

# **EULAR evidence based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT).**

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**ABSTRACT:**

**OBJECTIVES:** To develop evidence based recommendations for the management of systemic glucocorticoid (GC) therapy in rheumatic diseases.

**METHODS:** The multidisciplinary guideline development group from 11 European countries, Canada and the USA consisted of 15 rheumatologists, 1 internist, 1 rheumatologist-epidemiologist, 1 health professional, 1 patient and 1 research fellow. Each participant contributed up to 10 propositions describing key clinical points concerning the use of GCs. The final recommendations were agreed using a Delphi consensus approach. A systematic literature search of PUBMED, EMBASE, CINAHL, and Cochrane Library was used to identify the best available research evidence to support each of the propositions. The strength of recommendation was given according to research evidence, clinical expertise and perceived patient preference.

**RESULTS:** The 10 propositions were generated through three Delphi rounds and included patient education, risk factors, adverse effects (AEs), concomitant therapy (i.e. non-steroidal anti-inflammatory drugs (NSAIDs), gastroprotection and cyclo-oxygenase-2 selective inhibitors (coxibs), calcium and vitamin D, bisphosphonates), and special safety advice (i.e. adrenal insufficiency, pregnancy, growth impairment). Of the 10 propositions, only 3 propositions were fully supported and 2 were partially supported by research evidence. The remaining propositions were supported by circumstantial evidence and/or by expert opinion alone. The strength of each recommendation differed according to level of evidence and clinical expertise.

**CONCLUSION:** Ten key recommendations for the management of systemic GC-therapy were formulated using a combination of systematically retrieved research evidence and expert consensus. For all propositions the evidence was evaluated and the strength of recommendation was provided. There are areas of importance that have little evidence (i.e. dosing and tapering strategies, timing, risk factors and AE-monitoring, perioperative GC-replacement) and need further research; therefore also a research agenda was formulated.

## **INTRODUCTION:**

Since 1948, glucocorticoids (GCs) have been widely used in medicine.<sup>1</sup> Although GCs soon became associated with the occurrence of adverse effects (AEs), they are still the most frequently used anti-inflammatory and immune-suppressive drugs in rheumatic diseases. Arguments against the use of GCs are often based on fear for toxicity, which originated in observations of AEs seen in patients using high doses of GCs. High dose is defined as higher than 30 mg prednisolone or equivalent, medium dose is defined as higher than 7.5 mg up to (and including) 30 mg, and low dose is defined as doses up to 7.5 mg.<sup>2</sup> Prednisolone and prednisone are the most commonly used GCs, but not the most potent one, i.e. methylprednisolone is 1.25 times as potent as prednisolone, and betamethasone and dexamethasone are about 6 times as potent.<sup>2</sup> Recent studies demonstrated the disease modifying potential of low dose GCs in rheumatoid arthritis (RA) and this has renewed the debate on the risk-benefit ratio of this treatment.<sup>3</sup> Current literature on the risk-benefit ratio of GCs is nevertheless inconsistent, and inappropriate use of GCs could lead to increased toxicity;<sup>4</sup> this emphasizes the need for clear statements on proper use of GCs. In addition, patients' perspective on toxicity might differ from physicians' perspective. Hence, a EULAR task force on GCs, including a patient, was formed to develop evidence based recommendations, to provide a tool for the better use and management of GC-therapy in rheumatic diseases.

## **METHODS:**

### **Participants**

The Taskforce on GCs is a multidisciplinary guideline development committee, which was endorsed by EULAR-ESCISIT. Twenty experts in the field of GCs (15 Rheumatologists, 1 Internist, 1 Rheumatologist-Epidemiologist, 1 Health Professional, 1 patient and 1 research fellow) from 11 European countries, Canada and the USA, participated in the process. The objectives were 1) to agree on 10 key propositions related to the safe use of GCs; 2) to identify and critically appraise research evidence for the risk-benefit ratio of GC-treatment; 3) to generate recommendations based on the best available evidence.

### **Experts' consensus and Delphi rounds**

As a first step, a general systematic search was performed aimed at identifying the current available follow-up studies in rheumatic disease populations which used low-to-medium dose GCs (up to 30 mg prednisolone or equivalent<sup>2</sup>) and reported AEs (appendix 1). This general systematic search was done of the literature published between 1966 and early 2006 using the Pubmed, Embase, and CINAHL databases. The results of this search were raw data, not corrected for disease activity or co-morbidity, and were reported at the first group meeting of the committee to facilitate the group discussion. Thereafter, each participant independently contributed up to 10 propositions related to key clinical aspects in the use of GCs in rheumatic diseases. The Delphi technique was used to reach consensus on the propositions, as follows. The initial propositions were assembled into a list and overlapping propositions were combined. The list was returned to the experts and they were asked to select the 10 most important propositions from the list. A proposition was accepted for the final list if over half the participants selected it in any round and removed if it received less than four votes. If a proposition received less than 50% of the votes but more than three votes, then it entered a second Delphi round. After two rounds, 10 propositions were agreed upon.

### **Systematic literature search of the propositions**

After agreement on the 10 propositions, proposition-specific searches were performed. Contrary to the general search, performed before the Delphi-procedure to facilitate group discussion, these searches were not limited to studies on low-to-medium dose GCs. They were done of the literature published between 1966 and mid 2006 using the Pubmed, Embase, and Cochrane databases. The CINAHL database was not used for the proposition specific search, since it did not produce additional search results in the general literature search. The search strategy consisted of a search string per proposition, which was based on a translation of the proposition into specific terms. Each search string consisted of terms for GCs and any possible term for the specific component of each proposition. For example, “osteoporosis”, “bone loss”, “vertebral deformity”, “vertebral deformities”, “fracture”, “fractures”, “bone mineral density”, and “bone density”, were used for searching osteoporosis related literature. Components were combined in a structured manner: terms related to Patient/domain, or Intervention/determinant, or Comparison, or Outcome (PICO)<sup>5</sup>, were combined to create a search string, which was sensitive enough to yield all available evidence (appendix 2). The search in the Cochrane library included the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and The Cochrane Central Register of Controlled Trials. Reference lists within reviews and systematic reviews were examined and any additional study meeting the inclusion criteria was included. The results of the proposition specific searches of the different databases were then combined and duplications excluded.

### **Inclusion / exclusion criteria**

Studies that described clinical aspects of GCs or clinical outcomes which were directly or indirectly relevant to a proposition were included. The main focus was on systematic reviews/meta-analyses, randomized controlled trials (RCTs)/controlled trials, uncontrolled trials (for example, one group intervention, quasi-experimental study), cohort studies, case-control studies, and cross sectional studies. Review articles were sometimes used to describe expert opinion, whereas case reports, editorials, and commentaries were excluded. Studies on healthy subjects or animals and studies in a non-European language were also excluded. Where evidence related to GC-use in non-rheumatic diseases was found, it was extrapolated to rheumatic diseases if assumed valid.

### **Categorizing evidence**

Categorization of evidence was according to the quality of study design (Table 1 shows the hierarchy of importance). Questions were answered using the best available evidence and adverse effects were evaluated irrespective of medical condition.

### **Approval of propositions and strength of recommendations**

After the literature search on each proposition, a first draft of the manuscript was written and the Task Force met to discuss each proposition. During this meeting the wording of a proposition could be adjusted by majority agreement only in order to clarify a specific proposition or to reduce any ambiguity. The 10 final propositions and the final adjusted manuscript were approved by all task force members. For each proposition the strength of recommendation (SOR) was graded using an (A–E) ordinal scale (A = fully recommended, B = strongly recommended, C = moderately recommended, D = weakly recommended, and E = not recommended) and a 0–100 mm visual analogue scale (VAS). Task force members were asked to consider both the quality of research evidence presented and their own clinical expertise while grading. For each proposition,

the mean VAS and 95% confidence interval (CI), and the percentage of strongly to fully recommended (A–B) propositions were calculated. This grading method has not been fully evaluated but it has been considered advantageous in giving SOR for procedures which cannot be assessed in RCTs; SOR has been used too in other EULAR recommendations.<sup>6</sup> For propositions with more than one statement or aspect, SOR was scored both for the whole proposition as well as for the individual parts. Throughout the paper, where prednisolone is mentioned, prednisone also applies, and vice versa.

### **Future research agenda**

Each Task force member proposed up to 10 topics for future research on the management of systemic GC-therapy in rheumatic diseases, based on current evidence and clinical experience. The Delphi method, including the same criteria as those for selecting the propositions, was used to reach consensus on the most important research topics.

## **RESULTS**

### **Study populations and types of research evidence**

The general search on AEs in patients on GCs yielded 4645 hits (MEDLINE 3176, EMBASE 2491, CINAHL 87), and 4140 hits minus duplications. Of these, only 40 studies met the inclusion criteria. Figure 1 and Table 2 show the different study populations and the estimated incidence of different types of AEs as derived from the studies reporting on dichotomous AE outcomes.

### **Experts' opinion approach**

The Delphi exercise was performed after the taskforce experts had discussed the results of the general literature search. Initially, 153 (partly overlapping) propositions were produced and after 2 anonymous Delphi rounds, 10 final propositions were agreed upon (Table 3).

### **Assesment of the propositions**

The proposition specific searches resulted in 5089 possibly useful studies. Of these studies, 165 were included to provide (circumstantial) evidence for the propositions (Table 4).

## **Recommendations**

**1. The adverse effects of glucocorticoid therapy should be considered and discussed with the patient before glucocorticoid therapy is started. This advice should be reinforced by giving information regarding glucocorticoid management. If glucocorticoids are to be used for a more prolonged period of time, a “glucocorticoid card” is to be issued to every patient, with the date of commencement of treatment, the initial dosage and the subsequent reductions and maintenance regimens.**

*Level of evidence: IV*

*Strength of recommendation (95% CI):*

- *Overall: 91 (86-96)*
- *Pre-treatment advice: 92 (85-100)*
- *Information: 88 (80-96)*
- *Glucocorticoid card: 78 (67-89)*

The taskforce experts recommend that the occurrence of AEs during GC-therapy (Table 2) should be categorized following WHO guidelines: very common (>1/10); common (>1/100); uncommon (>1/1000); rare (>1/10 000); very rare (<1/100 000).<sup>7</sup> Thorough explanation of common and very common AEs of therapy is an integral part of the management of any disease and of patient education. An AE-survey in a population based cohort of GC-users showed that 68% of patients who used GCs recalled discussing potential GC-related AEs with their practitioner.<sup>8</sup> This recall might be influenced by the perception of severity of GC-related AEs, which may differ amongst patients.<sup>9</sup> Patient perspective has been studied in patients who used other types of drugs than GCs. Cancer patients who used taxane chemotherapeuticum perceived symptom status and improvement to be more important than toxicity of this medication.<sup>10</sup> RA patients, who had to choose between different DMARDs (not including GCs), based their preference on safer short term AE profile,<sup>11</sup> and older patients with knee osteoarthritis preferred a lower risk of AE to treatment effectiveness too.<sup>12</sup> In Japanese patients with chronic diseases, non-adherence to prescribed medication was strongly associated with anxiety.<sup>13</sup> For patients who were treated with sumatriptan subcutaneously, important issues of this migraine therapy were safety and AEs.<sup>14</sup>

Whether discussion of possible AEs before GC-therapy has any beneficial effect on disease outcome, e.g. by improving patient compliance, is unclear because of lacking data regarding GCs. However, circumstantial evidence exists that general patient education, including discussing possible AEs of treatment, positively influences outcome of therapy. A controlled clinical study showed that a structured patient education program in 100 RA patients reduced disability and pain for 3 months, although this reduction was no longer seen after 12 months.<sup>15</sup> A quasi-experimental study of 183 RA patients who were taking MTX showed that knowledge of the toxicity and safe use of MTX was significantly improved by a patient education program utilizing a rheumatology nurse.<sup>16</sup> Patient education also proved to be beneficial for the outcome of therapy in diabetic patients,<sup>17</sup> in cancer patients,<sup>18</sup> and in ambulatory clinic population.<sup>19</sup> Patient education is not always beneficial, however. A controlled clinical study showed that knowledge about adverse effects of beta-blockers could produce anxiety,<sup>20</sup> so in giving information, individual patient psychological characteristics should be taken into account.

Patient education could therefore have an effect on outcome of drug therapy, but the format of patient education has not been investigated. No study looked at the use of information leaflets in long-term GC-therapy specifically, which also leaves this part of the recommendation to be supported by expert opinion only. It was nevertheless shown that information leaflets did not have an impact on incidence and reporting of adverse effects,<sup>21</sup> whereas it did help patients to recognize an adverse reaction due to drug consumption,<sup>22</sup> and it increased patients' recall of a surgical procedure,<sup>23,24</sup> and knowledge about asthma<sup>25</sup> or clinical trials.<sup>26</sup> Several factors showed to influence recall of written information: narrative style,<sup>27</sup> understandability and cultural relevance,<sup>28</sup> readability,<sup>29,30</sup> time after information supply,<sup>31-33</sup> patient's age,<sup>16,34,35</sup> IQ and cognitive function.<sup>34,35</sup> Besides the use of an information leaflet, other techniques also showed to be worthwhile options: supplemental pocket-cards,<sup>16</sup> patient information videos,<sup>36-38</sup> and multimedia, such as touch screen computers.<sup>39,40</sup>

In the final part of this recommendation the use of "glucocorticoid cards" is advocated. No evidence was found to corroborate this, but the use of a pocket card in methotrexate (MTX) users improved their knowledge on safety and toxicity of MTX-treatment.<sup>16</sup>

In conclusion, although there is no research based justification specific to AEs of GC-therapy (category IV), information and, if necessary, education of patients on AEs of their treatment is generally accepted to be an ethical prerequisite and worthwhile. One should realise that patients' perspective on AEs might differ from doctors' perspective; patient information

should include both perspectives. If next to oral information an additional source of information is considered, several factors that influence its usefulness, the specific individual patients' perspective and characteristics, and different techniques of providing information should be taken into account.

**2. Initial dose, dose reduction and long-term dosing depend on the underlying rheumatic disease, disease activity, risk factors and individual responsiveness of the patient. Timing may be important, with respect to the circadian rhythm of both the disease and the natural secretion of glucocorticoids.**

*Level of evidence: I-III*

*Strength of recommendation (95% CI):*

- *Overall: 83 (70-97)*
- *Dose regimens: 92 (83-100)*
- *Dose timing: 74 (59-89)*

The only rheumatic disease in which dosing schemes of GCs were compared is polymyalgia rheumatica (PMR)/giant cell arteritis (GCA): after initial medium dose, subsequent dose reduction depended on disease activity. In a retrospective study, the records of 91 patients with PMR or GCA were reviewed: mean initial prednisolone dose in PMR-patients was 18 mg/day and mean duration of treatment was 17 months. In patients with GCA mean initial dose was 31 mg/day and mean duration of treatment was 16 months. In both groups the GC-treatment was stopped within 24 months.<sup>41</sup> Dosing strategies were assessed in one retrospective and three prospective studies on short to intermediate term GC-treatment in PMR and GCA: patients needing low initial dosages had less relapses, lower maintenance dose, and experienced less toxicity.<sup>42-45</sup> In early RA (disease duration <2 years), the use of low-dose GCs is not based solely on disease activity, but also on long-term outcome. A meta-analysis on multiple RCTs in early RA has shown that low-dose GCs are joint sparing on the long-term and can therefore be categorized as DMARDs.<sup>3</sup> Different regimens with GCs have been used for joint sparing purposes in early RA, usually in combination with other DMARDs. These different schemes could result in different outcome of the treatment, but data is lacking.

A relation between dose strategies and risk factors, such as diabetes, hypertension, and osteoporosis, can only be shown indirectly. In several studies in renal transplant patients, including a prospective observational study<sup>46</sup> (category IIB), reduction of GC-dose was related to improved insulin sensitivity.<sup>46-48</sup> Hypertension was related to higher initial GC-dosage in a comparative study on liver transplant patients<sup>49</sup> (category III). High initial dose and long-term use of GCs are associated with osteoporosis; this relation is elaborated upon in proposition 6.

Specific abnormalities in the GC-receptor gene have been associated with either an increased or reduced receptor function in 6.6% and in 2.3% of a healthy elderly population, respectively. In this population there was no association with individual response to GC, but abnormalities in the GC-receptor may contribute to the variable sensitivity to GC-therapy observed in a normal population.<sup>50</sup> It is unknown whether an individual response is different among individuals for the same GC-dose, since no study was found on the relation between dose strategies and individual responsiveness of patients.

Timing of GC-administration might influence its efficacy. This assumption is based on the fact that both symptoms (such as morning stiffness) and clinical signs of RA<sup>51</sup> as well as several pro-inflammatory cytokines<sup>52</sup> vary within 24 hours and show a circadian flare in the

beginning of the day. Administration of GCs early in the morning<sup>53</sup> (category IB), or the use of modified release (MR) tablet formulation of prednisone, delivering the GC early in the morning (abstract)<sup>54</sup> gave more improvement of RA symptoms than conventional timing of GC-therapy.

In conclusion, there is category III evidence on dosing regimens of GCs in PMR/GCA and category IA evidence showing a benefit for the use of low-dose longterm GCs in early RA. The relation between risk factors, AEs, high GC-dosages and longterm GC-use was indirectly shown for diabetes (category IIB) and hypertension (category III). No studies were identified that show a relation between GC-dosing regimens and individual responsiveness (category IV). There is category IB data on a superior effect of circadian administration of GCs.

**3. When it is decided to start glucocorticoid treatment, comorbidities and risk factors for adverse effects should be evaluated and treated where indicated. These include hypertension, diabetes, peptic ulcer, recent fractures, presence of cataract or glaucoma, presence of (chronic) infections, dyslipidemia and co-medication with non-steroidal anti-inflammatory drugs.**

*Level of evidence: IV*

*Strength of recommendation (95% CI): 92 (87-96)*

The relation between the risk factors mentioned above and GCs is well-known, and literature on the AEs that are associated with the above mentioned risk factors has recently been reviewed.<sup>55</sup> Although it is common sense to treat risk factors to diminish the chance of GC-related AEs, no study looked directly at the effects of evaluation and treatment of the above mentioned risk factors before the start of GC-treatment. The rationale for pre-treatment screening and treatment is that these risk factors are also known AEs of GCs, so these conditions could deteriorate and cause complications during GC-treatment. Data on the deterioration of the following risk factors and AEs were found:

- Diabetes and hypertension:<sup>55</sup> these preexistent conditions may worsen during GC-pulse therapy<sup>56</sup> and diabetes has also been shown to worsen during longterm oral GC-therapy.<sup>57</sup>
- Peptic ulcer and concomitant NSAID use: Incidence of peptic ulcers was slightly increased by therapy with GCs alone in some studies,<sup>58-61</sup> but not in all.<sup>62</sup> Undoubtedly the risk of peptic ulcers increases when GCs are prescribed concomitant with NSAIDs.<sup>62</sup> Patients should be asked about the use of 'over the counter'- NSAIDs, since many patients use this approach.<sup>63</sup>
- Recent fractures: GCs increase the risk of fractures.<sup>64</sup> Unfortunately, the majority of patients on GC-therapy with osteoporotic fractures has not been prescribed bisphosphonates or other anti-osteoporotic therapy.<sup>65-67</sup> This indicates that, in many cases, neither bone mineral density nor fracture status is evaluated before the start of GC-therapy. Nevertheless, rheumatologists are increasingly aware of the risk of fractures<sup>68</sup> and they prescribe more frequently bisphosphonates than GC-prescribing internal medicine specialists do.<sup>69</sup>
- Glaucoma and cataract: GCs can increase ocular pressure, and thus may induce glaucoma in predisposed individuals. Pre-existing glaucoma<sup>70</sup> and age<sup>71</sup> increase this risk of worsening of glaucoma due to GCs. Ocular GCs are believed to be more prone to induce glaucoma.<sup>72</sup> Research data on the incidence of cataract with long-term low dose systemic GC-treatment is scarce,<sup>55</sup> but the occurrence of cataract is associated with longer term and higher dosed GC-use.<sup>8,60</sup>
- (Chronic) Infections: GCs increase the risk of infection<sup>73,74</sup> and may mask the symptoms of infection. No data on the usefulness or effect of systematic screening for infections before start of GC-therapy is available, but nevertheless it should be performed. It should be kept in mind that GCs could also have an effect on the screening-tests themselves, i.e. in a population with a high



prevalence of tuberculosis, only 29% of 112 RA patients, of whom 87% used prednisone  $\leq 7.5$ mg daily, had a positive mantoux test, versus 71% of the healthy matched control group.<sup>75</sup>

- Dyslipidemia: GCs may induce dyslipidemia,<sup>76</sup> but we found no studies on the effects of GC-treatment upon preexisting dyslipidemia. High disease activity in RA and SLE may deteriorate lipid levels,<sup>77,78</sup> while effective disease modifying therapy, including GCs, has been shown to improve the altered lipid spectrum.<sup>79-81</sup> Classical risk factors, such as lipid levels, nevertheless explain the higher risk of cardiovascular disease only partially, since the disease itself might increase the risk of cardiovascular disease.<sup>82</sup>

In conclusion, even though risk factors for GC-associated AEs are well-known and there is obvious face validity trying to prevent these from occurring by assessing and treating comorbidities and risk factors at baseline, there is no evidence to show that this is effective (category IV).

**4. For prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity. The reasons to continue glucocorticoid therapy should be regularly checked.**

*Level of evidence: IV*

*Strength of recommendation (95% CI): 81 (68-94)*

Since there is no evidence from appropriately designed studies to support this proposition, it is supported by expert opinion alone (category IV). Nevertheless, this proposition has obvious face validity since the occurrence of GC-related AEs, osteoporosis in particular (proposition 5 and 6), is dependent of dose and duration of therapy. Concomitant GC-sparing therapy like methotrexate was successful in facilitating GC-tapering in some but not all trials in PMR-patients.<sup>83-85</sup> The risk-benefit ratio of tapering and stopping GCs in RA has not been studied systematically. In a placebo-controlled RCT of 12 weeks, low dose GCs had a small effect on HPA function and all patients showed response to the ACTH-stimulation test the day after stopping treatment,<sup>86</sup> suggesting that the abrupt stopping of low dose GC-therapy in these patients did not result in HPA insufficiency.

**5. During treatment, patients should be monitored for body weight, blood pressure, peripheral oedema, cardiac insufficiency, serum lipids, blood and/or urine glucose and ocular pressure depending on individual patient's risk, glucocorticoid dose and duration.**

*Level of evidence: IV*

*Strength of recommendation (95% CI): 89 (81-97)*

Since there is no direct evidence from appropriately designed studies to support this proposition, it is supported by expert opinion alone (category IV). Certain parts of the proposition deserve further attention:

Firstly, risks of AEs during GC-treatment are related to GC-dose and duration of treatment, monitoring should be dependent on both variables. For instance, changes in both body weight and blood glucose have been shown to be time and dose dependent.<sup>8</sup> Additionally, a review on low-dose GCs in RA showed that the toxicity of low dosages was modest.<sup>55</sup> Furthermore, not all AEs mentioned in this proposition occur in low dose GC-therapy; the same review found no relation of low dose GCs with hypertension, peripheral oedema, cardiac insufficiency, dyslipidemia, or hyperglycaemia.<sup>55</sup> In line with this, a retrospective cohort study did not show a significant relation between GC-dosage lower than 5 mg/day and serious AEs.<sup>60</sup>

However, a recent analysis did show a relation between GC-dosage lower than or equal to 5 mg/day and pneumonia, hazard ratio 1.4 (1.1-1.6)<sup>74</sup>.

Secondly, monitoring for treatable and preventable AEs is especially useful if the AE is common (i.e. low number needed to screen), the AE is severe or has a significant impact on quality of life, the cost of screening is low, and scoring is feasible in daily clinical practice. A theoretical framework showing elements of the discussion on monitoring the above mentioned AEs is found in Table 5, based upon group consensus after discussing all propositions. However, also non-modifiable AEs should be assessed, as they could be important from the patient's perspective and could be a surrogate marker for other AEs (e.g. reflecting patient's sensitivity to GCs), alerting the physician.

**6. If a patient is started on prednisone  $\geq$  7.5 mg daily and continues on prednisone for more than 3 months, calcium and vitamin D supplementation should be prescribed.**

**Antiresorptive therapy with bisphosphonates to reduce the risk of glucocorticoid-induced osteoporosis should be based on risk factors, including bone mineral density measurement.**

*Level of evidence: I*

*Strength of recommendation (95% CI):*

- *Overall: 95 (89-100)*
- *Calcium and vitamin D: 95 (91-99)*
- *Bisphosphonates: 96 (92-99)*

Bone loss commences early after the start of GC-therapy;<sup>87</sup> further rationale for this proposition is given by a large case-control study that showed an increase of the risk of both vertebral and hip fractures in patients using prednisone 7.5 mg daily or more compared to patients using lower dosages.<sup>88</sup> Several European guidelines took 7.5 mg of prednisone or equivalent daily as a cutoff value for the decision to perform bone mineral density (BMD) measurements or the start of preventive treatment for osteoporosis.<sup>89,90</sup> Nevertheless, a meta-analysis showed already an increased risk of fractures for GC-dosages as low as 5 mg daily within 3 to 6 months of treatment.<sup>64</sup> In contrast, two studies that measured BMD in early RA patients didn't show a detrimental effect of low dose GCs,<sup>91,92</sup> which could indicate that GC-induced osteoporosis might not only be related to dose but could also be disease specific.<sup>93</sup>

There is no direct evidence to support this proposition entirely, but indirect evidence does: Calcium, vitamin D, and vitamin D analog supplementation have been shown to decrease GC-induced loss of BMD and to reduce fractures in several meta-analyses of RCTs (category IA). A meta-analysis of 5 trials (274 patients, duration 9-36 months) comparing therapy with calcium and vitamin D to calcium alone or to placebo in patients taking GCs (prednisone equivalent of 5.6 - 18.9 mg daily) demonstrated less bone loss with vitamin D and calcium.<sup>94</sup> A review that included two meta-analyses of 32 studies (1531 patients, mostly RCTs) in transplant-patients using high doses of GCs showed that active vitamin D3 analogues resulted in less bone loss and less fractures than no treatment, placebo, plain vitamin D3 and/or calcium.<sup>95</sup> Nevertheless, vitamin D and calcium do not totally prevent GC-induced bone loss, whereas bisphosphonates generally do. Bisphosphonates have been proven superior in increasing BMD compared to calcium and/or (active) vitamin D in a meta-analysis of 13 trials (842 patients, duration 6-24 months)<sup>96</sup> (category IA). Another meta-analysis showed that bisphosphonates were more effective in preserving bone and decreasing the risk of vertebral fractures than active vitamin D3 analogues.<sup>95</sup> This superiority in increasing BMD as well as in preventing fractures was also shown in both a

large RCT comparing the effects of alfacalcidol and alendronate,<sup>97</sup> as in a meta-analysis of 5 randomised placebo-controlled trials with etidronate in postmenopausal women.<sup>98</sup>

It has been justified by several studies that bisphosphonate therapy should be based on the following risk factors: decreased BMD, female gender, older age, postmenopausal status and low body mass index (BMI). A cross-sectional study in 394 female RA-patients from a county based register indicated that age >60 years, low BMI, and current use of GCs were risk factors for low BMD<sup>99</sup> (category IIB). A review of 2 RCTs (296 patients) on risedronate showed that both GC-dose and low BMD were predictors of fractures. Additionally, at the same BMD level, postmenopausal patients on GCs were more prone to get fractures than postmenopausal patients who were not receiving GCs<sup>100</sup> (category 1B). The ACR has published a clear guideline on the treatment of GC-induced osteoporosis<sup>101</sup> and algorithms have been proposed to decide whether or not to start with bisphosphonates based on GC-dosage, preexistent fractures, age and gender, menopause, and BMD-measurement<sup>90,102</sup> (Figure 2).

Preventive therapy against GC-induced osteoporosis in long-term GC-users is still inconsistently prescribed, however.<sup>103,104</sup> This might result in more osteoporosis-related morbidity than necessary.

In conclusion, this proposition is supported by indirect evidence (category IA), which shows a decreased incidence of fractures resulting from calcium and vitamin D supplementation, and an even better protective effect with bisphosphonates in patients on prolonged treatment with GCs. Decreased BMD is a good predictor of future fractures (category I B) and advanced age and low BMI are associated with low BMD (category IIB).

**7. Patients treated with glucocorticoids and concomitant non-steroidal anti-inflammatory drugs should be given appropriate gastro-protective medication, such as proton pump inhibitors or misoprostol, or alternatively could switch to a cyclo-oxygenase-2 selective inhibitor (coxib).**

*Level of evidence: I*

*Strength of recommendation (95% CI): 91 (84-98)*

No study investigated gastro-protective measures in GC-using patients specifically, but the rationale for this proposition is given by the fact that gastro-intestinal (GI) toxicity possibly increases by treatment with GCs alone (see proposition 3). This is corroborated by a post-marketing surveillance program of more than 11000 arthritis patients, that showed that osteoarthritis and RA patients are 2.5 to 5.5 times more likely than the general population to be hospitalized for GI events which are NSAID-related. In these patients independent risk factors are GC-use, NSAID dose, age, disability level, and previous NSAID-induced GI symptoms.<sup>105</sup> Strikingly, gastro protective agents (i.e. antacids, histamin<sub>2</sub>-receptor antagonists, proton pump inhibitors (PPI), and cytoprotective agents (i.e. misoprostol)) are used in only 35% to 40% of patients with multiple risk factors for gastrointestinal ulceration, such as advanced age, active disease, NSAID therapy concomitant with GCs, low dose aspirin or anti-coagulants.<sup>106</sup> Established risk factors for NSAID-associated gastrointestinal toxicity have been shown to be poor predictors of prescription of a coxib. In contrast, the prescribing physician's preference was an important determinant.<sup>107</sup>

Although not studied in GC-using patients specifically, several treatment regimens have been shown to be gastro-protective for conventional NSAID users. This indirect evidence shows that:

- Proton pump inhibitors and misoprostol reduce the risk of gastric and duodenal ulcers in patients taking conventional NSAIDs (category I B).<sup>108,109</sup>
- Coxibs cause less GI-toxicity than conventional NSAIDs in RA patients (category I B)<sup>110,111</sup>. Furthermore, in a subgroup of aspirin-using patients, celecoxib reduced gastric ulcers by 51% compared to conventional NSAIDs, whereas this reduction was 71% among patients not taking aspirin.<sup>112</sup>
- Conventional NSAIDs combined with PPI cause less dyspepsia than coxibs do, when both treatments are compared with conventional NSAIDs (category I A).<sup>113</sup>
- In deciding on the prescription of coxibs and conventional NSAIDs, cardiovascular risk factors should be taken into account.<sup>114-119</sup>

In conclusion, this proposition is supported by indirect evidence (category IA-IB).

**8. All patients on glucocorticoid therapy for longer than one month, who will undergo surgery, need perioperative management with adequate glucocorticoid replacement to overcome potential adrenal insufficiency.**

*Level of evidence: IV*

*Strength of recommendation (95% CI): 91 (84-99)*

Adrenal insufficiency due to surgical stress has already been described in the 1950's. {Slaney, 1957 2741 /id} As patients with RA and PMR are considered to have relative adrenal insufficiency,<sup>121</sup> they might be more prone to adrenal insufficiency at surgery. The incidence and duration of GC-induced adrenal insufficiency depends, apart from possible individual differences in sensitivity for GC, of two factors. First, type and dosage of GC: a single dose of 50 mg prednisone or equivalent depresses the hypothalamic-pituitary-adrenal axis for 1.25 to 1.5 days, a dose of 40 mg triamcinolone for 2.25 days, and a dose of 5 mg dexamethasone for 2.75 days.<sup>122</sup> Intramuscular administration of a single dose of 40 to 80 mg triamcinolone acetone depresses the hypothalamic-pituitary-adrenal axis for 2 to 4 weeks, and after 40 to 80 mg intramuscular methylprednisolone, suppression lasts 4 to 8 days.<sup>122</sup> After an intra articular injection with 20 to 160 mg of methylprednisolon, the hypothalamic-pituitary-adrenal axis function is suppressed for 1 day in half of the patients and recovers in 95 % of the patients within 2 weeks.<sup>123</sup> Second, duration of therapy: although, acute stopping without consequences of low dose GCs in ambulant RA patient seems possible (see proposition 4), for patients in stress, like those undergoing surgery, the case is completely different. In such circumstances acute cessation after a daily dose of 7.5 mg or more prednisolone or equivalent for at least 3 weeks could lead to problems.<sup>124</sup> Treatment of less than 3 weeks or alternate-day therapy does not exclude the risk of suppression of the hypothalamic-pituitary-adrenal axis,<sup>125,126</sup> but the risk is still dose depended.<sup>127</sup> Stopping GCs perioperatively because of fear for infections can cause severe harm to patients and should not be done without sound consideration of risk and benefit.

GC-replacement is recommended in case of surgery for patients at risk of adrenal insufficiency. A replacement scheme has been proposed for different (surgical) procedures:<sup>128</sup> 1. For moderate physical stress inducing procedures, a single dose of 100 mg hydrocortisone intravenously. 2. For major surgery, 100 mg hydrocortisone intravenously before anesthesia and every 8 hours four times thereafter. The dose can be tapered by half per day afterwards. Several other schemes of GC-replacement exist. However, at this moment there is insufficient evidence to propose any specific recommendation for different surgical procedures. Possibly, low dose schemes could be applied, given the fact that acute stopping of low dose GCs in RA patients had only a small effect on HPA function,<sup>86</sup> suggesting little or non adrenal suppression.

Although GC-replacement is recommended in patients at risk,<sup>129</sup> the necessity of suprphysiological replacement has been questioned by the result of a randomized double-blind study of 18 patients with known prednisone induced adrenal suppression (abnormal ACTH test) caused by chronic prednisone use, who underwent major surgery.<sup>130</sup> These patients did not experience hypotension due to adrenal insufficiency while only continuing daily GC-dose perioperatively, indicating adrenal suppression does not necessarily mean that there will be clinical signs of adrenal insufficiency. Other data, in 40 renal allograft recipients on long-term low dose GC-treatment with significant physiologic stress (i.e. sepsis, metabolic abnormalities, or surgery), suggests too that baseline GC-therapy might be sufficient to prevent adrenal insufficiency.<sup>131</sup>

In conclusion, since early studies show the occurrence of adrenal insufficiency during surgery, it is common to increase the dose of GCs around surgical interventions in patients on GCs for longer than one month. There is no research investigating this (category IV) and it seems that in certain circumstances the continuation of usual daily GC-dosages might be sufficient. Stopping of GC-therapy perioperatively should not be done.

## **9. Glucocorticoids during pregnancy have no additional risk for mother and child.**

*Level of evidence:*

- **Mother: IV**
- **Child: I-III**

*Strength of recommendation (95% CI): 87 (78-96)*

Safety of GC-usage during pregnancy has two aspects: safety for the mother and safety for the unborn child.

Firstly, the safety of GCs for the pregnant mother: AEs associated with the use of GCs are believed not to differ between a pregnant patient and a non-pregnant patient, but no evidence was found to support this (category IV). As pregnant or lactating women are more at risk for pregnancy-associated AEs (e.g. osteoporosis,<sup>132</sup> diabetes,<sup>133</sup> hypertension<sup>134</sup>), this risk could be increased by GC-therapy, but no data are available.

Secondly, the safety of GCs for the fetus and neonate. The ability to pass the placenta and the rate of metabolization (inactivation) within the placenta differ for different types of GCs. So different GCs have different indications during pregnancy. Dexamethasone can be used to treat fetal conditions such as immature lungs, because it is not metabolized well by the placenta nor predominantly protein bound and thus higher dosages are available to the fetus. Prednisone, prednisolone, and methylprednisolone, are less available to the fetus (10% of the maternal dose) and therefore these substances are preferred for the treatment of maternal disorders.<sup>135</sup> GCs prior to and during pregnancy do not seem to have a negative impact on the development of the fetus. GCs in high doses have caused cleft palate in experimental animal models and low birth weight in humans.<sup>136,137</sup> However, there is no evidence that in humans either prednisone or methylprednisolone are teratogenic (Food and Drug Administration risk category B,<sup>138</sup> the increased risk of cleft palate in animals was not confirmed in controlled studies in women in the first trimester, nor in the later trimesters).

In a large retrospective cohort of GC-treated pregnant asthma-patients no increased incidence of birth defects compared with the general population was found. Most women were receiving low-dose prednisone (the mean daily dose was 8 mg) and were taking GCs at the time of conception (category III).<sup>139</sup> An increased incidence of prematurity among neonates exposed to GCs in utero was shown by a RCT, which compared the effects of high dose GCs (0.5 to 0.8 mg

per kilogram of body weight per day) with those of aspirin (100 mg daily) or placebo to treat unexplained recurrent fetal loss in SLE patients with a history of recurrent fetal loss (category I B).<sup>140</sup> On the other hand, disease activity itself has been associated with increased risk of abortions in SLE.<sup>141,142</sup> GCs have been suggested to improve fetal survival in SLE-patients with lupus anti-coagulant,<sup>143,144</sup> but this was not confirmed by the above mentioned RCT.<sup>140</sup> Finally, the incidence of infection was not increased in neonates who were exposed to GCs in utero (category I B).<sup>145</sup>

During lactation, GCs are excreted minimally into breast milk<sup>146,147</sup> and breast feeding by women with low dose GC-therapy is generally considered to be safe.<sup>148</sup> Exposure of an infant can be further minimized if breast-feeding is avoided during the first 4 hours after GC-intake, because there is an equilibrium between the concentration of prednisolone in mother milk and serum.<sup>147</sup>

The influence of bisphosphonates on the fetus is not known, but concern exists for use in fertile and in pregnant women because of the very long half-life of these drugs, which are presumed to be able to cross the placenta.<sup>149</sup> Furthermore, fetal hypocalcemia has been reported once during bisphosphonate therapy.<sup>150</sup> Until now, the treatment of osteoporosis with a bisphosphonate has not proved to be teratogenic during pre and early pregnancy in a case series of 24 patients,<sup>149</sup> but caution seems warranted.

In conclusion: There is category IV evidence that GCs are safe for mothers during pregnancy. Category III indirect evidence shows that GCs are not teratogenic for the fetus, and there is category I B evidence that they do not contribute to perinatal infections. Category I B evidence exists that high dose GCs may contribute to fetal prematurity in SLE patients.

## **10. Children receiving glucocorticoids should be checked regularly for linear growth and considered for growth hormone replacement in case of growth impairment.**

*Level of evidence: I*

*Strength of recommendation (95% CI): 93 (85-100)*

GCs can cause growth retardation in children. The pathogenesis of this growth impairment is multifaceted. Several studies showed the negative effects of long-term GC-therapy on growth: Studies in juvenile idiopathic arthritis (JIA) (category III),<sup>151</sup> early onset Crohn's disease (category III),<sup>152</sup> and asthma patients (category II B).<sup>153</sup> In addition, the growth impairment remained long after GC-treatment had been stopped in cystic fibrosis patients (category I B).<sup>154</sup> Growth hormone replacement (GHR) can be used to prevent growth impairment due to GCs: increase of linear growth with GHR was shown in several studies of GC-using JIA-patients (category I - III),<sup>155-160</sup> and in studies of "slowly growing GC-treated patients" (category II),<sup>161,162</sup> The daily GC-doses used in these studies varied between 0.2 and 0.5 mg/kg prednisolone equivalent and the duration GHR-therapy was 2 to 4 years.

Contrary to oral GCs, topical GC-administration does not seem to induce growth impairment,<sup>163</sup> whereas there is doubt whether inhalation GCs might influence linear growth. In one study of asthma patients, inhalation GCs had a negative influence on linear growth,<sup>164</sup> but in a meta-analysis, this finding was not confirmed.<sup>153</sup> Alternate day GC-administration in JIA patients resulted in less inhibition of body growth than daily usage did.<sup>165</sup>

An extra feature of GHR is its effect on bone: an increase of bone mineral content (BMC) was shown in addition to an increase of linear growth (category III).<sup>166</sup>

If GHR is considered, referral to an experienced paediatrician is indicated and additional testing can confirm GH deficiency. The most frequently used test is the clonidine provocation test.<sup>167</sup> Additionally, the dexamethasone response test appears to be promising for the detection of

GH deficiency.<sup>168</sup> Routine usage of GHR in GC-using patients is hampered by several factors: the therapy exists of daily injections (subcutaneously or intramuscularly), the length gain is relatively small, and it is a very costly therapy (between 15,000 € and 50.000 €, depending on the weight of the individual child<sup>169</sup>).

In conclusion, there is evidence (category I B) that GCs may cause growth impairment in children, which can be treated with GHR (category I B). GH deficiency can be confirmed with provocation tests and GHR should be under expert supervision.

## DISCUSSION

This EULAR document is an attempt to give recommendations for the safer use of systemic GCs, in rheumatic diseases. A similar design was used as in earlier taskforces,<sup>170-173</sup> i.e. a combination of both evidence and expert opinion. The added value of this taskforce, like previous ones, is provided by the fact that they (a) are a broad representation of experts in the field of GCs within and outside Europe; (b) use recent research data; and (c) use a thorough evidence based format. This format was applied in this taskforce and generated 10 key propositions on the use of GCs by anonymous Delphi procedure, which was followed by a systematic search for evidence per proposition. The order of propositions in the paper does not reflect importance, neither does the level of evidence of propositions, but reflects the logical order of patient management. Finally, both the level of evidence of the studies in support of each proposition as well as the strength of each recommendation are described. The benefits of this approach are reduction of personal bias, good external validity and generalisability, and clear identification of areas of clinical practice where more research data are required.<sup>174</sup> These propositions aim promoting the safer use of GCs among physicians and patients alike and they will form the basis for further EULAR research and education.

An important part of the methodology of these recommendations is the use of the VAS and ordinal scales for the grading of the recommendations. The mean values of the scaling give a clear indication of the support of the taskforce for each proposition, and the confidence intervals show the degree of agreement within the taskforce. The same method has been used by a recent taskforce<sup>171</sup> and proved to be very adequate for procedures which cannot be, or have not been, assessed in RCTs, but need to be upgraded according to expert opinion.<sup>6</sup> The latter is of great importance for these recommendations, since evidence on the safety or AEs of GCs lacks comparative studies of high quality, such as RCTs.

These recommendations have some limitations. First, the search strategy could have been too specific and relevant studies might have been overlooked. Search results were often overwhelming, since GCs are used quite extensively. Therefore, search strings might have been more specific than ideally useful. Second, the selection of circumstantial evidence in the absence of direct evidence has some degree of subjectivity. Third, in literature the evidence hierarchy has focused on treatment efficacy, whereas evidence on safety is better graded by other study types than RCTs. The above mentioned grading methodology tries to overcome this problem, but other grading systems might be preferred for grading studies on safety in the future.

The literature search showed that studies on GCs lack systemic assessment of AEs, that AEs often are poorly described, let alone defined, which made it difficult to provide direct evidence for most propositions. It is therefore advised to monitor a well defined list of AEs in a standardised manner in future studies. Standardised scoring for most AEs has however yet to be developed. Hypertension, diabetes, osteoporosis, gastric ulcer, cataract, glaucoma, infections, and dyslipidemia are AEs that merit monitoring. Optimal ways of implementation of monitoring and

its effect also are to be studied, including patients' perspectives. To point out the most important topics for future research on GCs a research agenda of 11 research questions has been formulated through 2 additional Delphi rounds (Table 6).

These recommendations, with all their limitations, are meant to give physicians some guidance for daily clinical practice. For this purpose also, some additional practice points were formulated by the taskforce (Box 1).

### **Box 1: Additional practical points**

**(During the process of formulating and discussing each proposition, several topics arose that merit extra emphasis).**

- Starting GC-therapy before a clear diagnosis has been made, may hamper the making of a diagnosis.
- Worries of patients about GC-induced AEs are likely to differ from those of physicians.
- Faster tapering of GCs than described in schemes in the literature might often be possible.
- Avoid concomitant therapy with NSAIDs in patients on a daily dose >10 mg prednisolone or equivalent.
- Patients on GCs possibly are more prone to get fractures than postmenopausal patients not on GCs with the same BMD-levels/T-scores.
- Reminders on the use of anti-osteoporosis medication reduce the occurrence of fractures in high risk patients.
- Adrenal suppression by GC, mirrored by an abnormal ACTH stimulation test, does not always predict signs and symptoms of adrenal insufficiency

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Table 1. Level of evidence

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I-A	Meta-analysis of randomised controlled trials
I-B	Randomised controlled trial
II-A	Controlled study without randomization
II-B	Quasi-experimental study
III	Descriptive studies (comparative, correlation, case-control)
IV	Expert committee reports/opinions and/or clinical opinion of respected authorities

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Table 2. Reported AEs in GC-treated patients with rheumatic diseases. (Results of the general search)

Type of AE:	Median: (25 <sup>th</sup> -75 <sup>th</sup> percentiles) (AEs per 100 patient years)
Cardiovascular (dyslipidemia, water and electrolyte imbalance, oedema, renal and heart dysfunction, hypertension)	15 (3-28)
Infectious (viral, bacterial, skin infections)	15 (3-15)
Gastro-intestinal (peptic ulcer disease, pancreatitis)	10 (4-20)
Psychological and behavioral (minor mood disturbances, steroid psychosis)	9 (2-236)
Endocrine & metabolic (glucose intolerance and diabetes, fat redistribution, interference with hormone secretion)	7 (3-34)
Dermatological (Cutaneous atrophy, acne, hirsutism, alopecia)	5 (2-80)
Musculoskeletal (osteoporosis, osteonecrosis, myopathy)	4 (3-9)
Ophthalmological (Glaucoma, cataract)	4 (0-5)

This table summarizes reported AEs in studies (n = 18) of the general search of patients using GCs (n= 963) for a rheumatic disease. Only those studies of patients who were using GCs up to 30 mg prednisolone or equivalent and reporting dichotomous AE outcomes were included in the data of the table, which was used as introductory information for the taskforce. Raw data, not corrected for disease activity, co-morbidity and the frequency of AEs in the contrast group, if present, were used. So not all AEs can be specifically attributed to the use of GCs; common events may be overestimated and less common ones underestimated. For instance, cardiovascular events are poorly correlated with GC-use. Types of AEs were divided into different groups (as has been published before<sup>55</sup>) and per group AEs per 100 patient years were derived by dividing the number of AEs by the duration of follow up in years, times 100. Mean daily GC-dose was 8 mg and the average duration of studies was 19.6 months.

Table 3. Experts' propositions developed throughout 3 Delphi rounds including the strength of recommendation.

Proposition		SOR		Evidence level of data
		VAS 100 (95% CI)	A+B %	
1 a	The adverse effects of glucocorticoid therapy should be considered and discussed with the patient before glucocorticoid therapy is started.	92 (85-100)	93	IV
1 b	This advice should be reinforced by giving information regarding glucocorticoid management.	88 (80-96)	93	IV
1 c	If glucocorticoids are to be used for a more prolonged period of time, a "glucocorticoid card" is to be issued to every patient, with the date of commencement of treatment, the initial dosage and the subsequent reductions and maintenance regimens.	78 (67-89)	79	IV
1	Full proposition (1A + 1B + 1C)	91 (86-96)	92	
2 a	Initial dose, dose reduction and long-term dosing depend on the underlying rheumatic disease, disease activity, risk factors and individual responsiveness of the patient.	92 (83-100)	86	IA-III
2 b	Timing may be important, with respect to the circadian rhythm of both the disease and the natural secretion of glucocorticoids.	74 (59-89)	57	-
2	Full proposition (2A + 2B)	83 (70-97)	85	
3	When it is decided to start glucocorticoid treatment, comorbidities and risk factors for adverse effects should be evaluated and treated where indicated. These include hypertension, diabetes, peptic ulcer, recent fractures, presence of cataract or glaucoma, presence of (chronic) infections, dyslipidemia and co-medication with non-steroidal anti-inflammatory drugs.	92 (87-96)	100	IV
4	For prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity. The reasons to continue glucocorticoid therapy should be regularly checked.	81 (68-94)	86	IV
5	During treatment, patients should be monitored for body weight, blood pressure, peripheral oedema, cardiac insufficiency, serum lipids, blood and/or urine glucose and ocular pressure depending on individual patient's risk, glucocorticoid dose and duration.	89 (81-97)	93	IV
6a	If a patient is started on prednisone $\geq 7.5$ mg daily and continues on prednisone for more than 3 months, calcium and vitamin D supplementation should be prescribed.	95 (91-99)	100	IA
6b	Antiresorptive therapy with bisphosphonates to reduce the risk of glucocorticoid-induced osteoporosis should be based on risk factors, including bone mineral density measurement.	96 (92-99)	93	IB-III
6	Full proposition (6A + 6B)	95 (89-100)	100	
7	Patients treated with glucocorticoids and concomitant non-steroidal anti-inflammatory drugs should be given appropriate gastro-protective medication, such as proton pump inhibitors or misoprostol, or alternatively could switch to a cyclo-oxygenase-2 selective inhibitor.	91 (84-98)	93	1A-IB
8	All patients on glucocorticoid therapy for longer than 1 month, who will undergo surgery, need perioperative management with adequate glucocorticoid replacement to overcome potential adrenal insufficiency.	91 (84-99)	93	IV
9	Glucocorticoids during pregnancy have no additional risk for mother and child.	87 (78-96)	86	IB-III
10	Children receiving glucocorticoids should be checked regularly for linear growth and considered for growth hormone replacement in case of growth impairment.	93 (85-100)	93	IB

\*A+B%, percentage of the taskforce members that strongly to fully recommended this proposition, based on an A - E ordinal scale; CI, confidence interval; SOR, strength of recommendation; VAS, visual analogue scale (0–100 mm, 0 = not recommended at all, 100 = fully recommended).

Table 4. Evidence delivered by the proposition-specific searches.

Proposition	Proposition-specific search, n studies:	N studies meeting inclusion criteria:	Type of evidence *
1	2699	34	Circumstantial
2	556	16	Partially direct
3	464	29	Circumstantial
4	131	4	Circumstantial
5	401	4	Circumstantial
6	71	19	Indirect
7	157	15	Indirect
8	303	13	Circumstantial
9	86	19	Partially indirect and partially direct
10	221	19	Indirect
<b>Total</b>	5089	172 (165 minus duplicates)	

\* Indirect = Data indirectly supports the proposition / Circumstantial = No data directly or indirectly supports the proposition, but there is circumstantial data which is useful to the proposition. Partially direct = part of the proposition is directly supported by data.

Table 5. Theoretical framework of criteria which can be used to decide whether monitoring for specific AEs is useful.

	<b>Number needed to screen?</b> (1/prevalence per year)	<b>Severity?</b> (Low / moderate / high)	<b>Cost of screening?</b> (Low / moderate / high)	<b>Feasibility of scoring?</b> (Low / moderate / high)
<b>Body weight</b>	1.5 <sup>8</sup>	Low	Low	High
<b>Blood pressure</b>	?	Moderate	Low	High
<b>Peripheral oedema</b>	?	Low	Low	High
<b>Heart failure</b>	?	High	Moderate	Moderate*
<b>Dyslipidemia</b>	?	Moderate	Moderate	Moderate*
<b>Blood/urine glucose</b>	12.5 <sup>8</sup>	Moderate	Moderate	High
<b>Glaucoma</b>	18.1 <sup>60</sup>	Moderate	Moderate	Moderate*

\* Scoring in daily practice depends on presence of accurate laboratory tests and / or eye pressure measurement equipment.

Table 6. Research agenda developed throughout 2 Delphi rounds.

1	What is the perception of patients, general physicians and rheumatologists on efficacy, safety and management of glucocorticoid therapy in rheumatic diseases? (exploring perceptions and environmental factors as barriers for the effective and safe use of glucocorticoids).
2	What is the influence of low dose glucocorticoid therapy on lipid profile and other cardiovascular risk factors in relation to active inflammation?
3	What is the pathophysiology of the skin side effects due to the use of glucocorticoids, and how can these be prevented?
4	What is the ideal timing of glucocorticoid treatment regarding safety as well as efficacy?
5	Regarding the use of glucocorticoids in early RA: is continuous low dose as effective as a step down dose (starting high and then tapering)?
6	Can we define biomarkers (including genetics) that predict glucocorticoid toxicity?
7	What is the best strategy for prediction, detection and prevention of glucocorticoid-associated cataract and glaucoma?
8	The mechanisms behind individual responsiveness and glucocorticoid resistance should be investigated and the clinical implications clarified.
9	Do glucocorticoids also inhibit radiographic progression in patients with long standing rheumatoid arthritis?
10	What is the pathophysiological mechanism of steroid myopathy and can we prevent this; is there a role for specific exercises?
11	Which genomic and non-genomic mechanisms of glucocorticoid actions are responsible for wanted and adverse effects, respectively?





## Appendix 2:

### Searchstrings proposition 1:

#### Part 1A.

**“The adverse effects of glucocorticoid therapy should be considered before glucocorticoid therapy is started...”**

Intervention / determinant: [patient education]

Outcome: [adverse effects]

#### Part 1B.

**“...This advice should be reinforced by giving information regarding glucocorticoid medication...”**

Intervention / determinant: [patients information] AND [information leaflets]

**Part 1C. “...If glucocorticoids are to be used for a more prolonged period of time a “glucocorticoid card” is to be issued to every patient, with the date of commencement of treatment, the initial dosage and the subsequent reductions and maintenance regimens.”**

Patient: [GC]

Intervention: [steroid card]

Database:	Searchstring:	Number of studies:
Pubmed	Part 1A: ("patient education"[Title/Abstract] OR "informed consent"[Title/Abstract] OR "patient instruction"[Title/Abstract] OR "patient perspective"[Title/Abstract] OR "patients perspective"[Title/Abstract] OR "patients viewpoint"[Title/Abstract] OR "patients viewpoint"[Title/Abstract] OR "patients' viewpoint") AND ("self report"[Title/Abstract] OR "adverse event"[Title/Abstract] OR "adverse effects"[Title/Abstract] OR "adverse effect"[Title/Abstract] OR "adverse effects"[Title/Abstract] OR "side-effect"[Title/Abstract] OR "side-effects"[Title/Abstract] OR "unwanted effect"[Title/Abstract] OR "unwanted effects"[Title/Abstract])	1256
	Part 1B: ("information leaflet"[Title/Abstract] OR "written information"[Title/Abstract] OR "information booklet"[Title/Abstract] OR "information brochure"[Title/Abstract] OR "information folders"[Title/Abstract] OR "information pamphlets"[Title/Abstract] AND ("patient education"[Title/Abstract] OR "informed consent"[Title/Abstract] OR "patient instruction"[Title/Abstract])	122
	Part 1C: ("steroid card"[Title/Abstract] OR "medication card"[Title/Abstract] OR "information card"[Title/Abstract] OR "information leaflets"[Title/Abstract] OR "written information"[Title/Abstract] OR "information booklet"[Title/Abstract] OR "information brochure"[Title/Abstract] OR "information folder"[Title/Abstract] OR "information folder"[Title/Abstract] OR "information pamphlet"[Title/Abstract] AND ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR *cortisone*[Title/Abstract] OR "Glucocorticoids/adverse effects"[MESH] OR "Glucocorticoids/therapeutic use"[MESH])	3
Embase	Part 1A: ((('patient education'/mj OR 'informed consent'/mj OR 'patient instruction' OR 'patient perspective' OR 'patients perspective' OR 'patient viewpoint' OR 'patients viewpoint') AND ('self report'/mj OR 'adverse event' OR 'adverse effects' OR 'adverse effect'/mj OR 'adverse effects' OR 'side-effect'/mj OR 'side-effects' OR 'unwanted effect' OR 'unwanted effects')) AND [english]/lim AND [humans]/lim AND [embase]/lim	166
	Part 1B: (('information leaflet' OR 'written information' OR 'information booklet' OR 'information brochure' OR 'information folders' OR 'information pamphlets') AND ('patient education'/de OR 'informed consent'/de OR 'patient instruction') AND [humans]/lim AND [embase]/lim	181
	Part 1C: ("steroid card" OR "medication card" OR "information card" OR "information leaflets" OR "written information" OR "information booklet" OR "information brochure" OR "information folder" OR "information folder" OR "information pamphlet" ) AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR *cortisone*):ti:ab:kw AND [humans]/lim AND [embase]/lim	1
Cochrane	Part 1A: ("patient education" OR "informed consent" OR "patient instruction" OR "patient perspective" OR "patients perspective" OR "patient viewpoint" OR "patients viewpoint") AND ("self report" OR "adverse event" OR "adverse effects" OR "adverse effect" OR "adverse effects" OR "side-effect" OR "side-effects" OR "unwanted effect" OR "unwanted effects"):ti:ab:kw	942
	Part 1B: ("information leaflet" OR "written information" OR "information booklet" OR "information brochure" OR "information folders" OR "information pamphlets") AND ("patient education" OR "informed consent" OR "patient instruction"):ti:ab:kw	27
	Part 1C: ("steroid card" OR "medication card" OR "information card" OR "information leaflets" OR "written information" OR "information booklet" OR "information brochure" OR "information folder" OR	1



<b>Total number of studies minus duplicates:</b>	556
<b>Part 2A:</b>	512
<b>Part 2B:</b>	54
<b>Part 2C:</b>	3

### Searchstrings proposition 3:

Intervention / comparison: Risk factors before start GC-therapy.

Outcome: prediction of (above mentioned) AEs.

Database:	Searchstring:	Number of studies:
Pubmed	((("risk factor"[title/abstract] OR "risk factors"[title/abstract]) AND (baseline[title/abstract] OR (therapy[title/abstract] AND (before[title/abstract] OR begin[title/abstract] OR start[title/abstract] OR "prior to"[title/abstract]))) OR ("predictor"[title/abstract] OR "predictors"[title/abstract]) AND (osteoporosis[Title/Abstract] OR "bone loss"[title/abstract] OR "Vertebral deformity"[Title/Abstract] OR "Vertebral deformities"[Title/Abstract] OR "fracture"[Title/Abstract] OR "fractures"[Title/Abstract] OR "bone mineral density"[Title/Abstract] OR "bone density"[Title/Abstract] OR osteonecrosis[Title/Abstract] OR "avascular necrosis"[Title/Abstract] OR "muscle weakness"[Title/Abstract] OR myopathy[Title/Abstract] OR "diabetes mellitus"[title/abstract] OR "blood glucose"[title/abstract] OR "fasting glucose"[title/abstract] OR "urine glucose"[title/abstract] OR glycosuria[title/abstract] OR urinalysis[title/abstract] OR "glucose intolerance"[Title/Abstract] OR "glucose tolerance"[Title/Abstract] OR hyperglycaemia[title/abstract] OR "body weight"[title/abstract] OR "weight gain"[Title/Abstract] OR "adipositas"[Title/Abstract] OR "fat redistribution"[Title/Abstract] OR "Fat distribution"[Title/Abstract] OR "buffalo hump"[Title/Abstract] OR "serum lipids"[title/abstract] OR dyslipidemia[title/abstract] OR dyslipidaemia[title/abstract] OR dyslipidemias[title/abstract] OR dyslipidaemias[title/abstract] OR hyperlipidemias[title/abstract] OR hyperlipidaemias[title/abstract] OR hypercholesterolaemia[title/abstract] OR atherosclerosis[Title/Abstract] OR arteriosclerosis[Title/Abstract] OR "atherosclerotic plaque"[Title/Abstract] OR "coronary artery disease"[Title/Abstract] OR "angina pectoris" [title/abstract] OR "myocardial infarction"[title/abstract] OR hypertension[title/abstract] OR "blood pressure"[title/abstract] OR oedema[title/abstract] OR edema[title/abstract] OR "cardiac insufficiency"[title/abstract] OR "heart failure"[title/abstract] OR "swollen ankles"[title/abstract] OR "electrolyte disorder"[Title/Abstract] OR "electrolyte balance"[title/abstract] OR "electrolyte imbalance"[title/abstract] OR "fluid disorder"[Title/Abstract] OR "fluid retention"[Title/Abstract] OR hypernatremia[Title/Abstract] OR hypernatraemia[Title/Abstract] OR hypokalaemia[Title/Abstract] OR hypokalemia[Title/Abstract] OR "Cushing syndrome"[Title/Abstract] OR "facial fullness" [Title/Abstract] OR "facial swelling"[Title/Abstract] OR "moon face"[Title/Abstract] OR "cutaneous atrophy"[Title/Abstract] OR "skin atrophy"[Title/Abstract] OR "skin hemorrhage"[Title/Abstract] OR "skin bleeding"[Title/Abstract] OR purpura[Title/Abstract] OR striae[Title/Abstract] OR "easy bruisability"[Title/Abstract] OR "easy bruising"[Title/Abstract] OR "wound healing"[Title/Abstract] OR acne[Title/Abstract] OR "hair loss"[Title/Abstract] OR hirsutism[Title/Abstract] OR alopecia[Title/Abstract] OR "gastric ulcer"[title/abstract] OR "gastroduodenal ulcer"[title/abstract] OR "stomach ulcer"[title/abstract] OR "peptic ulcer"[title/abstract] OR "peptic ulcer disease"[title/abstract] OR dyspepsia[title/abstract] OR dysfagia[title/abstract] OR "deglutition disorders"[title/abstract] OR "gastric hemorrhage"[title/abstract] OR "stomach hemorrhage"[title/abstract] OR "gastroduodenal hemorrhage"[title/abstract] OR cataract[title/abstract] OR glaucoma[title/abstract] OR "ocular pressure"[title/abstract] OR "intraocular pressure"[title/abstract] OR (infection[title/abstract] AND (viral[title/abstract] OR bacterial[title/abstract] OR fungal[title/abstract] OR respiratory[title/abstract] OR urinary[title/abstract] OR skin[title/abstract])) OR candida[title/abstract] OR "non-steroidal anti-inflammatory agents"[title/abstract] OR NSAID[title/abstract]))	220
Embase	((("risk factor" OR "risk factors") AND (baseline OR (therapy AND (before OR begin OR start OR "prior to")))) OR ("predictor" OR "predictors") AND (osteoporosis OR "bone loss" OR "Vertebral deformity" OR "Vertebral deformities" OR "fracture" OR "fractures" OR "bone mineral density" OR "bone density" OR osteonecrosis OR "avascular necrosis" OR "muscle weakness" OR myopathy OR "diabetes mellitus" OR "blood glucose" OR "fasting glucose" OR "urine glucose" OR glycosuria OR urinalysis OR "glucose intolerance" OR "glucose tolerance" OR hyperglycaemia OR "body weight" OR "weight gain" OR "adipositas" OR "fat redistribution" OR "Fat distribution" OR "buffalo hump" OR "serum lipids" OR dyslipidemia OR dyslipidaemia OR dyslipidemias OR dyslipidaemias OR hyperlipidemias OR hyperlipidaemias OR hypercholesterolaemia OR atherosclerosis OR arteriosclerosis OR "atherosclerotic plaque" OR "coronary artery disease" OR "angina pectoris" OR "myocardial infarction" OR hypertension OR "blood pressure" OR oedema OR edema OR "cardiac insufficiency" OR "heart failure" OR "swollen ankles" OR "electrolyte disorder" OR "electrolyte balance" OR "electrolyte imbalance" OR "fluid disorder" OR "fluid retention" OR hypernatremia OR hypernatraemia OR hypokalaemia OR hypokalemia OR "Cushing syndrome" OR "facial fullness" OR "facial swelling" OR "moon face" OR "cutaneous atrophy" OR "skin atrophy" OR "skin hemorrhage" OR "skin bleeding" OR purpura OR striae OR "easy bruisability" OR "easy bruising" OR "wound healing" OR acne OR "hair loss" OR hirsutism OR alopecia OR "gastric ulcer" OR "gastroduodenal ulcer" OR "stomach ulcer" OR "peptic ulcer" OR "peptic ulcer disease" OR dyspepsia OR dysfagia OR "deglutition disorders" OR "gastric hemorrhage" OR "stomach hemorrhage" OR "gastroduodenal hemorrhage" OR cataract OR glaucoma OR "ocular pressure" OR "intraocular pressure" OR (infection AND (viral OR bacterial OR fungal OR respiratory OR urinary OR skin)) OR candida OR "non-steroidal anti-inflammatory agents" OR NSAID):ti:ab AND [humans]/lim AND [embase]/lim	251
Cochrane	((("risk factor" OR "risk factors") AND (baseline OR (therapy AND (before OR begin OR start OR "prior to")))) OR ("predictor" OR "predictors") AND (osteoporosis OR "bone loss" OR "Vertebral deformity" OR "Vertebral deformities" OR "fracture" OR "fractures" OR "bone mineral density" OR "bone density" OR osteonecrosis OR "avascular necrosis" OR	0

	<p>"muscle weakness" OR myopathy OR "diabetes mellitus" OR "blood glucose" OR "fasting glucose" OR "urine glucose" OR glycosuria OR urinalysis OR "glucose intolerance" OR "glucose tolerance" OR hyperglycaemia OR "body weight" OR "weight gain" OR "adipositas" OR "fat redistribution" OR "Fat distribution" OR "buffalo hump" OR "serum lipids" OR dyslipidemia OR dyslipidaemia OR dyslipidemias OR dyslipidaemias OR hyperlipidemias OR hyperlipidaemias OR hypercholesterolaemia OR atherosclerosis OR arteriosclerosis OR "atherosclerotic plaque" OR "coronary artery disease" OR "angina pectoris" OR "myocardial infarction" OR hypertension OR "blood pressure" OR oedema OR edema OR "cardiac insufficiency" OR "heart failure" OR "swollen ankles" OR "electrolyte disorder" OR "electrolyte balance" OR "electrolyte imbalance" OR "fluid disorder" OR "fluid retention" OR hypernatremia OR hypernatraemia OR hypokalaemia OR hypokalemia OR "Cushing syndrome" OR "facial fullness" OR "facial swelling" OR "moon face" OR "cutaneous atrophy" OR "skin atrophy" OR "skin hemorrhage" OR "skin bleeding" OR purpura OR striae OR "easy bruisability" OR "easy bruising" OR "wound healing" OR acne OR "hair loss" OR hirsutism OR alopecia OR "gastric ulcer" OR "gastroduodenal ulcer" OR "stomach ulcer" OR "peptic ulcer" OR "peptic ulcer disease" OR dyspepsia OR dysphagia OR "deglutition disorders" OR "gastric hemorrhage" OR "stomach hemorrhage" OR "gastroduodenal hemorrhage" OR cataract OR glaucoma OR "ocular pressure" OR "intraocular pressure" OR (infection AND (viral OR bacterial OR fungal OR respiratory OR urinary OR skin)) OR candida OR "non-steroidal anti-inflammatory agents" OR NSAID) :ti:ab:kw</p>	
<b>Total number of studies minus duplicates:</b>		464

### Searchstrings proposition 4:

Patient / Domain: [Rheumatic diseases AND GCs]

Intervention / Determinant: [long-term treatment]

Database:	Searchstring:	Number of studies:
Pubmed	("rheumatoid arthritis"[Title/Abstract] OR "arthritis, rheumatoid"[MeSH Terms] OR "polymyalgia rheumatica" [Title/Abstract] OR "polymyalgia rheumatica"[MeSH Terms] OR vasculit*[Title/Abstract] OR "vasculitis"[MeSH Terms] OR "systemic lupus erythematosus"[Title/Abstract] OR "lupus erythematosus, systemic"[MeSH Terms] OR "polymyositis"[Title/Abstract] OR "polymyositis"[MeSH Terms] OR "dermatomyositis"[Title/Abstract] OR "rheumatic disease"[Title/Abstract] OR "Rheumatic Diseases"[MeSH]) AND ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract]) AND ("long-term treatment"[Title/Abstract] OR "chronic treatment"[Title/Abstract] OR "long-term therapy"[Title/Abstract] OR "chronic therapy"[Title/Abstract])	109
Embase	((("rheumatoid arthritis" OR "polymyalgia rheumatica" OR "polymyalgia rheumatica" OR vasculit* OR "systemic lupus erythematosus" OR "lupus erythematosus, systemic" OR "polymyositis" OR "dermatomyositis" OR "rheumatic disease" OR "Rheumatic Diseases") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("long-term treatment" OR "chronic treatment" OR "long-term therapy" OR "chronic therapy")):ti :ab	42
Cochrane	((("rheumatoid arthritis" OR "polymyalgia rheumatica" OR "polymyalgia rheumatica" OR vasculit* OR "systemic lupus erythematosus" OR "lupus erythematosus, systemic" OR "polymyositis" OR "dermatomyositis" OR "rheumatic disease" OR "Rheumatic Diseases") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("long-term treatment" OR "chronic treatment" OR "long-term therapy" OR "chronic therapy")):ti:ab:kw	0
<b>Total number of studies minus duplicates:</b>		131

## Searchstrings proposition 5:

Patient / domain: rheumatic patient

Intervention / determinant: Monitoring (for body weight, BP, etc...) during GC-treatment.

Outcome: Body weight, blood pressure, etc..

Database:	Searchstring:	Number of studies:
Pubmed	("rheumatoid arthritis"[Title/Abstract] OR "arthritis, rheumatoid"[MeSH Terms] OR "polymyalgia rheumatica"[Title/Abstract] OR "polymyalgia rheumatica"[MeSH Terms] OR vasculit*[Title/Abstract] OR "vasculitis"[MeSH Terms] OR "systemic lupus erythematosus"[Title/Abstract] OR "lupus erythematosus, systemic"[MeSH Terms] OR "polymyositis"[Title/Abstract] OR "polymyositis"[MeSH Terms] OR "dermatomyositis"[Title/Abstract] OR "rheumatic disease"[Title/Abstract] OR "Rheumatic Diseases"[MeSH]) AND (evaluation[title/abstract] OR monitoring[title/abstract] OR assessment[title/abstract] OR control[title/abstract] OR evaluating[title/abstract] OR measurement[title/abstract] OR metaphylaxis[title/abstract] OR screening[title/abstract] OR surveillance[title/abstract] AND ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract]) AND ("diabetes mellitus"[title/abstract] OR "blood glucose"[title/abstract] OR "fasting glucose"[title/abstract] OR "urine glucose"[title/abstract] OR glycosuria[title/abstract] OR urinalysis[title/abstract] OR "glucose intolerance"[Title/Abstract] OR "glucose tolerance"[Title/Abstract] OR hyperglycaemia[title/abstract] OR "body weight"[title/abstract] OR "weight gain"[Title/Abstract] OR "adipositas"[Title/Abstract] OR "fat redistribution"[Title/Abstract] OR "Fat distribution"[Title/Abstract] OR "buffalo hump"[Title/Abstract] OR "serum lipids"[title/abstract] OR dyslipidemia[title/abstract] OR dyslipidaemia[title/abstract] OR dyslipidemias[title/abstract] OR dyslipidaemias[title/abstract] OR hyperlipidemias[title/abstract] OR hyperlipidaemias[title/abstract] OR hypercholesterolaemia[title/abstract] OR atherosclerosis[Title/Abstract] OR arteriosclerosis[Title/Abstract] OR "atherosclerotic plaque"[Title/Abstract] OR "coronary artery disease"[Title/Abstract] OR "angina pectoris"[title/abstract] OR "myocardial infarction"[title/abstract] OR hypertension[title/abstract] OR "blood pressure"[title/abstract] OR oedema[title/abstract] OR edema[title/abstract] OR "cardiac insufficiency"[title/abstract] OR "heart failure"[title/abstract] OR "swollen ankles"[title/abstract] OR "electrolyte disorder"[Title/Abstract] OR "electrolyte balance"[title/abstract] OR "electrolyte imbalance"[title/abstract] OR "fluid disorder"[Title/Abstract] OR "fluid retention"[Title/Abstract] OR hypernatremia[Title/Abstract] OR hypernatraemia[Title/Abstract] OR hypokalaemia[Title/Abstract] OR hypokalemia[Title/Abstract] OR "Cushing syndrome"[Title/Abstract] OR "facial fullness" [Title/Abstract] OR "facial swelling"[Title/Abstract] OR "moon face"[Title/Abstract] OR glaucoma[title/abstract] OR "ocular pressure"[title/abstract] OR "intraocular pressure"[title/abstract])	181
Embase	((("rheumatoid arthritis" OR "polymyalgia rheumatica" OR "polymyalgia rheumatica" OR vasculit* OR "systemic lupus erythematosus" OR "lupus erythematosus, systemic" OR "polymyositis" OR "dermatomyositis" OR "rheumatic disease" OR "Rheumatic Diseases") AND (evaluation OR monitoring OR assessment OR control OR evaluating OR measurement OR metaphylaxis OR screening OR surveillance) AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("diabetes mellitus" OR "blood glucose" OR "fasting glucose" OR "urine glucose" OR glycosuria OR urinalysis OR "glucose intolerance" OR "glucose tolerance" OR hyperglycaemia OR "body weight" OR "weight gain" OR "adipositas" OR "fat redistribution" OR "Fat distribution" OR "buffalo hump" OR "serum lipids" OR dyslipidemia OR dyslipidaemia OR dyslipidemias OR dyslipidaemias OR hyperlipidemias OR hyperlipidaemias OR hypercholesterolaemia OR atherosclerosis OR arteriosclerosis OR "atherosclerotic plaque" OR "coronary artery disease" OR "angina pectoris" OR "myocardial infarction" OR hypertension OR "blood pressure" OR oedema OR edema OR "cardiac insufficiency" OR "heart failure" OR "swollen ankles" OR "electrolyte disorder" OR "electrolyte balance" OR "electrolyte imbalance" OR "fluid disorder" OR "fluid retention" OR hypernatremia OR hypernatraemia OR hypokalaemia OR hypokalemia OR "Cushing syndrome" OR "facial fullness" OR "facial swelling" OR "moon face" OR cataract OR glaucoma OR "ocular pressure" OR "intraocular pressure"))/MJ :ti:ab AND [humans]/lim AND [embase]/lim	83
Cochrane	((("rheumatoid arthritis" OR "polymyalgia rheumatica" OR "polymyalgia rheumatica" OR vasculit* OR "systemic lupus erythematosus" OR "lupus erythematosus, systemic" OR "polymyositis" OR "dermatomyositis" OR "rheumatic disease" OR "Rheumatic Diseases") AND (evaluation OR monitoring OR assessment OR control OR evaluating OR measurement OR metaphylaxis OR screening OR surveillance) AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("diabetes mellitus" OR "blood glucose" OR "fasting glucose" OR "urine glucose" OR glycosuria OR urinalysis OR "glucose intolerance" OR "glucose tolerance" OR hyperglycaemia OR "body weight" OR "weight gain" OR "adipositas" OR "fat redistribution" OR "Fat distribution" OR "buffalo hump" OR "serum lipids" OR dyslipidemia OR dyslipidaemia OR dyslipidemias OR dyslipidaemias OR hyperlipidemias OR hyperlipidaemias OR hypercholesterolaemia OR atherosclerosis OR arteriosclerosis OR "atherosclerotic plaque" OR "coronary artery disease" OR "angina pectoris" OR "myocardial infarction" OR hypertension OR "blood pressure" OR oedema OR edema OR "cardiac insufficiency" OR "heart failure" OR "swollen ankles" OR "electrolyte disorder" OR "electrolyte balance" OR "electrolyte imbalance" OR "fluid disorder" OR "fluid retention" OR hypernatremia OR hypernatraemia OR hypokalaemia OR hypokalemia OR "Cushing syndrome" OR "facial fullness" OR "facial swelling" OR "moon face" OR cataract OR glaucoma OR "ocular pressure" OR "intraocular pressure")):ti:ab:kw	137
<b>Total number of studies minus duplicates:</b>		<b>401</b>

## Searchstrings proposition 6:

Patient / Domain: [GC]

Intervention / Determinant: [calcium OR vitamin D OR bisphosphonates]

Outcome: [review / meta-analysis]

Database:	Searchstring:	Number of studies:
Pubmed	("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract] AND (bisphosphonate[Title/Abstract] OR bisphosphonates[Title/Abstract] OR alendronate[Title/Abstract] OR ibandronate[Title/Abstract] OR etidronate[Title/Abstract] OR risendronate[Title/Abstract] OR calcitonine[Title/Abstract] OR Calcium[Title/Abstract] OR "vitamin D"[Title/Abstract] OR "vitamin D3"[Title/Abstract] OR Hydroxycholecalciferols[Title/Abstract] OR alphacalcidol[Title/Abstract]) AND ((meta-analysis [pt] OR meta-analysis [tw] OR metanalysis [tw]) OR ((review [pt] OR guideline [pt] OR consensus [ti] OR guideline* [ti] OR literature [ti] OR overview [ti] OR review [ti]) AND ((Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])) OR (handsearch* [tw] OR search* [tw] OR searching [tw]) AND (hand [tw] OR manual [tw] OR electronic [tw] OR bibliographi* [tw] OR database* OR (Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw]))) OR ((synthesis [ti] OR overview [ti] OR review [ti] OR survey [ti]) AND (systematic [ti] OR critical [ti] OR methodologic [ti] OR quantitative [ti] OR qualitative [ti] OR literature [ti] OR evidence [ti] OR evidence-based [ti]))) BUTNOT (case* [ti] OR report [ti] OR editorial [pt] OR comment [pt] OR letter [pt])	34
Embase	("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND (bisphosphonate OR bisphosphonates OR alendronate OR ibandronate OR etidronate OR risendronate OR calcitonine OR Calcium OR "vitamin D" OR "vitamin D3" OR Hydroxycholecalciferols OR alphacalcidol) AND ((meta-analysis:it OR meta-analysis OR metanalysis) OR ((review:it OR guideline:it OR consensus:ti OR guideline*:ti OR literature:ti OR overview:ti OR review:ti) AND ((Cochrane OR Medline OR CINAHL OR (National AND Library)) OR (handsearch* OR search* OR searching) AND (hand OR manual OR electronic OR bibliographi* OR database* OR (Cochrane OR Medline OR CINAHL OR (National AND Library)))) OR ((synthesis:ti OR overview:ti OR review:ti OR survey:ti) AND (systematic:ti OR critical:ti OR methodologic:ti OR quantitative:ti OR qualitative:ti OR literature:ti OR evidence:ti OR evidence-based:ti))) NOT ((case*:ti OR report:ti OR editorial:it OR comment:it OR letter:it) NOT ((meta-analysis:it OR meta-analysis OR metanalysis) OR ((review:it OR guideline:it OR consensus:ti OR guideline*:ti OR literature:ti OR overview:ti OR review:ti) AND ((Cochrane OR Medline OR CINAHL OR (National AND Library)) OR (handsearch* OR search* OR searching) AND (hand OR manual OR electronic OR bibliographi* OR database* OR (Cochrane OR Medline OR CINAHL OR (National AND Library)))) OR ((synthesis:ti OR overview:ti OR review:ti OR survey:ti) AND (systematic:ti OR critical:ti OR methodologic:ti OR quantitative:ti OR qualitative:ti OR literature:ti OR evidence:ti OR evidence-based:ti))))):ti:ab	39
Cochrane	("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND (bisphosphonate OR bisphosphonates OR alendronate OR ibandronate OR etidronate OR risendronate OR calcitonine OR Calcium OR "vitamin D" OR "vitamin D3" OR Hydroxycholecalciferols OR alphacalcidol):ti:ab:kw	12
<b>Total number of studies minus duplicates:</b>		68



## Searchstrings proposition 7:

### Part 9A:

Patient / domain: [GC-using patients with concomitant NSAID]

Intervention / determinant: [gastro-protective measures]

### Part 9B:

Patient / domain: [NSAID-using patients]

Intervention / determinant: [gastro-protective measures]

Outcome: [Review OR Meta-analysis]

Database:	Searchstring:	Number of studies:
Pubmed	<p>Part 9A:            ("adrenal cortex hormones"[Title/Abstract] OR glucocort* [Title/Abstract] OR predniso* [Title/Abstract] OR cortison* [Title/Abstract] OR hydrocortison* [Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract]) AND ("non-steroidal anti-inflammatory agents"[title/abstract] OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR "anti-inflammatory agents, non-steroidal"[Pharmacological Action] OR NSAID[title/abstract]) AND (gastro-protective[title/abstract] OR gastroprotective[title/abstract] OR "gastro-protection"[title/abstract] OR gastroprotection[title/abstract] OR "proton pump inhibitor"[title/abstract] OR "proton pump inhibitors"[title/abstract] OR PPI[title/abstract] OR "COX-2 inhibitor"[title/abstract] OR Coxib[title/abstract] OR "cyclooxygenase 2 inhibitors"[title/abstract])</p> <p>Part 9B:            ("non-steroidal anti-inflammatory agents"[title/abstract] OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR "anti-inflammatory agents, non-steroidal"[Pharmacological Action] OR NSAID[title/abstract]) AND (gastro-protective[title/abstract] OR gastroprotective[title/abstract] OR "gastro-protection"[title/abstract] OR gastroprotection[title/abstract] OR "proton pump inhibitor"[title/abstract] OR "proton pump inhibitors"[title/abstract] OR PPI[title/abstract] OR "COX-2 inhibitor"[title/abstract] OR Coxib[title/abstract] OR "cyclooxygenase 2 inhibitors"[MESH] OR "cyclooxygenase 2 inhibitors"[title/abstract]) AND ((meta-analysis [pt] OR meta-analysis [tw] OR metanalysis [tw]) OR ((review [pt] OR guideline [pt] OR consensus [ti] OR guideline* [ti] OR literature [ti] OR overview [ti] OR review [ti]) AND ((Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])) OR (handsearch* [tw] OR search* [tw] OR searching [tw]) AND (hand [tw] OR manual [tw] OR electronic [tw] OR bibliographi* [tw] OR database* OR (Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw]))) OR ((synthesis [ti] OR overview [ti] OR review [ti] OR survey [ti]) AND (systematic [ti] OR critical [ti] OR methodologic [ti] OR quantitative [ti] OR qualitative [ti] OR literature [ti] OR evidence [ti] OR evidence-based [ti]))) BUTNOT (case* [ti] OR report [ti] OR editorial [pt] OR comment [pt] OR letter [pt])</p>	<p>48</p> <p>103</p>
Embase	<p>Part 9A:            ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("non-steroidal anti-inflammatory agents" OR NSAID OR NSAIDs) AND (gastro-protective OR gastroprotective OR "gastro-protection" OR gastroprotection OR "proton pump inhibitor" OR "proton pump inhibitors" OR PPI OR "COX-2 inhibitor" OR Coxib OR "cyclooxygenase 2 inhibitors"):ti:ab</p> <p>Part 9B:            ("non-steroidal anti-inflammatory agents" OR NSAID OR NSAIDs) :ti:ab AND (gastro-protective OR gastroprotective OR "gastro-protection" OR gastroprotection OR "proton pump inhibitor" OR "proton pump inhibitors" OR PPI OR "COX-2 inhibitor" OR Coxib OR "cyclooxygenase 2 inhibitors"):ti:ab AND ((meta-analysis:it OR meta-analysis OR metanalysis) OR ((review:it OR guideline:it OR consensus:ti OR guideline*:ti OR literature:ti OR overview:ti OR review:ti) AND ((Cochrane OR Medline OR CINAHL OR (National AND Library)) OR (handsearch* OR search* OR searching) AND (hand OR manual OR electronic OR bibliographi* OR database* OR (Cochrane OR Medline OR CINAHL OR (National AND Library)))) OR ((synthesis:ti OR overview:ti OR review:ti OR survey:ti) AND (systematic:ti OR critical:ti OR methodologic:ti OR quantitative:ti OR qualitative:ti OR literature:ti OR evidence:ti OR evidence-based:ti))) NOT ((case*:ti OR report:ti OR editorial:it OR comment:it OR letter:it) NOT ((meta-analysis:it OR meta-analysis OR metanalysis) OR ((review:it OR guideline:it OR consensus:ti OR guideline*:ti OR literature:ti OR overview:ti OR review:ti) AND ((Cochrane OR Medline OR CINAHL OR (National AND Library)) OR (handsearch* OR search* OR searching) AND (hand OR manual OR electronic OR bibliographi* OR database* OR (Cochrane OR Medline OR CINAHL OR (National AND Library)))) OR ((synthesis:ti OR overview:ti OR review:ti OR survey:ti) AND (systematic:ti OR critical:ti OR methodologic:ti OR quantitative:ti OR qualitative:ti OR literature:ti OR evidence:ti OR evidence-based:ti))))</p>	<p>6</p> <p>48</p>
Cochrane	<p>Part 9A:            ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("non-steroidal anti-inflammatory agents" OR NSAID OR NSAIDs) AND (gastro-protective OR gastroprotective OR "gastro-protection" OR gastroprotection OR "proton pump inhibitor" OR "proton pump inhibitors" OR PPI OR "COX-2 inhibitor" OR Coxib OR "cyclooxygenase 2 inhibitors"):ti:ab</p> <p>Part 9B:            ("non-steroidal anti-inflammatory agents" OR NSAID OR NSAIDs) :ti:ab AND (gastro-protective OR gastroprotective OR "gastro-protection" OR gastroprotection OR "proton pump inhibitor" OR "proton pump inhibitors" OR PPI OR "COX-2 inhibitor" OR Coxib OR "cyclooxygenase 2 inhibitors"):ti:ab:kw</p>	<p>2</p> <p>22</p>
<b>Total number of studies minus duplicates:</b>		157
<b>Part 9A:</b>		48
<b>Part 9B:</b>		111

## Searchstrings proposition 8:

Patients / Domain: [Long-term GCs]

Intervention / Comparison: [perioperative GC-substitution]

Outcome: [adrenal insufficiency due to surgical stress]

Database:	Searchstring:	Number of studies:
Pubmed	(("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract]) AND ("long-term"[Title/Abstract] OR "low-dose"[Title/Abstract] OR chronic[Title/Abstract])) OR ("substitution"[Title/Abstract] OR "replacement"[Title/Abstract] OR "perioperative"[Title/Abstract]) OR ("adrenal insufficiency"[Title/Abstract] OR "adrenal deficiency"[Title/Abstract] OR "adrenal crisis"[Title/Abstract] OR "adrenocortical insufficiency"[Title/Abstract] OR "adrenocortical deficiency"[Title/Abstract] OR surgery[Title/Abstract] OR "surgical stress"[Title/Abstract])	110
Embase	("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("long-term" OR "low-dose" OR chronic) AND ("substitution" OR "replacement" OR "perioperative") AND ("adrenal insufficiency" OR "adrenal deficiency" OR "adrenal crisis" OR "adrenocortical insufficiency" OR "adrenocortical deficiency" OR surgery OR "surgical stress"):ti:ab:kw AND [humans]/lim AND [embase]/lim	203
Cochrane	("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("long-term" OR "low-dose" OR chronic) AND ("substitution" OR "replacement" OR "perioperative") AND ("adrenal insufficiency" OR "adrenal deficiency" OR "adrenal crisis" OR "adrenocortical insufficiency" OR "adrenocortical deficiency" OR surgery OR "surgical stress"):ti:ab:kw	18
<b>Total number of studies minus duplicates:</b>		303

## Searchstrings proposition 9:

Patient / Domain: [rheumatic diseases and GCs]

Intervention / Determinant: [pregnancy]

Outcome: [Safety]

Database:	Searchstring:	Number of studies:
Pubmed	("rheumatoid arthritis"[Title/Abstract] OR "arthritis, rheumatoid"[MeSH Terms] OR "polymyalgia rheumatica" [Title/Abstract] OR "polymyalgia rheumatica"[MeSH Terms] OR vasculit*[Title/Abstract] OR "vasculitis"[MeSH Terms] OR "systemic lupus erythematosus"[Title/Abstract] OR "lupus erythematosus, systemic"[MeSH Terms] OR "polymyositis"[Title/Abstract] OR "polymyositis"[MeSH Terms] OR "dermatomyositis"[Title/Abstract] OR "rheumatic disease"[Title/Abstract] OR "Rheumatic Diseases"[MeSH]) AND ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract]) AND Pregnancy[Title/Abstract] AND ((safety[title/abstract] OR "adverse event"[Title/Abstract] OR "adverse effects"[Title/Abstract] OR "adverse effect"[Title/Abstract] OR "adverse effects"[Title/Abstract] OR side-effect*[Title/Abstract] OR "unwanted effect"[Title/Abstract] OR "unwanted effects"[Title/Abstract] OR complication*[Title/Abstract] OR morbidity[title/abstract] OR toxicity[title/abstract]))	51
Embase	("rheumatoid arthritis" OR "polymyalgia rheumatica" OR "polymyalgia rheumatica" OR vasculit* OR "systemic lupus erythematosus" OR "lupus erythematosus, systemic" OR "polymyositis" OR "dermatomyositis" OR "rheumatic disease" OR "Rheumatic Diseases") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND Pregnancy AND (safety OR "adverse event" OR "adverse effects" OR "adverse effect" OR "adverse effects" OR side-effect OR side-effects OR "unwanted effect" OR "unwanted effects" OR complication* OR morbidity OR toxicity):ti:ab	31
Cochrane	("rheumatoid arthritis" OR "polymyalgia rheumatica" OR "polymyalgia rheumatica" OR vasculit* OR "systemic lupus erythematosus" OR "lupus erythematosus, systemic" OR "polymyositis" OR "dermatomyositis" OR "rheumatic disease" OR "Rheumatic Diseases") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND Pregnancy AND (safety OR "adverse event" OR "adverse effects" OR "adverse effect" OR "adverse effects" OR side-effect OR side-effects OR "unwanted effect" OR "unwanted effects" OR complication* OR morbidity OR toxicity):ti:ab:kw	8
<b>Total number of studies minus duplicates:</b>		72

## Searchstrings proposition 10:

Patient / Domain: [Children that receive GCs]

Intervention / Determinant: [linear growth OR growth hormone]

Database:	Searchstring:	Number of studies:
Pubmed	Child*[Title/Abstract] AND ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract]) AND ("Growth impairment"[Title/Abstract] OR "growth hormone"[Title/Abstract])	176
Embase	(Child* AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("Growth impairment" OR "growth hormone")):ti:ab	106
Cochrane	(Child* AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("Growth impairment" OR "growth hormone")):ti:ab:kw	39
<b>Total number of studies minus duplicates:</b>		281