Review protocol for review question: How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022303705
1.	Review title	Radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression
2.	Review question	How effective are radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression?
3.	Objective	To establish effective radiological imaging techniques in the diagnosis 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) • 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 • MEDLINE & MEDLINE In-Process Searches will be restricted by: • Date: 1990 onwards (see rationale under Section 10)

ID	Field	Content
		• 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	Radiological imaging techniques in the diagnosis of spinal metastases, direct malignant infiltration of the spine or associated spinal cord compression

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
		  ○ 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/test	For diagnosis of spinal metastasis / direct infiltration: • MRI ○ T1 sequences (with/without contrast)

ID	Field	Content
		○ short T1 inversion recovery (STIR) sequences ○ T2 weighted sequences (to show the level and degree of compression of the cord / lesions within cord) ○ Whole spine imaging • CT (whole spine or other) • Image guided biopsy (for example for solitary metastasis) • Plain X-ray • FDG-PET-CT
8.	Comparator/Reference standard	For **test and treat studies** comparisons are: • Routine imaging versus sign/symptom directed • Delayed versus early imaging • Different test sequences in comparison with each other For **diagnostic accuracy studies** reference standard is: • Biopsy result / surgical pathology • Clinical and radiological follow up (if no surgery/biopsy done)
9.	Types of study to be included	For test and treat studies: experimental studies (where the investigator assigned intervention or control) including: • Randomised controlled trials • Non-randomised controlled trials • Systematic reviews/meta-analyses of controlled trials. For diagnostic accuracy studies, the following designs will be included: • Observational studies (where neither control nor intervention were assigned by the investigator) including: ○ Systematic reviews of diagnostic studies. ○ Diagnostic accuracy (cross-sectional) studies
10.	Other exclusion criteria	Inclusion: • Full text papers

ID	Field	Content
		Exclusion: • Conference abstracts • Articles published before 1990. MRI has regularly been used in diagnosis since the early 1990s – patient cohorts from pre-1990 are unlikely to representative of current cohorts. • 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)	For test and treat studies: • Overall survival • Disease-related morbidity • Neurological/functional status • Quality of life For diagnostic accuracy studies: • Sensitivity, specificity • Likelihood ratios • PPV, NPV
13.	Secondary outcomes (important outcomes)	• Pain • Time to treatment • Test-related morbidity, for example: ○ Consequences of false positives ○ Morbidity due to biopsy • Test failure (incomplete or cancelled test – for example, due to anxiety or claustrophobia during MRI)
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 inclu-

ID	Field	Content
		sion 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. 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. PICOTS will be extracted from each study. For prediction models, development stage and validation status will be extracted.
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. • 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. Quality assessment of diagnostic accuracy studies will be performed using the following checklist • QUADAS-2 for diagnostic accuracy studies

ID	Field	Content
		The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.

16.	Strategy for data synthesis	**Test and treat review**
		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.
		
		<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>
		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.
		
		Diagnostic review:

ID	Field	Content	
		Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where appropriate, meta-analysis of diagnostic test accuracy will be performed using the metandi package in STATA and Cochrane Review Manager software. Sensitivity, specificity, positive and negative likelihood ratios, with 95% CIs will be used as outcomes for diagnostic test accuracy. These diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies. PPV & NPV will be calculated by combining the summary estimates of sensitivity & specificity with prevalence estimates. <u>Validity (for both test & treat and diagnostic accuracy analyses)</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: • Myeloma versus other cancer types • Functional status / fitness for treatment 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

ID	Field	Content			
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	01/09/21			
22.	Anticipated completion date	23/08/23			
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 Institute for Health and Care Excellence (NICE) 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)	
25.	Review team members	NICE Technical Team	
26.	Funding sources/sponsor	This systematic review is being completed by 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: https://www.nice.org.uk/guidance/CG75	
29.	Other registration details	N/A	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=303705	
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	spinal metastases; malignant infiltration of the spine; spinal cord compression; cancer; radiology; imaging; diagnosis	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing

ID	Field	Content	
		☒	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	
37.	Relevant SRs	N/A	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CT: computed tomography; DARE: Database of Abstracts of Reviews of Effects; FDG-PET-CT: fluorodeoxyglucose-positron emission tomography-computed tomography; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; MRI: magnetic resonance imaging; NHS: National health service; NICE: National Institute for Health and Care Excellence; NPV: negative predictive value; PPV: positive predictive value; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation.