

## Metastatic spinal cord compression

### [J] Corticosteroids

*NICE guideline number tbc*

*Evidence reviews underpinning recommendations 1.8.1 to 1.8.7 in the NICE guideline*

*March 2023*

*Draft for consultation*

*This evidence review was developed by NICE*



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Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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# 1 Corticosteroids

## 2 Review question

3 How effective is corticosteroid therapy in managing the neurological consequences of meta-  
4 static spinal cord compression?

## 5 Introduction

6 Corticosteroids (typically dexamethasone) are routinely given to patients with MSCC with the  
7 intent to reduce tumour bulk or spinal cord swelling, relieve spinal cord pressure and improve  
8 treatment outcomes. They may result in a rapid improvement of neurological function but  
9 there is limited evidence about their longer-term benefits and harms. High-dose, long-  
10 duration treatment with corticosteroids can cause significant adverse effects. This evidence  
11 review aimed to summarise the balance of benefits and harms of corticosteroids in people  
12 with spinal cord or nerve root compression due to metastases or malignancy.

## 13 Summary of the protocol

14 See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PI-  
15 CO) characteristics of this review.

16 **Table 1: Summary of the protocol (PICO table)**

<b>Population</b>	Adults with spinal cord or nerve root compression because of: <ul style="list-style-type: none"><li>• metastatic spinal disease or</li><li>• direct malignant infiltration</li></ul>
<b>Intervention</b>	<ul style="list-style-type: none"><li>• Dexamethasone (oral or intravenous)</li></ul>
<b>Comparison</b>	<ul style="list-style-type: none"><li>• No dexamethasone</li><li>• Different regimens (for example different dosage or duration)</li></ul>
<b>Outcome</b>	<b>Critical</b> <ul style="list-style-type: none"><li>• Neurological and functional status including:<ul style="list-style-type: none"><li>○ Bowel and bladder function</li><li>○ Mobility or ambulatory status</li></ul></li><li>• Pain</li></ul> <b>Important</b> <ul style="list-style-type: none"><li>• Treatment related toxicity including:<ul style="list-style-type: none"><li>○ Steroid adverse effects</li><li>○ Tumour lysis syndrome (in haematological cancers)</li></ul></li></ul>

17 For further details see the review protocol in appendix A.

## 18 Methods and process

19 This evidence review was developed using the methods and process described in [Develop-](#)  
20 [ing NICE guidelines: the manual](#). Methods specific to this review question are described in  
21 the review protocol in appendix A and the methods document (supplementary document 1).

22 Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).

1 **Effectiveness evidence**

2 **Included studies**

3 Three randomised controlled trials were included in this review (Graham 2006, Sorensen  
4 1993, Vecht 1989).

5 The included studies are summarised in Table 2.

6 One trial compared high dose dexamethasone to no treatment (Sorensen 1993) and 2 trials  
7 compared high dose dexamethasone to low dose dexamethasone (Graham 2006 and Vecht  
8 1989).

9 One study was from Australia (Graham 2006) and the others from Denmark (Sorensen 1994)  
10 and the Netherlands (Vecht 1989).

11 See the literature search strategy in appendix B and study selection flow chart in appendix C.

12 **Excluded studies**

13 Studies not included in this review are listed, and reasons for their exclusion are provided in  
14 appendix K.

15 **Summary of included studies**

16 Summaries of the studies that were included in this review are presented in Table 2.

17 **Table 2: Summary of included studies**

Study	Population	Intervention	Comparison	Outcomes
Graham 2006  RCT  Australia	N=20  Age, mean, years (range): 66 (41 – 81). SD not reported.  Sex: female n=20, male n=14.	<u>High dose dexamethasone</u>  96 mg intravenous daily dexamethasone - days 0 - 2, then tapered to 0 mg by day 15.	<u>Low dose dexamethasone</u>  16 mg intravenous daily dexamethasone - days 0 - 2, then weaned to 0 mg by day 15.	Functional status  Treatment related toxicity
Sorensen 1994  RCT  Denmark	N=57  Age, years, median (range): High dose 60 (25-81); no treatment 64 (41-82).  Sex: female n=39, male n=18.	<u>High dose dexamethasone</u>  Intravenous bolus of 96 mg dexamethasone given immediately after myelography or MRI, then maintained on a 96 mg dose of dexamethasone for 3 days (given orally when possible in four divided doses). Treatment was then then tapered over 10 days.	<u>No treatment</u>  No details reported.	Functional status  Treatment related toxicity
Vecht 1989	N=37	<u>High dose dexamethasone</u>	<u>Low dose dexamethasone</u>	Functional status

Study	Population	Intervention	Comparison	Outcomes
RCT  Netherlands	Age, years, mean (SD): 61 (range 22-87). SD not reported.  Sex: female n=11; male n=26.	100 mg. No further details reported.	10 mg. No further details reported.	Pain

1 *mg: milligram; MRI: Magnetic Resonance Imaging; RCT: randomised controlled trial.*

2 See the full evidence tables in appendix D. No meta-analysis was conducted (and so there  
3 are no forest plots in appendix E).

#### 4 **Summary of the evidence**

##### 5 ***Dexamethasone verses no treatment***

6 Evidence comparing high dose dexamethasone to no treatment came from a single small  
7 RCT and ranged from low to moderate quality. For most outcomes there was no clinically  
8 important difference. There was a possible important benefit with dexamethasone at 6  
9 months (the 90% confidence intervals showed an important benefit, but the 95% confidence  
10 intervals included no effect): people in this arm were more likely to be alive and ambulant at  
11 6 months but by 1 year there was no difference. 11% of people taking high dose dexame-  
12 thasone experienced significant side effects compared to none in the no treatment arm.

##### 13 ***High verse low dose dexamethasone***

14 Evidence comparing low to high dose dexamethasone came from 2 small RCTs and ranged  
15 from low to high quality. There was no clinically important difference in any of the outcomes.

16 See appendix F for full GRADE tables.

#### 17 **Economic evidence**

##### 18 **Included studies**

19 A systematic review of the economic literature was conducted but no economic studies were  
20 identified which were applicable to this review question.

21 A single economic search was undertaken for all topics included in the scope of this guide-  
22 line. See supplement 2 for details.

##### 23 **Excluded studies**

24 Economic studies not included in this review are listed, and reasons for their exclusion are  
25 provided in supplement 2.

##### 26 **Summary of included economic evidence**

27 No economic studies were identified which were applicable to this review question.

##### 28 **Economic model**

29 No economic modelling was undertaken for this review because the committee agreed that  
30 other topics were higher priorities for economic evaluation.



## 1 **The committee's discussion and interpretation of the evidence**

### 2 **The outcomes that matter most**

3 Neurological status, functional status and pain were prioritised as critical outcomes by the  
4 committee. This is because spinal cord or nerve root compression is often accompanied by  
5 neurological and functional impairment and pain. Corticosteroids are typically used with the  
6 aim to alleviate these in the acute setting. The committee agreed that treatment related tox-  
7 icity was an important outcome because although corticosteroid related toxicity is a well  
8 known long term adverse effect, the medication would not usually be a long term treatment  
9 for this indication.

### 10 **The quality of the evidence**

11 The quality of the evidence was assessed using GRADE and ranged from low to high, with  
12 most of the evidence being of a low quality. This was predominately due to imprecision  
13 around the effect estimates: the evidence originated from 3 small studies.

14 Evidence was lacking for the adverse outcome of tumour lysis syndrome in people with hae-  
15 matological cancers.

16 For this reason, the committee used their expertise and experience to make the recommen-  
17 dations, while also taking into account the recommendations from the previous version of the  
18 guideline and their relevance to current practice.

### 19 **Benefits and harms**

20 The committee decided that it was important to make separate recommendations for people  
21 with haematological malignancy. For those with confirmed haematological malignancy with  
22 spinal metastases or direct malignant infiltration (DMI) of the spine, the committee agreed  
23 based on expertise that dexamethasone was indicated regardless of whether or not people  
24 have neurological symptoms (which is what corticosteroid treatment is usually aimed at alle-  
25 viating in the context of spinal cord compression). This is because corticosteroids in combi-  
26 nation with anticancer treatments such as bortezomib or thalidomide are commonly used for  
27 treating myeloma once a haematological malignancy is confirmed (see first-line treatment  
28 and subsequent therapy recommendations in [NICE guideline myeloma: diagnosis and man-  
29 agement](#)).

30 The committee agreed that a 16 mg dose of dexamethasone oral (or equivalent parenteral  
31 dose) to start with was current practice but were aware that in some cases a different corti-  
32 costeroid or a different dose may be used so they recommended that ongoing treatment  
33 should be discussed with the specialist team to allow for dose adjustments.

34 The committee discussed that corticosteroids ought to be avoided if a haematological malign-  
35 nancy is suspected but has not been confirmed, because their administration may have a  
36 direct anti-tumour effect on B-cell lymphoma and cause reduction in MRI abnormalities, mak-  
37 ing biopsy and histologic confirmation more difficult. Therefore, the committee based on ex-  
38 perience and expertise agreed that in these cases specialist haematological advice would be  
39 needed before corticosteroid treatment is started.

40 There was some evidence that functional status was improved with dexamethasone, but the  
41 studies were too small to draw clear conclusions: the 90% confidence intervals showed an  
42 important benefit in terms of ambulation and survival at 6 months, but the 95% confidence  
43 intervals included no effect. The committee noted that this was supported by their expertise  
44 and experience. They agreed that for people with MSCC with clinical symptoms or signs  
45 which are commonly neurological, steroids can reduce inflammation and promote stabilisa-

1 tion of blood vessel membranes at the compression site, consequently reducing back pain  
2 and neurologic deficits. The evidence also showed an increase in treatment-related signifi-  
3 cant toxicity but numbers in the trial were small so there was some uncertainty in these find-  
4 ings. The committee acknowledged that toxicity is a known adverse event of corticosteroids,  
5 and that they should be stopped once other treatment options, such as surgery or radiother-  
6 apy, are available and have been initiated. Corticosteroids would need to be reduced be-  
7 cause a sudden withdrawal may cause adverse events, such as a sharp fall in blood pres-  
8 sure, and affect blood glucose levels. They also decided that dexamethasone should be dis-  
9 continued if spinal metastases, DMI of the spine or MSCC are ruled out and corticosteroids  
10 should not be given to people with MSCC without neurological symptoms unless it is part of  
11 radiotherapy regimen or the person has severe pain or the person has a haematological ma-  
12 lignancy.

13 In situations where there are no other treatment options (because they have been tried and  
14 were not effective, the person is too unwell to tolerate other treatment, or giving another  
15 treatment is too risky) and symptoms return or worsen as dexamethasone is reduced, the  
16 committee agreed that it could be considered for longer.

17 One of the side effects of corticosteroid treatment is to increase blood glucose since these  
18 drugs promote glucose production in the liver and reduce the sensitivity of the cells to insulin  
19 so the committee recommended to monitor blood glucose. They also recommended to co-  
20 prescribe proton pump inhibitor (PPI) acid suppression to reduce the potential risk of peptic  
21 ulcer associated with corticosteroid therapy. They acknowledged that glucose monitoring and  
22 giving adjunct PPI treatment is common practice.

23 The committee acknowledged that the evidence was limited they noted that the use and  
24 mechanisms of action of corticosteroids treatments can be extrapolated from their use in  
25 other conditions that the committee could draw on from their expertise and they therefore did  
26 not prioritise this topic for a research recommendation.

## 27 **Cost effectiveness and resource use**

28 The committee agreed that the recommendations reflect current practice and that there will  
29 be no change in resource use as a result of these recommendations.

## 30 **Recommendations supported by this evidence review**

31 This evidence review supports recommendations 1.8.1 to 1.8.7 of the guideline.

## 32 **References – included studies**

### 33 **Effectiveness**

#### 34 **Graham 2006**

35 Graham P, Capp A, Delaney G et al. A pilot randomised comparison of dexamethasone 96  
36 mg vs 16 mg per day for malignant spinal-cord compression treated by radiotherapy: TROG  
37 01.05 Superdex study. *Clinical Oncology*, 18, 70-6, 2006

#### 38 **Sorensen 1994**

39 Sorensen P, Helweg-Larsen S, Mouridsen H, et al. Effect of high-dose dexamethasone in  
40 carcinomatous metastatic spinal cord compression treated with radiotherapy: A randomised  
41 trial. *European Journal of Cancer*, 30, 22-27, 1994

- 1 **Vecht 1989**
- 2 Vecht C, Haaxma-Reiche H, van Putten W, et al. Initial bolus of conventional versus high-
- 3 dose dexamethasone in metastatic spinal cord compression. *Neurology*, 39, 1255-7, 1989
- 4

# 1 Appendices

## 2 Appendix A Review protocols

3 **Review protocol for review question: How effective is corticosteroid therapy in managing the neurological consequences**  
4 **of metastatic spinal cord compression?**

5 **Table 3: Review protocol**

ID	Field	Content
0.	PROSPERO registration number	CRD42022303508
1.	Review title	Corticosteroid therapy in the management of neurological consequences of metastatic spinal cord compression
2.	Review question	How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?
3.	Objective	To establish the effectiveness of corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression
4.	Searches	<p>The following databases will be searched:</p> <ul style="list-style-type: none"><li>• Cochrane Central Register of Controlled Trials (CENTRAL)</li><li>• Cochrane Database of Systematic Reviews (CDSR)</li><li>• Cumulative Index to Nursing and Allied Health Literature (CINAHL)</li><li>• Database of Abstracts of Reviews of Effects (DARE)</li><li>• Embase</li><li>• Epistemonikos</li><li>• International Health Technology Assessment (IHTA) database</li><li>• MEDLINE &amp; MEDLINE In-Process</li></ul> <p>Searches will be restricted by:</p>

ID	Field	Content
		<ul style="list-style-type: none"> <li>• English language studies</li> <li>• Human studies</li> </ul> <p>Other searches: Inclusion lists of systematic reviews</p> <p>With the agreement of the guideline committee the searches will be re-run between 6-8 weeks before final submission of the review and further studies retrieved for inclusion.</p> <p>The full search strategies for MEDLINE database will be published in the final review.</p>
5.	Condition or domain being studied	Corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression
6.	Population	<p>Inclusion:</p> <p>Adults with spinal cord or nerve root compression because of:</p> <ul style="list-style-type: none"> <li>• metastatic spinal disease or</li> <li>• direct malignant infiltration</li> </ul> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>• Adults with spinal cord compression because of primary tumours of the spinal cord, meninges or nerve roots.</li> <li>• Adults with spinal cord compression because of non-malignant causes.</li> <li>• Adults with primary bone tumours of the spinal column.</li> <li>• Children and young people under the age of 18.</li> </ul>
7.	Intervention	Dexamethasone (oral or intravenous)
8.	Comparator	<ul style="list-style-type: none"> <li>• No dexamethasone</li> <li>• Different regimens (dosage and duration)</li> </ul>
9.	Types of study to be	Experimental studies (where the investigator assigned intervention or control) including:

ID	Field	Content
	included	<ul style="list-style-type: none"> <li>• Randomised controlled trials</li> <li>• Non-randomised controlled trials</li> <li>• Comparative observational studies (in the absence of RCTs)</li> <li>• Systematic reviews/meta-analyses of controlled trials.</li> </ul>
10.	Other exclusion criteria	<p>Inclusion:</p> <p>Full text papers</p> <p>Observational studies should adjust for baseline differences between patients in different intervention groups in their analyses</p> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>• Conference abstracts</li> <li>• Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/study quality.</li> <li>• Non-English language articles</li> </ul> <p>For NMA:</p> <p>Active interventions that are not part of the decision problem will not be considered in the analysis, unless they act as the sole connectors of the interventions of interest in the network.</p>
11.	Context	<p><a href="#">Metastatic spinal cord compression in adults: risk assessment, diagnosis and management</a> (2008) NICE guideline will be updated by this review question</p>
12.	Primary outcomes (critical outcomes)	<ul style="list-style-type: none"> <li>• Neurological &amp; functional status including: <ul style="list-style-type: none"> <li>○ Bowel &amp; bladder function</li> <li>○ Mobility or ambulatory status</li> </ul> </li> <li>• Pain</li> </ul>
13.	Secondary outcomes (important outcomes)	<ul style="list-style-type: none"> <li>• Treatment related toxicity including: <ul style="list-style-type: none"> <li>○ Steroid adverse effects</li> <li>○ Tumour lysis syndrome (in haematological cancers)</li> </ul> </li> </ul>

ID	Field	Content
14.	Data extraction (selection and coding)	<p>All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.</p> <p>Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol.</p> <p>Dual sifting will be performed on at least 10% of records; 90% agreement is required. The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary.</p> <p>Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion.</p> <p>Draft excluded studies will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.</p> <p>A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.</p>
15.	Risk of bias (quality) assessment	<p>Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual.</p> <p>ROBIS tool for systematic reviews Cochrane RoB tool v.2 for RCTs and quasi-RCTs</p> <p>The non-randomised study design appropriate checklist. For example Cochrane ROBINS-I tool for non-randomised controlled trials and cohort studies; the EPOC RoB tool for controlled before and after studies. The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.</p>

ID	Field	Content
16.	Strategy for data synthesis	<p>Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively.</p> <p><b>Data Synthesis</b> Where possible, pairwise meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events. Mean differences or standardised mean differences will be calculated for continuous outcomes.</p> <p>If sufficient RCTs are available forming a network of relevant interventions, network meta-analysis will be done using Metalnsight V3 (Owen, RK, Bradbury, N, Xin, Y, Cooper, N, Sutton, A. Metalnsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. Res Syn Meth. 2019; 10: 569-581)</p> <p><b>Heterogeneity</b> Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. In the case of serious or very serious unexplained heterogeneity (remaining after pre-specified subgroup and stratified analyses) meta-analysis will be done using a random effects model.</p> <p><b>Minimal important differences (MIDs)</b> Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes For risk ratios: 0.8 and 1.25.</p> <p>For continuous outcomes: MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD. For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries.</p> <p><b>Validity</b></p>



ID	Field	Content														
		The confidence in the findings across all available evidence will be 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: <a href="http://www.gradeworkinggroup.org/">http://www.gradeworkinggroup.org/</a>														
17.	Analysis of sub-groups	<p>Evidence will be stratified by:</p> <ul style="list-style-type: none"> <li>No pre-stratified analysis</li> </ul> <p>Evidence will be sub grouped by the following only in the event that there is significant heterogeneity in outcomes:</p> <ul style="list-style-type: none"> <li>Subgroups listed in the equality impact assessment form: age, race, sex &amp; socioeconomic status</li> <li>Primary cancer type</li> </ul> <p>Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.</p>														
18.	Type and method of review	<table border="1"> <tbody> <tr> <td><input checked="" type="checkbox"/></td> <td>Intervention</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Diagnostic</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Prognostic</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Qualitative</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Epidemiologic</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Service Delivery</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Other (please specify)</td> </tr> </tbody> </table>	<input checked="" type="checkbox"/>	Intervention	<input type="checkbox"/>	Diagnostic	<input type="checkbox"/>	Prognostic	<input type="checkbox"/>	Qualitative	<input type="checkbox"/>	Epidemiologic	<input type="checkbox"/>	Service Delivery	<input type="checkbox"/>	Other (please specify)
<input checked="" type="checkbox"/>	Intervention															
<input type="checkbox"/>	Diagnostic															
<input type="checkbox"/>	Prognostic															
<input type="checkbox"/>	Qualitative															
<input type="checkbox"/>	Epidemiologic															
<input type="checkbox"/>	Service Delivery															
<input type="checkbox"/>	Other (please specify)															
19.	Language	English														
20.	Country	England														
21.	Anticipated or actual start date	04 January 2022														
22.	Anticipated completion date	23 August 2023														

ID	Field	Content	Started	Completed
23.	Stage of review at time of this submission	Review stage		
		Preliminary searches	<input type="checkbox"/>	<input type="checkbox"/>
		Piloting of the study selection process	<input type="checkbox"/>	<input type="checkbox"/>
		Formal screening of search results against eligibility criteria	<input type="checkbox"/>	<input type="checkbox"/>
		Data extraction	<input type="checkbox"/>	<input type="checkbox"/>
		Risk of bias (quality) assessment	<input type="checkbox"/>	<input type="checkbox"/>
		Data analysis	<input type="checkbox"/>	<input type="checkbox"/>
24.	Named contact	5a. Named contact National Guideline Alliance		
		5b Named contact e-mail <a href="mailto:metastaticspinal@nice.org.uk">metastaticspinal@nice.org.uk</a>		
		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
25.	Review team members	NGA Technical Team		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the		

ID	Field	Content
		development of evidence-based recommendations in line with section 3 of <a href="#">Developing NICE guidelines: the manual</a> . Members of the guideline committee are available on the NICE website:.
29.	Other registration details	
30.	Reference/URL for published protocol	<a href="https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=303508">https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=303508</a>
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Corticosteroid therapy; MSCC; neurological consequences
33.	Details of existing review of same topic by same authors	None
34.	Current review status	<input checked="" type="checkbox"/> Ongoing
		<input type="checkbox"/> Completed but not published
		<input type="checkbox"/> Completed and published
		<input type="checkbox"/> Completed, published and being updated
		<input type="checkbox"/> Discontinued
35.	Additional information	None
36.	Details of final publication	<a href="http://www.nice.org.uk">www.nice.org.uk</a>

1 CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE:  
2 Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline  
3 Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

## Appendix B Search strategies (clinical / economic)

### Literature search strategies for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

Database: Medline – OVID interface

#	Searches
1	exp spinal cord neoplasms/ or Spinal Neoplasms/
2	((spine or spinal or vertebr*) adj2 (adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or neoplas* or tumor?r*)).tw.
3	((spine or spinal or vertebr*) and (metast* or oligometast*)).tw.
4	or/1-3
5	spinal cord compression/
6	((cauda equina or cervical* or cervicthoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) and (collaps* or compress* or pinch* or press*) and (adeno* or cancer* or carcinoma* or chordoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or oligometast* or tumor?r*)).tw.
7	(myelopath* or myeloradiculopath* or radiculopath*).tw,hw. or (radicular adj2 (disorder* or syndrome*)).tw.
8	(mescc or msc).tw.
9	or/5-8
10	((adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or metast* or oligometast* or neoplas* or tumor?r*) adj3 (escap* or infiltrat* or invasiv* or metast* or spread*) adj5 (cauda equina or cervical* or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoacic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr*)).tw.
11	4 or 9 or 10
12	Adrenal Cortex Hormones/
13	((adrenal or adeno*) adj2 (hormone* or steroid*)) or adrenocorticosteroid* or corticoid* or corticosteroid* or cortico steroid* or cortical steroid* or dermocorticosteroid*).tw.
14	exp dexamethasone/
15	(Adrecort or adrenocot or aeraseb* or aflucoson* or alfalyl or anaflogistico or aphtasolon or Arcodexan or arcodexan* or artrosone or auxiron or aziun or bidezol or bisu ds or calonat or cebedex or cetadexon or colofom or corson? or cortastat or cortidex or cortidexason or cortidrona or cortidrone or cortisumman or dacortina or dalalone or dalalone or danasone or decacortin or decadelton* or decaderm or decadion or decadrone or decadron or decadron or decadron or decadronal or decadrone or decaesadriil or decagel or decaject or decaject or decalix or decameth or decamethasone or decasone or decaspray or decaspray or decasterolone or decdan or decilone or decofluor or dectancyl or dekacort or delladec or deltafluoren or deltafluorene or dergramin or deronil or desacort or desacortone or desadrene or desalark or desameton* or desigdrone or de sone la or dexa cortisyl or dexa dabrosan or dexa korti or dexa scheros?n* or dexacen 4 or dexacen 4 or dexachel or dexacort or dexacortal or dexacorten or dexacortin or dexacortisyl or dexadabrosan or dexadecadrol or dexadrol or dexagel or dexagen or dexahelvacort or dexakorti or dexalien or dexalocal or dexame or dexamecortin or dexameson or dexamesone or dexametason* or dexameth or dexamethasone* or dexamethazon* or dexamethonium or dexamonozon or dexan or dexane or dexano or dexa p or dexapot or dexascheroson or dexascher-ozon* or dexason or dexasone or dexasone or dexinoral or dexionil or dexmethsone or dexona or dexone or dexone or dexone or dexpak or dexpak taperpak or dextelan or dextenza or dextrason or dexycu or dezone or dibasona or esacortene or exadion or exadione or firmalone or fluormethyl?prednisolone* or fluormone or fluorocort or fluorodelta or fluoro-methylprednisolone or fortacortin or gammacorten* or grosodexon* or hemady or hexad?ol or hexadecad?ol or hexadecadrol or hexad?ol or isnacort or isopto dex or isopto?maxidex or isoptodex or lokalison f or loverine or luxazone or marvidione or maxidex or maxidex or mediamethasone or megacortin or mephameson* or metasolon or metasolone or methazon ion or methazone ion or methazonion* or methylfluorprednisolone or metisone lafi or mexasone or millicorten or millicorten* or mk?125 or mymethasone or neoforderx or neoforderx or nisomethasone or novocort or oftan dexa or opticorten or opticortinol or oradex?n* or oradexon or orgadrone or ozurdex or pidexon or policort or posurdex or predni f tablinen or predni f or prednisolone or prodexona or prodexone or sanamethasone or santenson or santeson or sawasone or solurex or spoloven or sterasone or thilodexine or triamcimetil or vexamet or visumetazone or visumetha-zone).tw.
16	Or/12-15
17	11 and 16
18	(animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
19	17 not 18
20	limit 19 to english language

## Health economics search

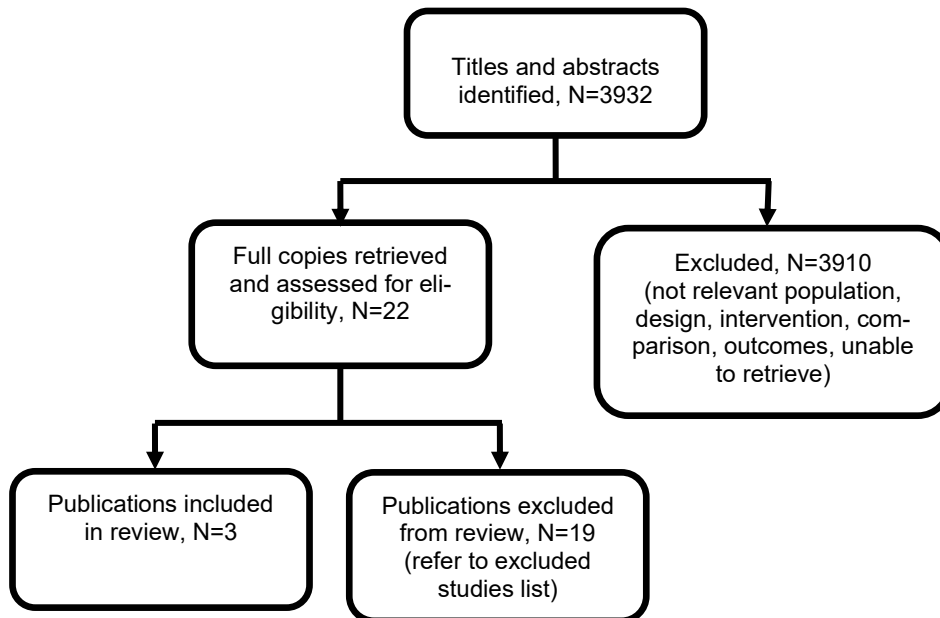
Database: Medline – OVID interface

#	Searches
1	exp Spinal Cord Neoplasms/ or Spinal Neoplasms/
2	((spine or spinal or vertebr*) adj2 (adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or neoplas* or tumo?r*)).tw.
3	((spine or spinal or vertebr*) and (metast* or oligometast*)).tw.
4	or/1-3
5	Spinal Cord Compression/
6	((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) and (collaps* or compress* or pinch* or press*) and (adeno* or cancer* or carcinoma* or chordoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or oligometast* or tumo?r*)).tw.
7	(myelopath* or myeloradiculopath* or radiculopath*).tw,hw. or (radicular adj2 (disorder* or syndrome*)).tw.
8	(mescc or msc).tw.
9	or/5-8
10	((adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or tumo?r*) adj3 (escap* or infiltrat* or invasiv* or metast* or spread*) adj5 (cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root))).tw.
11	or/4,9-10
12	Economics/ or Value of life/ or exp "Costs and Cost Analysis"/ or exp Economics, Hospital/ or exp Economics, Medical/ or Economics, Nursing/ or Economics, Pharmaceutical/ or exp "Fees and Charges"/ or exp Budgets/
13	(cost* or economic* or pharmacoeconomic*).ti.
14	(budget* or financ* or fee or fees or price* or pricing* or (value adj2 (money or monetary))).ti,ab.
15	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
16	or/12-15
17	11 and 16
18	limit 17 to english language
19	limit 18 to yr="2005 -Current"

## Appendix C Effectiveness evidence study selection

**Study selection for: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?**

**Figure 1: Study selection flow chart**



## Appendix D Evidence tables

### Evidence tables for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

**Table 4: Evidence tables**

#### Graham, 2006

Graham P, Capp A, Delaney G et al., A pilot randomised comparison of dexamethasone 96 mg vs 16 mg per day for malignant spinal-cord compression treated by radiotherapy: TROG 01.05 Superdex study. *Clinical oncology*, 18, 70-6, 2006

#### Study details

<b>Country/ies where study was carried out</b>	Australia
<b>Study type</b>	Randomised controlled trial (RCT) 8 recruiting hospitals.
<b>Study dates</b>	September 2001 - November 2003.
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• MRI evidence of MSCC and at least one of pain, weakness, sensory symptoms or sphincter disturbance symptoms.</li> <li>• Prior histological proof of malignancy.</li> <li>• Age &gt; 16 years</li> <li>• Eastern Co-operative Oncology Group (ECOG) performance status less than 4 before MSCC event.</li> <li>• Minimum power 1 out of 5.</li> <li>• Estimated minimum survival of 2 months.</li> <li>• Written informed consent.</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Prior radiotherapy (defined as being within one vertebral level).</li> <li>• Prior treatment for MSCC.</li> <li>• Multi-level MSCC or other central nervous system disease.</li> <li>• Lymphoma or myeloma histology.</li> <li>• Definite history of peptic ulceration or cardiac failure.</li> <li>• Pregnancy.</li> <li>• Ongoing nonsteroidal medication.</li> <li>• Patients undergoing surgery.</li> </ul>
<b>Patient characteristics</b>	Age, mean, years (range): 66 (41 – 81). Sex: female n=20, male n=14.

	<p>Primary site, n: Breast/prostate – high dose 5; low dose 6; total 11. Other (lung, gastrointestinal tract, renal, other) – high dose 4; low dose 5; all patients 9.</p> <p>Level, n: Cervical – high dose 0; low dose 1, all patients 1. Thoracic - high dose 8; low dose 7; all patients 15. Lumbar – high dose 1; low dose 3, all patients 4.</p> <p>Hours of dexamethasone pre-randomisation, n: 0 hours – high dose 7; low dose 6; all patients. 0 – 10 hours – high dose 2; low dose 3; all patients 5. &gt; 10 hours – high dose 0; low dose 2; all patients 2. &gt; 6 months from cancer diagnosis, n: high dose 3; low dose 6; all patients 9. Ambulant, n: high dose 6; low dose 9; all patients 15.</p>
<b>Intervention(s)/control</b>	<p>High dose dexamethasone = 96 mg intravenous daily dexamethasone - days 0 - 2, then weaned to 0 mg by day 15.</p> <p><i>versus</i></p> <p>Low dose dexamethasone = 16 mg intravenous daily dexamethasone - days 0 - 2, then weaned to 0 mg by day 15. More rapid reduction was permitted if steroid toxicity was diagnosed, and reductions could be ceased or reversed if neurological deterioration occurred with reducing dexamethasone dose. An increase above the day 0 dose was not permitted. Peptic ulcer prophylaxis consisted of cessation of any non-steroidal medication and commencement of omeprazole 40 mg daily reduced to 20 mg when the dexamethasone dose was less than 16 mg. Daily glucometer finger prick assays were undertaken. Patients with indwelling urinary catheters were prescribed trimethoprim 300 mg daily prophylactically, and nystatin drops were given orally to all patients. An appropriate laxative schedule was given. Radiation was given on megavoltage linear accelerators after simulation, using a minimum field width of 8 cm. The minimum supero-inferior tumour margin to field edge was 3 cm, typically one vertebral body. The dose was 30 Gy in 10 fractions prescribed at a depth of 5 cm. The first two fractions were to be given on consecutive days, including weekends.</p>
<b>Duration of follow-up</b>	12 months.
<b>Sources of funding</b>	Trans-Tasman Radiation Oncology Group (TROG); Cancer Council New South Wales.
<b>Sample size</b>	N=20. (96 mg group n=9; 16 mg group n=11).
<b>Other information</b>	<p>Patients had to be randomised within 12 hours of receiving more than 4 mg/24 h of dexamethasone or equivalent steroid.</p> <p>Serious adverse events defined as events that require hospitalisation or prolongation of an existing admission, life-threatening events or death within 30 days of study treatment.</p>



For the first 10 days, mean doses received were within 20% of scheduled doses. Beyond this time, a patient randomised to the low-dose arm remained on 12 mg because of neurological decline, thus influencing the mean upwards. Although compliance was satisfactory, there seemed to be a tendency to reduce steroid doses faster than the protocol specification in the high-dose group compared with the low-dose group.

Two out of six patients commencing radiotherapy on a Friday did not receive radiotherapy for two consecutive days at the commencement of treatment. Two patients received less than 30 Gy because of general deterioration (n=1) or death (n=1).

### Outcomes

Outcome	High dose dexamethasone (96mg), n=9	Low dose dexamethasone (16mg) n=11
Neurological and functional status - ambulation rate (patients ambulant at study entry, 1 month)	n=2/6	n=6/9
Treatment related toxicity - serious adverse effects - any	n=5/9	n=4/11
Treatment related toxicity - serious drug related adverse effects	n=1/9	n=0/11

### Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

**Sorensen, 1994**

Sorensen P, Helweg-Larsen S, Mouridsen H, et al. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: A randomised trial. *European Journal of Cancer*, 30, 22-27, 1994

**Study details**

<b>Country/ies where study was carried out</b>	Denmark.
<b>Study type</b>	Randomised controlled trial (RCT)
<b>Study dates</b>	May 1987 and April 1989.
<b>Inclusion criteria</b>	Patients referred for radiotherapy with compression of the spinal cord or cauda equina by epidural metastasis from a carcinoma. Diagnosis of spinal cord compression confirmed by myelography and, in some cases, by supplementary magnetic resonance imaging, with definition of the cranial and caudal margins of the epidural block.
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Patients with lymphoma.</li> <li>• Previous treatment for epidural metastasis.</li> <li>• Meningeal carcinomatosis.</li> <li>• Infectious disease</li> <li>• Patients with peptic ulcers in whom treatment with high-dose dexamethasone was considered inappropriate.</li> <li>• Patients who underwent surgery.</li> </ul> <p>Surgery was considered in patients without previously established diagnosis of cancer, and in a few patients with unstable vertebral lesions. In all other patients, radiotherapy was offered as the department's standard treatment.</p>
<b>Patient characteristics</b>	<p>Age, years, median (range): High dose 60 (25-81); no treatment 64 (41-82). Sex: female n=39, male n=18.</p> <p>Primary tumour site, n: Breast - Dexamethasone 18; no treatment 16. Gastrointestinal – Dexamethasone 3; no treatment 3. Prostrate - Dexamethasone 1; no treatment 4. Lung - Dexamethasone 2; no treatment 1. Sarcoma - Dexamethasone 1; no treatment 3. Melanoma - Dexamethasone 1; no treatment 1. Kidney - Dexamethasone 1; no treatment 0. Mesothelioma - Dexamethasone 0; no treatment 1. Thyroid - Dexamethasone 0; no treatment 1.</p>

	<p>Site of compression, n: Cervical - Dexamethasone 2; no treatment 1. Thoracic - Dexamethasone 17; no treatment 16. Lumbar - Dexamethasone 8; no treatment 13.</p> <p>Pre-treatment motor function, n: Ambulatory - Dexamethasone 17; no treatment 19. Paretic without gait - Dexamethasone 7; no treatment 8. Paraplegic - Dexamethasone 3; no treatment 3.</p>
<b>Intervention(s)/control</b>	<p>High dose dexamethasone = intravenous bolus of 96 mg given immediately after myelography or MRI, then maintained on a dose of 96 mg dexamethasone for 3 days (given orally where possible in four divided doses), and the treatment was then tapered over 10 days.</p> <p><i>versus</i></p> <p>No treatment = no details reported.</p> <p>Prophylactic medication against gastro-duodenal ulceration was not given routinely---only in patients with a history of peptic ulcers and in patients complaining of dyspepsia.</p> <p>Radiation therapy was delivered with 6 MV photon beams, administered in two parallel opposing anterior and posterior fields, encompassing one normal vertebra, cranial and caudal to the epidural block. A radiation dose of 28 Gy was given in fractions of 4 Gy on each of 7 consecutive days. The first dose of irradiation was given 1-20 h after myelography, usually within a few hours.</p>
<b>Duration of follow-up</b>	Every three months for two years or until death.
<b>Sources of funding</b>	Danish Cancer Research Foundation; Dexamethazone provided by Merck, Sharpe and Dhome, Denmark.
<b>Sample size</b>	N=59 randomised (2 patients excluded after randomisation, both from dexamethasone group due to ineligibility; dexamethasone group n=27; no treatment n=30).

**Outcomes**

<b>Outcome</b>	<b>High dose dexamethasone (96mg), n=27</b>	<b>No treatment n=30</b>
<b>Neurological and functional status - ambulation (preservation or restoration of gait, 3 months, number of patients)</b>	22/27	19/30
<b>Neurological and functional status - survival with gait function (6 months, number of patients)</b>	16/27	10/30

Outcome	High dose dexamethasone (96mg), n=27	No treatment n=30
Neurological and functional status - survival with gait function (1 year, number of patients)	8/27	6/30
Treatment related toxicity – ‘significant side-effects’ (number of patients)	n=3/27	n=0/30
Treatment related toxicity – discontinuation of dexamethasone therapy due to adverse events (number of patients)	n=2/27	n=0/30

**Critical appraisal – Cochrane RoB 2**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

**Vecht, 1989**

Vecht C, Haaxma-Reiche H, van Putten W, et al., Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. *Neurology* 39, 1255-7, 1989

**Study details**

Country/ies where study was carried out	Netherlands.
Study type	Randomised controlled trial (RCT)
Study dates	Not reported.

<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Histologically verified diagnosis of a primary tumour, either a carcinoma or a lymphoreticular malignancy.</li> <li>• Showing complete obstruction for contrast flow on myelography, which was performed on suspicion of metastatic epidural spinal cord compression.</li> </ul>
<b>Exclusion criteria</b>	Not reported.
<b>Patient characteristics</b>	<p>Age, years, mean (SD): 61 (range 22 -87). SD not reported.  Sex: female n=11; male n=26.  Pain, n: low dose 13/15; high dose 18/22; total 31/37  Paresthesia, n: low dose 4/15; high dose 6/21; total 10/36  Sensory level, n: low dose 13/15; high dose 12/21; total 25/36.</p> <p>Ambulation grade, n:  I – low dose 5/15; high dose 8/22; total; 13/37  II – low dose 2/15; high dose 6/22; total; 8/37  III – low dose 2/15; high dose 4/22; total; 6/37  IV - low dose 3/15; high dose 2/22; total; 5/37  V – low dose 10/15; high dose 2/22; total; 5/37</p> <p>Bladder dysfunction, n: low dose 10/15; high dose 6/19; total; 16/34</p> <p>Carcinoma, n: low dose 11/15; high dose 15/22; total; 26/37</p> <p>Lymphoreticular malignancy, n: conventional dose 4/15; high dose 7/22; total; 11/37</p>
<b>Intervention(s)/control</b>	<p>High dose dexamethasone = 100 mg dexamethasone</p> <p><i>versus</i></p> <p>Low dose dexamethasone = 10 mg dexamethasone.</p> <p>No further details reported.</p>
<b>Duration of follow-up</b>	1 week.
<b>Sources of funding</b>	Not reported.
<b>Sample size</b>	N=37 (100 mg group n=15; 10 mg group n=22).

**Outcomes**

<b>Outcome</b>	<b>High dose dexamethasone (100mg), n=22</b>	<b>Low dose dexamethasone (10 mg), n=15</b>
Neurological and functional status - change in bladder function at 3 hours (improved or stable)	n=21/22	n=15/15
Neurological and functional status - change in bladder function at 24 hours (improved or stable)	n=19/22	n=15/15
Neurological and functional status - change in bladder function at 1 week (improved or stable)	n=20/22	n=14/15
Neurological and functional status - ambulation rate (all patients) - 24 hours	n=14/22	n=6/15
Neurological and functional status - ambulation rate (all patients) - 1 week	n=11/20	n=7/13
Neurological and functional status - ambulation rate (patients ambulant at study entry, 1 month)	n=2/6	n=6/9
Neurological and functional status - change in ambulation (improved or stable) - 3 hours	n=21/21	n=13/14
Neurological and functional status - change in ambulation (improved or stable) - 24 hours	n=20/22	n=13/15
Neurological and functional status - change in ambulation (improved or stable) - 1 week	n=14/20	n=11/13
Pain - change in pain score (improved) - 3 hours	n=9/17	n=5/12
Pain - change in pain score (improved) - 24 hours	n=10/17	n=10/13
Pain - change in pain score (improved) - 1 week	n=11/14	n=10/11
Treatment related toxicity - serious adverse effects - any	n=5/9	n=4/11
Treatment related toxicity - serious drug related adverse effects	n=1/9	n=0/11

**Critical appraisal – Cochrane RoB 2**

<b>Section</b>	<b>Question</b>	<b>Answer</b>
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

## **Appendix E Forest plots**

**Forest plots for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?**

No meta-analysis was conducted for this review question and so there are no forest plots.



## Appendix F GRADE tables

GRADE tables for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?

Table 5: Evidence profile for comparison between high dose dexamethasone and no treatment

Quality assessment							No of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose dexamethasone	No treatment	Relative (95% CI)	Absolute		
<b>Neurological and functional status - ambulation (preservation or restoration of gait, 3 months)</b>												
1 (Sorensen 1994)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	22/27	19/30	RR 1.29 (0.93 to 1.78)	184 more per 1000 (from 44 fewer to 494 more)	MODERATE	CRITICAL
<b>Neurological and functional status - survival with gait function (6 months)</b>												
1 (Sorensen 1994)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	16/27	10/30	RR 1.78 (0.98 to 3.22)	260 more per 1000 (from 7 fewer to 740 more)	MODERATE	CRITICAL
<b>Neurological and functional status - survival with gait function (1 year)</b>												
1 (Sorensen 1994)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	8/27	6/30	RR 1.48 (0.59 to 3.72)	96 more per 1000 (from 82 fewer to 544 more)	LOW	CRITICAL
<b>Treatment related toxicity – ‘significant’ side effects</b>												
1 (Sorensen 1994)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	3/27	0/30	POR 8.93 (0.89 to 89.77)	110 more per 1000 (from 20 fewer to 240 more)	LOW	IMPORTANT
<b>Treatment related toxicity – discontinuation of dexamethasone therapy due to adverse events</b>												
1	random-	no serious	no serious in-	no serious indi-	very	none	2/27	0/30	POR 8.58	110 more per	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose dexamethasone	No treatment	Relative (95% CI)	Absolute		
(Sorensen 1994)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision <sup>2</sup>	none			(0.52 to 141.22)	1000 (from 8 fewer to 689 more)		

CI: confidence interval; NA: not applicable; POR: Peto odds ratio; RD: risk difference; RR: risk ratio

1 95% CI crosses 1 MID

2 95% CI crosses 2 MIDs

**Table 6: Evidence profile for comparison between high dose dexamethasone and low dose dexamethasone**

Quality assessment							No of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose dexamethasone versus	Low dose dexamethasone	Relative (95% CI)	Absolute		
<b>Neurological and functional status - change in bladder function (improved or stable) - 3 hours</b>												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/22	15/15	RR 0.96 (0.84 to 1.11)	40 fewer per 1000 (from 160 fewer to 110 more)	HIGH	CRITICAL
<b>Neurological and functional status - change in bladder function (improved or stable) - 24 hours</b>												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	19/22	15/15	RR 0.88 (0.72 to 1.06)	120 fewer per 1000 (from 280 fewer to 60 more)	MODERATE	CRITICAL
<b>Neurological and functional status - change in bladder function (improved or stable) - 1 week</b>												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/22	14/15	RR 0.97 (0.81 to 1.18)	28 fewer per 1000 (from 177 fewer to 168 more)	HIGH	CRITICAL
<b>Neurological and functional status - ambulation rate (all patients) - 24 hours</b>												

Quality assessment							No of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose dexamethasone versus	Low dose dexamethasone	Relative (95% CI)	Absolute		
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	14/22	6/15	RR 1.59 (0.79 to 3.19)	236 more per 1000 (from 84 fewer to 876 more)	LOW	CRITICAL
<b>Neurological and functional status - ambulation rate (all patients) - 1 week</b>												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	11/20	7/13	RR 1.02 (0.54 to 1.94)	11 more per 1000 (from 248 fewer to 506 more)	LOW	CRITICAL
<b>Neurological and functional status - ambulation rate (patients ambulant at study entry, 1 month)</b>												
1 (Graham 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	2/6	6/9	RR 0.5 (0.15 to 1.7)	333 fewer per 1000 (from 567 fewer to 467 more)	LOW	CRITICAL
<b>Neurological and functional status - change in ambulation (improved or stable) - 3 hours</b>												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	21/21	13/14	RR 1.09 (0.91 to 1.3)	84 more per 1000 (from 84 fewer to 279 more)	MODERATE	CRITICAL
<b>Neurological and functional status - change in ambulation (improved or stable) - 24 hours</b>												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	20/22	13/15	RR 1.05 (0.83 to 1.33)	43 more per 1000 (from 147 fewer to 286 more)	MODERATE	CRITICAL
<b>Neurological and functional status - change in ambulation (improved or stable) - 1 week</b>												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	14/20	11/13	RR 0.83 (0.57 to 1.2)	144 fewer per 1000 (from 364 fewer to 169 more)	MODERATE	CRITICAL
<b>Pain - change in pain score (improved) - 3 hours</b>												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	9/17	5/12	RR 1.27 (0.57 to 2.84)	113 more per 1000 (from 179 fewer to 767 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose dexamethasone versus	Low dose dexamethasone	Relative (95% CI)	Absolute		
<b>Pain - change in pain score (improved) - 24 hours</b>												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	10/17	10/13	RR 0.76 (0.47 to 1.26)	185 fewer per 1000 (from 408 fewer to 200 more)	LOW	CRITICAL
<b>Pain - change in pain score (improved) - 1 week</b>												
1 (Vecht 1989)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	11/14	10/11	RR 0.86 (0.62 to 1.2)	127 fewer per 1000 (from 345 fewer to 182 more)	MODERATE	CRITICAL
<b>Treatment related toxicity - serious adverse effects - any</b>												
1 (Graham 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	5/9	4/11	RR 1.53 (0.58 to 4.05)	193 more per 1000 (from 153 fewer to 1000 more)	LOW	IMPORTANT
<b>Treatment related toxicity - serious drug related adverse effects</b>												
1 (Graham 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	1/9	0/11	POR 9.23 (0.18 to 474.33)	110 more per 1000 (from 140 fewer to 360 more)	LOW	IMPORTANT

CI: confidence interval; NA: not applicable; POR: Peto odds ratio; RD: risk difference; RR: risk ratio

1 95% CI crosses 1 MID

2 95% CI crosses 2 MIDs

## **Appendix G Economic evidence study selection**

**Study selection for: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?**

No economic evidence was identified which was applicable to this review question.

## **Appendix H Economic evidence tables**

**Economic evidence tables for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?**

No evidence was identified which was applicable to this review question.

## **Appendix I Economic model**

**Economic model for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?**

No economic analysis was conducted for this review question.

## Appendix J Excluded studies

**Excluded studies for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?**

### Excluded effectiveness studies

**Table 7: Excluded studies and reasons for their exclusion –**

Study	Reason for exclusion
Al-Qurainy R and Collis E (2016) Metastatic spinal cord compression: Diagnosis and management. <i>BMJ (Online)</i> 353: i2539	Study design does not match review protocol – expert review/narrative. Checked for relevant studies
Chamberlain, Marc C, Sloan, Andrew, Vrionis, Frank et al. (2005) Systematic review of the diagnosis and management of malignant extradural spine cord compression: The Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. <i>Journal of clinical oncology</i> , 23, 7750-2	Study design does not match review protocol - commentary
Climent, Miguel A., Piulats, Josep M., Sanchez-Hernandez, Alfredo et al. (2012) Recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with metastatic castration-resistant prostate cancer. <i>Critical Reviews in Oncology/Hematology</i> 83(3): 341-352	Other protocol criteria - systematic review, checked for relevant studies
Dy, Sydney M, Asch, Steven M, Naeim, Arash et al. (2008) Evidence-based standards for cancer pain management. <i>Journal of clinical Oncology</i> 26(23): 3879-85	Other protocol criteria - systematic review, checked for relevant studies
George, Reena, Jeba, J., Leng, M. et al. (2007) Interventions for the treatment of metastatic extradural spinal cord compression. <i>Cochrane Database of Systematic Reviews</i> : cd006716	Other protocol criteria - duplicate publication - more recent version available
George, Reena, Jeba, Jenifer, Ramkumar, Govindaraj et al. (2015) Interventions for the treatment of metastatic extradural spinal cord compression in adults. <i>The Cochrane database of systematic reviews</i> : cd006716	Other protocol criteria - systematic review, checked for relevant studies
George, Reena, Jeba, Jenifer, Ramkumar, Govindraj et al. (2008) Interventions for the treatment of metastatic extradural spinal cord compression in adults. <i>The Cochrane database of systematic reviews</i> : cd006716	Other protocol criteria - duplicate publication - more recent version available
Hardy, Janet, Haywood, Alison, Rickett, Kirsty et al. (2021) Practice review: Evidence-based quality use of corticosteroids in the palliative care of	Other protocol criteria - systematic review, checked for relevant studies



Study	Reason for exclusion
patients with advanced cancer. Palliative Medicine 35(3): 461-472	
Haywood, Alison, Good, Phillip, Khan, Sohil et al. (2015) Corticosteroids for the management of cancer-related pain in adults. The Cochrane database of systematic reviews: cd010756	Other protocol criteria - systematic review, checked for relevant studies
Janjan, Nora, Bedwinek, John M., Hartsell, William F. et al. (2009) Therapeutic guidelines for the treatment of bone metastasis: A report from the American college of radiology appropriateness criteria expert panel on radiation oncology. Journal of Palliative Medicine 12(5): 417-426	Study design does not match review protocol – expert review/narrative. Checked for relevant studies
Klimo, Paul Jr; Kestle, John R; Schmidt, Meic H (2003) Treatment of metastatic spinal epidural disease: a review of the literature. Neurosurgical focus 15(5): e1	Other protocol criteria - systematic review, checked for relevant studies
Kumar, Abhishek, Weber, Michael H, Gokaslan, Ziya et al. (2017) Metastatic Spinal Cord Compression and Steroid Treatment: A Systematic Review. Clinical spine surgery 30(4): 156-163	Other protocol criteria - systematic review, checked for relevant studies
L'esperance, S, Vincent, F, Gaudreault, M et al. (2012) Treatment of metastatic spinal cord compression: cepo review and clinical recommendations. Current oncology (Toronto, Ont.) 19(6): e478-90	Other protocol criteria - systematic review, checked for relevant studies
Loblaw, D A and Laperriere, N J (1998) Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. Journal of Clinical Oncology 16, 1613-24	Other protocol criteria - systematic review, checked for relevant studies
Loblaw A, Perry J, Chambers A et al. (2005) Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 23(9): 2028-37	Other protocol criteria - systematic review, checked for relevant studies
Loblaw, D. A. and Laperriere, N. J. (1998) Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. Journal of Clinical Oncology 16: 1613-1624	Other protocol criteria - systematic review, checked for relevant studies
Oh, Daniel Chun-Suk, Rispoli, Leia, Ghosh, Priyanka et al. (2021) Epidural Steroid Injections for the Management of Spinal Malignancy-Related Pain: A Pragmatic Review and Retrospective Study. Pain practice : the official journal of World Institute of Pain 21(3): 285-298	Other protocol criteria - systematic review, checked for relevant studies
Skeoch, Gordon D, Tobin, Matthew K, Khan, Sajeel et al. (2017) Corticosteroid Treatment for	Other protocol criteria - systematic review, checked for relevant studies

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Study	Reason for exclusion
Metastatic Spinal Cord Compression: A Review. Global spine journal 7(3): 272-279	
Sorensen, S, Helweg-Larsen, S, Mouridsen, H et al. (1994) Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. European journal of cancer (Oxford, England : 1990) 30a(1): 22-7	Other protocol criteria - duplicate publication

## **Appendix K Research recommendations**

**Research recommendations for review question: How effective is corticosteroid therapy in managing the neurological consequences of metastatic spinal cord compression?**

No research recommendations were made for this review question.