects of GCs included from the initial three rounds. Although novel, this approach acknowledged the consistent data and results derived from the qualitative work conducted and drew from OMERACT principles and methodology, maintaining a minimum 70% threshold for consensus after weighting. Moreover, this adapted methodology enabled the inclusion of mood disturbance, fatigue, weight and sleep disturbance as domains; the approach and inclusion of these domains was positively received by patients and clinicians/researchers at the virtual workshop.

In all rounds of the Delphi exercise and final survey, patients highly ranked fatigue, which also featured prominently the prior qualitative work. Fatigue as an outcome of GC use warrants particular mention, as the patient experience of fatigue in this setting is multifaceted and complex. Discussions at the virtual workshop highlighted some important considerations for evaluating measurement tools incorporating fatigue. These included the overlap of fatigue with other GC effects such as mood and sleep disturbance, difficulties in separating fatigue attributed to GCs versus the underlying disease, and the bi-directional effect of GCs on fatigue in different contexts including GC dose, patient age, comorbidities, other medications and disease states.

The focus of OMERACT and the OMERACT GC group are outcomes in patients with Rheumatic diseases. Patient participation in the qualitative studies for candidate domain selection for the Delphi have included only patients with Rheumatic diseases. Responses from a small number of patients with other inflammatory conditions and clinicians/researchers with a focus on non-Rheumatic inflammatory disease were included in the Delphi process. Owing to the multisystem nature of Rheumatic disease, clinicians practicing outside of Rheumatic disease are often involved in the co-management of these patients. As the domain set has been developed for GC use in Rheumatic disease, however, further validation work would be required for this domain set to be used in non-Rheumatic inflammatory disease.

Although developed and endorsed by a multi-national group, the mandatory domains and endorsement at the virtual workshop were formulated and conducted in English. Further work to evaluate the relevance of these domains in non-English speakers will be important to its generalizability.

## Conclusion

Using OMERACT methodology, the GC Impact working group has developed the GC Impact core domain set, which was successfully endorsed at the OMERACT 2020 virtual workshop. Future work involves the collaboration between patients, clinicians and researchers in the identification, development, validation and integration of GC-specific measurement tools in future clinical trials.

## Declaration of Competing Interest

MD George reports grants from Bristol-Myers Squibb and personal fees from Dysimmune Diseases Foundation outside the submitted work.

M de Witt reports being a collaborating partner in the EU/IMI funded trial to investigate the efficacy and safety of low-dose GC in the elderly.

M Boers is principal investigator of the GLORIA trial on low-dose prednisolone or placebo in elderly RA patients, funded by the

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JA Singh has received consultant fees from Crealta/Horizon, Medisys, Fidia, Two labs Inc, Adept Field Solutions, Clinical Care options, Clearview healthcare partners, Putnam associates, Focus forward, Navigant consulting, Spherix, MediQ, UBM LLC, Trio Health, Medscape, WebMD, and Practice Point communications; and the National Institutes of Health and the American College of Rheumatology. JA Singh owns stock options in TPT Global Tech, Vaxart pharmaceuticals and Charlotte's Web Holdings, Inc. JAS previously owned stock options in Amarin, Viking and Moderna pharmaceuticals. JA Singh is on the speaker's bureau of Simply Speaking. JA Singh is a member of the executive of Outcomes Measures in Rheumatology (OMERACT), an organization that develops outcome measures in rheumatology and receives arms-length funding from 8 companies. JA Singh serves on the FDA Arthritis Advisory Committee. JAS is the chair of the Veterans Affairs Rheumatology Field Advisory Committee. JAS is the editor and the Director of the University of Alabama at Birmingham (UAB) Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis.

R Christensen reports honoraria paid to the Parker institute from: Lecture- Research Methods (Pfizer, DK; 2017), GRADE Lecture (Celgene, DK; 2017), Ad Board Lecture: CAM (Orkla Health, DK; 2017), Project Grant: "GreenWhistle" (Mundipharma, 2019), Lecture: Diet in RMD (Novartis, DK; 2019), Consultancy Report: Network MA's (Biogen, DK; 2017), Ad Board Lecture: GRADE (Lilly, DK; 2017), Consultancy Report: GRADE (Celgene, 2018), Lecture: Network MA's (LEO; 2020), outside the submitted work; and Musculoskeletal Statistics Unit, The Parker Institute is grateful for the financial support received from public and private foundations, companies and private individuals over the years. The Parker Institute is supported by a core grant from the Oak Foundation. R Christensen is a founding member of the Technical Advisory Group of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 8 companies.

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P Tugwell is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 8 companies.

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