Review protocol for review question: What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022303711
1.	Review title	Effective service configuration and delivery arrangements in the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression
2.	Review question	What service configuration and delivery arrangements are effective for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?
3.	Objective	To establish effective service configuration and delivery arrangements for the investigation and referral of adults with suspected or confirmed spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Cumulative Index to Nursing and Allied Health Literature (CINAHL) • Embase • Emcare • Epistemonikos • International Health Technology Assessment (IHTA) database

ID	Field	Content
		• MEDLINE & MEDLINE In-Process Searches will be restricted by: • Systematic review/meta-analysis study design filter • RCT/non-randomised controlled trials study design filter • Date: 1990 onwards (see rationale under Section 10) • English language studies • Human studies Other searches: • Reference searching • Citation searching • Inclusion lists of systematic reviews • Websites The searches will be re-run 6-8 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Service configuration and delivery arrangements in the investigation and referral of adults with suspected or confirmed MSCC

6.	Population	Inclusion:
		• Adults with suspected or confirmed
		  ○ metastatic spinal disease
		  ○ direct malignant infiltration of the spine.
		
		• Adults with suspected or confirmed spinal cord or nerve root compression because of
		  ○ metastatic spinal disease

ID	Field	Content
		○ direct malignant infiltration of the spine Exclusion: • Adults with spinal cord compression because of primary tumours of the spinal cord, meninges or nerve roots. • Adults with spinal cord compression because of non-malignant causes. • Adults with primary bone tumours of the spinal column. • Children and young people under the age of 18.
7.	Intervention	Any service delivery models (approaches, configurations of resources and services) for the investigation and referral of people with suspected malignant spinal cord compression or suspected spinal metastases. For example: • Delivery arrangements: ○ How and when investigations are done, for example: - 2 week wait pathway - Urgent investigation within 24 hours - 7 day scans ○ Where investigations are done, for example - Rapid diagnostic centres - Community diagnostic hubs - Emergency department ○ Who does investigations & how the workforce is managed - Role expansion or task shifting - Staffing models • Coordination of care and management of care processes, for example: ○ MSCC coordinators ○ Early involvement of oncology ○ Early involvement of relevant surgical department

ID	Field	Content
		○ Communication / referral between providers (for example from primary care) ○ Multidisciplinary teams • Coordination of investigations amongst different providers
8.	Comparator/Reference standard/Confounding factors	Interventions compared with: • Each other • Combinations of interventions
9.	Types of study to be included	Randomised controlled trials • Non-randomised comparative studies (including before and after designs) • Systematic reviews/meta-analyses. • Service evaluations and audits will be included in the absence of comparative randomised or non-randomised studies.
10.	Other exclusion criteria	Inclusion: • Full text papers Exclusion: • Conference abstracts • Articles published before 1990 (MRI became available in the early 1990s and is the key test for investigation of MSCC). • 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. • Non-English language articles
11.	Context	Metastatic spinal cord compression in adults: risk assessment, diagnosis and management (2008) NICE guideline will be updated by this review question
12.	Primary outcomes (critical outcomes)	• Overall survival • Quality of life • Patient satisfaction • Neurological and functional status including: ○ Bowel and bladder function

ID	Field	Content
		○ Mobility or ambulatory status ○ Time to paralysis (paralysis-free survival)
13.	Secondary outcomes (important outcomes)	• Emergency admission to hospital and length of hospital stay • Access to services: ○ Local availability (for example, time/distance travelled to access services) ○ Waiting times for services ○ Time to diagnosis ○ Time to treatment
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. 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. 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. 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.
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Appendix H

ID	Field	Content
		of Developing NICE guidelines: the manual: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • 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.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. <u>Data Synthesis</u> 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. If sufficient RCTs are available forming a network of relevant interventions, network meta-analysis will be done using MetaInsight V3 (Owen, RK, Bradbury, N, Xin, Y, Cooper, N, Sutton, A. MetaInsight: 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) <u>Heterogeneity</u> 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. <u>Minimal important differences (MIDs)</u>

ID	Field	Content	
		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. • 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. <u>Validity</u> 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: http://www.gradeworkinggroup.org/	
17.	Analysis of sub-groups	Evidence will be stratified by: • None Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Subgroups listed in the equality impact assessment form: age, race, sex & socioeconomic status 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.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative

ID	Field	Content		
		☐	Epidemiologic	
		☒	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	24 January 2022		
22.	Anticipated completion date	23 August 2023		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Alliance 5b Named contact e-mail metastaticspinal@nice.org.uk 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		

ID	Field	Content	
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 development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=303711	
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	Metastatic spinal cord compression, service, delivery, early rehabilitation and management.	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published

ID	Field	Content	
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	
	Relevant papers	N/A	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimal important difference; MSCC: metastatic spinal cord compression; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation