Research Protocol
Imaging for detection of osteomyelitis (HTA 16/103/03)

Produced by Centre for Reviews and Dissemination (CRD), University of York

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Title of project

Imaging for detection of osteomyelitis: a systematic review and meta-analysis

Important note

This protocol has not yet been approved by the advisory board for this project, and so is subject to change.

Plain English Summary

Osteomyelitis is an infection of the bone and bone marrow. Left untreated, it may result in bone infarction, loss of limb or joint function, growth disturbance in children and, in extreme cases, require amputation of the affected limb.

The main diagnostic tool is a bone biopsy or aspiration of a pus collection but these are invasive, slow to analyse and painful. Diagnostic imaging may help improve diagnosis, by improving targeting of biopsies, or replacing them. A range of diagnostic imaging methods are available, including X-rays, magnetic resonance imaging (MRI) scans, computed tomography (CT) scans, positron emission tomography (PET) scans and ultrasound. The methods each have their advantages and disadvantages. Existing review evidence in this field is limited, and generally focuses on one type of imaging test or has been restricted to patients with diabetic foot ulcers. There is a need for a comprehensive systematic review of the accuracy of these diagnostic methods.

The aim of this project is to systematically review the literature on diagnostic imaging techniques for the diagnosis of osteomyelitis. The various different imaging techniques will be compared to determine which has the best diagnostic accuracy properties across the range of types and locations of osteomyelitis and types of patient. This will account for practical issues such as ease of access to and interpretation of tests, and exposure to ionising radiation.

A systematic review of all studies reporting diagnostic accuracy data for any diagnostic imaging test for osteomyelitis will be performed. All types of patients and types of osteomyelitis will be included. The review will follow the recommendations in CRD's guidance on the conduct of a systematic review. A diagnostic meta-analysis will be performed to estimate the diagnostic accuracy of the imaging tests. The diagnostic accuracy of these tests will be compared. The practical value of the tests will be compared, balancing diagnostic accuracy with practical issues including cost, access to machinery, and ease of interpretation and radiation exposure.

1 Decision problem

The purpose of this review project is to assess and compare the diagnostic accuracy and clinical and practical value of the various imaging tests that may be used to detect osteomyelitis including, but not limited to: X-rays, MRI and PET scans, and ultrasound.

1.1 Background

1.1.1 Osteomyelitis

Osteomyelitis is an infection of the bone and bone marrow (1). Left untreated, it may result in bone infarction, loss in limb or joint function, and in extreme cases require amputation of the affected limb. If the infection spreads, it may lead to potentially fatal septicaemia (2). In children, osteomyelitis may also inhibit limb growth, requiring extensive orthopaedic intervention in later childhood. Staphylococcus aureus is the most common organism causing osteomyelitis, but other common organisms such as streptococcus or E. coli may also be responsible in some cases; aggressive organisms such as PVL-positive staphylococcus are increasingly seen (3). Bone infections occur most commonly in people younger than 20 or older than 50 years. It accounts for around 1% of all childhood hospital admissions. The incidence of osteomyelitis has increased over the past decades, notably in children and in patients greater than 60 years of age. This growing incidence has been associated with increased prevalence of methicillin-resistant Staphylococcus Aureus (MRSA) in children and an increase in diabetes-related infections in adults (4).

Osteomyelitis may be acute, subacute or chronic, and is divided between haematogenous osteomyelitis, where infection transfers from a remote location in the body via the blood stream, and contiguous osteomyelitis where infected material comes into direct contact with the bone (5). Haematogenous type is more common in children whilst contiguous type is more common in adults, usually as result of trauma or surgery (5). Osteomyelitis is also common in people with vascular deficiency, such as adults with diabetes, as a complication of diabetic foot ulcers (6). Osteomyelitis

may lead to infection of the adjacent joint (septic arthritis) or occur secondary to septic arthritis by contiguous spread.

Patients usually present with a range of symptoms including swelling, joint pain and fever. These symptoms are often not specific to osteomyelitis, leading to delays in correct diagnosis. Blood tests are used initially to assess inflammatory markers indicative of infection in the body, including white blood cell count, C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (7). Where these tests show evidence of possible infection patients are referred for further diagnostic testing. The most accurate diagnostic tool is a bone biopsy or aspiration of a pus collection from the bone or tissue surrounding the bone, with a microbiological assessment of the sample to identify the organism causing the infection. Biopsies are invasive and painful and generally require local or general anaesthetic (5, 8). The analysis of the results may take several days. Alternative diagnostic tools include blood or tissue cultures which are less accurate, but useful in identifying the organism causing an infection in the body which enables selection of the appropriate antibiotic for treatment. The primary treatment for osteomyelitis is through a course of antibiotics, but surgery may also be used (9).

1.1.2 Diagnostic imaging for osteomyelitis

Diagnostic imaging of the affected area before performing a biopsy may help improve diagnosis, and avoid unnecessary biopsies in people who may have an infection but are unlikely to have osteomyelitis. A range of diagnostic imaging methods are available, including X-rays, magnetic resonance imaging (MRI) scans, computed tomography (CT) scans, scintigraphy, positron emission tomography (PET) scans, single-photon emission computed tomography (SPECT) and ultrasound (9-12). These imaging methods each have their advantages and disadvantages.

X-rays are easily available and cheap to perform, but cannot detect osteomyelitis in its early stages. X-rays may be most useful in identifying other causes of the patient's symptoms, such as bone fractures (11). MRI scans are probably most widely recommended and used. They are more accurate than X-rays, and able to detect osteomyelitis in its early stages, but are expensive to perform (12). PET scans and bone scintigraphy may be more diagnostically accurate than MRI scans, but are more expensive and less widely available than MRI or X-rays (11, 13). These methods expose patients to ionising radiation. Ultrasound avoids the radiation exposure, and is readily available, but its diagnostic accuracy is currently uncertain (12). There is also a distinction between methods that provide two-dimensional images (X-ray, scintigraphy) and those producing three-dimensional images

(PET, MRI, CT, SPECT). Some tests (such as MRI) may be unsuitable for patients with hip replacements or other indwelling metalwork.

1.1.3 Current diagnostic and treatment practice

Once osteomyelitis is suspected on the basis of physical examination and blood tests an MRI scan is currently generally recommended as the imaging test of choice, because it can detect osteomyelitis early, and it can identify pus collections within bone that might require surgical drainage. X-rays are not usually recommended, because of their failure to detect early osteomyelitis, but may be used to rule out or confirm bone fractures or other causes of symptoms. CT scans, scintigraphy and PET scans are less widely recommended, but are an alternative for patients for whom MRI scans are not possible.

Ultrasonography is suggested as an alternative to radiological tests (9, 11, 12, 14, 15) and is widely used in paediatric practice to exclude joint effusions and pus collection next to bone (15). This is especially helpful in young children (under 6 years) who would require a general anaesthetic for MRI. Ultrasound is also used to guide aspiration and biopsy.

Little formal guidance (such as guidelines produced by NICE) exists for which imaging techniques to use to diagnose osteomyelitis. The only current NICE guidance is for the treatment of diabetic foot ulcers. In those patients an X-ray is recommended followed by an MRI scan if osteomyelitis is suspected but not confirmed by X-ray. Antigranulocyte Fab fragment antibody scintigraphy should not be used in patients with diabetic foot ulcers (16). Recommendations have also been published in the USA (17, 18).

Osteomyelitis is treated with a four to six-week course of antibiotics (19-21). Treatment is initially intravenous, switching to oral antibiotics after around two weeks. The choice of antibiotics will depend on the infecting organism, as determined by biopsies and other tests, and the patient's medical history. Surgery may also be used for debridement of necrotic tissue and affected bone, to drain pus and to reduce bacterial load (21).

1.1.4 Pathway to diagnosis in the NHS

There are a number of ways in which a patient might be referred for imaging to diagnose osteomyelitis. Patients may present with fever and be admitted as inpatients, or may be referred directly by their GP to an Orthopaedic clinic. This pathway to clinic is slower than presenting directly to A&E and such patients often have less virulent infection or subacute osteomyelitis. Patients may be referred from other hospitals; particularly if they lack the facilities to treat children (e.g. if the hospital does not offer MRI under general anaesthesia). Patients presenting with acute symptoms may have a

musculoskeletal issue (often limping or joint pains) or non-specific systemic symptoms and sepsis (e.g. immune deficient patients due to underlying chronic condition). Generally unwell patients with sepsis are more difficult to diagnose because they might be in intensive care and joint symptoms could initially be missed while the focus is on treating severe symptoms.

1.1.5 Existing review evidence

Preliminary searches suggest that, to date, seven systematic reviews or meta-analyses have been performed to assess diagnostic imaging techniques for osteomyelitis (22-27). However, most of these can be considered to be out of date, with only two published since 2010 (25, 27). Three of the reviews included only patients with osteomyelitis of the foot (primarily as a consequence of diabetes) (22, 23, 25), and three included only PET scans or scintigraphy (25-27). Only one review (from 2005) considered diagnosis of osteomyelitis at a range of sites using a range of imaging tools (24). None of the reviews discussed diagnostic accuracy in children, and it was unclear whether any reviews included studies of children. In general, these reviews concluded that either MRI or PET scans were good diagnostic tools for osteomyelitis.

1.2 Aims and objectives

The overall aim is to systematically review the literature of studies of diagnostic imaging for osteomyelitis, in order to identify the techniques with the best diagnostic accuracy, and the greatest clinical utility, across the range of types of disease and patients.

The key objectives are:

a) To perform a systematic review of all studies reporting the diagnostic accuracy of any relevant imaging test, or combination of tests used to detect osteomyelitis.

b) To perform diagnostic meta-analyses of identified studies to formally assess their diagnostic accuracy.

c) To investigate diagnostic accuracy across the range of different types of osteomyelitis and types of patient.

d) To compare the diagnostic accuracy of diagnostic tests both statistically and pragmatically, accounting for key factors such as availability of machinery, radiation exposure, and acceptability to patients.

e) To provide useful guidance as to which imaging tests should be preferred, according to type of disease and patient in the UK.

2 Methods

2.1 Systematic review of diagnostic accuracy

A systematic review of the clinical effectiveness will be performed following the general principles recommended in CRD's guidance and the PRISMA statement. The protocol details have been registered on PROSPERO (number CRD42017068511), an international database of prospectively registered systematic reviews in health and social care (http://www.crd.york.ac.uk/prospero/).

2.2 Search strategy

Comprehensive, systematic searching of bibliographic databases will be undertaken by an experienced information specialist in order to identify all relevant diagnostic accuracy studies. As a minimum the following databases will be searched: MEDLINE, EMBASE, CINAHL and CENTRAL. Searches for existing reviews and guidelines will also be performed.

The search strategy will include relevant text-word searches for terms that appear in the titles and/or abstracts of database records, along with relevant indexed keywords (such as Medical Subject Headings, MeSH). Search terms for "osteomyelitis" will be combined with terms to identity diagnostic imaging techniques (including general terms such as "diagnostic imaging" and names of specific tests, such as MRI and computed tomography). No date or language limits will be applied. A sample search strategy for Ovid MEDLINE is provided in Appendix 1. Reference lists of relevant systematic reviews will be manually searched to ensure all relevant studies in previous reviews are included. Abstracts from relevant recent conferences (such as UK Radiological Congress, European Congress of Radiology) will also be consulted.

2.3 Study selection

Titles and abstracts of studies will be independently assessed for inclusion by two research fellows using the inclusion criteria outlined below. Disagreements will be resolved through discussion and, where necessary, consultation with a third researcher. The full text of potentially relevant papers will be obtained and these will be assessed for inclusion, again by two researchers.

2.4 Inclusion and exclusion criteria

This review will include any prospective or retrospective diagnostic accuracy study, or study from which diagnostic accuracy data may be extracted.

2.4.1 Participants

Participants will be any person with suspected osteomyelitis (based on symptoms or blood tests) who is eligible for an imaging test and further diagnostic testing. No restrictions will be made for age or disease aetiology. Participants of particular interest are:

- Children (under 18)
- People with diabetic foot ulcers

2.4.2 Index tests

Index tests considered will be any diagnostic imaging technique that could potentially identify osteomyelitis. This will include, but is not limited to:

- X-rays,
- Magnetic resonance imaging (MRI),
- Computed tomography (CT),
- Positron emission tomography (PET),
- Single-positron emission computed tomography (SPECT),
- Ultrasound.

Combinations of these tests will be included. Variations on these tests will be included, such as variations in the radioisotopes used, and differences in MRI protocols or contrast use. The clinical experts on the project team and advisory board will assess the potential index tests identified through database searching to determine if any are ineligible because they are out of date, or no longer used in the UK. A cut-off date for studies (which may differ between tests) may be used there are clinical reasons to think the test methods or accuracy have changed over time.

2.4.3 Reference standards

The preferred reference standard is bone biopsy with microbiologically confirmed osteomyelitis. Other accepted reference standards will be: confirmation of osteomyelitis by pus aspiration or other histopathology tests, prior to antibiotic intake, or by surgery.

As biopsies are invasive, clinical follow-up of at least six months with no signs or symptoms of osteomyelitis will be accepted as confirmation of the absence of osteomyelitis. Similarly clinical evidence that the symptoms have another cause will be accepted as confirmation of the absence of osteomyelitis.

In order to avoid potential bias through overestimation of diagnostic accuracy, studies will be excluded if a positive osteomyelitis diagnosis is made by using a second imaging test, or by clinical follow-up alone, without biopsy or other microbiological testing. Studies reporting insufficient data to calculate sensitivity and specificity will also be excluded. These will be reported in a table of excluded studies.

2.4.4 Outcomes

The primary outcome will be the diagnostic accuracy of the imaging test compared to the reference standard. This will be expressed in terms of sensitivity (percentage of people with osteomyelitis with a positive diagnostic test result) and specificity (percentage of people without osteomyelitis with a negative test result). Diagnostic accuracy will also be expressed in terms of positive and negative likelihood ratios, and positive and negative predictive values. Comparative diagnostic accuracy between imaging tests will be expressed in terms of summary diagnostic odds ratios, and areas under summary receiver operating characteristic (ROC) curves.

2.4.5 Implementation of imaging tests

The statistical diagnostic accuracy of the imaging tests will not be the only factor to consider when selecting a suitable test for use in practice. Therefore, alongside studies reporting formal diagnostic accuracy, studies reporting information on the broader implementation and acceptability of tests will be reviewed. As part of the search process studies reporting data or other information in any of the following areas will be included:

- cost of imaging tests,
- availability of tests (e.g. access to machinery),
- accuracy of interpretation of test results (such as inter-rater reliability),
- radiation exposure,
- patient opinions and experience.

2.4.6 Study designs

Any study which considers an imaging test or tests for osteomyelitis which reports data on any of specified outcomes will be included. Therefore studies reporting any of: diagnostic accuracy data, other quantitative data (such as costs or radiation exposure data) or qualitative data (such as author, clinical expert or patient opinions) will be included. Only studies explicitly considering testing for osteomyelitis will be included. Studies reporting on characteristics of the diagnostic tests more broadly will be excluded. Studies in low-income countries will be excluded, to ensure relevance to the UK health setting.

The following types of reports will be excluded: editorials and opinions; case reports; reports focusing only on technical aspects of imaging tests (such as technical descriptions or specifications of machinery). We will select the most recent or most complete report in cases of multiple reports for a given study or when we cannot exclude the possibility of overlapping populations.

2.5 Data extraction

A data extraction form will be developed, and piloted on a small selection of studies. Data extracted will include details of patient characteristics, diagnostic tests, and reference standard tests. Data will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Given the anticipated high volume of studies, authors will not be contacted if relevant data appears to be unreported. Where multiple publications report on the same study only the most recent data will be extracted.

Patient characteristics will be extracted, including: age, diabetic status, location of osteomyelitis, and reason for referral. Data on study intervention will be extracted (e.g. characteristics of imaging test used, diagnostic cut-off and thresholds) and data on exclusions from study/analysis with reasons will be recorded. Diagnostic accuracy data will be extracted in terms of numbers of people. The numbers of true positive, true negative, false positive and false negative test results will be extracted, if reported. If not reported, sensitivity and specificity estimates (with their 95% confidence intervals) or other reported diagnostic accuracy data will be extracted. For other quantitative outcomes data will be extracted either as numbers of events, means or standard deviations, or as summaries such as risks or odds, depending on reporting.

For the implementation review it is anticipated that most data will be qualitative in nature. The main findings of those studies will be extracted and tabulated to inform a narrative synthesis. Where quantitative data are available these will be extracted and tabulated.

2.6 Quality assessment

The quality and potential for bias of the included diagnostic accuracy studies will be assessed using the QUADAS-2 tool designed for diagnostic accuracy studies and modified as appropriate (28). A potential bias of particular relevance in this review is verification bias, where patients do not always receive the reference standard test. This could occur as, owing to their invasive nature, patients may not receive a biopsy, and so their true osteomyelitis diagnosis may be uncertain. Incorporation bias may also be an issue, if the imaging test under scrutiny is used in combination with other diagnostic tests and may consequently overestimate the accuracy of the imaging test (29). Sensitivity analyses will be performed to examine the impact of potentially biased studies.

No formal quality assessment will be performed for studies reporting information other than diagnostic accuracy, because the wide variety of types of studies that may be included. The general quality of these studies will be considered.

2.7 Synthesis and meta-analysis

2.7.1 Diagnostic meta-analysis

For each diagnostic imaging test data will be synthesised in meta-analyses across studies using logistic regression modelling (30). This approach fits a statistical model that regresses index test outcome (positive or negative for osteomyelitis) against whether each person does or does not have confirmed osteomyelitis, based on the reference standard. This has been shown (30) to be equivalent to both bivariate meta-analysis and to hierarchical summary receiver operating characteristic (HSROC) analysis, which are the methods most commonly used in diagnostic meta-analyses (31, 32). It also accounts for correlation between sensitivity and specificity, and that these may vary if different test thresholds are used across studies. This proposed model is known as a "one-stage" approach because it analyses summary diagnostic accuracy across all studies simultaneously. It provides a more flexible approach than conventional bivariate or HSROC analysis. In particular, it permits the inclusion of extra terms in the model to identify subgroups of studies or participants, and to compare different imaging tests.

Studies will be pooled if there are three or more studies eligible for the analysis. Random effects models will be used to account for potential heterogeneity in diagnostic accuracy across studies. Results will be presented as summary sensitivity and specificity estimates, with 95% confidence regions, plotted in ROC space, as summary ROC curves, and as forest plots.

Where there are too few studies for a meta-analysis, or the studies are deemed too diverse for meta-analysis to be suitable, the reported diagnostic accuracy from each available study will be presented in tables and on ROC plots, and compared across studies, tests and subgroups.

2.7.2 Subgroup analyses

Separate meta-analyses will be conducted for each diagnostic imaging test and, where sufficient data are available, according to the following sub-categories of patients:

- Age (young children (for example, <8), older children (9-18), adults (18-60), older adults (>60))
- Cause of osteomyelitis (haematogenous, contiguous, trauma, surgical, diabetes-related, other)
- Acute, subacute or chronic osteomyelitis
- Anatomical site (long bone, spinal, foot and ankle, pelvis, other)
- Patients with hip replacements or other indwelling metalwork

Subgroup analyses will also be performed to assess the impact of different study characteristics:

- Subtypes of imaging test (e.g. due to use of different radioisotopes)

- Choice of reference standard (biopsy, or clinical and surgical follow-up)
- Study quality

These analyses will place particular focus on how patients in the NHS are likely to present for osteomyelitis diagnosis. Where sufficient published data exist we will seek to estimate the diagnostic accuracy of the imaging tests in the following key categories of patients:

- Patients with acute symptoms (such as would be admitted as inpatients)
- Patients with sepsis
- Patients with milder or chronic symptoms (such as would be referred by a GP)
- Patients with concomitant diseases (such as cancer)
- Patients with diabetes

Analyses will be performed separately for adults and children

Analyses within subgroups will be performed using the logistic regression analysis approach discussed above. Separate analyses will be performed for each subgroup. Where sufficient data are available subgroup characteristics will be included as parameters in the logistic regression models, to assess the difference in diagnostic accuracy across subgroups.

2.7.3 Comparison of imaging tests

Diagnostic tests will be compared by examining summary diagnostic odds ratios derived from the logistic regression models and by comparing summary ROC curves. In general, a larger diagnostic accuracy indicates a better performance, but this may not be the case if ROC curves cross, in which case we will consider the trade-off between sensitivity and specificity. Where there are sufficient data these comparisons will be made in each of the subgroups listed above.

Where studies report diagnostic accuracy data for two or more imaging tests on the same patient population these tests will be compared within study by comparing sensitivity, specificity and diagnostic odds ratio estimates. If sufficient studies are available these difference in within-study diagnostic accuracy will be pooled across studies in meta-analyses.

2.8 Implementation review

For studies reporting qualitative data on implementation of diagnostic tests (such as clinical or patient opinions) these data will be synthesised using a narrative synthesis approach. We will tabulate the findings of the included studies. Studies will be categorised according to the diagnostic test used, and the subgroups listed above, where feasible. Studies will be compared to identify any consistent themes in their results or, conversely, to identify areas of controversy. Areas where little or no data have been published will be identified.

Where quantitative data are presented, these will be tabulated across studies, and categorised by diagnostic test and patient subgroups, where feasible. Meta-analyses will be performed to synthesise results if sufficient data are available. Data on cost and radiation exposure will be combined with results from the diagnostic accuracy meta-analyses to investigate the potential trade-off between diagnostic accuracy, costs and radiation exposure. This will be achieved, if sufficient data are available, through the use of simulation studies which simulate populations with possible osteomyelitis, the outcomes of imaging tests (based on the results of the meta-analyses) and potential costs, radiation exposure and numbers of cancers caused. Diagnostic tests will be compared to evaluate costs, radiation exposure and cancers caused per misdiagnosis avoided (if more accurate tests have higher costs and/or radiation exposure). Where data to perform these analyses are not identified in the main search, pragmatic searches will be used to find relevant literature on radiation exposure from the imaging tests and consequent risk of cancer, and on costs of the tests.

3 Dissemination and projected outputs

The primary output will be a report submitted to the HTA. This will be accompanied by one or two peer-reviewed academic journals reporting the detailed results of the systematic review. How results are published will depend on the extent of the identified evidence. For example, it may be appropriate to publish results separately for adults and children, or for patients with diabetes. One peer-reviewed journal article will be produced providing a summary of the review and practical guidance for clinicians and radiographers. All papers will be submitted to general medical journals and/or journals likely to reach an audience of osteomyelitis specialists and radiographers (European Journal of Radiology, Paediatric Radiology)

Results will be presented to appropriate clinical audiences at conferences, (such as UK Radiological Congress, European Congress of Radiology). Results may be presented at other conferences as part of the team's usual conference attendance.

Major UK and European societies likely to be interested in this project will be informed of progress, including the Royal College of Radiologists, the British Institute of Radiology, European Bone and Joint Infection Society, European Society of Musculoskeletal Radiology. They will be sent a short summary of the review findings with a link to the HTA report.

4 Plan of investigation and timetable

The project will run for fifteen months, starting in July 1 2017. The project will follow the standard systematic review process, commencing with a protocol and PROSPERO registration and proceeding to database searching, screening and study selection, data extraction and quality assessment, and meta-analyses. Key milestones for the project are summarised in the table below.

Activity	**Month of project**														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Preparation and preliminary searches															
Main database searches															
Screening of results															
Obtaining full papers and secondary screening															
Selection of studies															
Data extraction															
Quality assessment															
Synthesis and meta-analysis															
Update search and review															
Write report															
Write journal articles															

5 Additional information

5.1 Research team

The research team is divided between a systematic review group at CRD in York, and clinical advisors in Leeds, as follows:

- Mark Simmonds (CRD)
    - Principal investigator: overall project management and statistical analysis
- Alexis Llewellyn (CRD)
- Teumzghi Mebrahtu (CRD)
    - Systematic reviewers, will perform all aspects of the review and write report and publications
- Melissa Harden (CRD)
    - Information specialist, will manage database searches and citation libraries
- Nerys Woollacott (CRD)
    - Provide expertise on HTA systematic review projects

- Jeannette Kraft (Leeds)
- Andrew Grainger (Leeds)
    - Clinical advisors, providing advice on all clinical aspects of osteomyelitis diagnosis and treatment in adults (Grainger) and children (Kraft)

5.2 Advisory board

This project will recruit a clinical advisory board to advise on practical aspects of the project and ensure the research remains relevant to patients, clinicians and the NHS. Currently this board consists of three clinicians with specialty in osteomyelitis treatment and radiography. Two or three patient representatives will also be invited to join. The board will meet three times during the course of the project.

5.3 Public and Patient Involvement

Two or three patient representatives who have received diagnostic imaging for suspected osteomyelitis (including a parent of a child patient) will be recruited to join the advisory board, from among the patients seen in practice by Drs Kraft and Grainger

5.4 Funding

The project is funded by the National Institute for Health Research (NIHR).

Project number HTA 16/103/03

5.5 Registration

This protocol is registered on PROSPERO (number CRD42017068511).

5.6 Conflicts of interest

M Simmonds, N Woolacott, J Kraft, A Llewellyn, T Mebrahtu and M Harden have no conflicts of interest to declare.

A Grainger declares the following potential conflicts of interest:

He receives lecturer fees from GE medical (ultrasound), is a consultant for Medivir AB, and has received research equipment from Siemens medical in the past.

5.7 Copyright

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