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# The Prediction and Monitoring of Toxicity Associated with Long-Term Systemic Glucocorticoid Therapy

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## Abstract

Glucocorticoids are often required for adequate control of inflammation in many serious inflammatory diseases; common indications for long-term treatment include polymyalgia rheumatica, giant cell arteritis, asthma and chronic obstructive pulmonary disease. Long-term glucocorticoid therapy is, however, associated with many adverse effects involving skin, gastrointestinal, eye, skeletal muscle, bone, adrenal, cardio-metabolic and neuropsychiatric systems. This balance between benefits and risks of glucocorticoids is important for clinical practice and glucocorticoid-related adverse effects can significantly impair health-related quality of life. Understanding the nature and mechanisms of glucocorticoid-related adverse effects may inform how patients are monitored for toxicity and identify those groups, such as older people, that may need closer monitoring. For clinical trials in diseases commonly treated with glucocorticoids, standardised measurement of glucocorticoid-related adverse effects would facilitate future evidence synthesis and meta-analysis.

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## Keywords

Glucocorticoids

Adverse effects

Giant cell arteritis

Polymyalgia rheumatica

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## Introduction

The glucocorticoids (GCs) are steroid hormones produced by the adrenal cortex. A certain constitutive level of circulating cortisol (endogenous GC) is required to maintain health. Cortisol levels increase during the physiological stress response, eliciting a multitude of systemic effects. Although the effects of the stress response may be adaptive in the short term, the elevation of GC levels is deleterious over the longer term. Overproduction of cortisol results in characteristic multi-system effects including hypertension, diabetes, accelerated atherosclerosis, electrolyte disturbance, fat redistribution, osteoporosis, skin

thinning, impaired healing and muscle wasting (Table 1).

**Table 1**

**Q1**

Risk factors and monitoring tests for glucocorticoid-related adverse effects

GC-related adverse effects: organ system	Effects	Risk factors	Possible monitoring tests or intervention
Skin	<ul style="list-style-type: none"> <li>– Thinning</li> <li>– Bruising</li> <li>– Impaired healing</li> </ul>	<ul style="list-style-type: none"> <li>– Older age</li> <li>– Comorbidities (diabetes or where skin integrity is compromised)</li> <li>– High cumulative <b>doseGC dose</b></li> </ul>	<ul style="list-style-type: none"> <li>– Confocal laser microscopy</li> <li>– Ultrasound</li> <li>– Evaporimetry</li> <li>– Optical coherence tomography</li> <li>– Dermaphot® imaging</li> </ul>
Gastro-intestinal	<ul style="list-style-type: none"> <li>– Ulceration</li> <li>– Impaired healing</li> </ul>	<ul style="list-style-type: none"> <li>– Older age</li> <li>– Cotreatment with NSAIDs</li> <li>– High daily and cumulative <b>doseGC dose</b></li> </ul>	<ul style="list-style-type: none"> <li>– Haemoglobin levels<sup>a</sup></li> <li>– Prophylactic gastroprotective treatment if clinically indicated<sup>a</sup></li> </ul>
Eye	<ul style="list-style-type: none"> <li>– Cataract</li> <li>– Glaucoma</li> </ul>	<ul style="list-style-type: none"> <li>– Older age</li> <li>– High cumulative <b>doseGC dose</b></li> </ul>	<ul style="list-style-type: none"> <li>– Eye examination including tonometry<sup>a</sup></li> </ul>
Skeletal muscle	<ul style="list-style-type: none"> <li>– Myopathy</li> </ul>	<ul style="list-style-type: none"> <li>– Older age</li> <li>– Physically inactive</li> <li>– High cumulative <b>doseGC dose</b></li> </ul>	<ul style="list-style-type: none"> <li>– Muscle strength testing</li> <li>– Muscle biopsy</li> <li>– CT/MRI scan for muscle cross sectional area</li> <li>– Patient questioning</li> </ul>
Bone	<ul style="list-style-type: none"> <li>– Osteoporosis</li> <li>– Osteonecrosis</li> </ul>	<ul style="list-style-type: none"> <li>– Older age</li> </ul>	<ul style="list-style-type: none"> <li>– Bone mineral density<sup>a</sup></li> <li>– Bone protection therapy<sup>a</sup></li> </ul>
Adrenal	<ul style="list-style-type: none"> <li>– Suppression of endogenous GC production</li> </ul>	<ul style="list-style-type: none"> <li>– Basal cortisol levels &lt;386 nmol/L</li> <li>– Total GC dose &gt;8.5 g</li> <li>– GC treatment duration</li> </ul>	<ul style="list-style-type: none"> <li>– Slow reduction in GC dose<sup>a</sup></li> <li>– ACTH stimulation test</li> </ul>

		>19 months	
Metabolic	<ul style="list-style-type: none"> <li>– Diabetes</li> <li>– Weight gain</li> <li>– Hyperglycaemia</li> </ul>	<ul style="list-style-type: none"> <li>– Older age</li> <li>– Cumulative <del>dose</del>GC dose <math>\geq 1.8</math> g</li> <li>– Female</li> <li>– Family history</li> </ul>	<ul style="list-style-type: none"> <li>– Fasting blood glucose test<sup>a</sup></li> <li>– Oral glucose tolerance test<sup>a</sup></li> <li>– Weight and height<sup>a</sup></li> </ul>
Cardiovascular disease	<ul style="list-style-type: none"> <li>– Accelerated atherosclerosis</li> <li>– Hypertension</li> <li>– Hypercholesterolaemia</li> </ul>	<ul style="list-style-type: none"> <li>– High cumulative <del>dose</del>GC dose</li> <li>– Presence of CVD risk factors prior to GC therapy</li> <li>– Hypertension</li> </ul>	<ul style="list-style-type: none"> <li>– Screening for hypertension pre-GC treatment<sup>a</sup></li> <li>– Blood pressure</li> <li>– Lipid profile</li> </ul>
Neuropsychiatric	<ul style="list-style-type: none"> <li>– Anxiety</li> <li>– Depression</li> <li>– Psychosis</li> </ul>	<ul style="list-style-type: none"> <li>– <del>Women</del>Female</li> <li>– Alcoholism</li> <li>– Family history of depression</li> <li>– High <del>dose</del>GC dose</li> </ul>	<ul style="list-style-type: none"> <li>– Patient questioning<sup>a</sup></li> <li>– Questionnaires</li> <li>– Pharmacotherapy</li> </ul>
Infection	<ul style="list-style-type: none"> <li>– Impaired neutrophil function</li> </ul>	<ul style="list-style-type: none"> <li>– Additional immunosuppressive treatments</li> </ul>	<ul style="list-style-type: none"> <li><del>None</del>– None</li> <li><del>Low</del>– Low threshold of suspicion for investigation of sepsis</li> </ul>

<sup>a</sup>See clinical practice guidelines from EULAR and/or BSR

Exogenous GCs have been utilised since the 1950s [ 1 ] for their potent immunosuppressive and anti-inflammatory effects; the most commonly prescribed oral GC is prednisolone or its pro-drug prednisone. Long-term GC therapy is associated with many adverse effects (AEs) that are often related to daily or cumulative GC dose; hence, the development of ‘steroid-sparing’ agents for many autoimmune rheumatic diseases, such as rheumatoid arthritis (RA). Although steroid-sparing agents have substantially reduced the amount of GCs prescribed in RA, low-dose GC therapy is still commonly used as part of combination therapy [ 2 ]. For polymyalgia rheumatica (PMR) and giant cell arteritis (GCA), however, GCs are still the cornerstone of therapy and often given as monotherapy. The short-term benefit of GCs in controlling the inflammatory disease is traded off against the risk of AEs (and resulting impact on health-related quality of life; HRQoL) in the longer term. Many GC-related

AEs are very costly; e.g. \$18,357.90 for a bone fracture per year per episode [3]. Measurement of GC-related AEs, and their impact on patients, is important for establishing both the overall clinical effectiveness and the cost-effectiveness of any treatment strategies intended to reduce total GC exposure. Reducing GC-related AEs is also an important part of the rationale for developing novel diagnostics for GCA and PMR, as well as other serious diseases requiring long-term GC therapy.

## Glucocorticoid-Related Adverse Effects

It is difficult to quantify the precise risk of GC-related AEs because of confounding by indication: because of the greater burden of inflammation, patients with more severe disease are both more likely to receive higher doses of GCs, and at greater risk of complications such as accelerated atherosclerosis and myopathy. These complications could be due to the disease as well as due to GCs. Here we use the term ‘GC-related’ AE to acknowledge this potential confounding, in contrast to ‘GC toxicity’ by which we mean the toxicity directly caused by GCs.

Although single randomised controlled trials (RCTs) are not usually powered to detect significant reductions in any particular GC-related AE, if a common set of secondary outcome measures (core outcome measurement set) were employed across all RCTs for a particular condition, meta-analysis may provide rich information that could inform clinical practice [4]. Indeed, there have been recent proposals for ‘core adverse events’ to be considered in formulating core outcome measurement sets in some disease areas [5]. It may even be possible to meta-analyse across different indications [6]. In order to select the most meaningful outcome measures, however, it is necessary to understand the nature and pathophysiology of GC toxicity. Here, rather than producing an exhaustive review, we focus on the AEs that are not so well covered by existing guidelines: skin, wound healing and gastric ulcers, eye, myopathy, bone, adrenal suppression, diabetes mellitus, weight gain, cardiovascular disease, neuropsychiatric, and infection.

## Nature and Pathophysiology of Glucocorticoid Toxicities

## Skin

The cutaneous manifestations of GC excess include telangiectasiae, atrophic striae, easy bruising, poor wound healing, increased transepidermal water loss and skin thinning [7, 8]. Skin thinning was reported in 85 % of young hypercortisolaemic patients and is a characteristic factor that suggests Cushing's syndrome rather than simple obesity [9]. The mechanisms of GC toxicity to the skin include reduced epidermal keratinocyte/dermal fibroblast proliferation, impaired collagen processing and decreased extracellular matrix protein/epidermal lipid expression [10, 11].

Effects of GC on the skin can include dryness, itching, burning and eczema [12]. In a survey of patients receiving oral GC therapy for 60 days or more, 60 % of participants reported skin changes that were bothersome [13]. Skin changes can have substantial psychological effects and therefore affect patients' HRQoL [14]. Current EULAR recommendations do not advocate routine monitoring of skin thinning for low-dose oral GCs taken for less than 6 months [2, 15]. However, although skin thinning/bruising was reported by 70 % of GC users receiving  $\geq 10$  mg prednisone daily for 18 months, skin thinning/bruising and acne were also significantly associated with longer durations of low-dose ( $\leq 7.5$  mg/day prednisone) GC treatment [13]. In a survey of 213 asthma specialists, skin thinning/bruising was the second most frequently reported AE relating to inhaled GC use, particularly in older patients [16]. Besides age, other risk factors for GC-related skin toxicity include comorbidities such as diabetes [17] where skin integrity is already compromised [18, 19].

Given the paucity of detailed data on skin changes in those taking GCs for rheumatic disease, it is suggested that skin thinning is assessed in future RCTs in this area. Methods to accurately evaluate GC-induced skin atrophy include confocal laser microscopy, ultrasound, optical coherence tomography (OCT) and evaporimetry [20, 21]. Although readily accessible, the Dermaphot® imaging and scoring system is more subjective and less sensitive than OCT for detection of subclinical epidermal thinning [20] with feasibility limited to monitoring visible GC-related skin AE such as telangiectasias.

There is the potential to use topical agents to reduce the unwanted effects of GCs on the skin [22]; 'steroid-sparing' (immunosuppressive or

immunomodulatory) agents may be given either topically or systemically [23]. Selective GC receptor agonists (SEGRAs) have also been suggested for topical use [24], but no clinical trial data are yet available.

## Wound Healing and Gastric Ulcers

Chronic wounds and associated infections represent a substantial economic burden, costing the US >\$25 billion annually and particularly affecting older people [25]. GCs disrupt multiple signalling pathways that are delicately orchestrated during normal repair, causing dysregulation of intercellular cross-talk, proliferation, differentiation, migration, re-epithelialisation and extracellular matrix remodelling [10, 26, 27]. Gastric ulceration is an important GC-related AE, particularly in individuals co-prescribed non-steroidal anti-inflammatory drugs (NSAIDs) [10, 28]. Older patients are at higher risk of delayed wound healing [29, 30], suggesting that this group may require greater caution. Even low-dose prednisone is associated with gastric ulceration when taken in the long term, although some of the data pre-dates widespread use of modern gastroprotective therapy [31]. Since wound healing and peptic ulcers are important to both patients and rheumatologists [32], EULAR recommendations advise routine monitoring (e.g. checking haemoglobin levels) in patients exposed to long-term GC therapy and prophylactic gastroprotective treatment (e.g. proton pump inhibitors) where necessary [15]. However, gastroprotective treatment remains underused in older patients prescribed GC therapy in the community [33].

## Eye

Cataract and glaucoma constitute a significant burden on national healthcare costs [34]. Cataract surgery costs €700 per eye in Europe [35] and €5000 per quality-adjusted life year gained with both eyes operated on [36]. For glaucoma, the annual average cost per patient is €700–1000 based on disease severity [37].

GC therapy is associated with both cataract (particularly posterior subcapsular cataract) and glaucoma [28, 35]. In a study using the national database of the German Collaborative Arthritis Centre, the prevalence of self-reported cataract was higher for any GC users (including those taking <5 mg prednisone daily) whereas the prevalence of self-reported glaucoma was only increased in those

taking >7.5 mg daily [38]. In a nested case-control analysis within a historic RA cohort, long-term, low-dose prednisone treatment was significantly associated with development of cataract [31].

Recommendations regarding ocular monitoring for GC toxicity vary. Previous EULAR recommendations advise baseline screening and ongoing monitoring for both cataract and glaucoma in patients receiving GCs for rheumatic disease [39], but for low-dose GC therapy only baseline screening for glaucoma is recommended [15]. For patients with systemic lupus erythematosus (SLE) receiving long-term GC therapy, at least a baseline eye assessment is recommended [40]. However, a chart review of 170 patients with SLE taking long-term GC therapy revealed that 20 % had never undergone an eye assessment; of those who had ever had an eye assessment, 29 % had cataract and 3 % glaucoma; development of cataract was associated with age, disease duration and cumulative GC dose [34].

Limitations of routinely collected clinical data such as this include screening/detection bias: both over-detection (since cataract is extremely common in older people) and under-detection (for example, in the UK ocular monitoring tends to be carried out by opticians, but intraocular pressure monitoring is not funded except in those with defined risk factors for glaucoma; consequently, tonometry is not always performed). Since both glaucoma and cataract are readily treatable, there are strong arguments for implementation of systematic ocular screening in long-term GC therapy.

## Myopathy

GC-induced myopathy typically affects the proximal skeletal muscles and is characterised by weakness and atrophy [41]. Multiple complex mechanisms are involved [42]. GCs inhibit the pathways involved in protein synthesis, such as transportation of amino acids into the muscle, and also increase muscle proteolysis through the ubiquitin/proteasome pathway. Both patients with rheumatic diseases on GC therapy and rheumatologists listed myopathy amongst the top 10 most worrisome GC-induced AE [32].

GC-related myopathy can be difficult to distinguish clinically from the symptoms and consequences of rheumatic diseases themselves, such as atrophy

related to muscle disuse. In GCA patients receiving high-dose oral GCs, myopathy was listed as an AE in 3/39 patients in a 2-year trial [43] but in 0/27 patients in a 78-week trial [44]. Yet in a third trial, 20/21 GCA patients reported 'subjective muscle weakness' [45]. In an observational study of patients with PMR using the Rochester Epidemiology Project database, 6/232 (2.6 %) patients with PMR had myopathy (5/175 of those receiving GCs and 1/57 of those receiving NSAIDs only); myopathy was defined as 'physician's diagnosis supported by documented proximal muscle weakness' [46]. Interpretation is hampered by the lack of standardised definitions and monitoring for GC-related myopathy in clinical practice. EULAR only recommends that GC-related muscle weakness should be assessed 'through questioning' at the start and end of the treatment in clinical trials [15]. It is unclear whether this is a sufficiently sensitive monitoring method.

Muscle strength tests that have been used to assess weakness in patients receiving GCs include maximum voluntary contraction of the quadriceps [47]. Functional tests include the stepper test (number of steps completed in 10 s), although reliability and variability data is limited [48]. Muscle biopsies arguably represent a gold standard for tissue changes, with characteristic changes of GC myopathy including reduced cross-sectional area of type II muscle fibres, in contrast to disuse atrophy which preferentially affects type I fibres [47]. However, there are logistical difficulties in obtaining muscle biopsies; imaging is a logical alternative for measuring muscle atrophy. In a small study, CT and MRI gave equivalent results for detecting a reduction in mid-thigh muscle cross-sectional area (CSA) following 20–60 mg/day GC treatment [49]. Higher cumulative GC doses are associated both with reduced muscle strength [50] and with reduced mid-thigh muscle CSA [49]. Other risk factors for GC-related myopathy include older age and physical inactivity [51]. Strategies for treating GC-related myopathy, if detected, include GC dose reduction if possible [50] and exercise programmes [52, 53].

## Bone

Osteoporosis is frequently highly ranked as a GC-mediated AE of significant concern to both patients and clinicians [13, 32]. Bone mineral density (BMD) decreases even with low-dose GCs [54, 55] and fracture risk increases with cumulative GC therapy [13]. Fractures are associated with substantial

morbidity and associated healthcare costs [56], particularly in the elderly [57]. Current recommendations advise assessment of risk factors for osteoporosis/fracture, for example by using the FRAX tool; while there is good evidence for several pharmacological treatments such as bisphosphonates [58••], this type of high-level evidence was not available recommendations regarding monitoring and for non-pharmacological treatments [59].

GC-mediated osteoporosis results largely from decreased bone formation, in contrast to postmenopausal osteoporosis which is characterised by increased bone turnover [60]. GCs inhibit osteoblast activity and direct osteoblast precursor cell differentiation towards adipogenesis rather than osteoblastogenesis [61, 62]. Concomitantly, osteoclast differentiation is promoted while apoptosis is suppressed [63], leading to decreased bone mass, impaired bone microstructure and increased fracture risk.

A recent systematic review of observational studies of long-term oral GC therapy found that in over 80 % of these studies, fewer than 40 % of patients received BMD testing or bone-protecting pharmacotherapy [64].

## Adrenal Suppression

Adrenocorticotrophic hormone (ACTH) is released from the anterior pituitary gland and stimulates cortisol synthesis in the adrenal cortex. Cortisol acts via the GC receptor in a physiological negative-feedback loop on the hypothalamo-pituitary-adrenal (HPA) axis to inhibit further cortisol synthesis [65].

Exogenous GCs inhibit the HPA axis in the same way [10]. Long-term GC treatment may cause sustained low ACTH levels, leading to adrenal atrophy [66]. GC-related adrenal suppression may cause clinically significant adrenal insufficiency in the face of physiological stressors such as intercurrent illness or surgery [67].

About half of patients receiving long-term GCs fail an ACTH stimulation test, which measures cortisol levels following injection with synthetic ACTH [68, 69]. A large longitudinal study conducted between 1984 and 2009 found that 49 % of GCA patients failed an ACTH test when their GC dose reached 5 mg/day [68]. Amongst these patients, it took a mean duration of 14 months for adrenal function to return to normal. Moreover, in RA patients prescribed

low-dose GC treatment (7.5 mg/day prednisolone) for 3 months, cortisol levels pre-, 30 min post- and 60 min post-ACTH test were reduced by 28%, 34% and 35 %, respectively [69]. EULAR does not currently recommend monitoring adrenal function in routine clinical practice during either low- or high-dose GC treatment [15, 70]. However, it is recommended that in patients taking >7.5 mg prednisolone-equivalent daily for >3 weeks, clinicians should be aware of the risk of adrenal suppression and that a slow reduction in dose should be followed prior to cessation [70••]. Risk factors for iatrogenic adrenal suppression in one study included a total GC dose >8.5 g, a duration of treatment >19 months and basal cortisol levels <386 nmol/L [68]. However, interpretation of ACTH stimulation test results and definition of what is a clinically significant suppression is not always straightforward. The low-dose ACTH test (1 µg of tetracosactide) is more sensitive than the standard 250 µg test [71, 72]. Suggestions for screening for iatrogenic adrenal suppression have been published elsewhere [73••].

## Diabetes Mellitus

Diabetes mellitus (DM) is the top most worrisome GC-related AE amongst rheumatologists and third most worrisome amongst patients with rheumatic diseases [32]. Insulin resistance (IR) precedes development of DM and is induced by GCs via several mechanisms [74]. These include increased transactivation of gluconeogenesis enzymes which increase hepatic glucose synthesis and glycogen deposition. This results in hyperglycaemia [10], inhibition of insulin signalling in fat, liver and muscle cells by suppression of insulin receptor substrate transcription [74], pancreatic β-cell dysfunction mediated via the GC receptor [75] and increased proteolysis and lipolysis, causing increased release of amino acids and free fatty acids [74]. Given that DM can cause further health complications and increased mortality [76], the prevention of this GC-mediated condition is crucial.

Evidence suggests that the risk of developing DM is dose dependent, with few events of GC-induced DM reported in patients on low-dose GCs [15, 77] but more in patients on medium- and high-dose GCs. In two separate studies, 7/124 of PMR patients and 2/40 of RA patients receiving an average daily dose of 10 mg prednisolone/day developed DM [46, 78]. Moreover, 7/19 of GCA patients on high-dose GCs developed DM, and a further 2/19 developed glucose

intolerance [43]. High-dose GCs induced DM in 16/127 of patients with SLE [79].

According to EULAR recommendations, patients with rheumatic diseases taking long-term or high-dose GC should be monitored by measuring fasting blood glucose levels and through an oral glucose tolerance test (OGTT) at the start and end of therapy [15, 70••]. In PMR and GCA, the British Society for Rheumatology (BSR) simply recommends 3-monthly glucose testing [80, 81]. If a patient already has diabetes or pre-diabetes at the start of GC therapy, very careful monitoring should be implemented during treatment. Older patients and those with a family history of DM appear to be at increased risk [46, 79].

## Weight Gain

Weight gain affects about 80 % of patients receiving long-term high-dose GCs [13]. A study of low-dose GC reported weight gain in fewer (4/93) patients [77]. Weight gain contributes to the risk of GC-induced DM [74]; EULAR and the BSR recommend monitoring weight during follow-up [15, 80, 81]. For patients with rheumatic diseases, weight gain ranks highly amongst worrisome GC-related AE [32] and anecdotally can have a major impact on HRQoL. It is unknown whether patients' concern of weight gain reduces adherence to GC therapy.

## Cardiovascular Disease

Cardiovascular disease (CVD) is associated both with inflammatory rheumatic disease and with GC therapy [82–85], and is of major concern to patients and rheumatologists [32]. Cardiovascular events (CVE) are associated with cumulative GC dose [86], but clinical trials data on low-dose GCs in RA appear reassuring, at least over the short term [77, 78, 86, 87]. EULAR recommend that carotid intima-media thickness (IMT; an indicator of atherosclerosis) should be measured at the start and end of clinical trials [15], although this is problematic in GCA/PMR since active GCA may itself cause an increase in IMT [87]. Analysis of routinely collected clinical data [88] may yield more precise estimates of the magnitude of elevated risk of CVE in GC-using versus non-GC-using patients with rheumatic disease, but this does not address the problem of confounding by indication (i.e. disease severity, which is difficult to measure precisely). Furthermore, in GCA, the disease itself might

directly cause CVE [89]. EULAR and the BSR recommend screening for hypertension and other CVD risk factors prior to commencing GC therapy in all patients with inflammatory diseases [15, 70, 81]. It could be argued that patients receiving long-term GCs should have a lower threshold for starting cholesterol-lowering medication, but this must be balanced against the burden of polypharmacy for patients.

## Neuropsychiatric

GC treatment has been associated with anxiety, depression, mood swings, sleep disturbances and psychosis, but prediction is difficult. Regarding low-dose GC, the existing data appear reassuring [78, 90, 91] and it is important to bear in mind the benefits of effectively treating disease; depression may be ameliorated by low-dose GCs in RA [77]. In contrast, patients receiving high-dose GCs appear more likely to experience neuropsychiatric symptoms, although confounding by indication limits interpretation of existing data. In a meta-analysis, psychosis and mood swings were the most common GC-related AE (20 %) in RA, PMR and inflammatory bowel disease patients [92]. The data, however, are plagued by inconsistency in defining and assessing neuropsychiatric AEs, and the severity of the reported neuropsychiatric AE is often unclear [43–45]. In clinical trials, standardised assessment tools would add valuable data. A recent study identified that diabetic women taking GCs were twice as likely to report depressive symptoms as those not taking GCs, when assessed using the Hospital Anxiety and Depression Scale [93]. Neuropsychiatric disturbances can occur as early as the first week of GC treatment or even after treatment has ceased [94]. If suspected, a reduction in GC dose is recommended (if possible) and pharmacological intervention may also be warranted [94].

## Infection

Infections are less common in RA patients receiving low-dose GC: 3–32 % [77, 78, 91] compared to older patients being treated for PMR or GCA 10–52 % [43, 46, 95]. With GC treatment, neutrophils show reduced adhesion to endothelial monolayers [96]. Laboratory analysis of blood samples from GC-treated patients tends to reveal a high neutrophil count since the GCs cause the neutrophils to demarginate. Detection of sepsis can also be delayed because of

these GC-induced changes in neutrophil count and because GCs inhibit the febrile response to infection. Patients receiving GCs should undergo the same precautions as those taking other immunosuppressants, such as vaccination and a low threshold of suspicion of infection [70••]. Older age and other GC-related complications such as DM, skin thinning and impaired healing are likely to confer additional risk.

## Health-Related Quality of Life and Utility

While it may be important for trials of GC-sparing agents to accurately measure every possible GC-related AE (Table 1), this is unlikely to be feasible for large pragmatic trials or for longitudinal observational studies of representative patients with GCA/PMR because the burden of assessments might be too great for older, frailer patients. Any core adverse events outcome measurement set relating to GC therapy would need to take feasibility and parsimony into consideration.

When modelling the clinical and cost-effectiveness of novel diagnostics or therapeutics where ‘steroid-sparing’ is a major aim, it is challenging to separately include every GC-related AEs, and all of their consequences on patients’ health state and health care utilisation. However, rheumatology registries (e.g. BSRBR, ACR RCR, etc.) and triallists could consider collecting HRQoL data that would reflect GC therapy as well as disease-related AEs. This would be attractive because it would incorporate the trade-off between medication benefits and AEs that is well understood by patients undergoing treatment. Any instrument measuring HRQoL specifically in GC-treated diseases would require robust qualitative work as a foundation. Until such instruments are developed, established HRQoL instruments such as the EQ-5D available from [www.euroqol.org](http://www.euroqol.org) [97] or the SF-6D available from <https://www.shef.ac.uk/scharr/sections/heds/mvh/sf-6d> [98] could be employed to capture the combined impact of all GC-related AE in a particular population. EQ-5D is the most commonly used HRQoL instrument and has been found to be a responsive measure in detecting deterioration in health in a number of health conditions including RA [99]. SF-6D is generated from the SF-36 or the SF-12 questionnaires, which are widely used in clinical studies as a measure of general health, and have been shown to be appropriate for patients with RA [100, 101]. The descriptive systems of both EQ-5D and SF-6D capture overall health and

should incorporate both health benefits and adverse events. EQ-5D was shown to identify adverse events to drug therapy and comorbidities [ 102, 103 •] while condition-specific health measures could not [ 104 ]. Another advantage of those HRQoL instruments is that they can be used to generate utility and ultimately quality-adjusted life years, which is the primary outcome for economic evaluation in the NICE reference case [ 105 ]. The combination of answers to EQ-5D (or respectively SF-6D) leads to a health profile that can be converted into a utility using standard weights representing a societal valuation of quality of life on a preference-based utility scale. The utility represents patients' overall quality of life and when multiplied by the time spent in each health state it generates quality-adjusted life years (QALYs). The way AEs are effectively incorporated in HRQoL as well as the relationship of AEs and health care utilisation still needs further analysis [ 106 ]; systematically collected HRQoL data could be combined with costs data to determine cost-effectiveness using a decision analysis model. This may yield important information to support the use of 'steroid sparing' therapies when both treatment arms achieve similar levels of inflammatory disease control.

## Conclusions

GC therapy is widespread and its risks are well known, although many of these risks are difficult to accurately quantify from current published data. The common theme is that risks of almost all GC-related AE increase with age. Data from clinical trials in RA cannot necessarily be extrapolated to infer risks of GC therapy in older people with PMR or GCA. Monitoring and mitigation of these GC-related AE requires an understanding of the pathophysiological mechanisms involved. The variations in arrangements for monitoring of the AEs of long-term GC therapy contrasts with the comparatively rigid protocols developed for monitoring of GC-sparing agents such as methotrexate, which are generally considered safer than long-term GCs. Development and economic evaluation of any novel diagnostic and therapeutic strategies to reduce GC-related AE will require careful selection of relevant, validated outcome measures that capture the impact of GC-related AE on HRQoL in order to facilitate robust clinical and cost-effectiveness evaluation.

## Compliance with Ethics Guidelines

*Conflict of Interest* Emma Harris, Ana Tiganescu, Sandy Tubeuf and Sarah Louise Mackie declare no conflicts of interest.

*Human and Animal Rights and Informed Consent* This article does not contain any studies with human or animal subjects performed by any of the authors.

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