National Institute for Health and Care Excellence

Final

Rheumatoid arthritis in adults: diagnosis and management

Evidence review H Glucocorticoids

NICE guideline NG100

Evidence review

July 2018

Final

This evidence review was developed by the National Guideline Centre

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1.1 Review question: In adults with rheumatoid arthritis, what is the clinical and cost effectiveness of adding short-term glucocorticoid treatment when initiating a new disease-modifying anti-rheumatic drug (DMARD)?

1.2 Introduction

DMARDs do not provide immediate relief of symptoms and take weeks or months to have an effect. While a person is waiting for a DMARD to work, symptoms may be relieved with glucocorticoids. This is often known as bridging treatment. Current practice on glucocorticoid use alongside DMARDs is variable and there is no agreement about the best approach. Most people with rheumatoid arthritis (RA) receive glucocorticoids at or shortly after diagnosis. The 2016 National Clinical Audit for Rheumatoid Arthritis and Early Inflammatory Arthritis reported that 78% of people diagnosed with rheumatoid arthritis in England and Wales were treated with glucocorticoids at the time they were given a working diagnosis, rising to 86% over the first 6 weeks. The audit did not report on the dosing or mode of administration of glucocorticoids.

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults with RA who are undergoing initiation of DMARD therapy for the first time and people who are undergoing initiation of new DMARD therapy following loss of response to previous DMARD
Interventions	• Prednisolone/prednisone – oral • Methylprednisolone – intravenous (IV) or intramuscular (IM) or intra-articular (IA) • Triamcinolone – IM or IA Studies where the glucocorticoid regimens used are not specifically aiming at remission induction will be excluded: • over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months) • IM/IA glucocorticoids administered more than3 times or over course of more than 3 months • IV glucocorticoids administered more than 3 times or over course of more than 1 week)
Comparison	Placebo or no glucocorticoid treatment
Outcomes	CRITICAL • Disease Activity Score (continuous) at 1 month • Disease Activity Score (continuous) at 3 months • Quality of life (continuous) at 1 month • Quality of life ((continuous) at 3 months • Function (continuous) at 1 month

	• Function (continuous) at 3 months IMPORTANT • Remission (dichotomous) at 1 or 3 months • Low disease activity (dichotomous) at 1 or 3 months • Pain (continuous) at 1 or 3 months • Continuing glucocorticoid use (dichotomous) at 12 months • Radiological progression (continuous) at 12 months • Adverse events (psychosis, hyperglycaemia, weight gain, insomnia, infection; dichotomous) at longest reported time point • Drug discontinuation due to adverse events (dichotomous) at longest reported time point while glucocorticoids being used • Drug discontinuation due to inefficacy (dichotomous) at longest reported time point while glucocorticoids being used
Study design	Randomised controlled trials (RCTs) Systematic reviews of RCTs

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[7] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

A search was conducted for randomised controlled trials and systematic reviews of randomised controlled trials comparing glucocorticoid treatment with placebo or no treatment in adults with RA. Five RCTs were included in the review;[19,25,32,71,73] these are summarised in Table 2 below. Four studies compared glucocorticoids with placebo, and 1 study compared glucocorticoid treatment with no glucocorticoid treatment. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.5.2 Excluded studies

A Cochrane review on the effects of glucocorticoids on radiological progression in rheumatoid arthritis by Kirwan et al. in 2007 was not included in this review because the protocol allowed inclusion of studies of any adults with a diagnosis of rheumatoid arthritis while the protocols for the guideline reviews focused specifically on people with rheumatoid arthritis who were initiating a new DMARD. However the included studies were checked for inclusion in this review.

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of randomised controlled trials included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Glucocorticoid **versus placebo**				
Corkill 1990[19]	Glucocorticoid versus placebo 8 week treatment Glucocorticoid: 120mg IM methylprednisolone at weeks 0, 4 and 8	People with classic or definite RA who require DMARD therapy Age (mean): 54 N=59	• Discontinuation: adverse events at 24 weeks • Discontinuation: inefficacy at 24 weeks	DMARD: Sodium aurothiomalate (gold) therapy
Ding 2012[25]	Glucocorticoid versus placebo 12 week treatment Glucocorticoid: oral prednisone (half of group received a low dose and half a medium dose)	People with RA for less than 2 years duration. Not used DMARDs in previous 3 months. Age at RA onset (mean): 43 N=266	• Discontinuation: adverse events at 12 weeks • Discontinuation: inefficacy at 12 weeks	DMARDs: methotrexate and leflunomide.
Gough 1994[32]	Glucocorticoid versus placebo 12 week treatment Glucocorticoid: 120mg IM methylprednisolone at 0, 4 and 12 weeks.	People with RA requiring DMARD treatment Age (mean): 54 N=20	• Discontinuation: adverse events at 3 months • Discontinuation: inefficacy at 3 months	DMARD: sulfasalazine. No other glucocorticoid permitted during study.
van Gestel 1995[71]	Glucocorticoid versus placebo 12 week treatment Glucocorticoid: oral prednisone 10mg/day	People with definite or classical RA for whom at least 1 DMARD had failed Age (mean): 57 N=40	• Discontinuation: adverse events at 12 weeks • Discontinuation: inefficacy at 12 weeks	DMARD: IM aurothioglucose. NSAIDs permitted.
Glucocorticoid **versus no** glucocorticoid				
Verschueren 2017[73]	Glucocorticoid versus usual care. Oral 30mg prednisolone step-down scheme for 34 weeks.	'Low-risk' people with RA for ≤1 year, DMARD naive. Age (mean): 51 N=90	• Radiological progression at 12 months • Adverse events: infection at 16 weeks	DMARD: methotrexate

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: glucocorticoid versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Glucocorticoids versus placebo (95% CI)
Disease Activity Score at 4 or 12 weeks - not reported	-	-	-	-	-
Quality of life at 4 or 12 weeks - not reported	-	-	-	-	-
Function at 4 or 12 weeks - not reported	-	-	-	-	-
Discontinuation: inefficacy	351 (4 studies) 12-24 weeks	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.24 (0.05 to 1.16)	40 per 1000	30 fewer per 1000 (from 70 fewer to 10 more)[3]
Discontinuation: adverse events	355 (4 studies) 12-24 weeks	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	Peto OR 0.27 (0.08 to 0.95)	55 per 1000	40 fewer per 1000 (from 90 fewer to 10 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
3 Absolute effect calculated using risk difference

Table 4: Clinical evidence summary: glucocorticoid versus no glucocorticoid

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (no glucocorticoids)	Risk difference with Glucocorticoids (95% CI)
Disease Activity Score at 4 or 12 weeks - not reported	-	-	-	-	-

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control (no glucocorticoids)	Risk difference with Glucocorticoids (95% CI)
Quality of life at 4 or 12 weeks - not reported	-	-	-	-	-
Function at 4 or 12 weeks - not reported	-	-	-	-	-
Radiological progression at 12 months Change in SvdH via X-ray. Scale from: 0 to 448.	82 (1 study) 1 years	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean radiological progression at 12 months in the control groups was 0.2	The mean radiological progression at 12 months in the intervention groups was 0.1 higher (0.08 lower to 0.28 higher)
Adverse events: infection	90 (1 study) 16 weeks	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.15 (0 to 7.46)	21 per 1000	20 fewer per 1000 (from 80 fewer to 40 more)[3]

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Risk difference used to calculate absolute effect

See appendix F for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

1.6.2 Excluded studies

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix G.

1.6.3 Unit costs

Table 5: UK costs of glucocorticoids

Drug	Dosage – Unit	Cost (£)
Methylprednisolone acetate suspension	120mg per 3ml – 1 vial	8.96
Prednisolone	2.5mg – 30 tablets	1.42
	5mg – 28 tablets	0.86
	10mg – 30 tablets	1.90
	20mg – 30 tablets	3.80

Source: NHS Drug Tariff September 2016[53]

1.7 Resource costs

The recommendations made in this review are not expected to have a substantial impact on resources.

1.8 Evidence statements

1.8.1 Clinical evidence statements

- Glucocorticoid versus placebo

Evidence from 4 studies in people starting a new DMARD, though not necessarily their first DMARD suggested a clinically important benefit of glucocorticoid treatment in terms of fewer discontinuations due to inefficacy and adverse events at 12 to 24 weeks (low to very low quality; n=385). No evidence was available for disease activity, quality of life or function.

- Glucocorticoid versus no glucocorticoid

Evidence from 1 study in people starting their first DMARD suggested a clinically important benefit of glucocorticoid treatment in terms of fewer infections at 16 weeks and a clinically important harm through radiological progression at 1 year, but there was considerable uncertainty in this effect estimates, limiting the ability to draw firm conclusions (low to very low quality; n=90). No evidence was available for disease activity, quality of life or function.

1.8.2 Health economic evidence statements

No relevant economic evaluations were identified.

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1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

Glucocorticoid treatment is used to rapidly improve symptoms of disease activity; therefore, the most critical outcome was agreed to be the Disease Activity Score (DAS). Other critical outcomes were agreed as quality of life and function. Both 1-month and 3-month outcome data was sought for many of the outcomes. The committee agreed that improvement in the short term, for example 1 month, is most useful for decision-making, as glucocorticoids are expected to have an effect soon after administration. However, DMARD treatment can take longer than 1 month to take effect and so the maintenance of any glucocorticoid effect at 3 months is also of interest.

The important outcomes were agreed as the number of people achieving remission and low disease activity, using DAS thresholds. The committee agreed that data reported in this format is not as informative as continuous DAS data but still gives an indication of symptom relief and disease activity improvement. Other important outcomes were pain, radiological progression, number of people continuing glucocorticoid use, adverse events, drug discontinuation due to inefficacy and drug discontinuation due to adverse events.

1.9.1.2 The quality of the evidence

No data on the critical outcomes were identified in evidence that met the review protocol for either of the reviews. Data for the critical outcomes were not able to be extracted on a number of occasions due to incomplete reporting (for example, reporting effect sizes without standard deviations, standard errors or confidence intervals; and reporting in figures only).

The available evidence for both of the reviews was of low or very low quality for all outcomes that were able to be extracted. For the comparison of glucocorticoid versus placebo, there were 385 participants across 4 studies, the evidence available for discontinuation due to inefficacy and discontinuation due to adverse events was of low or very low quality. All outcomes were downgraded on quality due to risk of bias and imprecision. Selection bias was the most common cause of risk of bias due to limited baseline comparability of treatment groups. For the comparison of glucocorticoid versus no glucocorticoid, there were 90 participants in 1 study, the evidence for radiological progression and adverse events (infection) was of low or very low quality. The evidence was considered high risk of bias due to lack of blinding. For the comparison of different dosing regimens, very low quality evidence was available for discontinuation due to adverse events and discontinuation due to inefficacy. Selection bias was the most common cause of risk of bias due to limited comparability of treatment groups.

1.9.1.3 Benefits and harms

Glucocorticoid versus no glucocorticoid/placebo

The committee agreed that the evidence on the effect of adding glucocorticoids when starting a new DMARD regimen was modest. There appeared to be a clinically important benefit in terms of fewer discontinuations due to inefficacy or adverse events when glucocorticoids were used, which suggested that glucocorticoids were well tolerated and improved efficacy. Overall, the evidence comprised some limited data on a small number of important outcomes and no data for any of the critical outcomes. However, the evidence did not suggest that glucocorticoid treatment is *not* effective, but more so that effectiveness was inconclusive due to lack of good quality evidence.

The committee discussed the 2 recommendations in the previous rheumatoid arthritis in adults: management [51] (2009) NICE guidance (CG79) that related to bridging treatment with glucocorticoids. The evidence was not considered convincing enough to warrant a recommendation to offer glucocorticoid treatment to all people as a bridge therapy in the early stage of DMARD treatment. In addition, it was noted that people with a low DAS at presentation may be prescribed DMARD treatment but do not necessarily require additional symptomatic treatment via glucocorticoids. Therefore, the wording of the previous recommendation to offer DMARDs in combination with glucocorticoids was edited to remove glucocorticoid treatment at this stage of the pathway.

Based on the evidence reviewed and group consensus, the committee agreed, however, that the recommendation from CG79 to 'consider' short-term glucocorticoid treatment to rapidly improve symptoms should be maintained. The rationale behind this recommendation, alongside the evidence, was that people with a high DAS may gain benefit from the effect of glucocorticoid treatment when starting a new DMARD. Committee consensus was that the anti-inflammatory effect of glucocorticoid treatment is effective for treating synovitis (active inflammation in a joint) and reducing DAS, which is important in the weeks or months before DMARD treatment takes effect. The lay representatives on the committee also emphasised the importance of bridging glucocorticoids in this period. At diagnosis, most people have a high DAS score and the lay members felt that glucocorticoids play an important role in controlling disease activity rapidly, not only to improve disease outcomes but also to provide rapid relief from pain, fatigue and other symptoms.

The previous 'consider' recommendation was also amended to clarify that the relevant population is all people starting a new DMARD, rather than just people who are newly diagnosed with rheumatoid arthritis. When existing DMARDs are replaced or new DMARDs are added to a regimen in the event of inadequate response, there may be the same need for rapid control of disease symptoms as when starting DMARDs for the first time.

As noted above, glucocorticoids may not be necessary for all people receiving a new DMARD; for example, people newly diagnosed with RA with low disease activity levels may not require bridging therapy with glucocorticoids. This should be considered as part of shared decision-making between clinicians and people with rheumatoid arthritis.

Glucocorticoid dosing

The committee considered that the glucocorticoid dose comparison review did not contain enough evidence to support any recommendation about dosing regimens. The committee agreed that no firm conclusions could be drawn from the single comparison from 1 study with no critical outcomes reported. A consensus recommendation was not considered appropriate for this comparison due to the variability in current practice regarding bridging glucocorticoid regimens.

Further research

The lack of good quality evidence also led the committee to make a research recommendation to determine the effectiveness of glucocorticoid treatment in people with rheumatoid arthritis initiating a new DMARD. The objective of this research would be to establish whether glucocorticoid therapy is effective for symptom control in the period before a DMARD takes full effect. The committee agreed that further research into different bridging glucocorticoid regimens (dose and mode of administration) was also needed as there was considerable uncertainty in this area not answered by the review.

1.9.2 Cost effectiveness and resource use

No relevant published health economic evidence was identified.

The committee noted that the use of glucocorticoids as a bridging treatment is covered by NICE guidance CG79. The unit costs of glucocorticoids were presented to the committee. The committee highlighted that although their unit cost is relatively low, follow-up costs due to adverse events may increase the NHS use in a small group of people.

The committee agreed that based on a lack of clinical evidence and no cost-effectiveness evidence, to remove the recommendation to offer glucocorticoids as part of a combination of DMARDs. The committee agreed, based on consensus, to maintain a recommendation that would allow consideration of short-term treatment with glucocorticoids (oral, intramuscular or intra-articular) in people commencing new DMARD treatment to rapidly improve symptoms. The committee considered that some people, such as those with a high DAS, may benefit from the effect of glucocorticoid treatment when starting a new DMARD. Overall, the committee concluded that these amended recommendations would not result in any additional spending for the NHS.

1.9.3 Other factors the committee took into account

The management of rheumatoid arthritis in pregnancy was identified as an equalities issue in the equalities impact assessment. The committee agreed that it should be an individualised and consultant-led service, with involvement of obstetric services and broader rheumatology MDT as indicated. People with rheumatoid arthritis and their rheumatology team need to consider many aspects of each individuals care. These include pre-conception advice and management of pharmacological therapies, assessment of potential impact of disease on the pregnancy, advice on disease course during pregnancy, and discussions regarding the disease and its treatment in the post-partum period. Particular attention should be paid to therapeutic management of rheumatoid arthritis to ensure potentially teratogenic therapies are not continued in the pre-conception stage or into early pregnancy. Alternative management strategies should be considered, depending on each person's level of disease control and symptoms, for the duration of the pregnancy.

2 Glucocorticoid regimen for people with rheumatoid arthritis

2.1 Review question: In adults with rheumatoid arthritis, when initiating a new DMARD, which short-term glucocorticoid regimen is most clinically and cost effective?

2.2 Introduction

DMARDs do not provide immediate relief of symptoms and take weeks or months to have an effect. While a person is waiting for a DMARD to work, symptoms may be relieved with glucocorticoids. This is often known as bridging treatment. Current practice on glucocorticoid use alongside DMARDs is variable and there is no agreement about the best approach. Most people with rheumatoid arthritis receive glucocorticoids at or shortly after diagnosis. The 2016 National Clinical Audit for Rheumatoid Arthritis and Early Inflammatory Arthritis reported that 78% of people diagnosed with rheumatoid arthritis in England and Wales were treated with glucocorticoids at the time they were given a working diagnosis, rising to 86% over the first 6 weeks. The audit did not report on the dosing or mode of administration of glucocorticoids.

2.3 PICO table

For full details, see the review protocol in appendix A.

Table 6: PICO characteristics of review question

Population	People with rheumatoid arthritis who are undergoing initiation of DMARD therapy for the first time and people who are undergoing initiation of a new DMARD therapy following loss of response to previous DMARD
Interventions	• High dose – IV administration, oral administration more than 40mg/day • Medium dose – IM/IA administration, oral administration 10-40mg/day • Low dose – oral administration less than 10 mg/day Where oral dose varied during the study, the dose regimen was assigned according to the starting oral dose. Studies where the glucocorticoid regimens did not specifically aim at remission induction will be excluded: • Over a long treatment duration (continuous oral glucocorticoid without tapering to zero commenced before 6 months and completed before 12 months) • IM/IA glucocorticoids administered more than 3 times or over course of more than 3 months • IV glucocorticoid administered more than 3 times or over course of more than 1 week
Comparison	Comparison of different dosage regimens
Outcomes	CRITICAL • Disease Activity Score (continuous) at 1 month and 3 months • Quality of life (for example, EQ5D, SF-36, RA Quality of Life instrument, patient global assessment as per OMERACT method; continuous) at 1 month and 3 months • Function (for example, Health Assessment Questionnaire, activities of daily living; continuous) at 1 month and 3 months

	IMPORTANT • Remission (dichotomous) at 1 and 3 months • Low disease activity (dichotomous) at 1 and 3 months • Pain (for example, visual analogue scale; continuous) at 1 and 3 months • Continuing glucocorticoid use (dichotomous) at 12 months • Radiological progression (continuous) at 12 months • Adverse events (psychosis, hyperglycaemia, weight gain, insomnia, infection; dichotomous) at longest reported time point • Drug discontinuation due to adverse events (dichotomous) at longest reported time point • Drug discontinuation due to inefficacy (dichotomous) at longest reported time point
Study design	RCTs Systematic reviews of RCTs

2.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[7] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

2.5 Clinical evidence

2.5.1 Included studies

A search was conducted for randomised controlled trials and systematic reviews of randomised controlled trials comparing varying doses of glucocorticoid treatment to each other in adults with rheumatoid arthritis. One RCT was included in the review;[25] it is summarised in the summary of clinical studies in Table 7 below.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

2.5.2 Excluded studies

See the excluded studies list in appendix I.

2.5.3 Summary of randomised controlled trials included in the evidence review

Table 7: Clinical studies included

Study	Intervention and comparison	Population	Outcomes	Comments
Ding 2012[25]	Low dose glucocorticoid versus medium dose glucocorticoid 12 week treatment Low dose: 7.5mg per day oral	People with RA for less than 2 years duration. Not used DMARDs in previous 3 months. Age at RA onset (mean): 42	Discontinuation: adverse events at 12 weeks Discontinuation: inefficacy at 12 weeks	N=176 DMARDs: methotrexate and leflunomide. Suitable therapy such as NSAIDs allowed.

Study	Intervention and comparison	Population	Outcomes	Comments
	prednisone. Medium dose: 15mg per day oral prednisone			

See appendix D for full evidence tables.

2.5.4 Quality assessment of clinical studies included in the evidence review

Table 8: Clinical evidence summary: low dose versus medium dose

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medium dose	Risk difference with Low dose glucocorticoids versus medium dose glucocorticoids (95% CI)
Disease Activity Score at 4 or 12 weeks - not reported	-	-	-	-	-
Quality of life at 4 or 12 weeks - not reported	-	-	-	-	-
Function at 4 or 12 weeks - not reported	-	-	-	-	-
Discontinuation: inefficacy	172 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	Peto OR 7.39 (0.15 to 372.38)	0 per 1000	12 more per 1000 (from 20 fewer to 40 more)[1]
Discontinuation: adverse events	174 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW[2,3] due to risk of bias, imprecision	RR 0.51 (0.05 to 5.54)	23 per 1000	11 fewer per 1000 (from 22 fewer to 103 more)

1 Calculated from risk difference
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

See appendix F for full GRADE tables.

2.6 Economic evidence

2.6.1 Included studies

No relevant health economic studies were identified.

2.6.2 Excluded studies

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix G.

2.6.3 Unit costs

Table 9: UK costs of glucocorticoids

Drug	Dosage – Unit	Cost (£)
Methylprednisolone acetate suspension	120mg per 3ml – 1 vial	8.96
Prednisolone	2.5mg – 30 tablets	1.42
	5mg – 28 tablets	0.86
	10mg – 30 tablets	1.90
	20mg – 30 tablets	3.80
	25mg – 56 tablets	75.00

Source: NHS Drug Tariff September 2016

2.7 Resource costs

The recommendations made in this review are not expected to have a substantial impact on resources.

2.8 Evidence statements

2.8.1 Clinical evidence statements

- Low dose versus medium dose glucocorticoid treatment

Evidence from 1 study indicated a clinically important benefit for low dose glucocorticoid treatment in terms of fewer discontinuations due to adverse events and no clinical difference between groups for discontinuation due to inefficacy, both at 12 weeks (very low quality; n=174 and 172). However, there was considerable uncertainty in these effect estimates, limiting the ability to draw firm conclusions. No evidence was available for disease activity, quality of life or function.

2.8.2 Health economic evidence statements

No relevant economic evaluations were identified.

2.9 The committee's discussion of the evidence

2.9.1 Interpreting the evidence

2.9.1.1 The outcomes that matter most

Glucocorticoid treatment is used to rapidly improve symptoms of disease activity; therefore, the most critical outcome was agreed to be the Disease Activity Score (DAS). Other critical outcomes were agreed as quality of life and function. Both 1-month and 3-month outcome data was sought for many of the outcomes. The committee agreed that improvement in the short term, for example, 1 month, is most useful for decision-making, as glucocorticoids are expected to have an effect soon after administration. However, DMARD treatment can take longer than 1 month to take effect and so the maintenance of any glucocorticoid effect at 3 months is also of interest.

The important outcomes were agreed as the number of people achieving remission and low disease activity, using DAS thresholds. The committee agreed that data reported in this format is not as informative as continuous DAS data but still give an indication of symptom relief and disease activity improvement. Other important outcomes were pain, radiological progression, number of people continuing glucocorticoid use, adverse events, drug discontinuation due to inefficacy and drug discontinuation due to adverse events.

2.9.1.2 The quality of the evidence

No data on the critical outcomes were identified in evidence that met the review protocol for either of the reviews. Data for the critical outcomes were not able to be extracted on a number of occasions due to incomplete reporting (for example, reporting effect sizes without standard deviations, standard errors or confidence intervals; and reporting in figures only).

The available evidence for both of the reviews was of low or very low quality for all outcomes that were able to be extracted. For the comparison of glucocorticoid versus placebo, low or very low quality evidence was available for discontinuation due to inefficacy and discontinuation due to adverse events. All outcomes were downgraded on quality due to risk of bias and imprecision. Selection bias was the most common cause of risk of bias due to limited comparability of treatment groups. For the comparison of glucocorticoid versus no glucocorticoid, low or very low quality evidence was available for radiological progression and adverse events (infection). The evidence was considered high risk of bias due to lack of blinding. For the comparison of different dosing regimens, very low quality evidence was available for discontinuation due to adverse events and discontinuation due to inefficacy. Selection bias was the most common cause of risk of bias due to limited comparability of treatment groups.

The committee were aware of a 2007 Cochrane review entitled Effects of glucocorticoids in on radiological progression in rheumatoid arthritis by Kirwan et al, which was unable to be included due to differences in the review protocols. The Cochrane review was not included in this review because the protocol allowed inclusion of any adults with a diagnosis of rheumatoid arthritis while the protocols for the guideline reviews focussed specifically on people with rheumatoid arthritis who were initiating a new DMARD. Trials were only included if the only difference between the arms was the use of glucocorticoids and the DMARD regimen used in each arm was the same. Trials were also excluded in accordance with the protocol if participants were not commencing a new DMARD, where the duration of glucocorticoid treatment was not considered 'short term', or for the glucocorticoid regimen review, where the glucocorticoid regimens compared in the trials were deemed to be similar in total dose. These protocol restrictions were agreed by the committee as important to ensure the review specifically addressed the key area of uncertainty. All references from the

Cochrane review were checked for inclusion, but many of the studies included were ineligible for inclusion for these reasons.

2.9.1.3 Benefits and harms

Glucocorticoid versus no glucocorticoid/placebo

The committee agreed that the evidence on the effect of adding glucocorticoids when starting a new DMARD regimen was modest. There appeared to be a clinically important benefit in terms of fewer discontinuations due to inefficacy or adverse events when glucocorticoids were used, which suggested that glucocorticoids were well tolerated and improved efficacy. Overall, the evidence comprised some limited data on a small number of important outcomes and no data for any of the critical outcomes. However, the evidence did not suggest that glucocorticoid treatment is ineffective, but more so that effectiveness was inconclusive due to lack of good quality evidence.

The committee incorporated the 2 recommendations in the previous rheumatoid arthritis in adults: management [51] (2009) NICE guidance (CG79) that related to bridging treatment with glucocorticoids into dicussions. The guideline evidence was considered strong enough to warrant a recommendation to consider glucocorticoid treatment to people as a bridge therapy in the early stage of DMARD treatment. In addition, it was noted that people with a low DAS at presentation may be prescribed DMARD treatment but do not necessarily require additional symptomatic treatment via glucocorticoids. Therefore, the wording of the previous recommendation to offer DMARDs in combination with glucocorticoids was edited to remove glucocorticoid treatment at this stage of the pathway.

Based on the evidence reviewed and group consensus through the the committee's expertise and experience, it was agreed that the recommendation from CG79 to 'consider' short-term glucocorticoid treatment to rapidly improve symptoms should be maintained. The rationale behind this recommendation, alongside the evidence, was that people with a high DAS may gain benefit from the effect of glucocorticoid treatment when starting a new DMARD. The committee's expertise and experience indicated was that the anti-inflammatory effect of glucocorticoid treatment is effective for treating synovitis (active inflammation in a joint) and reducing DAS, which is important in the weeks or months before DMARD treatment takes effect. The lay representatives on the committee also emphasised the importance of bridging glucocorticoids in this period. At diagnosis, most people have a high DAS score, and the lay members felt that glucocorticoids play an important role in controlling disease activity rapidly, not only to improve disease outcomes but also to provide rapid relief from pain, fatigue and other symptoms.

The previous 'consider' recommendation was also amended to clarify that the relevant population is all people starting a new DMARD, rather than just people who are newly diagnosed with rheumatoid arthritis. When existing DMARDs are replaced or new DMARDs are added to a regimen in the event of inadequate response, there may be the same need for rapid control of disease symptoms as when starting DMARDs for the first time.

As noted above, glucocorticoids may not be necessary for all people receiving a new DMARD; for example, people newly diagnosed with RA with low disease activity levels may not require bridging therapy with glucocorticoids. The committee therefore agreed that this should be considered as part of shared decision-making between clinicians and people with rheumatoid arthritis.

Glucocorticoid dosing

The committee considered that the glucocorticoid dose comparison review did not contain enough evidence to support any recommendation about dosing regimens. The committee

agreed that no firm conclusions could be drawn from the single comparison from 1 study with no critical outcomes reported. A consensus recommendation was not considered appropriate for this comparison due to the variability in current practice regarding bridging glucocorticoid regimens.

Further research

The lack of good quality evidence also led the committee to make a research recommendation to determine the effectiveness of glucocorticoid treatment in people with rheumatoid arthritis initiating a new DMARD. The objective of this research would be to establish whether glucocorticoid therapy is effective for symptom control in the period before a DMARD takes full effect. The committee agreed that further research into different bridging glucocorticoid regimens (dose and mode of administration) was also needed as there was considerable uncertainty in this area not answered by the review.

2.9.2 Cost effectiveness and resource use

No relevant published health economic evidence was identified.

The committee noted that the use of glucocorticoids as a bridging treatment is covered by NICE guidance CG79. The unit costs of glucocorticoids were presented to the committee. The committee highlighted that although their unit cost is relatively low, follow-up costs due to adverse events may increase the NHS use in a small group of people.

The committee agreed that based on a lack of clinical evidence and no cost-effectiveness evidence to remove the recommendation to offer glucocorticoids as part of a combination of DMARDs. The committee agreed based on consensus to maintain a recommendation that would allow consideration of short-term treatment with glucocorticoids (oral, intramuscular or intra-articular) in people commencing new DMARD treatment to rapidly improve symptoms. The committee considered that some people, such as those with a high DAS, may benefit from the effect of glucocorticoid treatment when starting a new DMARD. Overall, the committee concluded that these amended recommendations would not result in any additional spending for the NHS.

2.9.3 Other factors the committee took into account

The management of rheumatoid arthritis in pregnancy was identified as an equalities issue in the equalities impact assessment. No studies were found that reported on only pregnant women or presented data for a pregnant women subgroup. The committee agreed that it should be an individualised and consultant-led service, with involvement of obstetric services and broader rheumatology MDT as indicated. People with rheumatoid arthritis and their rheumatology team need to consider many aspects of each individuals care. These include pre-conception advice and management of pharmacological therapies, assessment of potential impact of disease on the pregnancy, advice on disease course during pregnancy, and discussions regarding the disease and its treatment in the post-partum period. Particular attention should be paid to therapeutic management of rheumatoid arthritis to ensure potentially teratogenic therapies are not continued in the pre-conception stage or into early pregnancy. Alternative management strategies should be considered, depending on each person's level of disease control and symptoms, for the duration of the pregnancy.

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Appendices

Appendix A: Review protocols

Table 10: Review protocol: short-term glucocorticoids (compared with placebo)

In adults with rheumatoid arthritis, what is the clinical and cost effectiveness of adding short-term glucocorticoids (compared with placebo) when initiating a new DMARD?

ID	Field	Content
I	Review question	In adults with rheumatoid arthritis, what is the clinical and cost effectiveness of adding short-term glucocorticoids (compared with placebo or no glucocorticoid treatment) when initiating a new DMARD? (To determine whether all patients should be offered glucocorticoids when initiating a new DMARD for control of active disease).
II	Type of review question	Intervention
III	Objective of the review	This review seeks to determine whether all people with active rheumatoid arthritis should be offered glucocorticoids when initiating a new DMARD for control of active disease.
IV	Eligibility criteria – population / disease / condition / issue / domain	Adults with rheumatoid arthritis who are commencing a new DMARD. The initiation of any conventional or biologic DMARDs will be considered. Studies in patients who are undergoing initiation of DMARD therapy for the first time and patients who are undergoing initiation of new DMARD following loss of response to previous DMARD will be combined in the analysis. In the latter case, the new DMARD may be in addition or in place of previous DMARD. No requirement as to background medication (for example, analgesics). Pregnant women will be treated as a stratum.
V	Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Glucocorticoids: Prednisolone/prednisone – oral Methylprednisolone – intravenous (IV) or intramuscular (IM) or intra-articular (IA) Triamcinolone – IM or IA Data for all glucocorticoids will be pooled within each of the above comparisons, regardless of particular drug, mode of administration or dose.
VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	Comparison of glucocorticoid against placebo. Comparison of glucocorticoid against no corticoglucocorticoid treatment.
VII	Outcomes and prioritisation	CRITICAL • Disease Activity Score (continuous) at 4 weeks & 12 weeks • Quality of life (for example, EQ5D, SF-36, RA Quality of Life instrument, patient global assessment as per OMERACT method)

ID	Field	Content
		(continuous) at 4 weeks and 12 weeks • Function (for example, Health Assessment Questionnaire, activities of daily living) (continuous) at 4 weeks and 12 weeks IMPORTANT • Low disease activity (dichotomous) at 4 weeks & 12 weeks • Remission (dichotomous) at 4 weeks & 12 weeks • Pain (for example, visual analogue scale; continuous) at 4 weeks & 12 weeks • Continuing glucocorticoid use (dichotomous) at 12 months • Radiological progression (continuous) at 12 months • Adverse events (psychosis, hyperglycaemia, weight gain, insomnia, infection; dichotomous) at longest reported time point while glucocorticoids were being prescribed • Discontinuation due to adverse events (dichotomous) at longest reported time point while glucocorticoids were being prescribed • Discontinuation due to inefficacy (dichotomous) at longest reported time point while glucocorticoids were being prescribed
VIII	Eligibility criteria – study design	Systematic Review RCT
IX	Other inclusion exclusion criteria	Studies where the glucocorticoid regimens used are not specifically aiming at remission induction will be excluded: • over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months) • IM/IA glucocorticoids administered more than3 times or over course of more than 3 months IV glucocorticoids administered more than 3 times or over course of more than 1 week)
X	Proposed sensitivity / subgroup analysis, or meta-regression	For the short term (4 & 12 week) time points above, where a study reports multiple time points, the closest time point to the specified time point will be extracted. Data will not be extracted if it is > 12 weeks. For the long term (12-month) time points above, the longest time point reported will be extracted. Data will not be extracted if it is less than 12 months. Subgroup analyses if there is heterogeneity: Mode of administration within dose class (IV v IM v IA v oral)
XI	Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists will be double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus could not be reached, for more information please see the separate methods report for this guideline.
XII	Data management (software)	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome. • Endnote will be used for bibliography, citations, sifting and reference management.
XIII	Information sources – databases and dates	Cilnical search databases: Medline, Embase and the Cochrane Library. Date limits for search: None

ID	Field	Content
		Language: English Health economics search databases: Medline, Embase, NHSEED and HTA Date limits for search: Medline and Embase from 2014 NHSEED and HTA from 2001 Language: English
XIV	Identify if an update	This review is an update of a clinical area covered in NICE guideline: Rheumatoid arthritis in adults: management[51] published in 2009. However the protocol for this updated review differed from the previous review and thus the search was undertaken for all years.
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10014
XVI	Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
XVII	Search strategy – for one database	For details, please see appendix B
XVIII	Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
XIX	Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
XX	Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
XXIV	Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale / context – what is known	For details, please see the introduction to the evidence review.

ID	Field	Content
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee (https://www.nice.org.uk/guidance/indevelopment/gid-ng10014/documents) developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Stephen Ward in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual
XXVII	Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XXVIII	Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XXIX	Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	Not registered

Table 11: Review protocol for regimens of short-term glucocorticoids

In adults with rheumatoid arthritis, when initiating a new DMARD, which short-term glucocorticoid regimen is most clinically and cost effective?

ID	Field	Content
I	Review question	In adults with rheumatoid arthritis, when initiating a new DMARD, which short-term glucocorticoid regime is most clinically and cost effective? (If short-term glucocorticoids are effective compared with placebo/no glucocorticoids, to determine which dosage regime and length of treatment is most effective.)
II	Type of review question	Intervention
III	Objective of the review	This review seeks to determine whether all people with active rheumatoid arthritis should be offered glucocorticoid when initiating a new DMARD for control of active disease.
IV	Eligibility criteria – population / disease / condition / issue / domain	Adults with rheumatoid arthritis who are commencing a new DMARD. The initiation of any conventional or biologic DMARDs will be considered. Studies in patients who are undergoing initiation of DMARD therapy for the first time and patients who are undergoing initiation of new DMARD following loss of response to previous DMARD will be combined in the analysis. In the latter case, the new DMARD may be in addition or in place of previous DMARD. No requirement as to background medication (for example, analgesics). Pregnant women will be treated as a stratum.
V	Eligibility criteria – intervention(s) / exposure(s) /	Glucocorticoid: Prednisolone/prednisone – oral

ID	Field	Content
	prognostic factor(s)	Methylprednisolone – intravenous (IV), intramuscular (IM) or intra-articular (IA) Triamcinolone – IM or IA Data will be pooled in a dose class, regardless of particular drug or mode of administration, as follows: High dose – IV administration, oral administration > 40mg/day Medium dose – IM/IA administration, oral administration 10-40mg/day Low dose – oral administration < 10 mg/day
VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	Comparison of glucocorticoid doses as defined in the intervention eligibility criteria above.
VII	Outcomes and prioritisation	CRITICAL • Disease Activity Score (continuous) at 4 weeks & 12 weeks • Quality of life (for example, EQ5D, SF-36, RA Quality of Life instrument, patient global assessment as per OMERACT method) (continuous) at 4 weeks and 12 weeks • Function (for example, Health Assessment Questionnaire, activities of daily living) (continuous) at 4 weeks and 12 weeks IMPORTANT • Low disease activity (dichotomous) at 4 weeks & 12 weeks • Remission (dichotomous) at 4 weeks & 12 weeks • Pain (for example, visual analogue scale; continuous) at 4 weeks & 12 weeks • Continuing glucocorticoid use (dichotomous) at 12 months • Radiological progression (continuous) at 12 months • Adverse events (psychosis, hyperglycaemia, weight gain, insomnia, infection; dichotomous) at longest reported time point while glucocorticoids were being prescribed • Discontinuation due to adverse events (dichotomous) at longest reported time point while glucocorticoids were being prescribed • Discontinuation due to inefficacy (dichotomous) at longest reported time point while glucocorticoids were being prescribed
VIII	Eligibility criteria – study design	Systematic Review RCT
IX	Other inclusion exclusion criteria	Studies where the glucocorticoid regimens used are not specifically aiming at remission induction will be excluded: • over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months) • IM/IA glucocorticoids administered more than3 times or over course of more than 3 months IV glucocorticoids administered more than 3 times or over course of more than 1 week)
X	Proposed sensitivity / subgroup analysis, or meta-regression	Sensitivity For the short term (4 & 12 week) time points above, where a study reports multiple time points, the closest time point to the specified time point will be extracted. Data will not be extracted if

ID	Field	Content
		it is > 12 weeks. For the long term (12-month) time points above, the longest time point reported will be extracted. Data will not be extracted if it is less than 12 months. Subgroup analyses if there is heterogeneity Mode of administration within dose class (IV v IM v IA v oral)
XI	Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists were double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus could not be reached, for more information please see the separate Methods report for this guideline
XII	Data management (software)	• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). • GRADEpro was used to assess the quality of evidence for each outcome. Endnote was used for bibliography, citations, sifting and reference management
XIII	Information sources – databases and dates	Databases: Medline, Embase and the Cochrane Library. Date limits for search: None Language: English
XIV	Identify if an update	Not an update
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10014
XVI	Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
XVII	Search strategy – for one database	For details, please see appendix B
XVIII	Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
XIX	Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
XX	Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
XXIV	Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.

ID	Field	Content
XXV	Rationale / context – what is known	For details, please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee (https://www.nice.org.uk/guidance/indevelopment/gid-ng10014/documents) developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Stephen Ward in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual
XXVII	Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XXVIII	Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
XXIX	Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	Not registered

Table 12: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	Populations, interventions and comparators must be as specified in the clinical review protocol above. Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).52 Inclusion and exclusion criteria If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic

Review question	All questions – health economic evidence
	evidence table will not be completed and it will not be included in the health economic evidence profile. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both, then there is discretion over whether it should be included. Where there is discretion The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. Setting: UK NHS (most applicable). OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example, Switzerland). Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. Health economic study type: Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. Year of analysis: The more recent the study, the more applicable it will be. Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly from before 2001 will be rated as 'Not applicable'. Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations. Quality and relevance of effectiveness data used in the health economic analysis: The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017. https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (Ovid)	1946 – 09 October 2017	Exclusions Randomised controlled trials Systematic review studies
Embase (Ovid)	1974 – 09 October 2017	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 10 of 12 CENTRAL to 2017 Issue 9 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp Arthritis, Rheumatoid/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/

15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	exp Glucocorticoids/
30.	(corticosteroid* or steroid* or glucocorticoid*).ti,ab.
31.	(prednisolone or deltacortril or deltastab or pevanti or methylprednisolone or medrone or depo-medrone or solu-medrone or prednisone or lodotra or triamcinolone or adcortyl or aureocort or kenalog).ti,ab.
32.	or/29-31
33.	28 and 32
34.	randomized controlled trial.pt.
35.	controlled clinical trial.pt.
36.	randomi#ed.ti,ab.
37.	placebo.ab.
38.	drug therapy.fs.
39.	randomly.ti,ab.
40.	trial.ab.
41.	groups.ab.
42.	or/34-41
43.	Clinical Trials as topic.sh.
44.	trial.ti.
45.	or/34-37,39,43-44
46.	Meta-Analysis/
47.	Meta-Analysis as Topic/
48.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
49.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
50.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
51.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
52.	(search* adj4 literature).ab.
53.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
54.	cochrane.jw.
55.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.

56.	or/46-55
57.	33 and (45 or 56)

Embase (Ovid) search terms

1.	exp *rheumatoid arthritis/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	exp *glucocorticoid/ or *corticosteroid/
28.	(corticosteroid* or steroid* or glucocorticoid*).ti,ab.
29.	(prednisolone or deltacortril or deltastab or pevanti or methylprednisolone or medrone or depo-medrone or solu-medrone or prednisone or lodotra or triamcinolone or adcortyl or aureocort or kenalog).ti,ab.
30.	or/27-29
31.	26 and 30
32.	random*.ti,ab.
33.	factorial*.ti,ab.
34.	(crossover* or cross over*).ti,ab.
35.	((doubl* or singl*) adj blind*).ti,ab.
36.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
37.	crossover procedure/
38.	single blind procedure/
39.	randomized controlled trial/
40.	double blind procedure/

41.	or/32-40
42.	systematic review/
43.	meta-analysis/
44.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
45.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
46.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
47.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
48.	(search* adj4 literature).ab.
49.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
50.	cochrane.jw.
51.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
52.	or/42-51
53.	31 and (41 or 52)

Cochrane Library (Wiley) search terms

#1.	[mh "Arthritis, Rheumatoid"]
#2.	(rheumatoid near/2 (arthritis or arthrosis)):ti,ab
#3.	(caplan* near/2 syndrome):ti,ab
#4.	(felty* near/2 syndrome):ti,ab
#5.	(rheumatoid near/2 factor):ti,ab
#6.	((inflammatory or idiopathic) near/2 arthritis):ti,ab
#7.	inflammatory polyarthritis:ti,ab
#8.	(or #1-#7)
#9.	[mh Glucocorticoids]
#10.	(corticosteroid* or steroid* or glucocorticoid*):ti,ab
#11.	(prednisolone or deltacortril or deltastab or pevanti or methylprednisolone or medrone or depo-medrone or solu-medrone or prednisone or lodotra or triamcinolone or adcortyl or aureocort or kenalog):ti,ab
#12.	#9 or #10 or #11
#13.	#8 and #12

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to rheumatoid arthritis population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies.

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 06 October 2017	Exclusions Health economics studies
Embase	2014– 06 October 2017	Exclusions

Database	Dates searched	Search filter used
		Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2001 – 06 October 2017 NHSEED - 2001 – 31 March 2015	None

Medline (Ovid) search terms

1.	exp Arthritis, Rheumatoid/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	Economics/
30.	Value of life/
31.	exp "Costs and Cost Analysis"/
32.	exp Economics, Hospital/
33.	exp Economics, Medical/
34.	Economics, Nursing/
35.	Economics, Pharmaceutical/
36.	exp "Fees and Charges"/
37.	exp Budgets/

38.	budget*.ti,ab.
39.	cost*.ti.
40.	(economic* or pharmaco?economic*).ti.
41.	(price* or pricing*).ti,ab.
42.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
43.	(financ* or fee or fees).ti,ab.
44.	(value adj2 (money or monetary)).ti,ab.
45.	or/29-44
46.	exp models, economic/
47.	*Models, Theoretical/
48.	*Models, Organizational/
49.	markov chains/
50.	monte carlo method/
51.	exp Decision Theory/
52.	(markov* or monte carlo).ti,ab.
53.	econom* model*.ti,ab.
54.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
55.	or/46-54
56.	28 and (45 or 55)

Embase (Ovid) search terms

1.	exp *rheumatoid arthritis/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/

22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	statistical model/
28.	exp economic aspect/
29.	27 and 28
30.	*theoretical model/
31.	*nonbiological model/
32.	stochastic model/
33.	decision theory/
34.	decision tree/
35.	monte carlo method/
36.	(markov* or monte carlo).ti,ab.
37.	econom* model*.ti,ab.
38.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
39.	or/29-38
40.	*health economics/
41.	exp *economic evaluation/
42.	exp *health care cost/
43.	exp *fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	26 and (39 or 53)

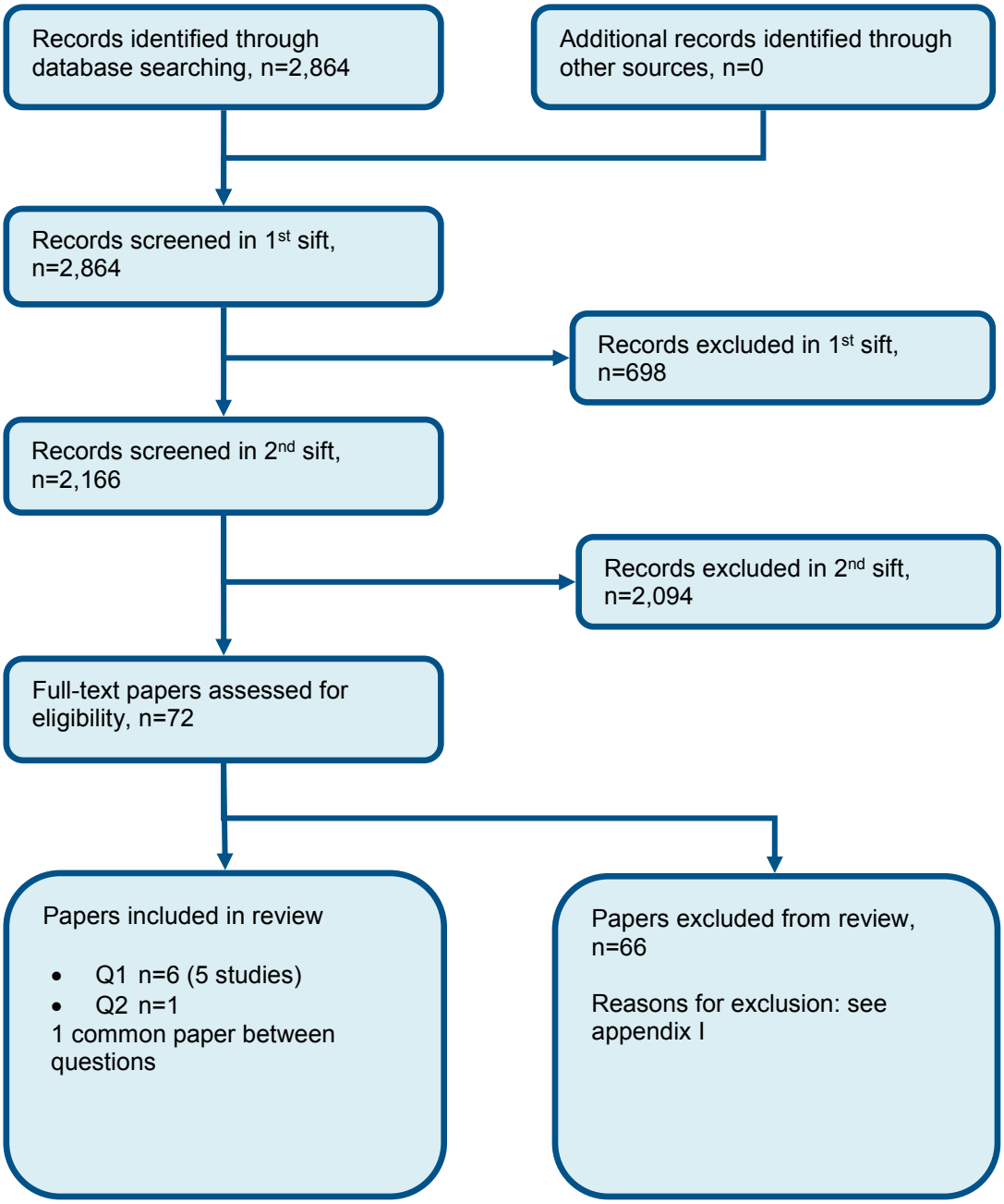
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Arthritis, Rheumatoid EXPLODE ALL TREES
#2.	((rheumatoid adj2 (arthritis or arthrosis)))
#3.	((caplan* adj2 syndrome))
#4.	((felty* adj2 syndrome))
#5.	((rheumatoid adj2 factor))
#6.	(((inflammatory or idiopathic) adj2 arthritis))

#7.	("inflammatory polyarthritis")
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the reviews of glucocorticoids for rheumatoid arthritis



Appendix D: Clinical evidence tables

Study	Corkill 1990[19]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=59)
Countries and setting	Conducted in United Kingdom
Line of therapy	Mixed line
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1958 revised ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Classic or definite RA who require DMARD therapy and have either persistent synovitis despite NSAID therapy for 3 months or progressive erosions on an X-ray plus an erythrocyte sedimentation rate (ESR) greater than 40mm/h.
Exclusion criteria	Previous treatment with gold, aged under 16 or over 80, proteinuria or glucocorticoid treatment within previous 2 months, insulin requiring or unstable diabetes, hospital inpatient care within prior 2 months.
Recruitment/selection of patients	Recruited from rheumatology clinics at Guy's, Lewisham and Royal Sussex County hospitals. Stratified to duration of RA (less than 1 year or more than 1 year) and age (less than 50 years or more than 50 years).
Age, gender and ethnicity	Age - Mean (SD): 54. Gender (M:F): 21 male, 38 female. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: glucocorticoid. 120mg IM methylprednisolone at weeks 0, 4 and 8. . Duration 8 weeks. Concurrent medication/care: Gold given as 10mg IM dose at week 0 followed by 50mg weekly until a total dose of 1g was reached. After which gold was continued at 50mg monthly. . Indirectness: No indirectness Further details: 1. Dose class (glucocorticoid v placebo comparison only): Medium dose (IM administration). 2. Duration of intervention use: Longer term use (>3 months oral, 2-3 doses IM/IV/IA) (3 doses IM). 3. Route of administration: IM (n=24) Intervention 2: Placebo. 0.9% saline given IM at 0, 4 and 8 weeks. . Duration 8 weeks. Concurrent

	medication/care: Gold given as 10mg IM dose at week 0 followed by 50mg weekly until a total dose of 1g was reached. After which gold was continued at 50mg monthly. . Indirectness: No indirectness Further details: 1. Dose class (glucocorticoid v placebo comparison only): Not applicable (Placebo). 2. Duration of intervention use: Longer term use (>3 months oral, 2-3 doses IM/IV/IA) (3 IM doses). 3. Route of administration: IM
Funding	Academic or government funding (Supported by the Arthritis Foundation of New Zealand and the Rose Hellaby Trust)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLUCOCORTICOID versus PLACEBO Protocol outcome 1: Drug discontinuation: adverse events at Longest time period reported - Actual outcome: Discontinuation: adverse events at 24 weeks; Group 1: 1/23, Group 2: 0/13 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar in terms of age, disease duration, number seropositive, no prior DMARD therapy, pain, grip strength, HAQ, joint count, haemoglobin, disease activity, glucose. Groups have differences in gender, ESR and Larson X-ray score. ; Group 1 Number missing: 12; Group 2 Number missing: 11 Protocol outcome 2: Drug discontinuation: inefficacy at Longest time period reported - Actual outcome: Discontinuation: inefficacy at 24 weeks; Group 1: 1/23, Group 2: 3/16 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar in terms of age, disease duration, nimber seropositive, no prior DMARD therapy, pain, grip strength, HAQ, joint count, haemoglobin, disease activity, glucose. Groups have differences in gender, ESR and Larson X-ray score. ; Group 1 Number missing: 12; Group 2 Number missing: 8	
Protocol outcomes not reported by the study	Disease Activity Score at 1 month; Disease Activity Score at 3 months; Quality of life at 3 months; Quality of life at 1 month; Function at 1 month; Function at 3 months; Pain at 3 months; Pain at 1 month; Radiological progression at 12+ months; Continuing glucocorticoid use at 12 months; Adverse events: psychosis at Longest time period reported; Adverse events: hyperglycaemia at Longest time period reported; Adverse events: weight gain at Longest time period reported; Adverse events: infection at Longest time period reported; Adverse events: insomnia at Longest time period reported; Remission at 1 month; Remission at 3 months; Low disease activity at 1 month; Low disease activity at 3 months

Study	Ding 2012[25]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=266)
Countries and setting	Conducted in China
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	People with RA for less than 2 years duration. No previous use of DMARDs or anti-malarial drugs or glucocorticoids in past 3 months allowed. Including 2 of following symptoms: >3 swollen joints, >8 tender joints, ≥45 minutes of morning stiffness, ≥28mm/h ESR, ≥1.5 times upper limit of normal of C-reactive protein level
Exclusion criteria	Other immune disorders, hypertension, diabetes, heart disease, osteoporosis, pre-existing liver disease, hematologic system disease, peptic ulcer, pregnancy or lactating, drug allergies, immunodepression contraindicated.
Recruitment/selection of patients	Recruited from The Affiliated Drum Tower Clinical Hospital of Nanjing University of Chinese Medicine.
Age, gender and ethnicity	Age - Mean (SD): Placebo group: 45 (14), low dose glucocorticoid group: 40 (19), medium dose glucocorticoid group: 44 (14). Gender (M:F): 39 male, 227 female. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=176) Intervention 1: glucocorticoid. Prednisone (half receiving 7.5mg/day and half receiving 15mg/day). Duration 12 weeks. Concurrent medication/care: Methotrexate at 10mg/week and leflunomide at 20mg/day. Suitable therapy such as NSAIDs used for adverse events. . Indirectness: No indirectness Further details: 1. Dose class (glucocorticoid v placebo comparison only): Not applicable (Half low dose and half medium dose). 2. Duration of intervention use: Short term use (<3 months oral, 1 dose IM/IV/IA) (3 months). 3. Route of administration: Oral (n=90) Intervention 2: Placebo. Placebo. Duration 12 weeks. Concurrent medication/care: Methotrexate at 10mg/week and leflunomide at 20mg/day. Suitable therapy such as NSAIDs used for adverse events. . Indirectness: No indirectness Further details: 1. Dose class (glucocorticoid v placebo comparison only): Not applicable (Placebo). 2.

	Duration of intervention use: Short term use (<3 months oral, 1 dose IM/IV/IA) (3 months). 3. Route of administration: Oral (n=88) Intervention 3: glucocorticoid - glucocorticoid low dose (oral > 10 mg/day). Prednisone: 7.5mg/day. Duration 12 weeks. Concurrent medication/care: Methotrexate at 10mg/week and leflunomide at 20mg/day. Suitable therapy such as NSAIDs used for adverse events. . Indirectness: No indirectness Further details: 1. Dose class (glucocorticoid v placebo comparison only): Low dose (7.5g/day). 2. Duration of intervention use: Short term use (<3 months oral, 1 dose IM/IV/IA) (12 weeks). 3. Route of administration: Oral (n=88) Intervention 4: glucocorticoid - glucocorticoid medium dose (IM, IA, oral 10-40 mg/day). Prednisone: 15mg/day. Duration 12 weeks. Concurrent medication/care: Methotrexate at 10mg/week and leflunomide at 20mg/day. Suitable therapy such as NSAIDs used for adverse events. . Indirectness: No indirectness Further details: 1. Dose class (glucocorticoid v placebo comparison only): Medium dose (15mg/day). 2. Duration of intervention use: Short term use (<3 months oral, 1 dose IM/IV/IA) (12 weeks). 3. Route of administration: Oral
Funding	Academic or government funding (Supported by grant ZKX08022 and YKK11101 from Nanjing Health Bureau, Jiang Su, China)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLUCOCORTICOID versus PLACEBO

Protocol outcome 1: Drug discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 3/174, Group 2: 6/86
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for gender, age at disease onset, duration of disease and DAS score before treatment. No details of previous RA treatment or rheumatoid factor status. ; Group 1 Number missing: 2; Group 2 Number missing: 4

Protocol outcome 2: Drug discontinuation: inefficacy at Longest time period reported
- Actual outcome: Discontinuation: inefficacy at 12 weeks; Group 1: 1/172, Group 2: 1/81
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for gender, age at disease onset, duration of disease and DAS score before treatment. No details of previous RA treatment or rheumatoid factor status. ; Group 1 Number missing: 4; Group 2 Number missing: 9

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLUCOCORTICOID LOW DOSE (ORAL > 10 MG/DAY) versus GLUCOCORTICOID MEDIUM DOSE (IM, IA, ORAL 10-40 MG/DAY)

Protocol outcome 1: Drug discontinuation: adverse events at Longest time period reported - Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 1/86, Group 2: 2/88 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for gender, age at disease onset, DAS score before treatment. Some difference in duration of disease. No details of previous RA treatment or rheumatoid factor status. ; Group 1 Number missing: 2; Group 2 Number missing: 0 Protocol outcome 2: Drug discontinuation: inefficacy at Longest time period reported - Actual outcome: Discontinuation: inefficacy at 12 weeks; Group 1: 1/86, Group 2: 0/86 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for gender, age at disease onset, DAS score before treatment. Some difference in duration of disease. No details of previous RA treatment or rheumatoid factor status. ; Group 1 Number missing: 2; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Disease Activity Score at 1 month; Disease Activity Score at 3 months; Quality of life at 3 months; Quality of life at 1 month; Function at 1 month; Function at 3 months; Pain at 3 months; Pain at 1 month; Radiological progression at 12+ months; Continuing glucocorticoid use at 12 months; Adverse events: psychosis at Longest time period reported; Adverse events: hyperglycaemia at Longest time period reported; Adverse events: weight gain at Longest time period reported; Adverse events: infection at Longest time period reported; Adverse events: insomnia at Longest time period reported; Remission at 1 month; Remission at 3 months; Low disease activity at 1 month; Low disease activity at 3 months

Study	Gough 1994[32]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in United Kingdom; Setting: Selly Oak Hospital arthritis clinic
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with RA requiring DMARD treatment. Not previously received glucocorticoid treatment .
Exclusion criteria	None detailed.
Recruitment/selection of patients	Recruited sequentially.
Age, gender and ethnicity	Age - Mean (range): glucocorticoid group: 56 (39-73), placebo group: 51 (41-67). Gender (M:F): 4 male, 16 female. . Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: glucocorticoid. 120mg intramuscular methylprednisolone at 0, 4 and 12 weeks. . Duration 12 weeks. Concurrent medication/care: No other glucocorticoids permitted during study. Salazopyrin EN commenced at 500mg daily and increased to 2g daily after 1 month. . Indirectness: No indirectness Further details: 1. Dose class (glucocorticoid v placebo comparison only): Medium dose (120mg IM). 2. Duration of intervention use: Longer term use (>3 months oral, 2-3 doses IM/IV/IA) (3 IM injections over 12 weeks). 3. Route of administration: IM (n=9) Intervention 2: Placebo. Normal saline IM at 0, 4 and 12 weeks. Duration 12 weeks. Concurrent medication/care: No glucocorticoids permitted during study. Salazopyrin EN commenced at 500mg daily and increased to 2g daily after 1 month. . Indirectness: No indirectness Further details: 1. Dose class (glucocorticoid v placebo comparison only): Not applicable (Placebo). 2. Duration of intervention use: Longer term use (>3 months oral, 2-3 doses IM/IV/IA) (3 IM over 12 weeks). 3. Route of administration: IM
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLUCOCORTICOID versus PLACEBO

Protocol outcome 1: Drug discontinuation: adverse events at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 3 months; Group 1: 0/11, Group 2: 0/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of duration of disease, joint score, CRP and RF positive. Small differences in gender, age. Larger differences in Ritchie. ESR and erosions present. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Drug discontinuation: inefficacy at Longest time period reported
- Actual outcome: Discontinuation: inefficacy at 3 months; Group 1: 0/11, Group 2: 0/9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of duration of disease, joint score, CRP and RF positive. Small differences in gender, age. Larger differences in Ritchie. ESR and erosions present. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Disease Activity Score at 1 month; Disease Activity Score at 3 months; Quality of life at 3 months; Quality of life at 1 month; Function at 1 month; Function at 3 months; Pain at 3 months; Pain at 1 month; Radiological progression at 12+ months; Continuing glucocorticoid use at 12 months; Adverse events: psychosis at Longest time period reported; Adverse events: hyperglycaemia at Longest time period reported; Adverse events: weight gain at Longest time period reported; Adverse events: infection at Longest time period reported; Adverse events: insomnia at Longest time period reported; Remission at 1 month; Remission at 3 months; Low disease activity at 1 month; Low disease activity at 3 months

Study	Van gestel 1995[71]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Netherlands
Line of therapy	Mixed line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: 1958 paper quoted with criteria for RA
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with definite or classical RA when treatment with parenteral gold was considered (generally due to failed treatment by a slow-acting antirheumatic drug). People fulfilled at least 3 of the following criteria: ≥5 tender joints, ≥3 swollen joints, >28mm/h ESR, ≥60 minutes of morning stiffness, Hb level below normal for person's age and gender.
Exclusion criteria	People with diseases or medication that may affect bone mass, women less than 3 years post-menopausal or had irregular cycles.
Recruitment/selection of patients	Recruited from out-patient population at the University of Nijmegen between 1988 and 1991.
Age, gender and ethnicity	Age - Median (IQR): glucocorticoid group: 57 (41-61), placebo group: 56 (42-65). Gender (M:F): Male: 12, Female: 28. Ethnicity: Not detailed
Further population details	
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: glucocorticoid. Prednisone 10mg/day for 12 weeks, tapered to 0mg per day by week 19. . Duration 20 weeks. Concurrent medication/care: IA glucocorticoid injections allowed with injected joint omitted from further evaluation. IM aurothioglucose at 10mg/week for week 1 and 50mg/week for weeks 2-20. Other DMARDs used were methotrexate (n=7) and sulphasalazine (n=3). . Indirectness: No indirectness Further details: 1. Dose class (glucocorticoid v placebo comparison only): Medium dose (10mg/day). 2. Duration of intervention use: Longer term use (>3 months oral, 2-3 doses IM/IV/IA) (20 weeks). 3. Route of administration: Oral (n=20) Intervention 2: Placebo. No details. Duration 20 weeks. Concurrent medication/care: IA injections with glucocorticoids allowed with injected joint omitted from further evaluation. IM aurothioglucose at 10mg/week for week 1 and 50mg/week for weeks 2-20. Other DMARDs used were methotrexate (n=4) and sulphasalazine (n=1). . Indirectness: No indirectness

	Further details: 1. Dose class (glucocorticoid v placebo comparison only): Not applicable (Placebo). 2. Duration of intervention use: Longer term use (>3 months oral, 2-3 doses IM/IV/IA) (20 weeks). 3. Route of administration: Oral
Funding	Academic or government funding (Supported by a grant from the Dutch League against Rheumatism)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLUCOCORTICOID versus PLACEBO Protocol outcome 1: Drug discontinuation: adverse events at Longest time period reported - Actual outcome: Discontinuation due to adverse events at 12 weeks; Group 1: 0/20, Group 2: 1/19 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Varying DMARDs on top of gold were utilised and placebo group given more glucocorticoid injections. Glucocorticoid group: other DMARDs used: methotrexate (n=7) and sulfasalazine (n=3) and IA glucocorticoids: 1 patient in one joint. Placebo group: Other DMARDs used: methotrexate (n=4) and sulfasalazine (n=1) and IA glucocorticoids: 4 patients in six joints. ; Baseline details: Similar in gender, age, rheumatoid factor positive, previous DMARD use, previous prednisone use, DAS score, functional capacity. Some difference in terms of disease duration and "X-ray total". ; Group 1 Number missing: 0; Group 2 Number missing: 1 Protocol outcome 2: Drug discontinuation: inefficacy at Longest time period reported - Actual outcome: Discontinuation due to inefficacy at 12 weeks; Group 1: 0/20, Group 2: 1/19 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Varying DMARDs on top of gold were utilised and placebo group given more glucocorticoid injections. Glucocorticoid group: other DMARDs used: methotrexate (n=7) and sulfasalazine (n=3) and IA glucocorticoids: 1 patient in one joint. Placebo group: Other DMARDs used: methotrexate (n=4) and sulfasalazine (n=1) and IA glucocorticoids: 4 patients in six joints. ; Baseline details: Similar in gender, age, rheumatoid factor positive, previous DMARD use, previous prednisone use, DAS score, functional capacity. Some difference in terms of disease duration and "X-ray total". ; Group 1 Number missing: 0; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Disease Activity Score at 1 month; Disease Activity Score at 3 months; Quality of life at 3 months; Quality of life at 1 month; Function at 1 month; Function at 3 months; Pain at 3 months; Pain at 1 month; Radiological progression at 12+ months; Continuing glucocorticoid use at 12 months; Adverse events: psychosis at Longest time period reported; Adverse events: hyperglycaemia at Longest time period reported; Adverse events: weight gain at Longest time period reported; Adverse events: infection at Longest time period reported; Adverse events: insomnia at Longest time period reported; Remission at 1 month; Remission at 3 months; Low disease activity at 1 month; Low disease activity at 3 months

Study (subsidiary papers)	Verschueren 2017[73] (Verschueren 2015[72], Verschueren 2015[74])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=289)
Countries and setting	Conducted in Belgium
Line of therapy	1st line
Duration of study	Intervention time: 34 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR 1987 criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with RA. Disease duration ≤1 year, DMARD naive. Assigned as "low-risk" based on satisfying one of the following definitions: 1) no erosions, ACPA negative and RF negative. 2) Erosions, ACPA negative, RF negative, DAS28 (CRP)≤3.2. 3) No erosions, ACPA negative and/or RF positive and DAS28 (CRP)≤3.2.
Exclusion criteria	Contraindications for intensive treatment with glucocorticoids.
Recruitment/selection of patients	Recruited from 2009 to 2013.
Age, gender and ethnicity	Age - Mean (SD): 51 years old. Gender (M:F): Male: 19 Female: 71. Ethnicity: Not detailed
Further population details	
Extra comments	People with controlled diabetes, osteoporosis, previous malignancy were not excluded.
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: glucocorticoid. Oral prednisolone step-down scheme from 30mg at the beginning to 5mg in week 28. Complete discontinuation by week 34. . Duration 34 weeks. Concurrent medication/care: 15mg methotrexate weekly. . Indirectness: No indirectness Further details: 1. Dose class (glucocorticoid v placebo comparison only): Medium dose (30mg daily). 2. Duration of intervention use: Longer term use (>3 months oral, 2-3 doses IM/IV/IA) (34 weeks). 3. Route of administration: Oral (n=47) Intervention 2: Usual care. No glucocorticoids allowed. Duration 34 weeks. Concurrent medication/care: 15mg methotrexate weekly. Indirectness: No indirectness Further details: 1. Dose class (glucocorticoid v placebo comparison only): Not applicable 2. Duration of intervention use: Not applicable 3. Route of administration: Not applicable
Funding	Academic or government funding (Flemish government grant. Lead author holds Pfizer Chair for Early Rheumatoid Arthritis Management at the KU Leuven.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLUCOCORTICOID versus USUAL CARE Protocol outcome 1: Radiological progression at 12+ months - Actual outcome: Sharp van der Heijde score at 12 months; Group 1: mean 0.3 (SD 0.5); n=38, Group 2: mean 0.2 (SD 0.3); n=44 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for DAS28, remission, disease activity, gender, disease duration, RF status, CCP, erosions, HAQ. ; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 5, Reason: Unclear Protocol outcome 2: Adverse events: infection at Longest time period reported - Actual outcome: Infection at 16 weeks; Group 1: 0/43, Group 2: 1/47 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for DAS28, remission, disease activity, gender, disease duration, RF status, CCP, erosions, HAQ. ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Disease Activity Score at 1 month; Disease Activity Score at 3 months; Quality of life at 3 months; Quality of life at 1 month; Function at 1 month; Function at 3 months; Pain at 3 months; Pain at 1 month; Continuing glucocorticoid use at 12 months; Adverse events: psychosis at Longest time period reported; Adverse events: hyperglycaemia at Longest time period reported; Adverse events: weight gain at Longest time period reported; Adverse events: insomnia at Longest time period reported; Drug discontinuation: adverse events at Longest time period reported; Drug discontinuation: inefficacy at Longest time period reported; Remission at 1 month; Remission at 3 months; Low disease activity at 1 month; Low disease activity at 3 months

Appendix E: Forest plots

E.1 Glucocorticoids versus placebo in people with rheumatoid arthritis

Figure 2: Discontinuation: inefficacy

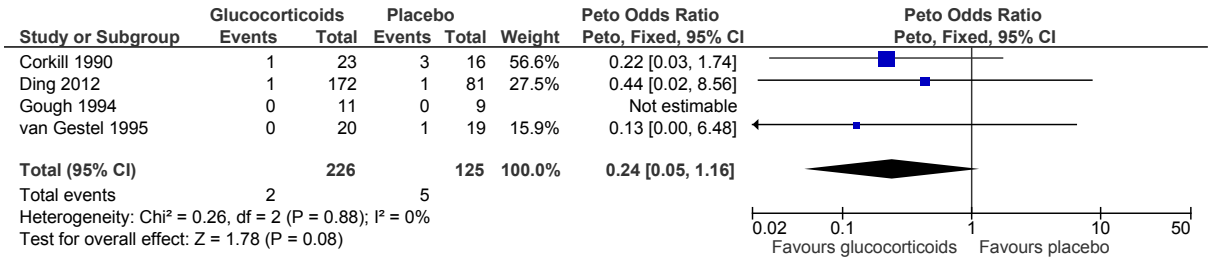
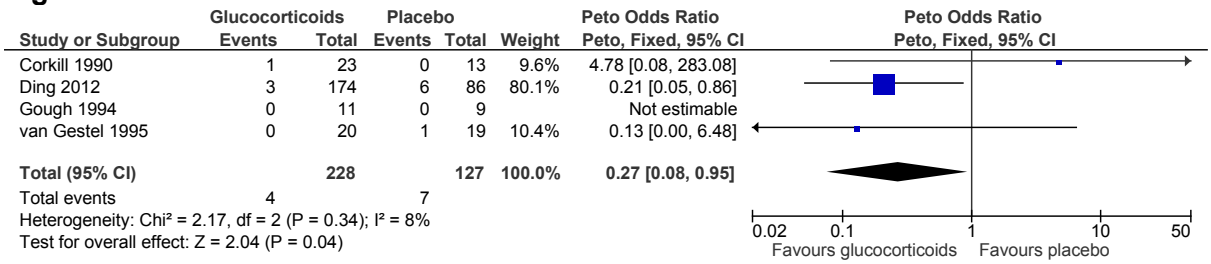


Figure 3: Discontinuation: adverse events



E.2 Glucocorticoids versus no glucocorticoids in people with rheumatoid arthritis

Figure 4: Radiological progression (change in SvdH) at 12+ months

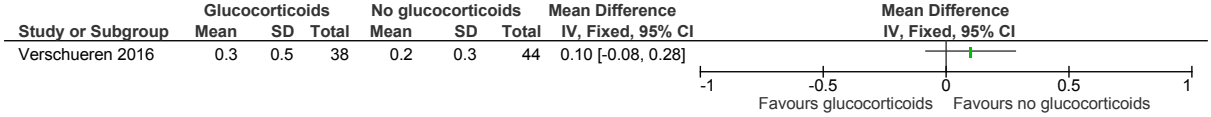
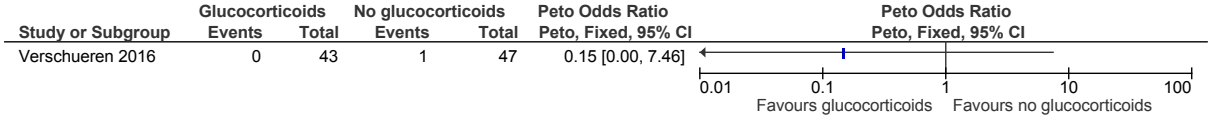


Figure 5: Adverse events: infection



E.3 Low dose glucocorticoids versus medium dose glucocorticoids in people with rheumatoid arthritis

Figure 6: Discontinuation: inefficacy

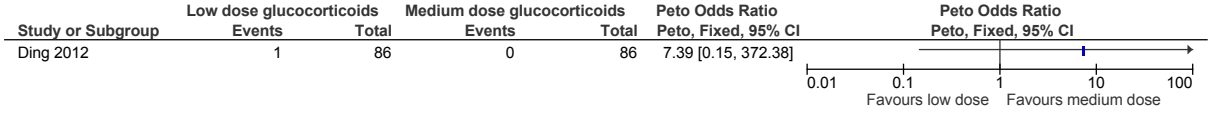
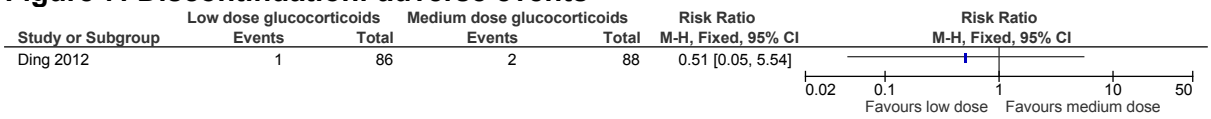


Figure 7: Discontinuation: adverse events



Appendix F: GRADE tables

Table 15: Clinical evidence profile: Glucocorticoids versus placebo for rheumatoid arthritis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glucocorticoids versus placebo	Control	Relative (95% CI)	Absolute		
Disease Activity Score at 4 or 12 weeks - not reported												
0	-	-	-	-	-	none	0	-	-	-		
Quality of life at 4 or 12 weeks - not reported												
0	-	-	-	-	-	none	0	-	-	-		
Function at 4 or 12 weeks - not reported												
0	-	-	-	-	-	none	0	-	-	-		
Discontinuation: inefficacy (follow-up 12-24 weeks)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/226 (0.88%)	5/125 (4%)	Peto OR 0.24 (0.05 to 1.16)	30 fewer per 1000 (from 70 fewer to 10 more)[3]	⊕OOO VERY LOW	IMPORTANT
Discontinuation: adverse events (follow-up 12-24 weeks)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/228 (1.8%)	7/127 (5.5%)	Peto OR 0.27 (0.08 to 0.95)	40 fewer per 1000 (from 90 fewer to 10 more)[3]	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effect calculated using risk difference

Table 16: Clinical evidence profile: Glucocorticoids versus no glucocorticoids for rheumatoid arthritis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glucocorticoids	Control (no glucocorticoids)	Relative (95% CI)	Absolute		
Disease Activity Score at 4 or 12 weeks - not reported												
0	-	-	-	-	-	none	0	-	-	-		
Quality of life at 4 or 12 weeks - not reported												
0	-	-	-	-	-	none	0	-	-	-		
Function at 4 or 12 weeks - not reported												
0	-	-	-	-	-	none	0	-	-	-		
Radiological progression at 12 months (follow-up mean 1 years; measured with: Change in SvdH via X-ray; range of scores: 0-448; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	38	-	MD 0.1 higher (0.08 lower to 0.28 higher)	⊕⊕OO LOW	IMPORTANT
Adverse events: infection (follow-up mean 16 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/43 (0%)	1/47 (2.1%)	Peto OR 0.15 (0 to 7.46)	20 fewer per 1000 (from 80 fewer to 40 more)[3]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Risk difference used to calculate absolute effect

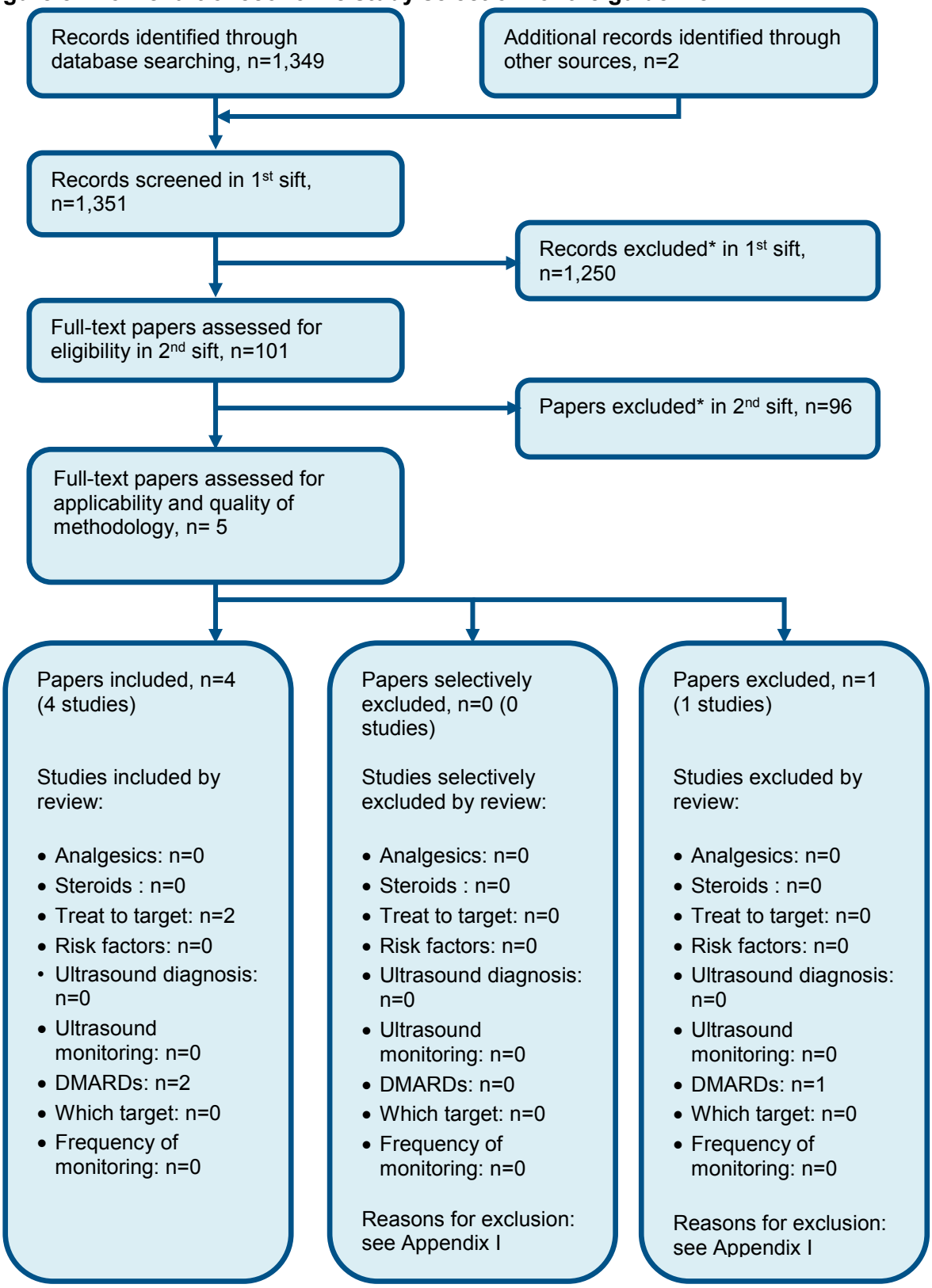
Table 17: Clinical evidence profile: Low dose glucocorticoids versus medium dose glucocorticoids for rheumatoid arthritis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose glucocorticoids versus medium dose glucocorticoids		Relative (95% CI)	Absolute		
Disease Activity Score at 4 or 12 weeks - not reported												
0	-	-	-	-	-	none	0	-	-	-		
Quality of life at 4 or 12 weeks - not reported												
0	-	-	-	-	-	none	0	-	-	-		
Function at 4 or 12 weeks - not reported												
0	-	-	-	-	-	none	0	-	-	-		
Discontinuation: inefficacy (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/86 (1.2%)	0/86 (0%)	Peto OR 7.39 (0.15 to 372.38)	12 more per 1000 (from 20 fewer to 40 more)[3]	⊕OOO VERY LOW	IMPORTANT
Discontinuation: adverse events (follow-up mean 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/86 (1.2%)	2/88 (2.3%)	RR 0.51 (0.05 to 5.54)	11 fewer per 1000 (from 22 fewer to 103 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Calculated from risk difference

Appendix G: Health economic evidence selection

Figure 8: Flow chart of economic study selection for the guideline



** Non-relevant population, intervention, comparison, design or setting; non-English language*

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 18: Studies excluded from the clinical review

Study	Exclusion reason
Akdemir 2016[1]	Inappropriate comparison
Allaart 2006[3]	Inappropriate comparison
Allaart 2007[2]	Inappropriate comparison
Axelsen 2015[4]	Inappropriate comparison
Bain 1972[5]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Bakker 2012[6]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Boers 2015[8]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Capell 2004[9]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Chamberlain 1976[10]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Choy 1993[11]	High oral glucocorticoid dose that would not be used in the UK
Choy 2005[12]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Choy 2008[13]	Concomitant glucocorticoid therapy in both treatment arms
Ciconelli 1996[14]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Claessen 2009[15]	Not guideline condition
Cochrane 1971[16]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD

Study	Exclusion reason
	following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Conaghan 2003[17]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Conrado 2016[18]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
De jong 2013[21]	Not guideline condition
De jong 2014[20]	Not guideline condition
De rotte 2014[22]	Incorrect study design
Den uyl 2012[24]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Den uyl 2014[23]	DMARD treatment varied between trial arms
Engvall 2008[26]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Ferraz 1992[27]	Incorrect interventions
Forslind 2009[28]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Frediani 2004[29]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Gerlag 2004[31]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Gerlag 2007[30]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Graudal 2014[33]	Not primary study
Hafstrom 2009[34]	Over long treatment duration (continuous oral glucocorticoids

Study	Exclusion reason
	without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Hansen 1987[36]	DMARD therapy varied between treatment groups
Hansen 1999[35]	DMARD regime varied between treatment arms
Harris 1983[37]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered. . Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Haugeberg 2011[38]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Jelinek 1991[39]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Jurgens 2013[40]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Jurgens 2014[41]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Kirwan 2004[43]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Kirwan 2006[42]	Commentary on previously published trial
Konijn 2016[44]	DMARD therapy varied between treatment groups
Laan 1993[45]	Relevant outcomes not reported at the correct time point
Lafforgue 1993[46]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Machold 2010[47]	Not guideline condition
Markusse 2016[48]	Inappropriate comparison

Study	Exclusion reason
Menon 2014[49]	Not review population
Montecucco 2012[50]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)
Ostergaard 1999[54]	DMARD regime varied between treatment arms
Pavelka 1992[55]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Radia 1988[56]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Rasch 2015[57]	Narrative review of studies using COBRA regimen
Scott 2016[58]	Secondary analysis of RCTs that were previously excluded
Seegobin 2014[59]	ACPA positive versus ACPA negative comparison
Shipley 1988[60]	Inappropriate comparison
Stock 2017[61]	Inappropriate population
Svensson 2003[62]	Inappropriate comparison
Ter wee 2015[63]	DMARD regime varied between treatment arms
Trampisch 2014[64]	Trial protocol
Van der kooij 2009[65]	DMARD therapy varied between treatment groups
Van der kooij 2009[66]	Inappropriate comparison
Van der veen 1992[67]	High dose glucocorticoid treatment versus high dose glucocorticoid treatment
Van der veen 1993[68]	High dose glucocorticoid treatment versus high dose glucocorticoid treatment
Van everdingen 2002[69]	Not starting new DMARD therapy
Van everdingen 2003[70]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Vischer 1986[75]	Incorrect interventions
Williams 1982[76]	Not Participants must be commencing a new DMARD, whether initiating DMARD therapy for the first time or initiating new DMARD following loss of response to previous DMARD. In the latter case, the new DMARD may be in addition or in place of previous DMARD. The initiation of any conventional or biologic DMARDs will be considered.
Wong 1990[77]	Over long treatment duration (continuous oral glucocorticoids without tapering to zero commenced before 6 months and completed before 12 months, IM/IA glucocorticoids administered > 3 times or over course of > 3 months, or IV glucocorticoids administered > 3 times or over course of > 1 week)

I.2 Excluded health economic studies

Table 19: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Appendix J: Research recommendations

J.1 Glucocorticoid bridge therapy

Research question: What is the clinical and cost effectiveness of short-term bridging treatment with glucocorticoids for adults with RA starting a new DMARD, including the most effective dosing strategy and mode of administration?

Why this is important:

All DMARDs have a slow onset of action. In some cases, response may not be seen for 2-3 months. In contrast glucocorticoids have an immediate effect on joint pain and swelling. In clinical practice, several different regimens are prescribed to 'bridge' the time between the initial prescription of DMARDs and the clinical response. However, good quality randomised controlled trial evidence demonstrating the effectiveness of glucocorticoids used as bridging treatment is limited and inconclusive. Further research is needed to inform recommendations for practice regarding whether bridging treatment with steroids should be used until the new DMARD begins to take effect.

The optimal dosing regimen and mode of administration for bridging glucocorticoids also needs to be established. While the anti-inflammatory response is dose dependent, side effects of glucocorticoids vary according to dose and duration of treatment.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People with active RA commencing a new DMARD Intervention(s):Oral prednisolone, or intramuscular (IM) methylprednisolone or triamcinolone Comparison: Each other in different doses, or placebo Outcome(s):Disease activity (DAS 28), Function (HAQ), Pain (VAS), quality of life, adverse events
Importance to patients or the population	Glucocorticoids are believed to provide rapid improvement in pain and disability in people with active RA. Lay members on the committee felt that steroids play an important role in controlling disease activity rapidly, not only to improve disease outcomes but also to provide rapid relief from pain, fatigue and other symptoms.
Relevance to NICE guidance	High quality research in this area may enable future updates of this guidance to make a strong recommendation on the use of glucocorticoids as bridging treatment which was not possible in the present guideline due to the lack of good quality evidence. Further research may also enable the guideline to make recommendations on the most effective dose and mode of administration.
Relevance to the NHS	People with RA who are prescribed glucocorticoids may be less dependent on medical services during DMARD initiation. Without this treatment they may require large doses of analgesia, and other intervention from primary and secondary care, physiotherapy and other allied health professionals until slow acting therapies are effective, which collectively can be much more expensive than the short-term additional cost of glucocorticoids. If evidence is able to demonstrate the beneficial effects of steroids as bridging therapy, and the best dose and mode of administration, use of other management strategies may reduce, thus reducing resource use.
National priorities	N/A
Current evidence base	A systematic review of the current evidence in chapter H found limited RCT evidence on critical outcomes and high quality evidence was lacking to inform a strong recommendation on the use of glucocorticoids as bridging treatment. No evidence was available to inform which regimen

	would be most effective.
Equality	None.
Study design	This would be best addressed by a randomised controlled trial of oral prednisolone versus IM methylprednisolone versus IM triamcinolone versus placebo with initiation of methotrexate (or other appropriate conventional DMARD) in people with active RA.
Feasibility	No major feasibility or ethical issues if it is made clear to patients they can withdraw for side effects or inefficacy.
Other comments	None
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.