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Clinical science

Measuring the impact of steroid therapy on health-related quality of life in patients with rheumatic diseases: international development of a glucocorticoid treatment–specific patient-reported outcome measure

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Abstract

Objectives: Glucocorticoids (GCs) ('steroids') are used to treat rheumatic diseases but adverse effects are common. We aimed to explore the impact of GC therapy on health-related quality of life (HRQoL), to inform the development of a treatment-specific patient-reported outcome measure (PROM) for use in clinical trials and practice.

Methods: Semi-structured qualitative interviews were conducted with patients from the UK, USA and Australia, treated for a rheumatic condition with GCs in the last 2 years. Purposive sampling was used to select participants with a range of demographic and disease features. An initial conceptual framework informed interview prompts and cues. Interviews elicited GC-related physical and psychological symptoms and salient aspects of HRQoL in relation to GC therapy. Interview data were analysed inductively to develop initial individual themes and domains. Candidate questionnaire items were developed and refined.

Results: Sixty semi-structured qualitative interviews were conducted (UK $n=34$, USA $n=10$, Australia $n=16$). The mean age was 58 years; 39/60 were female; and 18 rheumatic diseases were represented. Some 126 individual themes were identified and organized into six domains: physical symptoms; psychological symptoms; psychological impact of steroids; impact of steroids on participation; impact of steroids on relationships; and benefits of steroids. Candidate questionnaire items were tested and refined by piloting with patient research partners, iterative rounds of cognitive interviews and linguistic translatability assessment, informing a draft questionnaire.

Conclusion: We describe an international qualitative study to develop candidate items for a treatment-specific PROM for patients with rheumatic diseases. A future survey will enable the validation of a final version of the PROM.

Keywords: rheumatic diseases, glucocorticoid steroids, quality of life, patient-reported outcomes

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Rheumatology key messages

- This study describes the impact of glucocorticoid (steroid) treatment on people with rheumatic conditions.
- There is no patient-reported outcome measure to assess steroid impact from the patient perspective.
- This work underpins the development of a treatment-specific, generic patient-reported outcome to measure steroid therapy impact.

Introduction

Glucocorticoids (GCs) are a class of CS ('steroid') widely used in the autoimmune rheumatic diseases to treat inflammatory arthritis, systemic vasculitis, connective tissue diseases (CTDs) and the crystal arthropathies [1–6].

GCs are key in the management of life- and organ-threatening rheumatic diseases [5, 7], but they have wide-ranging dose- and duration-dependent adverse effects [8] which are of great concern to patients and clinicians [9–13]. Adverse effects include depression, anxiety, weight gain, skin thinning, insomnia, and risk of diabetes, osteoporosis and infection, among many others [14–17].

The OMERACT Glucocorticoid Impact Working Group has published a core domain set for GC impact on patients [18] and has identified the need for a patient-reported outcome measure (PROM) for effects of GC therapy in adults with inflammatory diseases [19]. Following on from this, the OMERACT Glucocorticoid Impact Working Group conducted a systematic review of 25 studies including both qualitative and quantitative studies (7 qualitative and 18 survey studies) [20] to inform the development of both a core domain set for clinical trials involving GCs and a patient-reported outcome to measure impact of GCs on patients' health-related quality of life (HRQoL). The OMERACT systematic review included qualitative studies to provide a broader and more complete view of the patients' perspective. The numerous effects of GCs reported by patients fell into four cross-cutting themes: physical symptoms, psychological symptoms, effect on participation and contextual factors such as societal pressures relating to taking GCs.

Randomized controlled trials of novel therapies should assess efficacy based on outcomes of importance to both clinicians and patients. The patient perspective captured by validated PROMs provides valuable insights into the patient condition, which are not always captured by clinician-reported assessment tools [21]. Health-related quality of life is a multidimensional construct that includes physical, psychological and social functioning. Until recently, the only PROMs available to assess the HRQoL impacts of GC therapy have been generic measures of HRQoL intended to assess impacts of any disease, rather than the combination of impacts caused by GC therapy [22]. Guidance from the US Food and Drug Administration (FDA) on the development of patient-reported outcomes requires patient involvement at each stage of development of a PROM [23].

The development of a new PROM requires the use of mixed methods applied in three distinct phases: Phase 1—collection and analysis of qualitative data from patients, who have an understanding and personal experience of GCs that only they can describe, to inform PROM candidate items, with additional refinement via cognitive debriefing; Phase 2—item reduction and determination of underlying PROM scale structure and cross-sectional measurement properties; Phase 3—longitudinal and comparative analysis/verification of the new PROM's measurement properties. Phases 2 and 3 involve using quantitative methods within the context of a longitudinal survey. This study describes Phase 1 in the development of a treatment-specific PROM, to capture the impact of GC treatment on HRQoL from the patient perspective.

Methods

Study management

Members of the study steering committee included patient research partners, qualitative researchers, methodologists and rheumatology clinicians from the UK, USA and Australia. Following the FDA guidance [23], a conceptual framework was developed to describe the scope of the final PROM, based on steering committee input and literature review to describe potential areas of interest for inclusion. A conceptual framework also highlights subjects of importance to patients that may not be suitable for a PROM, e.g. contextual factors such as societal influence and interaction with clinicians. The conceptual framework was refined throughout the study based on interview content, to act as an evolving guide for the PROM development. An interview topic guide was also developed to include prompts and cues. Ethical approval was obtained in the UK (REC ref: 19/SW/0221), USA (IRB ref: 2019-0215) and Australia (CALHN ref: 12903). All participants provided informed consent.

Patient and public involvement

Patient research partners (P.R., C.S.) are study co-applicants and were involved in developing the initial research proposal, developing the conceptual framework, reviewing all patient-facing documents, reviewing interview prompts and cues, reviewing some of the interview transcripts for their interpretation of themes, reviewing the long-list of PRO candidate questions and wordings, reviewing the research results, and reviewing presentations and research dissemination, and are included as co-authors on all publications.

Participants

Participants were recruited from rheumatology clinics in the UK, USA and Australia. Participants were approached by their usual clinical team. Interested participants were then sent an information sheet by the non-clinical research team; after reading this, participants could either decline the study or take part. All participants gave written informed consent. Criteria for inclusion in the study were: clinician-diagnosed rheumatic condition; treatment with GCs for the rheumatic condition in the past 2 years; age 18 years or over; sufficient English language skills to participate in the interview; and capacity to provide informed consent. An *a priori* purposive sampling framework was developed by the study steering committee to obtain a broad sample of participants, with different demographic characteristics (age, race and sex), disease

features, duration of steroid therapy and current disease activity. Data were also captured on education level and employment status.

In-depth qualitative interviews

Informed consent was obtained prior to each semi-structured patient interview. Interviews, performed by experienced qualitative researchers in the UK (M.A.S.), USA (N.G.) and Australia (E.A.H.), were recorded, transcribed and anonymized. The interviews were used to determine the breadth of topics of importance to patients in relation to treatment with GCs, and the impact on HRQoL. Interviews continued until no new substantive themes arose, indicating data saturation [24]. Anonymized transcripts from the USA and Australia were sent to the UK. All study transcripts were organized by qualitative researchers (C.A., S.B.) within one NVivo database prior to analysis. Transcripts were systematically analysed using a modified framework method [25–27]. Coding was carried out using both an inductive (codes emerged during analysis) and deductive (codes anticipated) approach [28], in conjunction with the conceptual framework. Individual themes were identified and given a descriptive label; themes were then reduced and refined by J.C.R., J.D. and S.B., and patient partners C.S. and P.R. Individual themes were grouped into overarching domains related to development of a PROM to assess the impact of GC treatment for rheumatic conditions.

Candidate item development

A long-list of candidate items was developed based on the individual themes by J.C.R., J.D. and S.B. Items were added, removed or refined, to reduce overlap between items and improve the readability of each item. Piloting and further amendment was conducted in an iterative way by steering committee patient partners.

Cognitive interviews and linguistic evaluation

Serial cognitive interviews were conducted with patients in the UK, USA and Australia. Cognitive interviewing involves interviewers asking survey respondents to think out loud as they read through a questionnaire to assess understanding of each item from the respondent's perspective [29]. In this way, ambiguous or confusing items are amended, combined or removed.

In parallel, a face validity and linguistic assessment of the original English source text of the long list of candidate items was independently performed, in accordance with current industry standards and guidance from the FDA, by a specialist company (RWS Life Sciences, Buckinghamshire, UK).

Results

Qualitative interviews

Sixty semi-structured qualitative interviews were conducted (UK $n = 34$, USA $n = 10$, Australia $n = 16$). Mean participant age was 58 years; 39/60 were female. Eighteen rheumatic diseases were represented [AS, Behçet's disease, crystal arthropathy, eosinophilic granulomatosis with polyangiitis, GCA, granulomatosis with polyangiitis, IgG4-related disease, necrotizing myopathy, palindromic rheumatism, PM/DM, PMR, PsA, RA, synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome/chronic recurrent multifocal osteomyelitis (CRMO), sarcoidosis, sclerosing mesenteritis, SLE, Takayasu arteritis], grouped into five disease categories (systemic vasculitis, inflammatory arthritis, crystal arthropathy, CTD, other). Detailed demographic and GC use information is provided in Table 1. To preserve the anonymity of participants with often rare diseases, we have chosen to report age ranges rather than specific ages.

Analysis of interview transcripts identified 126 initial individual themes in relation to symptoms and impact of GCs on HRQoL. These were then refined through a process of discussion, amalgamation and refinement resulting in 51 individual themes within six overarching domains relevant to the development of a PROM: physical symptoms (Table 2); psychological symptoms (Table 3); psychological impact of steroids (Table 4); impact of steroids on participation (Table 4); impact of steroids on relationships (Table 4); benefits of steroids (Table 4). See Supplementary Table S1, available at *Rheumatology* online for the Data Saturation Table.

Additional themes of importance to patients were contextual factors, but these topics would not be included in the development of a PROM (for example patient education; confidence in clinicians; other people's concerns and perceptions including input from the media, friends and family; the patient's support network; and comorbidities). These areas of importance may be explored in future analyses.

Candidate item development

The 51 individual themes within the six PROM domains were recast into an initial list of 134 questionnaire candidate items (all individual themes resulted in one or more potential candidate items). An iterative process of refinement and reduction of items through patient partner review, two rounds of cognitive interviews and incorporation of the Translatability Assessment findings (see Supplementary Data S1, available at *Rheumatology* online) was then completed by the group (J.C.R., J.D. and S.B., and patient partners C.S. and P.R.).

Several items were excluded, combined or amended in response to discussions with patient research partners, the Steroid PRO Working Group, the linguistic translatability assessment, and cognitive interviews with patients in the UK, US and Australia. Illustrations of these changes are shown in Table 5. Items were reworded to improve clarity, and those that were judged to be similar in meaning were removed to reduce redundancy. Use of appropriate language was also a key consideration in item development, to avoid wording that can be perceived as derogatory (e.g. 'moon face' and 'buffalo hump').

The final long-form of the draft Steroid PRO consisted of 40 candidate items. An abridged version of the items retained is shown in Supplementary Table S2, available at *Rheumatology* online. The initial conceptual framework was refined during the qualitative work and the final version for this stage is shown in Fig. 1.

Discussion

This international qualitative study examined themes of importance to people who are receiving GCs for their rheumatic condition. This is the first study to develop candidate PROM items to represent the impact of GCs across the inflammatory rheumatic conditions using FDA-approved methods, including patient involvement at every stage [23]. The long-list of PROM questions developed through this process comprised

Table 1. Demographics and glucocorticoid use

		UK		Australia		USA		All Sites	
		n = 34		*n* = 16		*n* = 10		*n* = 60	
Sex	Male	14	41.2%	6	37.5%	1	10.0%	21	36%
	Female	20	58.8%	10	62.5%	9	90.0%	39	66%
Ethnicity	Asian/Asian British	0	0.0%	2	12.5%	0	0.0%	2	3%
	Black/African/ Caribbean/Black British	1	2.9%	0	0.0%	3	30.0%	4	7%
	Mixed/Multiple ethnic groups	1	2.9%	1	6.3%	0	0.0%	2	3%
	White	32	94.1%	13	81.3%	6	60.0%	51	86%
	Other ethnic group	0	0.0%	0	0.0%	1	10.0%	1	2%
Age (years)	18–39	5	14.7%	5	31.3%	4	40.0%	14	23%
	40–59	10	29.4%	2	12.5%	3	30.0%	15	25%
	60–79	15	44.1%	8	50.0%	3	30.0%	26	43%
	80+	4	11.8%	1	6.3%	0	0.0%	5	8%
Mean (SD) age, years		61	(16.14)	56	(17.83)	50	(15.62)	58	(17.01)
Rheumatic disease(s)	Systemic vasculitis	13	34.2%	5	31.3%	1	10.0%	19	30%
	Inflammatory arthritis	14	36.8%	1	6.3%	1	10.0%	16	25%
	Crystal arthropathy	0	0.0%	0	0.0%	2	20.0%	2	3%
	CTD	4	10.5%	8	50.0%	5	50.0%	17	27%
	Other	7	18.4%	2	12.5%	1	10.0%	10	16%
Dose of oral glucocorticoids in the last 7 days (mg/day)	≥30	1	2.9%	0	0.0%	1	10.0%	2	3%
	>7.5 and <30	6	17.6%	4	25.0%	1	10.0%	11	18%
	>0 and ≤7.5	14	41.2%	6	37.5%	5	50.0%	24	40%
	0	13	38.2%	6	37.5%	3	30.0%	23	38%
Maximum duration of glucocorticoid use	<6 weeks	5	14.7%	0	0.0%	1	10.0%	6	10%
	6 weeks to 6 months	2	5.9%	1	6.3%	1	10.0%	4	7%
	6 months to 2 years	10	29.4%	4	25.0%	3	30.0%	17	28%
	2–5 years	11	32.4%	2	12.5%	2	20.0%	15	25%
	>5 years	6	17.6%	9	56.3%	3	30.0%	18	30%
Maximum glucocorticoid dose (mg/day) where known (*n* = 55)	≥30	24	70.6%	6	54.5%	8	80%	38	69%
	>7.5 to <30	7	20.6%	5	45.5%	2	20%	14	25%
	≤7.5	3	8.8%	0	0%	0	0%	3	5%
Educational level	No formal qualifications	4	12%	0	0%	0	0%	4	7%
	School/high school qualifications	7	21%	4	25%	6	60%	17	28%
	Vocational/employment related qualifications	9	26%	4	25%	0	0%	13	22%
	College/university degree or higher qualifications	14	41%	8	50%	4	40%	26	43%
Employment status	Employed with income	9	26%	8	50%	1	10%	18	30%
	Employed without income (volunteer)	9	26%	8	50%	1	10%	18	30%
	Unemployed	2	6%	0	0%	0	0%	2	3%
	Homemaker/carer	0	0%	1	6%	2	20%	3	5%
	Disabled (unable to work)	1	3%	1	6%	1	10%	3	5%
	Retired	5	15%	0	0%	3	30%	8	13%
	Full-time student	17	50%	6	38%	2	20%	25	42%

six key domains: physical symptoms, psychological symptoms, psychological impact of steroids, impact of steroids on relationships, impact of steroids on participation and benefits of steroids, resulting in 40 candidate questionnaire items.

This study was informed by the OMERACT Glucocorticoid Impact Working Group, which highlighted the need for a PROM to measure GC impact [19, 20]. The study findings mirror the themes identified in the systematic review conducted by the OMERACT Glucocorticoid Impact Working Group, of physical symptoms, psychological symptoms, effect on participation and contextual factors [support (or lack of) from family and friends, support (or lack of) from community/media, self-management and mastery]. This study also highlighted the benefits of GC therapy. This led to an

Table 2. Physical effects of GC therapy

A: Appetite and hunger
It gives you a big appetite. You're always hungry, like you're never full yourself. You have to eat, eat, eat, but that's what steroid does (USA, F, 60–79, Crystal arthropathy, White Hispanic)
B: Body appearance change
I can feel… like little fat rolls on my neck which I didn't have before and my, erm, my sort of like my back and my neck just, you know, between my, above my shoulder blades that all feels quite fleshy and fat… I'm getting a lot of fat under my chin and what not… I don't like that. (UK, F, 18–39, TA, White English/Welsh/Scottish/N. Irish/British)
C: Bone and joint symptoms
Right now, I have AVN. I have it, I believe I have it on my left knee, my right ankle, and both my shoulders. And I believe there are signs of AVN on my hip. (USA, M, 18–39, SLE, White Hispanic)
D: Changes in dental health
… another thing I've noticed with the steroids is my teeth, my teeth have got very, very sensitive. (UK, F, 18–39, TA, White English/Welsh/Scottish/N. Irish/British)
E: Changes in vision
… my long-distance vision was becoming blurry… It developed over those two months [on steroids]… I went to get my sight checked, and… my cataracts had really taken off from when I had my eyes checked midyear last year. (Aus, F, 60–79, GCA, English/Welsh/Scottish/N. Irish/British—English)
F: Cramping in the hands
Every now and again, there's a—it's almost like my hand goes into some sort of spasm, and I can't—it just doesn't flow… I'd be trying to write, and it just wasn't flowing. (Aus, F, 60–79, GCA, English/Welsh/Scottish/N. Irish/British—English)
G: Skin changes
… acne is a very big thing with the prednisone. So maybe a month-and-a-half after, I started to really see acne on my face and skin… the bruising would show more… The cuts would show more. Your skin takes longer to heal when you're on these medications. (USA, F, 18–39, Inflammatory myositis, Black/African/Caribbean/Black British—Caribbean)
H: Increased energy
So I was like, you know, I was wired all day long is the only way to describe it really… You know, I did decorating, two o'clock in the morning, because I couldn't sleep. (UK, F, 40–59, EGPA, White English/Welsh/Scottish/N. Irish/British)
I: Hair changes
My hair is thinning dreadfully. I really don't know if I'm going to lose it or it's just going to thin, but it's not just thinning. The texture, it's gone very lightweight and flyaway. It's almost like it's dead. (Aus, F, 60–79, GCA, English/Welsh/Scottish/N. Irish/British—English)
J: Weight gain
I have excessive weight gain. Health-wise, I'm now pre-diabetic. Yeah. So definitely. And mentally also because of my size and my weight. I was never this weight before. So definitely that part could mess with you mentally. (USA, F, 18–39, SLE, Black/African/Caribbean/Black British—Caribbean)
K: High blood pressure
… so what they did um, supplied me err straightaway with err a course of um blood pressure tablets.… I said 'Well why?', and they said 'That's probably the steroids doing that, giving you the high blood pressure'. (UK, M, 40–59, GPA, White, English/Welsh/Scottish/N. Irish/British)
L: Osteoporosis
As a result of, of the duration of my steroids, I have also now got osteoporosis, which is probably the result four years and three months on steroids. (UK F, 60–79, PMR, White Irish)
M: Hot flushes
… when I was on the higher dose of steroids, the side effects, I did get—like my body temperature, I think I got quite hot quite easily. So hot flushes and things like that. (Aus, F, 18–39, GPA, Multiple ethnic background—White, Māori)
N: Fatigue
… my memory [of IV steroids], apart from feeling really awful was my mind just racing and being absolutely exhausted and not able to sleep because your mind doesn't stop, it's goes round and round and you're exhausted and you just end up waking up, if you got any shut-eye at all. (UK, F, 40–59, RA, Other white—Mixed European)
O: Facial changes
I used to feel, I used to see the bloatiness in my face… You can see the difference in your face shape. It's just like your whole face kind of puffs out. (USA, F, 40–59, RA, White Irish)
P: Muscle symptoms
I noticed that perhaps I didn't have a lot of strength in my thigh and buttock muscles… eventually I saw [Consultant]… he said, 'Oh well, you know, possible steroid myopathy'. Well hell's teeth surely he would… he should know. And like he saw that my leg muscles were all weak. (UK, F, 60–79, RA & PMR, White English/Welsh/Scottish/N. Irish/British)
Q: Physical dependence on steroids
I've never been on heroin, but I would say coming off steroids must equate [with] trying to come off, you know, a drug… I knew that in order to get off them it had to be a slow progress. So I did it and reduced them gradually as I could, but it was not comfortable, it was not pain free, and it was difficult. (UK, F, 60–79, PMR, White Irish)
R: Fungal infections
I asked [Doctor], would the steroids give me fungal nail and she said yes. (UK, F, 60–79, PMR, White English/Welsh/Scottish/N. Irish/British)
S: Impact on clothes
… it just is very frustrating because then you have to buy more clothes. I have a wardrobe right now that goes four different sizes as my weight goes up and down and up and down… I love wearing dresses, and in the summertime, I won't do it unless they're long dresses because of the bruising and the scarring on my legs. That's basically where all my bruising and scarring is, so I don't wear shorts during the summer unless I'm on a beach somewhere. (USA, F, 40–59, SLE, White—Other white background)

To preserve the anonymity of participants with often rare diseases, we have chosen to report age ranges rather than specific ages. Aus: Australia (Aus); M: male; F: female; AVN: avascular necrosis; BD: Behçet's disease; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; TA: Takayasu arteritis.

Table 3. Psychological effects of GC therapy

A: Agitation
I was very anxious and agitated and didn't have enough rest. (USA, F, 60–79, GPA, White Spanish/French/German/Russian)
B: Anger or irritation
I was irritable, like I was easy to get annoyed, and I think I actually got annoyed. . . it's like a change in personality. (Aus, F, 60–79, GCA, English/Welsh/Scottish/N. Irish/British—English)
C: Anxiety
It will give you some kind of anxiety. That's what I will say. It will give you anxiety and I would say it could mess with you. (USA, F, 18–39, SLE, Black/African/Caribbean/Black British—Caribbean)
D: Difficulty thinking clearly
. . . that feeling that my brain is just so foggy that I have to concentrate fiercely to function. I just felt like my brain wasn't functioning quite right. I was in a sort of dreamlike haze all the time. (USA, F, 60–79, GPA, White Spanish/French/German/Russian)
E: Mind racing
My memory. . . was my mind just racing and being absolutely exhausted and not able to sleep because your mind doesn't stop, it's goes round and round and you're exhausted. (UK, F, 40–59, RA, Other white—Mixed European)
F: Low mood
It makes you feel down. It makes you feel depressed. You don't want to socialise, because you're not you. (Aus, F, 40–59, inflammatory myositis, Italian)
G: Mood swings
. . . when I was on the higher dose. . . my mood was—sometime I was very angry on something, like little thing and everything. So yeah, the mood swing because of the steroids. (Aus, M, GPA, 18–39, Indian)
H: Paranoid thoughts
I imagined that people were following me and hiding, er, from me and. . . I behaved very strangely. . . . if we went into a restaurant or, or, a café or somewhere, I couldn't stay in there. I kept imagining that people were looking at me. . . it was most strange. (UK, F, 80+, PMR, White English/Welsh/Scottish/N. Irish/British)
I: Pressure of speech
I can't be quiet. I'm just talkative. My mother knows that I'm on it because she's like, yeah, you're going. I'm very talkative. It's like, oh that just prednisone. (USA, F, 18–39, SLE, Black/African/Caribbean/Black British—Caribbean)
J: Risk taking
I already planned out what I was going to do with this money, that money, this money—and somehow I overdraft my bank account by $500. I spent over then what I should. And in 20 years, I've never done that. (USA, F, 40–59, Crystal arthropathy, Black/African/Caribbean/Black; Any other Black/African/Caribbean British)

To preserve the anonymity of participants with often rare diseases, we have chosen to report age ranges rather than specific ages. Aus: Australia (Aus); M: male; F: female; BD: Behçet's disease; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; TA: Takayasu arteritis.

additional psychological burden on patients, who reported needing to weigh up the benefits of GCs *vs* the negative effects on HRQoL. Additional contextual factors identified included the impact of patient education, medical professionals' concerns about GCs and comorbidities. Patients taking GC therapy can have concerns about the increased risk of infection [30], particularly during the COVID-19 pandemic [31], and concerns about secondary conditions, e.g. osteoporosis.

The strengths of this study include sampling participants across a range of rheumatic conditions from three different continents. Participants also had a range of different current GC dosages and treatment durations. The breadth of participant ages and educational levels is a further strength; a potential limitation is that there is a low prevalence rate of those with Asian heritage, and high prevalence of people of white heritage in the UK, which could reduce the variety of reported experiences. A linguistic evaluation has been performed, with adaptations made to the questionnaire items to ensure formal translations into other languages will be possible in the future (Supplementary Data S1, available at *Rheumatology* online). One limitation is that this study was performed with only English-speaking people from the UK, USA and Australia. It is possible that people from other countries or people who speak languages other than English may report different themes of importance in relation to GC impact. Once this tool has been validated for use in these three countries, cross-cultural validation will be required if the tool is to be used in other countries—involving adaptation to ensure conceptual equivalence and validation to confirm psychometric equivalence.

This work will underpin the first generic PROM to measure GC impact from the patients' perspective. A disease-specific GC impact PROM has been developed for lupus: the Systemic Lupus Erythematosus Steroid Questionnaire (SSQ) [32]. The SSQ has been designed using similarly robust methodology, and covers similar domains, tailored specifically for patients with SLE. However, it has not been validated for use in patients with other inflammatory rheumatic diseases and there is a need for an instrument with broader utility across diseases. The Glucocorticoid Toxicity Index (GTI) is a clinician-reported composite outcome measure that assesses GC-relevant outcomes of importance as prioritized by clinicians [33]. It was developed based on the consensus of experts from a broad range of medical specialties. A GC impact PROM will therefore be complementary to the GTI.

This work may also be relevant to patients with non-rheumatic conditions. Study participants were included with a broad range of multi-system diseases, for example patients with respiratory and gastric involvement (see Supplementary Table S3, available at *Rheumatology* online, for patients who reported also taking GCs for non-rheumatic conditions). The themes reported in this study are similar to those observed in qualitative studies on the impact of GCs in asthma and inflammatory bowel disease [34–38]. Cross-condition validation will be required to explore this further, with the potential that a future GC impact PROM may also be acceptable and effective for use in non-rheumatic inflammatory conditions.

If we wish to reduce or mitigate the combined adverse effects of GC therapy on the lives of patients with rheumatic diseases, it is important to be able to measure the patient

Table 4. Impact of GC therapy on participation, impact of GC therapy on relationships, psychological impact of GC therapy, and benefits of GC therapy

Impact of steroids on participation
A: Activities
I find socially I'm reluctant to go out and meeting people except the very close, er, friends.. . . we used to do a lot of socializing, dancing, etc., which I've found now I'm reluctant to do. (UK, M, 60–79, GPA, White English/Welsh/Scottish/N Irish/British)
B: Social life
You don't feel like doing anything. You don't want to socialise because you're not comfortable in yourself. You can't go out with friends and have a coffee with them, because you just don't want to. You don't feel good in yourself. (Aus, F, 40–59, Inflammatory myositis, Italian)
C: Work and education
I felt like I was constantly trying to catch up at work and I was getting behind in my workload. . . But I couldn't, how could I say I feel really, a little bit depressed and I can't sleep, so I don't feel like I can work properly. (UK, F, 18–39, BD, White English/Welsh/Scottish/N. Irish/British)
Impact of steroids on relationships
D: Friends and acquaintances
I think steroids, period, affects your life, your relationships because steroid is an immunosuppressant. So you don't even want to be around other people at that point because you don't even want to get sick. (USA, F, 18–39, Inflammatory myositis, Black/African/Caribbean/Black British—Caribbean)
E: Family
. . . my husband. . . commented that I seemed angry and grumpy, and frustrated and upset. I was like, it's not you, and I'm sorry, I've just had five days of steroid and I feel gross, and I'm tired, and I'm flaring, and I tried to do stuff with the family and it was great, but now I have literally no reserves left. (Aus, F, 18–39, SLE, English/Welsh/Scottish/Northern Irish/British; Australian)
F: Relationship
But the wife will say I'm a little bit moody. Yeah I get, I get angry really quickly. (UK, M, 40–59, Inflammatory myositis, White English/Welsh/Scottish/N. Irish/British)
G: Work relationships
I've just started going back to work. . . I'm client-facing, so I feel quite self-conscious about my face and also it, it's made me put on a lot of weight. So I feel very self-conscious about my weight. (UK, F, 18–39, TA, White English/Welsh/Scottish/N. Irish/British)
Psychological impact of steroid therapy
H: Concern about low immune system
I know it suppresses your immune system to the point where you basically can catch anything, any virus, anything, you could get really ill. (USA, F, 18–39, SLE, Black/African/Caribbean/Black British—Caribbean)
I: Concern about side effects
Because of the severity it has on your body and on your organs and the side effects from it. So the more you take, I think the more damage you do your body. (USA, F, 40–59, RA, White Irish)
J: Concern about secondary condition
You got all types of problems behind it that you never had before. That's the main thing, and they're serious problems. I mean serious problems. The weight gain, pre-diabetic—you could wind up being a diabetic. (USA, F, 18–39, SLE, Black/African/Caribbean/Black British—Caribbean)
K: Concern about use of steroids
Yeah I want to come off the steroids, because I know that they're not doing, long term they're not doing my body any good. (UK, M, 40–59, EGPA, White English/Welsh/Scottish/N. Irish/British)
L: Concern about weight
The problem I don't like with the steroids, is the weight gain and it doesn't matter, even when I, there was stages where I wasn't eating all day, because I, I had to control this weight. (UK, F, 40–59, EGPA, White English/Welsh/Scottish/N. Irish/British)
M: Dealing with increased medication load
I had prednisolone, and then I've got multiple other things to sort of pair with that, just to kind of like, deal with the side effects. (UK, F, 18–39, SLE, White English/Welsh/Scottish/N Irish/British)
N: Feeling dependent on steroids
Your body gets used to getting that extra steroid dose every day, and needs it to, to function properly. . . from a personal perspective, you become very aware of the fact that you feel dependent on something. (UK, M, 40–59, Sarcoidosis, Mixed/Multiple ethnic groups, Mixed White and Asian)
O: Having to weigh up pros and cons
I was very much relying on the prednisolone. So it's as if you know, you can't live without it, but you can't live with it. . . Love 'em or hate 'em, can't do without them, that. . . that's how I look upon these. (UK, F, 60–79, RA & PMR, White English/Welsh/Scottish/N. Irish/British)
P: Impact of appearance change
I then came a bit recluse. I think that's the word. Because I was a bit embarrassed of my appearance, so I just stuck with my family and didn't really do much outside. (Aus, F, 40–59, Inflammatory myositis, Italian)
Q: Loss of sense of self
My big thing with steroids is that they're frustrating because you know it's not your regular personality, you know it's not your regular look. (USA, F, 40–59, SLE, White—Other white background)
R: Low in mood because of steroid therapy
I don't want to take it, because I know what I went through before, and I don't want to go through it again. . . So it's a lot of tears. . . I feel down. I don't want to take them. (Aus, F, 40–59, Inflammatory myositis, Italian)
Benefits of steroids
S: Able to do activities
*The positives were that it worked for me and I regained my hearing, so I was able to function better in day-to-day life. (*Aus, F, 18–39, GPA, Multiple ethnic background—White, Māori)
T: Effective symptom control
Within about two or three days I was already starting to feel a lot better. I actually think it's a bit of a wonder drug, to be honest. Prednisolone anyway. (Aus F, 40–59, Inflammatory myositis, Mediterranean)

(continued)

Table 4. Continued

U: Pain relief
I was in so much pain with the inflammation and everything like, and the swelling, everything was just a relief to get rid of the pain. (UK, M, 40–59, AS, White English/Welsh/Scottish/N. Irish/British)
V: Psychological benefits
. . . it's done wonders for me . . .it has been transformative in that it's made my life very stable, I feel less socially anxious. (UK, M, 40–59, Sarcoidosis, Mixed white and Asian)

To preserve the anonymity of participants with often rare diseases, we have chosen to report age ranges rather than specific ages. Aus: Australia (Aus); M: male; F: female; BD: Behçet's disease; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; TA: Takayasu arteritis.

Table 5. Examples of feedback on the draft questionnaire and actions taken

Questionnaire feedback	Source[a]	Action taken
Item text 'I have felt comfortable with the dose of steroids that I'm taking' was questioned, as the patient experience is more about having to balance the benefits of GCs with the negative effects, so it is not a matter of feeling 'comfortable'	PRP	Item removed
The phrases 'moon face' (as an example of facial appearance change) and 'buffalo hump' (as an example of body shape change) could be perceived as derogatory	PRP	Combined in new item using neutral language: 'I was unhappy with my appearance. . .'
Item on 'functioning well': uncertainty about the reliable understanding of the word 'function'—as opposed to specific example, e.g. 'mobility'	IDWG	Item removed and more specific items and examples retained
Response categories—'rarely' and 'sometimes' were felt to be close in meaning	PRP	Response categories were retained for review in the large-scale survey
The activity 'keeping going' was felt to be vague, particularly when considering future translations	IDWG	Example deleted from the item
'I was able to live my life in the way that I wanted'—felt to be very similar to 'I could do all the things that are important. . .'	CI (UK, USA, Aus)	Item removed
Patients reported that it would be clearer if the instruction 'Please select <u>one</u> answer for each question' came after the stem 'Due to treatment with steroids, during the past 7 days. . .'	CI (Aus)	The stem structure was changed as suggested
'I lived my life to the full'—difficult to translate	LTA	Item removed
In the introduction: 'We are interested in your experience of being treated with glucocorticoids, known commonly as steroids'—difficult to translate into Arabic and IsiXhosa	LTA	'Glucocorticoids' removed; reworded as 'We are interested in your experience of being treated with steroids'
'I felt my underlying condition was under control'—'underlying condition' lacks clarity when translated into Hindi and Simplified Chinese	LTA, PRP	'Underlying condition' changed to 'medical condition' to address identified issues
'I was able to exercise as much as I wanted'—wanting to exercise was perceived to vary over time, particularly during disease flares, and this item could also provoke guilt about not wanting to exercise more. The item 'I could do all the things that were important to me' was preferred	CI (Aus, UK)	Item removed in favour of 'I could do all the things that were important. . .'

[a] Patient research partners (PRP); PRO Item Development Working Group (IDWG)—J.C.R., J.D., S.B.; Linguistic translatability assessment (LTA); Cognitive interviews (CI); Australia (Aus).

impact accurately. Here, we have reported the first stages in the development of a Steroid PRO intended to measure the impact of GCs in a range of rheumatic conditions from the patient perspective. Such a PROM, once developed, might be used to capture patient-relevant outcomes in future randomized controlled trials comparing different GC regimens. It could also have potential value in clinical practice, not only for benchmarking clinical services but also as a communication tool within the patient–clinician encounter [39, 40]. Future work will highlight the impact on patients of taking GCs, and therefore could be used to support shared decision-making processes regarding steroid-reduction and trial of alternative therapies where the impact of GC adverse effects is great.

The next steps will include further refinement and validation of the 40-item draft questionnaire to determine its measurement properties, including reducing the number of items, and determine the final scale structure.

GCs are relatively inexpensive and widely used due to their benefits in controlling inflammation, but their side effects are of clinical concern and can directly impact patients' HRQoL. The ability to measure the life impact of GC therapy in

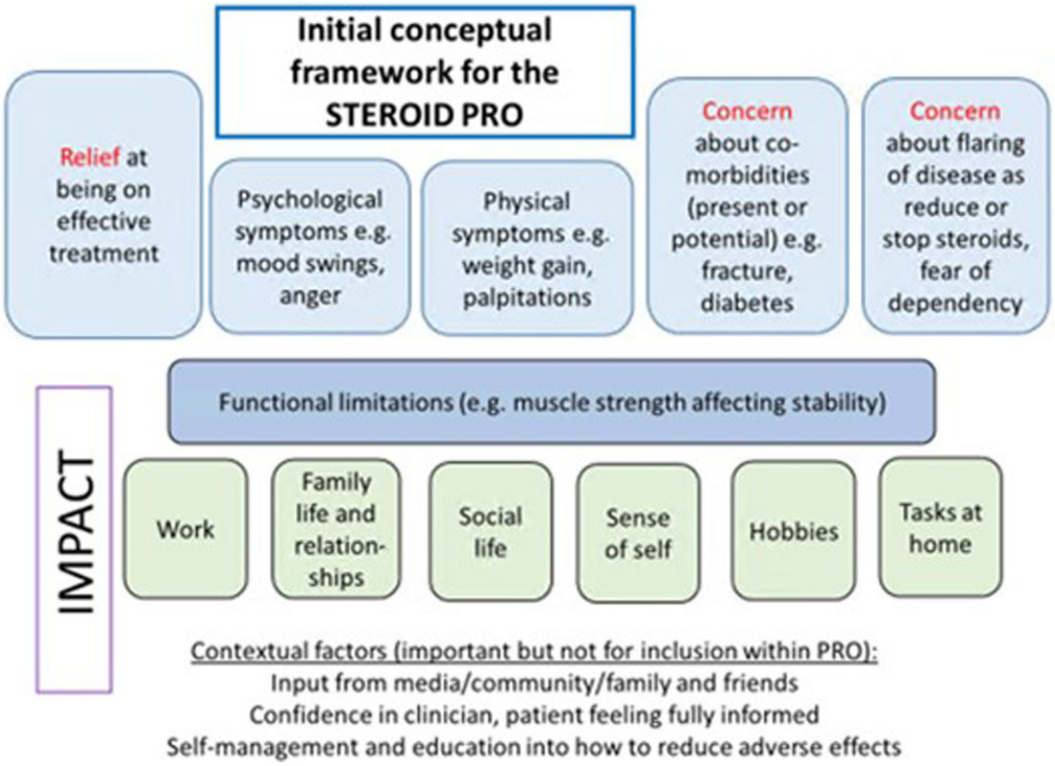

Figure 1. Initial conceptual framework

patients with rheumatic conditions will allow designers of future randomized clinical trials implementing new treatment strategies to measure the extent to which reduction in GC dosing improves HRQoL.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Contribution statement

S.B. contributed to the study design and study materials, analysis of qualitative interviews, conducted cognitive interviews in the UK, drafting and revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. M.A.S. contributed to the study design and study materials, analysis of qualitative interviews, revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. J.D. contributed to the study design and study materials, drafting and revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. P.R. (patient research partner) contributed to the study design and study materials, revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. C.S. (patient research partner) contributed to the study design and study materials, revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. M.N. contributed to the study design and study materials, revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. C.A. contributed to the study design and study materials, analysis of qualitative interviews and revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. R.J.B. contributed to the study design and study materials, revision of the manuscript for intellectual content and approved the final manuscript for submission for publication. J.T.L.C. contributed to the study design and study materials and revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. E.D. contributed to the study design and study materials and revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. N.G. contributed to the study design and study materials and revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. E.A.H. contributed to the study design and study materials, conducting of cognitive interviews at Australia site and revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. S.L. contributed to the study design and study materials and revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. I.N.-M. contributed to the study design and study materials, was study coordinator in USA, revised the manuscript for intellectual content, and approved the final manuscript for submission for publication. D.P.-F. contributed to the study design and study materials, was study coordinator in Australia, revised of the manuscript for intellectual content, and approved the final manuscript for submission for publication. C.R.

contributed to the study design and study materials, was study coordinator in Australia, revised the manuscript for intellectual content, and approved the final manuscript for submission for publication. J.T. contributed to the study design and study materials and revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. K.Y. contributed to the study design and study materials, conducted cognitive interviews in USA, revised the manuscript for intellectual content, and approved the final manuscript for submission for publication. S.L.M. contributed to the study design and study materials and revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication. S.G. was the lead investigator for the USA site, contributed to the study design and study materials, revised the manuscript for intellectual content, and approved the final manuscript for submission for publication. C.H. was the lead investigator for the Australia site, contributed to the study design and study materials, revised the manuscript for intellectual content, and approved the final manuscript for submission for publication. J.C.R. was the Chief Investigator, designed the study and study materials, led the grant application, oversaw the project and interpretation of the results, analysis of qualitative interviews, and drafting and revision of the manuscript for intellectual content, and approved the final manuscript for submission for publication.

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