Review protocol for review question: How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42021288035
1.	Review title	Radiotherapy for the management of spinal metastases, direct malignant infiltration or associated spinal cord compression
2.	Review question	How effective is radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?
3.	Objective	To establish the effectiveness of radiotherapy, including both fractionated and unfractionated radiotherapy, for the management of 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) • Database of Abstracts of Reviews of Effects (DARE) • Embase • Epistemonikos • International Health Technology Assessment (IHTA) database

ID	Field	Content
		• MEDLINE & MEDLINE In-Process Searches will be restricted by: • Date: 1990 onwards (see rationale under Section 10) • English language studies • Human studies Other searches: Inclusion lists of systematic reviews 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. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Radiotherapy in the management of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression.
6.	Population	Inclusion: Adults with: • metastatic spinal disease • direct malignant infiltration of the spine • Adults with confirmed spinal cord or nerve root compression because of metastatic spinal disease or direct malignant infiltration. Exclusion: • Adults with suspected metastatic spinal disease and suspected direct malignant infiltration of the spine. • Adults with spinal cord compression because of primary tumours of the spinal cord, meninges or nerve roots.

ID	Field	Content
		• 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	Radiotherapy (RT): • Unfractionated RT (including stereotactic techniques) • Fractionated RT
8.	Comparator	• No RT (with or without surgery) • Repeated single site treatments versus one multi-site treatment • Surgery with post-op RT versus RT alone • Different fractionation • Different dosage • Different RT technique
9.	Types of study to be included	Experimental studies (where the investigator assigned intervention or control) including: • Randomised controlled trials • Systematic reviews/meta-analyses of randomised controlled trials. In the absence of controlled trials reporting critical outcomes for each of the interventions & comparators, studies using the following designs will be included: Observational studies (where neither control nor intervention were assigned by the investigator) including: • Systematic reviews of observational studies. • Prospective and retrospective cohort studies • Case control studies • Before and after study or interrupted time series
10.	Other exclusion criteria	Inclusion: • Full text papers • Observational studies should adjust for baseline differences in patient groups in their analyses

ID	Field	Content
		Exclusion: • Conference abstracts • Articles published before 1990. MRI has regularly used in diagnosis since the early 1990s. IMRT was not commercially available until 1994. • 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 • Studies using qualitative methods only • 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)	• Health related quality of life
		• Neurological and functional status including:
		  ○ Bowel & bladder function
		  ○ Mobility or ambulatory status
		• Overall survival
		• Pain

13.	Secondary outcomes (important outcomes)	• Treatment related morbidity • Spinal stability (especially in those who did not have surgery) • Fitness for subsequent anti-cancer therapy
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. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary.

ID	Field	Content
		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. 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 Developing NICE guidelines: the manual. Quality assessment of individual studies will be performed using the following: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • ROBINS-I for non-randomised 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. Data Synthesis Where possible, pair wise 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.

ID	Field	Content
		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. 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. Validity 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: • Primary cancer type • Ambulant vs non ambulant patients • Bony instability / vertebral collapse on MRI 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.

ID	Field	Content			
18.	Type and method of review	X	Intervention		
			Diagnostic		
			Prognostic		
			Qualitative		
			Epidemiologic		
			Service Delivery		
			Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	01 November 2021			
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			

ID	Field	Content
		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 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	National Guideline Alliance. Radiotherapy for the management of spinal metastases, direct malignant infiltration or associated spinal cord compression. PROSPERO 2021 CRD42021288035 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021288035
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	Humans; Radiation Oncology; Spinal Cord Compression; Spinal Neoplasms

ID	Field	Content	
33.	Details of existing review of same topic by same authors		
34.	Current review status	X	Ongoing
			Completed but not published
			Completed and published
			Completed, published and being updated
			Discontinued
35.	Additional information		
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; 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