## 1. Title of the project:

Natural History of Spinal Metastases

## 2. Name of TAR team and project 'lead'

Produced by:

Warwick Evidence
Health Sciences Research Institute
Medical School
University of Warwick
Coventry
CV4 7AL

Lead Author:

Paul Sutcliffe[1]

Co-authors:

Martin Connock[1]
Rachel Court[1]
Ngianga-Bakwin Kandala[1]
Martin Underwood[1]
Aileen Clarke[1]

[1]Warwick Evidence, Health Sciences Research Institute University of Warwick

Correspondence to:

Dr Paul Sutcliffe

Date Completed: 4 May 2011

This project was commissioned by the NIHR HTA Programme as project number 10/91.

The views expressed in this protocol are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Conflicts of interest: The authors have no conflicts of interest.

## 3. Plain English Summary

When a cancer spreads to a new and different site in the body it very often locates in the bony skeleton. The commonest place for these new cancers in bone is in one or more vertebrae in which case they are called spinal metastases. Sometimes these spinal metastases do not cause symptoms, however they can be a source of severe pain or weakness in the vertebra which may fracture. Spinal metastases may also grow so that the spinal nerve cord that runs through the length of the vertebral column is compressed. When a vertebra fractures it may result in the spine becoming bent or twisted making every day movements more difficult, and there is a danger that vertebral fracture and collapse may also cause compression of the spinal cord. Compression of the spinal cord carries with it the risk of paralysis of body structures below the level of compression. If it were possible to predict which vertebrae were more likely to fracture then early targeted treatment might prevent, reduce or delay such events and the serious unwanted outcomes that might result. The present project aims to look at the scientific evidence about predicting vertebral fracture and spinal compression resulting from spinal metastases so as to find out whether accurate predictions can be made or whether further scientific research is required.

## 4. Decision problem

The objective of this short report is to determine if there is sufficient evidence in the literature deriving from natural history and imaging studies of patients known to have spinal metastases to identify those at high risk of progression to spinal compression and or to spinal collapse. In this context we will look for studies of spinal metastatic disease which identify candidate risk factors that can identify individuals or their vertebrae at risk of these undesirable outcomes. This will be done by systematic review, quality assessment and evidence synthesis of the relevant literature. The remit for this short report stated that the purpose was not to develop a decision rule (e.g. development of a multivariable risk prediction model (1)). However, studies that have developed such models will be included in the review. Ideal studies of this type will have prospectively studied a defined cohort of patients to identify risk factors independently associated with outcome (in this case spinal compression and or spinal collapse) and have prospectively tested the decision rule in a different and appropriate cohort of patients (2).

Other studies may consider patients whose vertebrae collapse without warning (e.g. asymptomatic spinal metastases) and these will be used to map the natural history.

### *4.1 Background*

#### Spinal Metastases

Metastatic cancer is the most common neoplasm involving the skeletal system (3). Prostate, lung and breast cancer all metastasise to bone and are all common accounting for more than 80% of cases of spinal metastatic bone disease (4). Spinal metastases can lead to significant morbidity due to neural compression, pain, and pathologic fracture. Pressure on the periosteum or adjacent neural structures can cause local or radiating pain (5).

The average time from original diagnosis of cancer to development of spinal metastases has been estimated to be ~32 months and the average time from detection of spinal metastases to spinal compression ~27 months (6). Average survival for patients with spinal cord compression has been reported to be 3 to 7 months with a 36% probability of survival to 12 months (6).

#### Epidemiology

Spinal metastasis is common in patients with cancer. Tse (7) reported that 60-70% of patients with systemic cancer develop spinal metastasis and 10% of these patients are symptomatic. Approximately 5 to 10% of cancer patients develop metastatic spinal cord compression (MSCC) during the course of their disease (8). Multiple myeloma (strictly spinal multiple myeloma is not metastatic, it will not be reviewed in

this report) or plasmacytoma, non-Hodgkins lymphoma, and renal cell cancers each account for 5 to 10% of cases (9).

## Treatment

Primary treatment has often relied on radiation therapy (10) with or without systemic chemotherapy or hormonal therapy. More recently systemic treatments with radionuclides (11;12) and bisphosphonates (13;14) have shown positive clinical outcomes. Denosumab has also been used for the prevention of fractures in postmenopausal women with osteoporosis (15) and has been considered for the use with spinal metastases (16). Although the availability of effective treatments has been reported, many studies have documented the lack of adequate pain management for these patients (17).

A large number of prospective trials have investigated the effectiveness of external beam radiation therapy for palliation of pain or control of progression of osseous metastatic disease (18-26). Local radiotherapy plays an important role in the management of bone metastases (27). Agarawal et al., (28) reported results from a meta-analysis of radiotherapy data finding that one month after treatment, over 40% of patients were likely to have 50% reduction in pain but that fewer than 30% were expected to have complete pain relief. Stereotactic single fraction "radio-surgery" has shown promise (29) and such new approaches for the treatment of vertebral metastases using very steep dose gradients from intensity-modulated radiotherapy (IMRT) have been proposed (30).

Radiofrequency ablation (RFA) is an image-guided minimally invasive treatment for solid tumours (4). Patients who are not responding to conventional treatment frequently have a contraindication to initial or repeat radiation, and those who have limited disease, may benefit from palliation with RFA. RFA can safely palliate pain from bone metastases (4). RFA has been used for patients with persistent pain from a solitary focus of metastatic disease who have been treated, or in localized disease where a more local ablative therapy can be performed as an alternative to external beam radiotherapy (31;32).

Percutaneous image-guided procedures for providing local tumour ablative therapy such as ethanol injection (33), vertebroplasty (34;35) and RFA (36;37) have also shown some promise in the treatment of metastatic bone lesions.

A question remains about when treatment should start and whether asymptomatic metastases should be treated prophylactically.

## Spinal cord compression

Spinal cord compression is a critical condition which requires emergency care to prevent loss of neurological function and to reverse established deficits (38). Surgical indication can include bony compression and spinal instability (39). Surgery is often restricted to patients with involvement of one spinal segment with a good performance status and expected life span of >3 months (8).

## Management

In November 2008 NICE issued a clinical guideline for the diagnosis and management of adults at risk of and with metastatic spinal cord compression (40). The guidelines contained treatment algorithms for patients with symptoms suggestive of spinal metastases. The guideline proposed the patient treatment pathways shown in Figure 1.

Radiation therapy and different forms of surgery are the primary methods for treating spinal cord compression. High-dose steroids are administered with radiation treatment and tapered gradually with completion of treatment (38). Surgical interventions include decompression and fixation for the following indications: spinal instability or bony compression, intraspinal bony fragment, impending sphincter dysfunction; single site cord compression, radioresistant tumour; neurological progression during or after radiation treatment or a previously radiated site that has received a maximum cord tolerance dose (9;39).

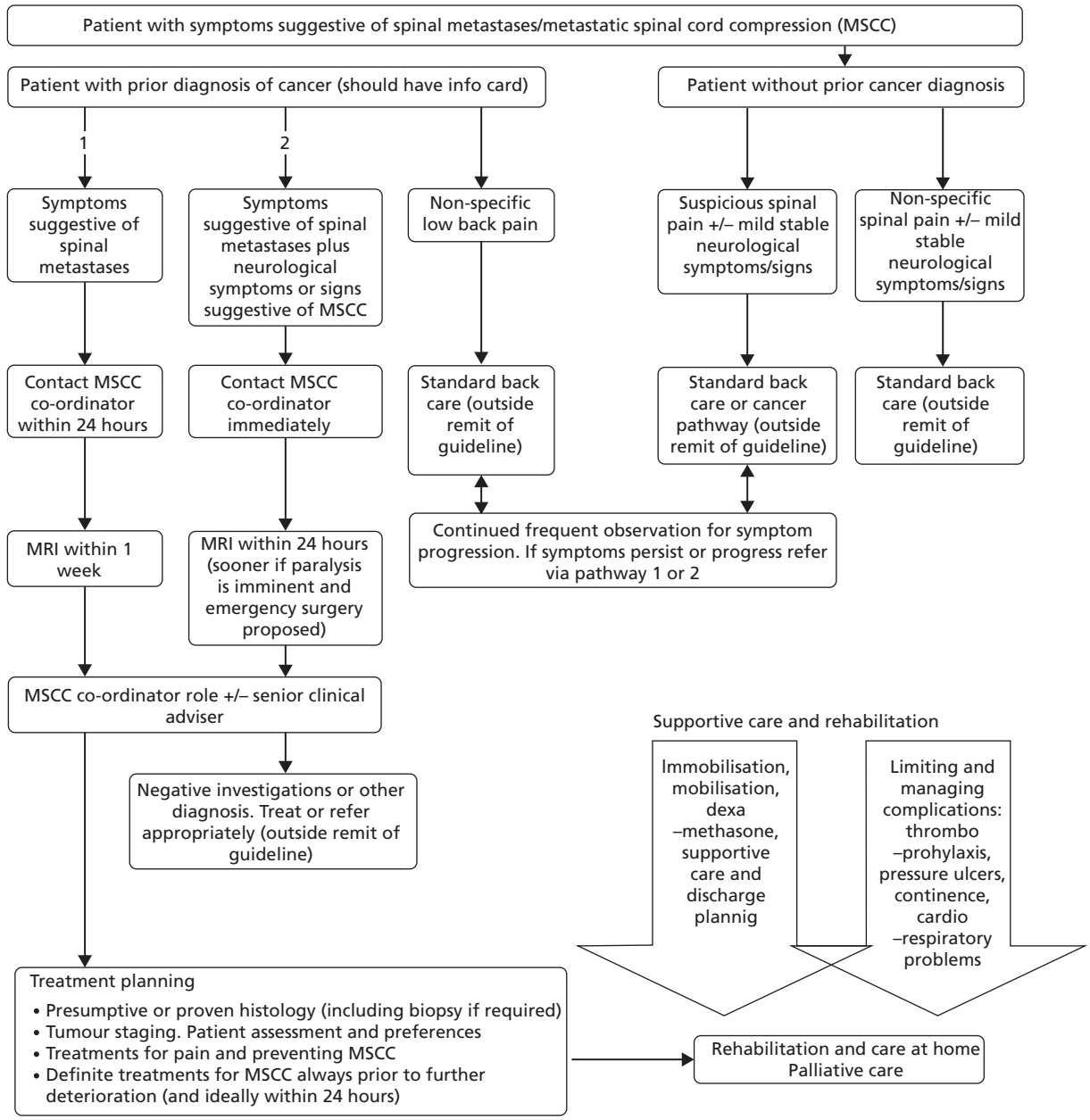


**FIGURE 1** Patient treatment pathways for diagnosis and management of adults at risk of and with metastatic spinal cord compression. Redrawn from (40)

## *Imaging and detection*

Spinal metastases may be asymptomatic and detected during routine examination of cancer patients, but suspicious clinical examination or suggestive symptoms such as pain, are more likely to lead to investigation and detection. Detection and localisation of bony metastases is undertaken using various imaging technologies including: radiography, CT scanning, PET with [$^{18}$F] labelled 2 fluoro 2 deoxy-glucose, MRI, and bone scintigraphy using Tc-99m methylene diphosphonate (41-43). There is active discussion in the literature regarding which method or combination of methods (e.g. integrated CT / PET) is most useful and appropriate; nevertheless no method achieves 100% sensitivity or specificity; equivocal images are encountered and methods may yield discordant results. Equivocal diagnoses can be refuted or supported using bone biopsy and or fine needle aspiration, but these procedures are not routinely undertaken. There appear to be no guidelines that recommend specific imaging modalities, however NICE guideline

75 (40) for diagnosis and management of adults at risk of and with metastatic spinal cord compression recommends that MRI imaging should be undertaken very soon after diagnosis or suspected diagnosis.

### *Types of prognostic studies*

In our preliminary scoping searches of the published literature it has become clear it would be impossible to investigate "natural history" without treatment. Although older literature may describe the development of spinal metastases without treatment, the population in these studies are not likely to be representative because imaging modalities will differ from those of today and patients included are likely to be only those with well-developed disease. It has also become clear that the natural history and progression of spinal metastases is likely to be influenced by numerous factors including type of primary tumour (breast, kidney, lung, prostate and myeloma) and current and previous anti-cancer treatments received. A further consideration is whether metastases are osteolytic or osteoblastic. This means that the review team anticipate that there may be several types of progression and each may be associated with different prognostic factors. In other words, progression and risk will have some degree of specificity for the particular primary cancer concerned. Identification of candidate predictors of spinal compression and of spinal collapse will require examination of a wide variety of studies and study designs that are not well indexed in electronic databases and not generally well described within the titles and abstracts of published studies.

Scoping searches have revealed that four main types of prognostic study have been undertaken with regard to metastatic spinal metastases. These comprise:

- Attempts to determine the risk factors which allow the identification of patients most suitable for surgical intervention (e.g. scoring schemes such as Tokuhashi (44;45); Tomita (46) and others). Some of these studies are specific for metastases derived from particular primary tumours (e.g. lung, breast etc);
- Attempts to identify risk factors for survival of patients not considered suitable for radical surgery and who should therefore receive various forms of palliative care (47);
- Attempts to identify risk factors important in determining the survival of patients after surgical interventions for spinal cord compression and or vertebral compression fracture(s) (48;49) (e.g. vertebrectomy and reconstruction, vertebroplasty, kyphoplasty, radiofrequency ablation);
- Assessment of risk factors of clinical or imaging technologies for progression of metastatic spinal metastases to spinal cord compression and or to vertebral compression fracture(s) (50;51). These studies will be the focus of the current short report. As such they might serve several purposes: for example to inform the choice about potential pre-emptive intervention(s) so as to avoid or delay more radical surgical intervention; to bring forward radical interventions before patient health deteriorates to the extent that they are no longer suitable candidates for these interventions; to categorise patients into those more or less suitable for earlier or later radical intervention.

An ideal simple natural history study would be one which follows up patients that have spinal metastases to see how many progress to vertebral collapse or cord compression, especially if factors predictive of these events are recorded.

Scoping searches identified a 2011 systematic review (52) that looked at the evidence about potential predictors of instability and impending instability of the thoracolumbar spine in patients with spinal metastases. The authors included fourteen primary studies which they rated as of good quality and identified the following potential predictors of instability: tumour size, a larger cross sectional area of bone defect, increased force of spinal loading, decreased bone density, posterior location of the tumour within the vertebrae, destruction of the costovertebral joint, pedicle destruction in the thoracolumbar spine, increased axial rigidity, and sagittal spinal deformity. However, much of the work (64%) reported in this review was of biomechanical post mortem studies and the authors were unable to reach definitive conclusions, they commented that this research area required improved research methodology.

## Report methods for synthesis of evidence

The current short report aims to provide an evidence-based perspective on the natural history of metastatic spinal lesions to be able to identify patients at high risk of progression or spinal collapse, either clinically or using imaging investigations.

A systematic review of the evidence for predictive utility of candidate risk factors will be undertaken following the general principles recommended in the PRISMA statement (53;54).

Reviews will also be identified and included in the current report.

### *5.1 Identification and selection of studies*

Initial scoping searches have been carried out to assess the volume and type of literature relating to the assessment question. The yield of studies that describe spinal metastases, their progression and the imaging modalities employed in detecting and monitoring disease progression, is numbered in thousands. A narrative synthesis of the evidence on disease progression in relation to all metastases is therefore not feasible within the time constraints of this project, especially since progression of metastases will differ depending on primary tumour.

#### Search strategy

Difficulties can be encountered when literature searching for prognostic studies. There are no widely acknowledged optimal search strategies for searching literature for prognostic studies (55). Strategies for searching Medline and Embase for prognostic studies have been developed and tested, the most sensitive of which range in sensitivity from 82.3% in Medline (56) to 98.7 in Embase (57).

Scoping searches have been undertaken to inform the development of the search strategy. An iterative procedure was used, with input from clinical advisors and previous HTA and systematic reviews (e.g. Cooper et al., 2011 (58), National Collaborating Centre for Cancer 2008, Sutcliffe et al., 2009 (59)). A copy of the search strategy that is likely to be used in the major databases is provided in Appendix 1. This draft search strategy developed for MEDLINE will be adapted as appropriate for other databases. This strategy covers the concepts of metastatic spinal lesions, adults and outcomes (spinal cord compression, vertebral compression, vertebral collapse, or progression of vertebral collapse). The addition of other concepts to this strategy such as natural history, technologies and prediction or prognosis, will be developed as the project progresses. Search filters for prognosis have been identified and assessed.

The search strategy will comprise the following main elements:

- Searching of electronic bibliographic databases
- Contact with experts in the field
- Scrutiny of references of included studies

#### Databases will include

MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Database of Systematic Reviews; CENTRAL; DARE, NHS EED, HTA databases (NHS-CRD); Science Citation Index and Conference Proceedings (Web of Science); UKCRN Portfolio Database; Current Controlled Trials; Clinical Trials.gov.

The search strategy will not include limits for study design, as all types of study will be screened for potential inclusion.

In addition, the reference lists of relevant articles will be checked and various health services research related resources will be consulted via the Internet. These are likely to include HTA organisations, guideline producing bodies, generic research and trials registers. Citation searches of included studies will be

undertaken using the Web of Science citation search facility. The reference lists of included studies and relevant review articles will also be checked.

## *Inclusion of relevant studies*

Titles and abstracts of retrieved studies will be examined for inclusion by two reviewers independently. Disagreement will be resolved by retrieval of the fill publication and consensus agreement. The following inclusion criteria will be used:

### Study design

Prospective or retrospective case series, cohort or case-control studies (case studies will be excluded).

### Population

Adult patients with vertebral metastases at risk of developing (or who have developed) metastatic spinal cord compression, vertebral collapse or progression of vertebral collapse.

### Intervention/Technologies

Diagnostic/prognostic methods, including clinical features and/or imaging technologies (MRI, CT, PET, Technetium-99m scintigraphy, X-rays).

### Comparator

None or another diagnostic/prognostic method.

### Outcomes

Spinal cord compression, vertebral compression, vertebral collapse, or progression of vertebral collapse.

Due to the potential plethora of retrieved studies, the difficulties in identifying prognostic studies (i.e. full texts are often required to be able to confidently evaluate whether a prognostic paper meet the inclusion criteria) and constraints of time in a short report, some modification of the above PICO may be required. If necessary due to time constraints we will focus on breast and prostate cancer.

### Exclusion criteria

- Animal models and post-mortem studies
- Preclinical and biological studies
- Editorials, opinions
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality
- Studies not in English, French and German
- Studies where a majority of patients (>50%) is suffering from multiple myeloma

A record of all papers rejected at full text stage and reasons for exclusion will be documented.

## *Data extraction strategy*

The full data will be extracted independently by one reviewer using a data extraction form informed by the NHS Centre for Reviews and Dissemination (60) and previous HTAs involving prognosis (e.g. Sutcliffe et al., 2009 (59), see Appendix 2). Studies that give rise to uncertainty will be reviewed by a second researcher, and any disagreements will be resolved by discussion. Further discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Summary tables will be developed which list all clinical assessments, imaging, and other technologies which may inform prognosis of metastatic spinal lesions reported in the literature, with details of their prognostic value, where adequate information is available. We will not develop a prediction rule or other prognostic tool, but will provide information to assess whether the current evidence base allows such development without further data collection.

Data will be extracted to allow quality assessment of the included studies (see below).

### *Quality assessment strategy*

The quality of conduct and reporting of prognostic studies has received some criticism (2;61). Surveys indicate that the vast majority of such studies appear to have been undertaken on an ad hoc or opportunistic basis in absence of a defined research question or clear protocol for the design, conduct and analysis of the study. Common weaknesses include lack of information about whether outcomes, populations, and test cut-off were defined before data were collected. Selective reporting of analyses is also a common problem (61).

Due to these anticipated deficiencies the proposed systematic review will put emphasis on assessment of quality of primary studies and will attempt to incorporate quality findings into the evidence synthesis. For example, sensitivity analyses will be undertaken to assess the robustness of any meta-analysis conclusions to the inclusion/exclusion of low quality studies (i.e. those at most risk of bias). Quality assessment of included studies will be informed using the guidelines suggested by Hayden and colleagues as appropriate for prognosis studies (62) (Appendix 3) and modified as necessary according to Sutcliffe et al., (2009) (59) (further details are provided below and in Appendix 4). The risk of bias will be illustrated using the Cochrane Review Manager risk-of-bias tool (63).

There are no widely agreed criteria for quality assessing prognostic studies (Altman, 2001 (55)). Factors which need to be considered in the assessment of prognostic studies include: internal validity, external validity, statistical validity, evaluation of the model, and the clinical usefulness of the model (64-68). As there is an element of subjectivity in quality assessment, as well as a need for attention to detail as reporting methods and formats vary widely, disagreement between reviewers is not uncommon. Two team members will undertake quality assessment. Regular discussion meetings will therefore be arranged to resolve any uncertainty between the two members. A third team member will be asked to attend the meetings when agreement cannot be reached. A statistician will provide additional support in interpreting the statistical models and to validate the quality assessment scores assigned by the two reviewers.

In determining how to approach quality assessment in this short report we identified some systematic reviews of prognostic studies (18;66;67;69;70) to see how the issue had been addressed. The value of an overall quality score, which mixes different issues, has been questioned (71). Common themes in these earlier reviews were internal, external and statistical validity.

Hayden et al., (62) appraised how authors of reviews of prognostic studies had assessed study quality and provided recommendations as to the domains that should be considered, and also the questions which might contribute to the assessment of each domain. Domains proposed by Hayden to assess potential biases in prognostic studies were:

- Study population
- Study attrition
- Prognostic factor measurement
- Outcome measurement
- Confounding measurement and account
- Analysis

Within each of these categories, questions are proposed by Hayden et al., (62) to help assess the extent of possible biases. In line with the previous HTA work undertaken by Sutcliffe et al., (2009) (59) we propose to adapt these to make the questions relevant to the disease area, the types of studies available, and also to clarify the meaning of each question in the context of the short report. The resulting quality assessment tool which we may use is provided in Appendix 4.

In consultation with clinical and statistical advisors, other quality assessment checklists may need to be developed based on the quality assessment instruments used in published systematic reviews and in the literature of prognostic factors. A further example of a prognostic studies quality assessment checklist

is presented in Appendix 5. Validation studies will be assessed using relevant criteria from the quality assessment tool developed by the research team for prognostic models (particularly model evaluation) and the results reported together with the original model.

RCTs and systematic reviews will be quality assessed using an adapted checklist proposed by the NHS Centre for Reviews and Dissemination (60) (see Appendix 6).

### *Methods of analysis/synthesis*

Data will be tabulated and discussed in a narrative review. Each tumour type will be looked at separately.

Meta-analyses of prognostic results will be considered for each risk factor if it is deemed clinically meaningful to synthesise studies. Where meta-analysis is appropriate, for each risk factor of interest, effect estimates will be pooled across trials using a random effects meta-analysis model; this model takes into account between-study heterogeneity in effect estimates, which we believe is likely to occur. Primarily we will seek to synthesise odds ratio estimates (adjusted and unadjusted). But if relative risks are reported, then these will be synthesised if it is appropriate to do so. Heterogeneity across studies will be examined using the $\chi^2$ test statistic and $I^2$ statistic (which gives the percentage of the total variability in the data due to between-study heterogeneity) and the tau-squared statistic (which gives an estimate of the between-study variance). Each random-effects analysis will be summarised by reporting the mean prognostic effect estimate and its confidence interval; also we will provide a 95% prediction interval for the prognostic effect in a new study (72), so as to reveal how the effect may vary in different contexts and populations (73). This is important in order to identify the probability that each potential risk factor would actually have prognostic value in practice. If there are sufficient numbers of studies, sub-group analyses and/or meta-regression will be used to explore whether the following pre-specified variables explain any of the heterogeneity: bone density, population parameters, tumour type, imaging modality used, outcome event, length of follow up, and study quality (risk of bias).

It is possible that primary studies have been undertaken and published that have computed hazard ratios that compare populations categorised according to risk factor. Should such studies exist, random-effect meta-analysis using the extracted hazard ratios will be undertaken as above and when judged appropriate. Fitting parametric distributions to the reported Kaplan-Meier plots would be considered in order to illustrate the results from disparate studies should meta-analysis be considered inappropriate.

All the above models and analyses will be undertaken in a frequentist framework using the STATA software (74). Where it is not appropriate to pool data, studies will be tabulated and described separately.

For each meta-analysis containing 10 or more studies, the likelihood of publication bias will be investigated through the construction of contour-enhanced funnel plots (63;75). These help distinguish publication bias from other causes of asymmetry. We recognise that, especially where heterogeneity exists, publication bias may be one of a number of reasons for any small-study effects identified.

## Report methods for synthesising evidence of cost-effectiveness

Not applicable for this remit.

## Expertise in this TAR team

Warwick Evidence is a newly developed technology assessment group located within Warwick Medical School. Warwick Evidence brings together experts in clinical and cost effectiveness reviewing, medical statistics, health economics and modelling. The team planned for the work includes: Dr Paul Sutcliff and Dr Martin Connock who are experienced senior systematic reviewers; Ms Rachel Court, information specialist;

Professor Aileen Clarke, professor of health services research; Professor Martin Underwood, professor of primary care and clinical specialist with an interest in back pain; Dr Kandala, principal research fellow in demography and medical statistics; and additional clinical specialists, Professor Charles Hutchinson, Mr Philip Sell and Professor Charles Greenough. Ms Amy Grove will provide project management support.

## Competing interests of authors

None of the authors have any competing interests, although Professor Underwood has been involved in NICE guidelines on back pain.

## Timetable/milestones

The project will be undertaken in phases, including: literature search, study selection, data abstraction and critical appraisal, evidence synthesis, and dissemination of the results. The project is currently planned to be completed in 3 months, once approval of the protocol has been confirmed and after pilot/scoping searches have been completed. Research Team Meetings will be conducted where appropriate via teleconferencing to minimise costs and reduce our carbon footprint. There will be weekly sub-team meetings and monthly expert consultation (via the telephone/email).

Draft protocol finalised TBC

Commissioning decision TBC

Progress report TBC

Draft assessment report TBC

Assessment report 31 October 2011

The proposed draft timelines are shown below:

| Project Tasks | Aug 2011 | Sept 2011 | Oct 2011 |
|---|---|---|---|
| Protocol confirmation | | | |
| Searching and collecting studies | | | |
| Study assessment, data extraction | | | |
| Evidence synthesis | | | |
| Progress report to NCCHTA | | | |
| Writing draft report | | | |
| Peer review | | | |
| Final report and paper writing | | | |

## 10.1. APPENDICES

### APPENDIX 1 DRAFT SEARCH STRATEGY

### Medline via Ovid interface, searched on 19/05/2011

| | |
|---|---|
| Spinal Neoplasms/ | 9801 |
| ((spine or spinal or vertebr* or cervical spine or cervical vertebrae or thoracic or lumbar or sacral or sacrum or coccyx) adj3 (metasta* or lesion* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)).mp. | 33803 |
| 1 or 2 | 33803 |
| metasta*.mp. | 297575 |
| exp Neoplasm Metastasis/ | 134650 |
| 4 or 5 | 302301 |
| 3 and 6 | 7718 |
| limit 7 to (english language and humans and "all adult (19 plus years)") | 3980 |
| Fractures, Compression/ | 697 |
| Spinal Cord Compression/ | 8636 |
| Polyradiculopathy/ | 2044 |
| Spinal Fractures/ | 8239 |
| exp Paralysis/ | 63791 |
| ((spine or spinal or vertebra* or cord) adj5 (collapse* or compression or fractur* or instability)).mp. | 27635 |
| compression fracture*.mp. | 1924 |
| (cauda equina or polyradicul*).mp. | 10451 |
| (paralysis or paraly?ed or plegia or paraplegi* or hemiplegi* or quadriplegi* or tetraplegi*).mp. | 83273 |
| (fracture adj3 progression).mp. | 35 |
| 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 | 126217 |
| 8 and 19 | 984 |

mp. searches the fields: [mp=title, original title, abstract, name of substance word, subject heading word]

## APPENDIX 2 DATA EXTRACTION FORM

## Data extraction tables

Note this table will be piloted and it is anticipated will be used for all included studies whether natural history or prognosis.

### *Paper ID*

1st Author: Year: Ref ID:

Reviewer:

### *1. Study Design*

**A.** Cohort = 1 Case control = 3 Case series = 2 Other = 4

**B.** Retrospective = 1 Prospective = 2

### *2. Treatment received by population in study prior to assessment of candidate risk factors*

| | |
|---|---|
| 0 = None / not reported | 1 = Watchful waiting/ active monitoring |
| 2 = Surgical radical resection (spondectomy) | 3 = Surgical reconstruction |
| 4 = Laminectomy | 5 = Transpedicular approach |
| 6 = Posterior approach | 7 = Costotransversectomy approach |
| 8 = Lateral extracavitary approach | 9 = Minimally invasive endoscopic approach |
| 10 = Kyphoplasty | 11 = Radiotherapy |
| 12 = Radiation therapy | 13 = Robotic radiation therapy |
| 14 = Stereotactic radiation therapy | 15 = Intensity-modulated radiation therapy |
| 16 = Spinal stabilization | 17 = Medication |
| 18 = Other/mixed | |

### *3. Imaging modalities used to detect metastases and to monitor progression to outcomes of interest*

| Imaging modalities | No. patients (%) |
|---|---|

### *4. If treatments received according to prediction criteria and relevant outcomes have been reported these details will be extracted and recorded*

| Treatments received post prediction | Outcomes reported |
|---|---|

## 5. Baseline study characteristics

| Paper | Method | Study participation | Outcomes |
|---|---|---|---|
| Author<br>Country<br>Journal | Aim:<br>*Was primary aim of paper to assess prognosis?*<br>*Was primary aim of paper to assess natural history*<br>Study design:<br>Sample size:<br>*Initial:*<br>*In Analysis:*<br>Inclusion criteria:<br>Start and finish dates:<br>Time to event analysis conducted (Cox regression) and/or logistic regression:<br>Diagnosis of spinal metastases: | Age:<br>Median –<br>Mean –<br>Range –<br>Distribution –<br>Sex:<br>Racial characteristics:<br>Type of primary tumours:<br>Non-osseous metastases present (distribution, number, not reported):<br>Completeness of data:<br>Withdrawals and losses to follow up: | Endpoints:<br>Risk factors:<br>Length of follow-up:<br>Median –<br>Mean –<br>Range –<br>Results reported at X years –<br>New collapse of vertebrae:<br>Progression of previously collapsed vertebrae:<br>Compression of spinal cord (proposed causes e.g. bone fragment, growth of metastases):<br>Overall survival:<br>Quality of life:<br>Pain: |

## 6. Primary disease and metastases

| Primary disease | No. of Vertebrae and location | Primary disease | No. of Vertebrae and location |
|---|---|---|---|
| Myeloma | | Breast Cancer | |
| Renal Cell Carcinoma | | Lung cancer | |
| Malignant lymphoma | | Prostate Cancer | |

## 7. Potential predictors of instability

| Candidate Risk Factor | Yes/no/not reported | Specify |
|---|---|---|
| Tumor size | | |
| Larger cross-sectional area of bone defect | | |
| Increased force of spinal loading | | |
| Decreased bone density | | |
| Location of the tumour within the vertebrae | | |
| Destruction of the costovertebral joint | | |
| Pedicle destruction in the thoracolumbar spine | | |
| Increased axial rigidity | | |
| Sagittal spinal deformity | | |
| Magnitude of spinal loading | | |
| Tumour location within the spine / site of involved vertebrae | | |

continued

| Candidate Risk Factor | Yes/no/not reported | Specify |
|---|---|---|
| Tumour type | | |
| Blood calcium level | | |
| Lesion type (e.g. lytic / blastic / mixed) | | |
| Other(s) | | |

*Note:* Adapted from Weber *et al.*, 2011 (52)

## *8. Evaluation of risk factor effect on outcome (univariate analyses)*

| Candidate Risk Factor | Mode of analysis (logistic regression/ time event) | Adjusted or unadjusted odds ratio/hazard ratio and 95% CI | P value |
|---|---|---|---|
| General health scale | | | |
| No. extraspinal bone metastases foci | | | |
| No. metastases in the vertebral bodies | | | |
| Metastases to the major internal organs | | | |
| Primary site of the cancer | | | |
| Spinal cord palsy | | | |
| Performance index (Karnovsky score) | | | |
| Subluxation | | | |
| Other(s) specify..... ..... | | | |

**Author's conclusion:**

**Reviewer's conclusion:**

## *9. Evaluation of risk factor effect on outcome (multivariate analyses)*

Number of factors (prognostic markers) in final model?

| Candidate Risk Factor<br>Risk factors (prognostic markers) in proposed models? | Mode of analysis (logistic regression/ time event) | Adjusted or unadjusted odds ratio/hazard ratio and 95% CI | P value |
|---|---|---|---|
| Specify identity of combined variables (and relative weighting as appropriate) Model 1 | | | |
| Specify identity of combined variables (and relative weighting as appropriate) Model 2 | | | |
| Continue as required | | | |

**Author's conclusion:**

**Reviewer's conclusion:**

## *Summary Conclusions*

## APPENDIX 3 ASSESSMENT OF RISK OF BIAS IN PROGNOSTIC STUDIES (HAYDEN ET AL., (62))

| Potential Bias | Items To Be Considered for Assessment of Potential Opportunity for Bias |
|---|---|
| Study participation<br>The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results.<br>Yes<br>Partly<br>No<br>Unsure | The source population or population of interest is adequately described for key characteristics.<br>The sampling frame and recruitment are adequately described, possibly including methods to identify the sample (number and type used, e.g., referral patterns in health care), period of recruitment, and place of recruitment (setting and geographic location)<br>Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).<br>There is adequate participation in the study by eligible individuals.<br>The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics. |
| Study attrition<br>Loss to follow-up (from sample to study) is not associated with key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias.<br>Yes<br>Partly<br>No<br>Unsure | Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.<br>Attempts to collect information on participants who dropped out of the study are described.<br>Reasons for loss to follow-up are provided.<br>Participants lost to follow-up are adequately described for key characteristics.<br>There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not. |
| Prognostic factor measurement<br>The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias.<br>Yes<br>Partly<br>No<br>Unsure | A clear definition or description of the prognostic factor measured is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).<br>Continuous variables are reported or appropriate (i.e., not data-dependent) cut-points are used.<br>The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).<br>Adequate proportion of the study sample has complete data for prognostic factors.<br>The method and setting of measurement are the same for all study participants.<br>Appropriate methods are used if imputation is used for missing prognostic factor data. |
| Outcome measurement<br>The outcome of interest is adequately measured in study participants to sufficiently limit bias.<br>Yes<br>Partly<br>No<br>Unsure | A clear definition of the outcome of interest is provided, including duration of follow-up and level and extent of the outcome construct.<br>The outcome measure and method used are adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).<br>The method and setting of measurement are the same for all study participants. |

| Potential Bias | Items To Be Considered for Assessment of Potential Opportunity for Bias |
|---|---|
| Confounding measurement and account<br>Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.<br>Yes<br>Partly<br>No<br>Unsure | All important confounders, including treatments (key variables in conceptual model), are measured.<br>Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).<br>Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).<br>The method and setting of confounding measurement are the same for all study participants.<br>Appropriate methods are used if imputation is used for missing confounder data.<br>Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).<br>Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment). |
| Analysis<br>The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results.<br>Yes<br>Partly<br>No<br>Unsure | There is sufficient presentation of data to assess the adequacy of the analysis.<br>The strategy for model building (i.e., inclusion of variables) is appropriate and is based on a conceptual framework or model.<br>The selected model is adequate for the design of the study.<br>There is no selective reporting of results. |

## APPENDIX 4 QUALITY ASSESSMENT FORM:

## Assessing quality of prognostic studies on the basis of framework of potential biases (based on Hayden *et al.*, (62); see Appendix 3)

First Author: Year: ID: Reviewer:

| Potential bias | Items to be considered for assessment of potential opportunity for bias | Yes | Partly | No | Unsure | NA |
|---|---|---|---|---|---|---|
| **Study population** | Inclusion and exclusion criteria are adequately described (including pre-treatment, diagnosis (primary and metastases), start/finish date recruitment | | | | | |
| | Baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics: XX (where relevant) | | | | | |
| | Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results | | | | | |
| **Study attrition** | Statement as to exclusions due to missing data: – baseline variables | | | | | |
| | – loss to follow-up | | | | | |
| | Statement as to the possible effect on the results from missing data | | | | | |
| | Loss to follow-up is not associated with key characteristics | | | | | |
| **Prognostic factor measurement** | Clear definition of the prognostic factors measured is provided *(e.g. imaging modality method, measurement described)* | | | | | |
| | Specified instrument and personnel for measurement non-vertebral factors | | | | | |
| | Continuous variables are reported or appropriate *(i.e., not data-dependent)* cut-points are used | | | | | |
| | Blinding: were estimators of risk factor status and of outcomes blinded? | | | | | |
| | The prognostic factor(s) of interest is (are) adequately measured in study participants to sufficiently limit potential bias | | | | | |
| **Outcome** | Is the outcome clearly defined? | | | | | |
| **Confounding measurement and account** | Do the authors address potential confounders? | | | | | |
| **Analysis** | There is sufficient presentation of data to assess the adequacy of the analysis | | | | | |
| | The statistical analysis is appropriate for the study design of the study, limiting potential for the presentation of invalid results | | | | | |
| | TOTAL NUMBER OF TICKS TO THE MAIN QUESTIONS (GREEN BOXES) | | | | | |

*Note:* The above table was adapted from: Sutcliffe *et al.*, 2009 (59)

**Overall opinion of study quality =**

# APPENDIX 5 AN EXAMPLE OF QUALITY ASSESSMENT OF PREDICTIVE MODELS

## Quality assessment of predictive models

A. External validity

(i) Was the model generated on a community- or hospital-based population? Patients admitted to hospitals are not representative of all patients with stroke in the community, and different hospitals admit different types of stroke patient. Models generated on hospital-based patients may therefore not be applicable to other stroke patients.

(ii) Were patients with transient ischaemic attacks and subarachnoid haemorrhages included? (prognostic factors for these may be different from those for stroke)

(iii) Were there major exclusion criteria (such as age, sex, or type of stroke) that may limit generalisability?

(iv) Was there a description of the cohort of patients (e.g. age, sex, treatment) on which the models were developed so that clinicians could assess how similar it was to their own patients?

B. Internal validity

(i) Was an inception cohort established? Prognosis should be studied in patients who are at a similar stage in the disease process (an 'inception cohort') since factors that affect prognosis may vary with the time since stroke. Studies in which patients were seen within one week of onset were defined as having the most adequate inception cohort.

(ii) Were an adequate number of patients in the inception cohort followed up to minimise bias? We arbitrarily defined losses of less than 10% of the original cohort as adequate.

(iii) Were baseline data collected prospectively? Data collected retrospectively (e.g. from case notes may be less accurate than prospectively collected data).

(iv) Were references made to the outcomes' validity and reliability?

(v) Were outcomes assessed at appropriate times? Outcomes should be assessed at a fixed time after stroke onset so that all patients are at a similar stage in the disease process, and long-term outcomes (>30 days) are more meaningful.

(vi) Were some potentially important predictors not entered into the model? Models that do not include variables known to be important independent predictors are probably less reliable than those that do. It was difficult to define which factors were important in prognosis before completing this systematic review. However, age and stroke severity were likely to be important in prognosis and so we documented whether these variables were entered into the analysis.

(vii) Were the predictive variables clearly defined, clinically valid, and was reference made to their reliability?

C. Statistical validity

(i) Was the sample size adequate as defined by an EPV of 10 or more? Were interaction terms included for any variables? Was some form of stepwise analysis used and if not was collinearity between the variables assessed? Multiple regression can produce spurious results if all the variables are simply entered into a model and certain highly predictive variables are strongly correlated with each other (collinearity). This is less problematic in stepwise regression.

D. Evaluation of the model

(i) Was the final model validated on the data that were used to generate the model (internal validation)? Models that do not produce accurate predictions on the patients who were used to generate it are clearly unreliable.

(i) Was the final model validated on patients who were not used to generate the model (external validation)? Models that predict well on the patients who were used to produce the model may still not provide accurate predictions on other patients. The accuracy must also be tested in an independent cohort of patients, ideally, on several independent cohorts to assess its generalisability.

(iii) Are the model's predictions better than predictions based on clinical judgement? If prognostic models are to be used in clinical practice, they should be at least as good as clinical judgement.

(iv) Was the effect of using the model in clinical practice established? If the model's predictions are to be used in clinical practice, their effect on patient outcome should be evaluated. This is best done in randomised trials. The use of a model may harm patients if, for example, patients who are falsely predicted to have a poor outcome are given hazardous treatments or alternatively are left untreated because treatment is judged to be futile.

E. The ease of use (practicality) of the model

(i) Were the data required to make predictions easily available?

Models that include complex variables or those that are not available when the clinician needs to make a prediction are unhelpful. Variables were defined as complex after discussion between the two authors.

(ii) Was the actual model and the coding of variables described so that it could be used?

(iii) Were confidence intervals given for the predictions? Models that only give point estimates for the probability of an outcome can give a false impression of accuracy. Clinicians need to know whether the confidence interval for a prediction is sufficiently narrow to allow a specific prognosis to be given.

*Note:* The above text was based on the Systematic review of prognostic models in patients with acute stroke produced by Counsell et al., 2001 (66)

## APPENDIX 6 QUALITY ASSESSMENT OF RCTS AND REVIEWS

### Quality assessment of RCTs

| Questions | Yes/No |
|---|---|
| Was the method used to assign participants to the treatment groups really random? | |
| What method of assignment was used? | |
| Was the allocation of treatment concealed? | |
| What method was used to conceal treatment allocation? | |
| Was the number of participants who were randomised stated? | |
| Were details of baseline comparability presented? | |
| Was baseline comparability achieved? | |
| Were the eligibility criteria for study entry specified? | |
| Were any co-interventions identified that may influence the outcomes for each group? | |
| Were the outcome assessors blinded to the treatment allocations? | |
| Were the individuals who administered the intervention blinded to the treatment allocation? | |
| Were the participants who received the intervention blinded to the treatment allocation? | |
| Was the success of the blinding procedure assessed? | |
| Were at least 80% of the participants originally included in the randomised process followed up in the final analysis? | |
| Were the reasons for withdrawal stated? | |
| Was an intention-to-treat analysis included? | |

Y – item addressed; N – no; ? – not enough information or not clear; NA – not applicable

*Note:* The above checklist was taken from the NHS Centre for Reviews and Dissemination (60)

## Quality Assessment of Reviews

| Questions | Yes/No |
|---|---|
| Were the search methods used to find evidence on the primary research question stated? | |
| Was the search for evidence reasonably comprehensive? | |
| Were the criteria used for deciding which studies to include reported? | |
| Was bias in the selection of studies avoided? (e.g., language restrictions not applied, unpublished trials included) | |
| Were the criteria used for assessing the validity of the included studies reported? | |
| Was the validity of all studies referred to in the text assessed using appropriate criteria? | |
| Summary – was review systematic? | |
| Were the methods used to combine the findings of the relevant studies reported? | |
| Were the findings of the relevant studies combined appropriately relative to the primary question of the overview? *(If no attempt has been made to combine the findings, and no statement is made regarding the inappropriateness of combining them, score "no". If a summary (general) estimate is given anywhere in the abstract, discussion or summary section of the paper and it is not reported how that estimate was derived, score "no" even if there is a statement regarding the limitations of combining the findings of the studies reviewed. If in doubt, score "?")* | |
| Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview? | |

Y – item addressed; N – no; P – partially; ? – not enough information or not clear; NA – not applicable

*Note:* The above table is adapted from: Oxman and Guyatt's (1991) index of methodological quality (76) as published by Kelly *et al*., (77)

## 10.2. TEAM MEMBERS' CONTRIBUTIONS

### Research team: Warwick Evidence

Lead: Dr. Paul Sutcliffe
Title: Senior Research Fellow
Address: Health Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry CV4 7AL
Tel: 02476 574505
Fax: 02476 528375
Email: p.a.sutcliffe@warwick.ac.uk
Speciality: Co-ordinate review process, protocol development, abstract assessment for eligibility, development of quality assessment tool, quality assessment of trials, data extraction, data entry, data analysis and review of natural history of metastatic spinal lesions review, and review of various technologies to predict collapse of vertebrae containing metastatic spinal lesions. Report writing.

All correspondence should be sent to Dr. Paul Sutcliffe (Lead)

Name: Professor Aileen Clarke
Title: Director of Warwick Evidence
Address: Health Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry CV4 7AL
Tel: 02476 150189
Fax: 02476 528375
Email: Aileen.Clarke@warwick.ac.uk
Speciality: Co-ordinate review process, protocol development, data analysis and synthesis of findings. Report writing.

Name: Dr. Martin Connock
Title: Senior Research Fellow
Address: Health Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry CV4 7AL
Tel: 02476 574940
Fax: 02476 528375
Email: M.Connock@warwick.ac.uk
Speciality: Protocol development, abstract assessment for eligibility, development of quality assessment tool, quality assessment of trials, data extraction, data entry, data analysis and review development of natural history of metastatic spinal lesions review, and review of various technologies to predict collapse of vertebrae containing metastatic spinal lesions. Report writing.

Name: Dr. Ngianga-Bakwin Kandala
Title: Principal Research Fellow
Address: Health Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry CV4 7AL
Tel: 02476 575054
Fax: 02476 528375
Email: N-B.Kandala@warwick.ac.uk
Speciality: Protocol development, abstract assessment for eligibility, development of quality assessment tool, quality assessment of trials, data extraction, data entry, data analysis, and statistical advisor.

Name: Rachel Court
Title: Information specialist
Address: Health Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry CV4 7AL
Tel: 02476 574639
Fax: 02476 528375
Email: R.A.Court@warwick.ac.uk
Speciality: Protocol development, develop search strategy and undertake the electronic literature searches.

Name: Amy Grove
Title: Project Manager
Address: Health Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry CV4 7AL
Tel: 02476 528375
Fax: 02476 528375
Email: to be confirmed
Speciality: Retrieval of papers and help in preparing and formatting the report.

## Clinical Advisors

Speciality of clinical advisors: Protocol development, help interpret data, provide a methodological, policy and clinical perspective on data and review development of background information and clinical effectiveness and review of report drafts.

Professor Martin Underwood
Health Sciences Research Institute
Warwick Medical School
University of Warwick
Coventry
CV4 7AL
Tel: 02476 574664
Email: M.Underwood@warwick.ac.uk

Professor Charles Hutchinson
Clinical Sciences Research Institute
Room 10107
University of Warwick
University Hospital of Coventry and Warwickshire
Clifford Bridge Road
Coventry
CV2 2DX
Tel: 02476968667
Email: C.E.Hutchinson@warwick.ac.uk

Mr Phillip Sell
Trauma & Spinal Orthopaedics
University Hospitals of Leicester
Department of orthopaedics
Gwendolen Road
Leicester
Leicestershire

LE5 4QF
Telephone: 0116 258 8171
Email address: psell2.spine@tiscali.co.uk

Professor Charles Greenough
The James Cook University Hospital
Marton Road
Middlesbrough
Cleveland
TS4 3BW
Email address: Charles.Greenough@stees.nhs.uk

We acknowledge the importance of our specialist clinical advisors on this piece of work. The aim of the advisory group is to help clarify issues and provide advice on the clinical relevance and scientific quality of the review. It is anticipated that clinical advisors on this panel will be consulted either individually, or as a group at various stages during the review (approximately 2–3 meetings/teleconferences over period of report). In addition, the review team will keep in regular contact with the clinical advisors by email and telephone. The clinical advisors will be contacted when greater clarification of complex studies is required. The clinical advisors will be involved in reading drafts and will be authors on the current review.

## REFERENCE LIST

1. Riley RD, Sauerbrei W, Altman DG. Prognostic markers in cancer: the evolution of evidence from single studies to meta-analysis, and beyond. *Br J Cancer* 2009 Apr 21;**100**(8):1219–29.
2. Hemingway H, Riley RD, Altman DG. Ten steps towards improving prognosis research. *BMJ* 2009;**339**:b4184.
3. Stoll BA, Parbhoo S. *Bone metastases: Monitoring and treatment*. 2 ed. New York: Raven Press; 1983.
4. Dupuy DE, Liu D, Hartfeil D, Hanna L, Blume JD, Ahrar K, *et al.* Percutaneous radiofrequency ablation of painful osseous metastases: a multicenter American College of Radiology Imaging Network trial. *Cancer* 2010 Feb 15;**116**(4):989–97.
5. Twycross RG. Management of pain in skeletal metastases. *Clin Orthop Relat Res* 1995 Mar;(312):187-96.
6. Boogerd W, van der Sande JJ. Diagnosis and treatment of spinal cord compression in malignant disease. *Cancer Treatment Reviews* 1993;**19**:129–50.
7. Tse V. Spinal Metastases and Metastatic disease to the Spine and Related Structures. 2009. Available from: URL: http://medicine.medscape.com/article/1157987-overview#a1099 [Accessed april 2011]
8. Rades D, Stalpers LJ, Veninga T, Schulte R, Hoskin PJ, Obralic N, *et al.* Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *J Clin Oncol 2005* May 20;**23**(15):3366–75.
9. Prasad D, Schiff D. Malignant spinal-cord compression. *Lancet Oncol* 2005 Jan;**6**(1):15–24.
10. Janjan NA. Radiation for bone metastases: conventional techniques and the role of systemic radiopharmaceuticals. *Cancer* 1997 Oct 15;**80**(8 Suppl):1628–45.
11. Quilty PM, Kirk D, Bolger JJ, Dearnaley DP, Lewington VJ, Mason MD, *et al.* A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol* 1994 Apr;**31**(1):33–40.

12. Serafini AN, Houston SJ, Resche I, Quick DP, Grund FM, Ell PJ, *et al.* Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol* 1998 Apr;**16**(4):1574–81.

13. Hortobagyi GB, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *New England Journal of Medicine* 1999;**12**:1785–91.

14. Conte PF, Latreille J, Mauriac L, Calabresi F, Santos R, Campos D, *et al.* Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. *J Clin Oncol* 1996 Sep;14(9):2552-9.

15. Cummings SR, San MJ, McClung MR, Siris ES, Eastell R, Reid IR, *et al.* Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009 Aug 20;**361**(8):756–65.

16. Santini D, Fratto ME, Vincenzi B, Napoli N, Galluzzo S, Tantardini M, *et al.* Denosumab: the era of targeted therapies in bone metastatic diseases. [Review] [59 refs]. *Current Cancer Drug Targets* 2009 Nov;**9**(7):834–42.

17. Cleeland CS. The measurement of pain from metastatic bone disease: capturing the patient's experience. *Clin Cancer Res* 2006 Oct 15;**12**(20 Pt 2):6236s–42s.

18. Riley RD, Burchill SA, Abrams KR, Heney D, Sutton AJ, Jones DR, *et al.* A systematic review of molecular and biological markers in tumours of the Ewing's sarcoma family. *Eur J Cancer* 2003 Jan;**39**(1):19–30.

19. Madsen EL. Painful bone metastasis: efficacy of radiotherapy assessed by the patients: a randomized trial comparing 4 Gy X 6 versus 10 Gy X 2. *Int J Radiat Oncol Biol Phys* 1983 Dec;**9**(12):1775–9.

20. Blitzer PH. Reanalysis of then RTOG study of the palliation of symptomatic osseous metastasis. *Cancer* 1984;**55**:1468–72.

21. Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986 Aug;**6**(4):247–55.

22. Arcangeli G, Micheli A, Arcangeli G, Giannarelli D, La PO, Tollis A, *et al.* The responsiveness of bone metastases to radiotherapy: the effect of site, histology and radiation dose on pain relief. *Radiother Oncol* 1989 Feb;14(2):95–101.

23. Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clin Oncol (R Coll Radiol)* 1989 Nov;**1**(2):59–62.

24. Poulter CA, Cosmatos D, Rubin P, Urtasun R, Cooper JS, Kuske RR, *et al.* A report of RTOG 8206: a phase III study of whether the addition of single dose hemibody irradiation to standard fractionated local field irradiation is more effective than local field irradiation alone in the treatment of symptomatic osseous metastases. *Int J Radiat Oncol Biol Phys* 1992;**23**(1):207–14.

25. Arcangeli G, Giovinazzo G, Saracino B, D'Angelo L, Giannarelli D, Arcangeli G, *et al.* Radiation therapy in the management of symptomatic bone metastases: the effect of total dose and histology on pain relief and response duration. *Int J Radiat Oncol Biol Phys* 1998 Dec 1;**42**(5):1119–26.

26. Ratanatharathorn V, Powers WE, Moss WT, Perez CA. Bone metastasis: review and critical analysis of random allocation trials of local field treatment. *Int J Radiat Oncol Biol Phys* 1999;**44**:1–18.

27. Bates T. A review of local radiotherapy in the treatment of bone metastases and cord compression. *Int J Radiat Oncol Biol Phys* 1992;**23**(1):217–21.

28. Agarawal JP, Swangsilpa T, van der Linden Y, Rades D, Jeremic B, Hoskin PJ. The role of external beam radiotherapy in the management of bone metastases. *Clin Oncol (R Coll Radiol)* 2006 Dec;**18**(10):747–60.

29. Gerszten PC, Burton SA, Ozhasoglu C, Welch WC. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. *Spine (Phila Pa 1976)* 2007 Jan 15;**32**(2):193–9.

30. Inoue T, Oh RJ, Shiomi H. New approach for treatment of vertebral metastases using intensity-modulated radiotherapy. *Strahlenther Onkol* 2011 Feb;**187**(2):108–13.

31. Callstrom MR, Atwell TD, Charboneau JW, Farrell MA, Goetz MP, Rubin J, *et al.* Painful metastases involving bone: percutaneous image-guided cryoablation--prospective trial interim analysis. *Radiology* 2006 Nov;**241**(2):572–80.

32. Goetz MP, Callstrom MR, Charboneau JW, Farrell MA, Maus TP, Welch TJ, *et al.* Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. *J Clin Oncol* 2004 Jan 15;**22**(2):300–6.

33. Gangi A, Kastler B, Klinkert A, Dietemann JL. Injection of alcohol into bone metastases under CT guidance. *J Comput Assist Tomogr* 1994 Nov;**18**(6):932–5.

34. Levine SA, Perin LA, Hayes D, Hayes WS. An evidence-based evaluation of percutaneous vertebroplasty. *Manag Care* 2000 Mar;**9**(3):56–60, 63.

35. Taylor RS, Taylor RJ, Fritzell P. Balloon kyphoplasty and vertebroplasty for vertebral compression fractures: a comparative systematic review of efficacy and safety. *Spine (Phila Pa 1976)* 2006 Nov 1;**31**(23):2747–55.

36. Dupuy DE, Hong R, Oliver B, Goldberg SN. Radiofrequency ablation of spinal tumors: temperature distribution in the spinal canal. *AJR Am J Roentgenol* 2000 Nov;**175**(5):1263–6.

37. Rosenthal DI, Hornicek FJ, Wolf MW, Jennings LC, Gebhardt MC, Mankin HJ. Percutaneous radiofrequency coagulation of osteoid osteoma compared with operative treatment. *J Bone Joint Surg Am* 1998;**80**:815–21.

38. Sejpal SV, Bhate A, Small W. Palliative radiation therapy in the management of brain metastases, spinal cord compression, and bone metastases. *Semin Intervent Radiol* 2007 Dec;**24**(4):363–74.

39. Loblaw DA, Perry J, Chambers A, Laperriere NJ. 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. *J Clin Oncol* 2005 Mar 20;**23**(9):2028–37.

40. Metastatic spinal cord compression; diagnosis and management of adults at risk of and with metastatic spinal cord compression. 2008. URL: http://guidance.nice.org.uk/CG75/Guidance/pdf/English [Accessed april 2011]

41. Bilsky MH, Lis E, Raizer J, Lee H, Boland P. The diagnosis and treatment of metastatic spinal tumor. *Oncologist* 1999;**4**(6):459–69.

42. Morris PG, Lynch C, Feeney JN, Patil S, Howard J, Larson SM, *et al.* Integrated positron emission tomography/computed tomography may render bone scintigraphy unnecessary to investigate suspected metastatic breast cancer. *J Clin Oncol* 2010 Jul 1;**28**(19):3154–9.

43. Tiwari BP, Jangra S, Nair N, Tongaonkar HB, Basu S. Complimentary role of FDG-PET imaging and skeletal scintigraphy in the evaluation of patients of prostate carcinoma. *Indian J Cancer* 2010 Oct;**47**(4):385–90.

44. Tokuhashi Y, Matsuzaki H, Toriyama S, Kawano H, Ohsaka S. Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. *Spine (Phila Pa 1976)* 1990 Nov;**15**(11):1110–3.

45. Tokuhashi Y, Matsuzaki H, Oda H, Oshima M, Ryu J. A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. *Spine (Phila Pa 1976)* 2005 Oct 1;**30**(19):2186–91.

46. Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamaru T. Surgical strategy for spinal metastases. *Spine* (Phila Pa 1976 ) 2001 Feb 1;**26**(3):298–306.

47. Prognostic factors for patients with spinal metastases from lung cancer. 2011. Available from: URL: http://www.medscape.com/viewarticle/540597_3 [accessed april 2011]

48. Chaichana KL, Pendleton C, Wolinsky JP, Gokaslan ZL, Sciubba DM. Vertebral compression fractures in patients presenting with metastatic epidural spinal cord compression. *Neurosurgery* 2009 Aug;**65**(2):267–74.

49. Sciubba DM, Gokaslan ZL, Suk I, Suki D, Maldaun MV, McCutcheon IE, *et al.* Positive and negative prognostic variables for patients undergoing spine surgery for metastatic breast disease. *Eur Spine J* 2007 Oct;**16**(10):1659–67.

50. Rose PS, Laufer I, Boland P, Hanover A, Bilsky M, Yamada J, *et al.* Risk of fracture after single fraction image-guided itensity modulated radiation therapy to spinal metastases. *J Clin Oncol* 2011;**27**(30):5075–9.

51. Taneichi H, Kaneda K, Takeda N, Abumi K, Satoh S. Risk factors and probability of vertebral body collapse in metastases of the thoracic and lumbar spine. *Spine (Phila Pa 1976)* 1997 Feb 1;**22**(3):239–45.

52. Weber MH, Burch S, Buckley J, Schmidt MH, Fehlings MG, Vrionis FD, *et al.* Instability and impending instability of the thoracolumbar spine in patients with spinal metastases: a systematic review. *Int J Oncol* 2011 Jan;**38**(1):5–12.

53. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009 Oct;**62**(10):1006–12.

54. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.

55. Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ* 2001 Jul 28;**323**(7306):224–8.

56. Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2004 Jun 9;**2**:23.

57. Wilczynski NL, Haynes RB. Optimal search strategies for detecting clinically sound prognostic studies in EMBASE: an analytic survey. *J Am Med Inform Assoc* 2005 Jul;**12**(4):481–5.

58. Cooper K, Meng Y, Harnan S, Ward S, Fitzgerald P. Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: systematic review and economic evaluation. *Health Technol Assess* 2011;**15**(4).

59. Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al.* Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review. *Health Technol Assess* 2009 Jan;**13**(5).

60. Khan KS, Ter Riet G, Galnville J, Snowdon AJ, Kleijnen J. Undertaking Systematic Reviews of Research on Effectiveness. CRD's Guidance for Carrying Out or Commissioning Reviews. 2nd Edition. (ISBN 1900640201) CRD Report No. 4. York: NHS Centre for Reviews and Dissemination (CRD), University of York. 2001. URL: http://www.york.ac.uk/inst/crd/report4.htm [Accessed april 2011].

61. Kyzas PA, Loizou KT, Ioannidis JP. Selective reporting biases in cancer prognostic factor studies. *J Natl Cancer Inst* 2005 Jul 20;**97**(14):1043–55.

62. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006 Mar 21;**144**(6):427–37.

63. Higgins JPT, Green S. Cochrane Handbook for Systematic Reveiws of Interventions version 5.1.0. 2011. Available from: URL: http://www.cochrane-handbook.org/ [Accessed april 2011].

64. Altman DG, Royston P. What do we mean by validating a prognostic model*? Stat Med* 2000 Feb 29;**19**(4):453–73.

65. Braitman LE, Davidoff F. Predicting clinical states in individual patients. *Ann Intern Med* 1996 Sep 1;**125**(5):406–12.

66. Counsell C, Dennis M. Systematic review of prognostic models in patients with acute stroke. *Cerebrovasc Dis* 2001;**12**(3):159–70.

67. Jacob M, Lewsey JD, Sharpin C, Gimson A, Rela M, van der Meulen JH. Systematic review and validation of prognostic models in liver transplantation. *Liver Transpl* 2005 Jul;**11**(7):814–25.

68. Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. *JAMA* 1994 Jul 20;**272**(3):234–7.

69. Meijer R, Ihnenfeldt DS, de Groot IJ, van LJ, Vermeulen M, de Haan RJ. Prognostic factors for ambulation and activities of daily living in the subacute phase after stroke. A systematic review of the literature. *Clin Rehabil* 2003 Mar;**17**(2):119–29.

70. Martin B, Paesmans M, Mascaux C, Berghmans T, Lothaire P, Meert AP, *et al.* Ki-67 expression and patients survival in lung cancer: systematic review of the literature with meta-analysis. *Br J Cancer* 2004 Dec 13;**91**(12):2018–25.

71. Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al.* Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy. *Health Technol Assess* 2006 Sep;**10**(34).

72. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc* 2009 Jan;**172**(1):137–59.

73. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;**342**:d549.

74. STATA Statistical analysis and software. 2011. URL: http://www.stata.com/ [accessed April 2011].

75. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008 Oct;**61**(10):991–6.

76. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991;**44**(11):1271–8.

77. Kelly KD, Travers A, Dorgan M, Slater L, Rowe BH. Evaluating the quality of systematic reviews in the emergency medicine literature. *Ann Emerg Med* 2001 Nov;**38**(5):518–26.