**Study Title:** Imaging in Paediatric Osteomyelitis (the PICBONE study): a multi-centre cohort study to understand the role of MRI and Ultrasound in the diagnosis of acute haematogenous osteomyelitis in children.

**Short title:** The PIC Bone Study

**Ethics Ref:** 23/WM/0027

**IRAS Project ID: 318114**

**Date and Version No:** V2.0_06Feb2024


| | |
|---|---|
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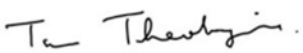
| **Sponsor:** | University of Oxford |
| **Funder:** | NIHR Health Technology Assessment (HTA) Programme |
| **Chief Investigator Signature:** |  |

There are no potential conflicts of interest.

**Confidentiality Statement**

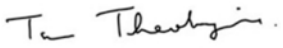
This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

**Trial Title:** Imaging in Paediatric Osteomyelitis (the PICBONE study): a multi-centre cohort study to understand the role of MRI and Ultrasound in the diagnosis of acute haematogenous osteomyelitis in children.

**Protocol Date and Version No**: 06 February 2024, Version number: V2.0

**Protocol signature page**

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Tim Theologis 

| **Principal Investigator** (Please print name) | **Signature** | **Site name or ID number** | **Date** |
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## 1. KEY CONTACTS

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|---|---|
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| **Funder** | National Institute for Health Research Health Technology Assessment Programme<br><br>htafunding@nihr.ac.uk |
| **Clinical Trials Unit** | Surgical Intervention Trials Unit,<br>Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS)<br>Botnar Research Centre, University of Oxford,<br>Windmill Road, OXFORD, OX3 7LD<br><br>situ@ndorms.ox.ac.uk |
| **Statistician** | Professor Gary Collins, PhD<br>Director of the Centre for Statistics in Medicine<br>Director of the UK EQUATOR Centre<br><br>Centre for Statistics in Medicine, NDORMS, Botnar Research Centre, University of Oxford, Windmill Road, Oxford, OX3 7LD, United Kingdom<br><br>gary.collins@csm.ox.ac.uk |
| **Committees** | Study Steering Committee (SSC)<br><br>Chair: Professor James Robb 07594710634; j.e.robb@btinternet.com |

## 2. LAY SUMMARY

Background:

When a child is brought to the emergency department with a painful limb without an obvious injury, doctors are typically faced with a dilemma between two diagnoses:

- A serious, though relatively uncommon, infection of their bones or joints OR
- A non-serious, though common, temporary swelling to their joints

Serious infections in bones are rare but can be limb and life threatening. They require urgent treatment (antibiotics) and sometimes surgery. Temporary joint swelling, however, is common and resolves without any intervention within a few days. The challenge is to quickly identify which child has an infection and which has joint swelling. Telling these apart is often not easy and involves x-rays and blood tests. Often, 'special tests' are also used, which are ultrasound and/or MRI (magnetic resonance imaging) scans. Doctors around the world are unsure about the best choice of test, particularly the 'special tests', and in what order tests should be performed when a bone infection is suspected.

A clear pathway outlining which tests to perform, and when they are needed, would help to ensure that bone infections are not missed. This would also reduce unnecessary tests on children who do not have an infection and get to a diagnosis more quickly.

Aims:

1. To understand how helpful 'special tests' (i.e. ultrasound and MRI scans) are in diagnosing bone and joint infections in children.

2. To create a pathway that doctors and nurses can use in emergency departments to aid the diagnosis of bone and joint infections.

Methods:

1. Learn from children who have previously been suspected to have bone and joint infection.

We will look at past records from at least 30 hospitals in the UK. These will tell us which tests were performed and when. We will work-out how useful the 'special tests' were at detecting bone infections and identify patterns in how and when tests should be performed. We will use the information to develop a pathway to investigate suspected bone infections.

2. Apply what we've learnt to diagnose future infections in children.

We will test how well the pathway that we develop works on data collected from a new group of children with suspected infections.

3. Determine the acceptability and concerns in treating bone and joint infection.

We will interview families to see if this pathway is acceptable to children, parents and doctors and assess how best to address children's and parents' needs and concerns.

## 3 SYNOPSIS

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|---|---|
| Study Title | Imaging in Paediatric Osteomyelitis (the PIC Bone study): a multi-centre cohort study to understand the role of MRI and Ultrasound in the diagnosis of acute haematogenous osteomyelitis in children. |
| Short title | The PIC Bone Study |
| Study registration | ISRCTN (International Standard Registered Clinical/soCial sTudy Number) registry. |
| Sponsor | Research Governance, Ethics and Assurance Team<br>Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB<br>rgea.sponsor@admin.ox..ac.uk |
| Funder | National Institute for Health Research Health (NIHR) Technology Assessment Programme (HTA)<br>NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)<br>University of Southampton Alpha House, Enterprise Road Southampton, SO16 7NS; netsmonitoring@nihr.ac.uk |
| Study Design | Multi-centre cohort study of children with suspected bone and/or joint infection (BJI) combining a retrospective cohort, a prospective validation cohort and a qualitative evaluation. |
| Study Participants | Prospective and Retrospective Studies:<br>Children and young people under 16 years old where BJI is part of the differential diagnosis even if the treating clinician believes this can be ruled out on the basis of the history and examination alone.<br>Qualitative Information Study:<br>Patients and families with a proven BJI and a sub-set of patients and families who have undergone investigations for suspected BJI but received other diagnoses. Also, health professionals involved with the care of children with a suspected BJI. |
| Sample Size | Prospective study: A minimum of 111 children with a proven BJI (from a sample of children with suspected BJI – anticipated to be 1500 children)<br>Retrospective study: A minimum of 444 children with a proven BJI (from a sample of children with suspected BJI - anticipated to be 6000 children).<br>Qualitative Information Study (identified as part of the prospective study): purposive sample of approximately 20 families with a proven BJI and a sub-set of patients/families who have undergone investigations for suspected BJI but received other diagnoses. We will also conduct focus groups and interviews with a purposive sample of approximately 12 health professionals. |
| Planned Study Period | 01 June 2022 to 31 March 2025<br>Total length of project: 34 months<br>Individual participant involvement: 15 months |
| Planned Recruitment period | Retrospective study: 16 June 2023 – 30 June 2024<br>Prospective study: 27 July 2023 – 30 June 2024 |

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|---|---|
| Primary objective | To estimate the sensitivity and specificity of MRI and USS in the investigation of BJI in children. |
| Secondary objective | To derive and validate a prediction model for the diagnosis of BJI in children, to determine the added value of MRI and USS imaging for use in the emergency, secondary and tertiary settings and to explore acceptability to children, parents and health practitioners. |
| Clinical Outcome | Presence or absence of proven BJI, which includes osteomyelitis and/or septic arthritis. |
| Qualitative Outcome | Experience through semi-structured qualitative interviews with children and parents, and focus groups and interviews with health professionals. |

## 4. ABBREVIATIONS

| | |
|---|---|
| BAPS-CASS | British Association of Paediatric Surgeons-Congenital Anomalies Surveillance System |
| BJI | Bone and/or Joint Infection |
| BOSS | British Orthopaedic Surveillance Study |
| BPSU | British Paediatric Surveillance Unit |
| BSCOS | British Society for Children's Orthopaedic Surgery |
| CI | Chief Investigator |
| CPinBOSS | Cerebral Palsy in the British Orthopaedic Surgery Surveillance Study |
| CRF | Case Report Form |
| ED | Emergency Department |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HRA | Health Research Authority |
| HTA | Health Technology Assessment |
| ICF | Informed Consent Form |
| MAR | Missing at Random |
| MCAR | Missing Completely at Random |
| MNAR | Missing Not at Random |
| MRI | Magnetic Resonance Imaging |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute of Health Research |
| NPV | Negative Predictive Value |
| BJI | Osteomyelitis |
| PERUKI | Paediatric Emergency Research in the UK and Ireland |
| PI | Principal Investigator |
| PIL | Participant/ Patient Information Leaflet |
| PPI | Patient and Public Involvement |
| PPV | Positive Predictive Value |
| RES | Research Ethics Service |
| R&D | NHS Trust R&D Department |
| REC | Research Ethics Committee |
| SMG | Study Management Group |
| SOP | Standard Operating Procedure |

| | |
|---|---|
| SSC | Study Steering Committee |
| STARD | Standards for Reporting of Diagnostic Accuracy Studies |
| UKOSS | UK Obstetric Surveillance System |
| USS | Ultrasound Scan |

## 5. BACKGROUND AND RATIONALE

### 5.1 Investigations in Osteomyelitis

Osteomyelitis is a bacterial infection of bone. In children, it is typically introduced through the blood (haematogenous) and usually affects the metaphyses, the part of the long bones which is adjacent to the joint. Acute osteomyelitis presents with symptoms of less than two weeks, including pain, loss of limb function, raised temperature and malaise. The infection frequently 'breaks out' into the adjacent joint, causing 'septic arthritis' (1). Osteomyelitis and septic arthritis in children are inextricably linked and considered together as 'osteoarticular infection' or bone and/or joint infection (BJI). **The abbreviation BJI in this document should be taken to indicate bone and/or joint infection**. The burden of BJI is significant, with data suggesting that approximately 1800 children (0-16 years old) are admitted to hospitals in England each year (https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18).

BJI presents two key challenges: (a) establish the diagnosis promptly and start antibiotic treatment; (b) decide whether surgical drainage of the infection is required. Untreated BJI rapidly progresses to irreversible joint cartilage and/or growth plate damage and bone destruction, leading to a limb threatening situation, while systemic sepsis can have life threatening implications. Early differentiation of BJI from less urgent conditions mimicking the symptoms is critical. The most common differential diagnosis is transient synovitis, which is a childhood disorder that spontaneously resolves over several days. Other differential diagnoses include occult fracture, benign or malignant bone tumour, bone marrow disease, inflammatory arthritis, non-infective osteitis, and soft tissue infections.

Following the onset of symptoms, the majority of patients present to the Emergency Department (2). Clinical work-up typically includes the history of the illness, clinical examination, routine blood tests and radiographs. However, despite this work-up, clinicians are frequently left facing difficulties in distinguishing BJI from the other potential causes, and therefore consider advanced imaging. Such imaging includes ultrasound scan (USS) and magnetic resonance imaging (MRI). USS is more readily accessible and can identify organised fluid collections within joints or tissues, but the overall diagnostic value is unknown. A recent Health Technology Assessment (HTA) review found a sensitivity of 95.6% and specificity of 80.7% using MRI to diagnose BJI in adults (3), though was unknown in children. Furthermore, the situation is more complex in children, because MRI often requires sedation or anaesthesia in children, which influences clinical decision making. Given these uncertainties, there is significant variation in the choice and timing of imaging in children, which delays treatment (2). Qualitative work undertaken as part of an observational study concerning childhood BJI, called the DINOSAUR study, demonstrated the frequent delay in diagnosis had a negative effect on the families' experience of healthcare (2). The main recommendations of the DINOSAUR study were that research should explore and evaluate strategies to improve the speed and accuracy of diagnosis among non-specialist providers at the initial point of contact.

In order to help clinicians differentiate between different causes of BJI, there are several rudimentary decision support tools, that use clinical, haematological, and biochemical parameters (2) (4) (5) (6) (7). However, these tools have been developed without methodological expertise in diagnostic accuracy and do not consider the role of imaging. The use of these tools is, therefore, limited.

### 5.2 Existing Evidence

A recent HTA review concerning imaging in BJI did not identify any studies relevant to children (3). Better guidance regarding the use of imaging to optimize the diagnosis of BJI in children is a priority of both clinicians and children and their families (2) (8) (9).

In preparation for this study, we surveyed the 'Paediatric Emergency Research in the UK and Ireland' (PERUKI) network. We identified that for every child admitted to hospital with suspected BJI, another 5 children were seen in the Emergency Department (ED) and discharged for whom BJI was a differential diagnosis. NHS Digital data indicates that there are 1800 admissions per year with suspected BJI, from which we infer that more than 10,000 children are investigated yearly for suspected BJI in UK Emergency Departments. Furthermore, we carried out a feasibility study (see 5.3 below) amongst children attending a tertiary hospital ED during 2018-20, from which we identified 323 children with suspected BJI. From these, we identified the proportion of those admitted, the number who underwent an MRI or USS and the timing and diagnostic outcome of imaging.

The DINOSAUR study investigated inpatient cases of children with suspected BJI, and demonstrated that one in three children underwent USS, and one in five underwent an MRI. The sequence and timing of these investigations varied (2). Abnormalities were identified in 70-80% of USS and 75-90% of MRI. However, the design of the DINOSAUR study did not allow evaluation of the diagnostic accuracy of imaging techniques. The data from our PERUKI network survey showed that 53% of admitted children underwent MRI and 72% USS. MRI provided the definitive diagnosis in 70% of cases and USS in 22%.

### 5.3 Feasibility Study

To support the development of this study, we carried out a retrospective study of children (0-16yrs) presenting to a tertiary hospital (Oxford University Hospitals) with suspected BJI. Electronic patient records of every ED attendance encounter (n=15,741) between October 2018 and January 2020 were obtained. These records were sorted according to the recorded "visit reason" and a search was performed to include all encounters where the visit reason included the terms: limp, limping child, abnormal gait, osteomyelitis, septic arthritis, swollen leg/joint, non-weight bearing, limb and joint pain. We assessed 516 records from which we excluded those with rheumatological diseases, known bone disease, superficial soft tissue infection, and musculoskeletal injury. 323 records were deemed to be suspected BJI encounters.

Clinical admission and progress notes, operation notes, discharge summaries and imaging reports were scrutinised to determine: the proportion of patients with suspected BJI admitted and not admitted, the number of patients in each sub-group who underwent an MRI or USS, and the diagnostic outcome of the imaging. Details on the age, sex, use of sedation or general anaesthetic for MRI and any adverse events were obtained. Definitive diagnosis of BJI was based upon a predetermined reference standard (see 5.4). The data to inform the reference standard were obtained from the patient electronic record.

### 5.4 Reference Standard for the diagnosis of Bone/Joint Infection

In defining the reference standard, we considered the DINOSAUR study and the previous HTA review of imaging in osteomyelitis (2, 3). A positive microbiological culture or polymerase chain reaction (PCR) from a relevant specimen (abscess, bone, joint fluid) provides definitive confirmation of BJI. However, a significant proportion of specimens in children with an infection do not grow bacteria (2). Therefore, a positive blood culture in the absence of another source of infection, or a specimen of joint fluid with WBC>50,000 are also considered as confirmation of BJI (3). In addition, conventional radiographs, although normal in >50% of children at initial presentation (2), show secondary changes related to BJI within approximately 7-10 days (10). Therefore, evidence of BJI on radiographs obtained at a later stage is accepted as confirmatory of the condition.

Establishing an alternative diagnosis, or resolution of symptoms without any antibiotic treatment or surgery, safely rules out the diagnosis of BJI, because spontaneous resolution of BJI is highly unlikely (11). Currently, approximately 30% of children undergo surgery (aspiration, biopsy) to 'rule out' BJI (2). Many of these procedures may be avoidable but are undertaken to prevent harm from delayed diagnosis when there is uncertainty. Understanding the sensitivity and specificity of diagnostic imaging, along with a clear decision tool that includes other diagnostic parameters, would be of great value.

The Paediatric Emergency Medicine Collaborative in the UK and Ireland (PERUKI) and the Australian Paediatric Emergency Medicine Research Collaborative have prioritised decision support tools, to help differentiate BJI from other diagnoses, amongst their top 10 most important research areas. The question that they have proposed is "In children with atraumatic limp (suspected infection), what is the best clinical decision rule for observation/investigation/management?" (8) (9).

## 6. OBJECTIVES AND OUTCOME MEASURES

**Primary Objective**

To estimate the sensitivity and specificity of MRI and USS in the investigation of BJI in children.

**Secondary Objectives**

To derive and validate a prediction model, for use in the acute presentation of the child, to determine the added value of MRI and USS imaging in the diagnosis of BJI in children.
Explore the acceptability of the diagnostic model to children, parents, and health practitioners.
To explore the diagnostic process and journey from the perspectives of children, parents, and health practitioners, considering the opportunities to enhance the patient/parent experience through semi-structured qualitative interviews with children and parents and focus groups with health professionals.

**Outcome Measure**

Primary: Presence or absence of proven BJI, which includes osteomyelitis and/or septic arthritis.
Secondary (qualitative interviews): experience through semi-structured qualitative interviews with children and parents and focus groups with health professionals.

## 7 STUDY DESIGN

The study is a multi-centre cohort study of children with suspected BJI combining a retrospective cohort and a prospective validation cohort. Similar selection criteria and data collection will be employed in both cohorts.
The study will consist of two phases:

1. A multicentre retrospective cohort study to establish the diagnostic accuracy of MRI and USS and to develop a prediction model for diagnosis.
2. A multicentre prospective cohort study to externally validate the prediction model.
3. In parallel, a qualitative study will inform the management of patients being investigated for BJI, including how best to address their information needs and how to support them during the process.

Our approach is pragmatic, allowing clinicians to decide on the choice, timing, and sequence of the investigations without changing their clinical practice. A study mandating USS and MRI investigation of all participants, in a pre-defined order, would have been methodologically ideal, though ethically unacceptable given the need for sedation or anaesthesia for MRI in young children.

**Qualitative study**
As part of the prospective cohort study, the central research team (qualitative) will conduct qualitative interviews with children and young people who have undergone clinical investigations for BJI, their parents and health professionals. This is important to learn how patients experience clinical investigations and the diagnostic processes, and to identify ways to avoid delays and enhance patient experience of diagnosis. Evidence from previous qualitative research, involving children diagnosed with BJI conducted as part of the DINOSAUR study, showed that parents prioritised receiving a quick and accurate diagnosis [2]. However, the DINOSAUR study focussed mostly on experiences of treatment for BJI. It did not examine how children and parents experienced the diagnostic process, or the perspectives of health professionals. There is some previous research on experiences of those undergoing imaging, but this has mostly focused on either adults [12] or children and young people in planned care or research settings [13, 14]. BJI is often diagnosed in urgent care settings, yet there is little understanding of the experiences of children and young people in these settings. Work is needed which focuses on how patients, their parents and health professionals experience the diagnostic pathway and investigations for BJI. This study will inform the management of patients being investigated for BJI and help to ensure that the process of diagnosis and imaging is acceptable. It will also explore the information needs of children and parents, to identify how best to support their care during the diagnostic process; in order to ameliorate pain and distress and minimise the use of general anaesthetics during MRIs [15].

**Setting:**
The cohort study will be conducted in NHS secondary care hospitals throughout the UK. The first cohort (retrospective) will be identified through Emergency Department (ED) records in participating centres. The second cohort (prospective) will also be recruited in ED or acute wards at the same centres. Support from PERUKI and the British Society for Children's Orthopaedic Surgery (BSCOS) will help facilitate recruitment and support the study.

We have considered the INCLUDE guidance in preparing the study. Diversity is particularly important, as diseases more frequent in different racial or ethnic groups may affect the diagnostic process of BJI (e.g. sickle cell disease, haemophilia). Furthermore, there is evidence that the incidence of BJI increases with

increasing socio-economic deprivation (12). In discussion with our PPI co-investigators, we will be targeting hospitals covering underserved and ethnically/racially diverse areas (e.g. East London, Birmingham) to ensure our sample is inclusive.

## 8. PARTICIPANT IDENTIFICATION

### 8.1 Study Participants

Children and young people under 15 years and 9 months old with a diagnosis of BJI suspected by the treating clinician.

### 8.2 Inclusion Criteria (all participants):

- The child is aged between 0-15 years.
- BJI is part of the differential diagnosis, even remotely, and even if the treating clinician believes BJI can be ruled out on the basis of the history and examination alone.
- The duration of symptoms is less than 2 weeks at the time of attendance to acute healthcare.
- Symptoms affecting the appendicular skeleton only.

### 8.3 Exclusion Criteria (Prospective cohort):

- There is evidence that the patient and/or parent/guardian would be unable to adhere to study procedures or complete follow-up, such as developmental delay or a developmental abnormality.

- Limited comprehension by the parent guardian of the English language. This will be assessed by the recruiting team at participating sites.

- Suspected infections affecting the axial skeleton (skull spine, or ribs).

- Traumatic aetiology of symptoms

## 9. PROTOCOL PROCEDURES

### 9.1 Screening, Eligibility Assessment and Recruitment

<u>9.1.1 Retrospective cohort:</u>

Site ED records will be screened for potential cases of BJI by the local clinical team. ED attendance codes/ keywords including, but not limited to, any of the key words limp, limping child, abnormal gait, osteomyelitis, septic arthritis, swollen leg/joint, non-weight bearing, limb and joint pain, transient synovitis will be reviewed. These predefined attendance codes/ keywords were derived during the feasibility study, but additional keywords can be identified and added by the participating centres. If the ED record indicates BJI as a differential diagnosis, the electronic patient record will be reviewed. Patient medical records, which include their admission and progress notes, operation notes, discharge summaries and imaging reports will be scrutinised.

<u>9.1.2 Prospective cohort (12 months recruitment – 3 months follow-up)</u>

Similar to the retrospective cohort, patients with suspected BJI (identified by one of the keywords above), will be identified in participating centres either in the Emergency Department, on admission or in the paediatric or paediatric orthopaedic department. Patients will be recruited when the treating clinician believes that the child may have a diagnosis of bone or joint infection (i.e. BJI is part of the differential diagnosis, even remotely and even if the treating clinician believes BJI can be ruled out on the basis of the history and examination alone).

A patient poster has been designed to let patients and their families know that the study is taking place in the hospital and to help improve recruitment.

9.1.3 Qualitative study

The qualitative study will run in approximately 15 of the sites involved in the prospective cohort study and explore the perspectives of children/young people, parents/carers, and health professionals on the diagnostic process for BJI. Participants from the prospective cohort will be invited to participate in this sub-study. See Section 9.9 for more details.

## 9.2 Informed Consent

Retrospective cohort

Participating centres will enter routinely captured anonymised medical records data into the study database. Data will be anonymised, and patient consent will not be required.

Prospective cohort

Children and their parents/guardians will be informed about the study by the clinical team. If the patient/parent/guardian is interested in participating in the study, they will be introduced to the research associate/practitioner assigned to the study. The research associate/practitioner will provide the family with the age-appropriate participant information sheet, parent/guardian information sheet, study 'explainer video' and a verbal explanation of the study. The qualitative sub-study will also be outlined to eligible families at participating sites. The child and their family will be given the opportunity to discuss any issues related to the study with the research associate. It will be emphasised that the study will not affect the child's treatment nor subject the child to extra investigations or hospital visits but will allow the clinical team or central research team to contact the family for confirmation of symptom resolution at 3 months.

The parent/guardian will then be asked to sign a consent form, and the child will be invited to complete an assent form. As part of the main study consent, families will be asked to indicate whether they are willing for their contact details, the age in whole years of the child, and their diagnosis (positive or negative for infection) to be shared with the qualitative team, and happy to be contacted to discuss this sub-study.

Assent will be sought from all children where the local clinical or research team assesses the child competent to understand the study information. We expect assent to almost universally be collected for children over 8 years of age. Assent forms do not substitute for the consent form. Assent should be taken where appropriate; however the absence of assent does not exclude the patient from the study if consent has been obtained from the parent/ legal representative. If the child actively declines participation, we will not include the child in the study.

Where electronic consent/assent is used and the parent/guardian has an email address they are willing to provide, an electronic version of the signed ICF will be automatically emailed to them. If the parent/guardian agrees, a copy of the assent form may also be emailed to the participant. If the parent/guardian does not have/does not provide an email address the local team will be able to print a copy of the signed consent/assent and provide this to the parent/guardian and participant. A copy of the electronic consent/assent form downloaded from the trial database should be placed in the Investigator Site File and a copy in the participant's medical record.

During the prospective study we will seek consent from participants and their family for future contact. This will allow for assessment of any long-term effects of BJI on bone growth and degenerative arthritis. Any studies involving long-term follow-up will seek separate funding and ethical approval and will be reported at a later time-point, separate to the monograph.

We have carefully considered the timing of consent for the subgroup of children admitted to hospital. Given the significant anxiety and worry associated with serious systemic illness for which surgery is often being considered, we propose to approach these families as they approach discharge from hospital, rather than seeking consent in the acute phase of the illness.

For those patients discharged from the ED or acute ward on their first day of attendance who require further time to consider the study, a member of the research team will follow up potential participants by phone, electronically or through the post (detailed below).

### 9.3 Enrolment

There is no randomisation of patients within this study.

Patients and their parent(s)/guardian will be provided with either the QR code/website address to access the study information portal or with written information about the study, during their visit to the hospital. The family will also be provided with a verbal explanation of the study by the assigned Associate Principal Investigator/clinician at the site. If interested in participating, they will be given the option of signing a consent and assent form immediately or have the option to consider later enrolment either on paper (through the post or email) or via a link directly to the database. To enrol after the hospital visit, the researcher will request a telephone number and/or an email address for the parent / guardian. For those parents sharing an e-mail address, this will be entered into the secure password-controlled study database, and a link will be shared to the online consent portal. A link to the study website will also be provided, where the family can find a study explainer animation clip, a summary of the prospective study, the qualitative sub-study and all the study information leaflets outlining what is involved. Contact details for the local PIC Bone team and for the study manager in Oxford are provided to allow the patient/parent to contact the team to ask any questions that they may have. After reviewing the study information, patients/parents can then enrol for the study via the e-consent and optional e-assent form.

Any patients and parent/guardians who are approached in the hospital and request more time to consider enrolment can be contacted by telephone/email during the week after discharge to discuss further. Should they wish to consent, the research team will send an e-consent link (as above).

Paper based information material and consent/assent forms will be available to parents who do not have access to email. This will be administered by post where necessary.

The central study manager will be alerted to the addition of new participants once they are added to the study database.

### 9.4 Blinding and code-breaking

No blinding or code breaking is required for this study.

### 9.5 Description of study intervention(s), comparators, and study procedures (clinical)

The study does not involve an intervention or comparator.

### 9.6 Description of data collection

Data relevant to establishing the reference standard and to developing and validating the prediction model will be collected for both the retrospective and prospective cohorts. These will be collected by the treating clinicians, retrieved from the medical records and will include as much of the information presented below as possible.

**A summary of the data collection is presented here:**

**Retrospective study**

Review of ED records, by performing an ED attendance search using keywords suggestive of BJI. Each site will be asked to start from 28 February 2020 and work backwards until 28 February 2018 or until the desired number of cases (as agreed with the site) is collected.

Outcomes of ED attendance:

Child discharged directly from ED on their first day of attendance: the medical record will be reviewed and details of clinical parameters and 'tests' will be collated. A review of the medical notes over the following 3 months will be performed to ensure that there was no subsequent diagnosis of BJI or an alternative diagnosis. If BJI, details pertaining to the reference standard will be collected.

Child admitted in hospital: the medical record will be reviewed and details of clinical parameters and 'tests' will be collated. A review of the medical notes over the following 3 months will be performed to elicit the diagnosis/ exclusion of BJI or an alternative diagnosis. If BJI, details pertaining to the reference standard will be collected.

**Prospective Study**

For children recruited from acute attendance by the clinical team/research associate/practitioner and once consent is in place:

- Collect baseline data upon recruitment.
- Review records for confirmation on final diagnosis (to include those with pending investigations at the time of discharge).
- Contact family for follow up at 3 months via phone/text/email (conducted by study management team).
- If family indicate further hospital attendance/treatment received elsewhere, study management team to contact local site to explore further.

#### 9.6.1 Baseline Information (retrospective and prospective studies)

This information will be collected for all children in the retrospective and prospective cohorts.

Data will be extracted from the routine medical record. Data fields have been chosen which may be useful in the diagnosis of BJI. These include patient factors (i.e. sex and age), disease factors (i.e. the duration of symptoms), haematological factors (i.e. White Blood count), and biochemical factors (i.e. the C-reactive protein). No additional information will be necessitated beyond that collected during routine care.

In particular, detail of the 'special tests' performed will be collected, along with the timing and outcome of the test and its position in the clinical timeline of the child. In addition, the access of sites to US and MRI on an urgent basis, particularly out-of-hours, will be recorded.

### 9.6.2 3-Month follow-up

For the **retrospective study**, follow-up data will be collected to confirm the diagnosis (as described above in 9.6).

For the **prospective study**, all patients will be followed up by review of the medical notes at the local site up to 3 months to confirm the diagnosis on the basis of the same reference standard. All families will be contacted by the central study team (Oxford) for a final follow up at 3 months via phone/email or text to check if the symptoms have resolved or to ensure that they did not seek treatment elsewhere. If these families report that they have been treated elsewhere, the central study team (Oxford) will inform the original recruiting site and request the site to contact the non-participating hospital or the general practitioner to collect appropriate data to ensure completeness of medical notes for the patient's care pathway.

### 9.6.3 Reference Standard for Diagnosis of BJI:

A. <u>Definitive Diagnosis of BJI (at least any ONE of the following):</u>

Positive histopathology sample indicative of infection from relevant tissue/fluid biopsy sample or surgical bone/joint specimen OR
Positive microbiology joint aspirate (bacterial growth indicating proven infection, positive Gram stain, pus cells combined with macroscopic appearance of pus) OR
Positive PCR joint aspirate with proven infection OR
Positive blood culture with no other source of infection AND subsequent localising signs on imaging OR
Joint aspirate >50,000 WBC OR

Evidence of osteomyelitis on two imaging modalities or confirmatory changes on follow-up imaging.

B. Uncertain Group

Children with negative or equivocal diagnostic investigations, who recovered following more than 24 hours of antibiotic treatment will be considered as a separate "uncertain" group. Less than 24 hours of treatment dose antibiotics or the use of long-term prophylactic antibiotics will be considered as 'no' antibiotic use, as neither could effectively treat an infection of bone or joint.

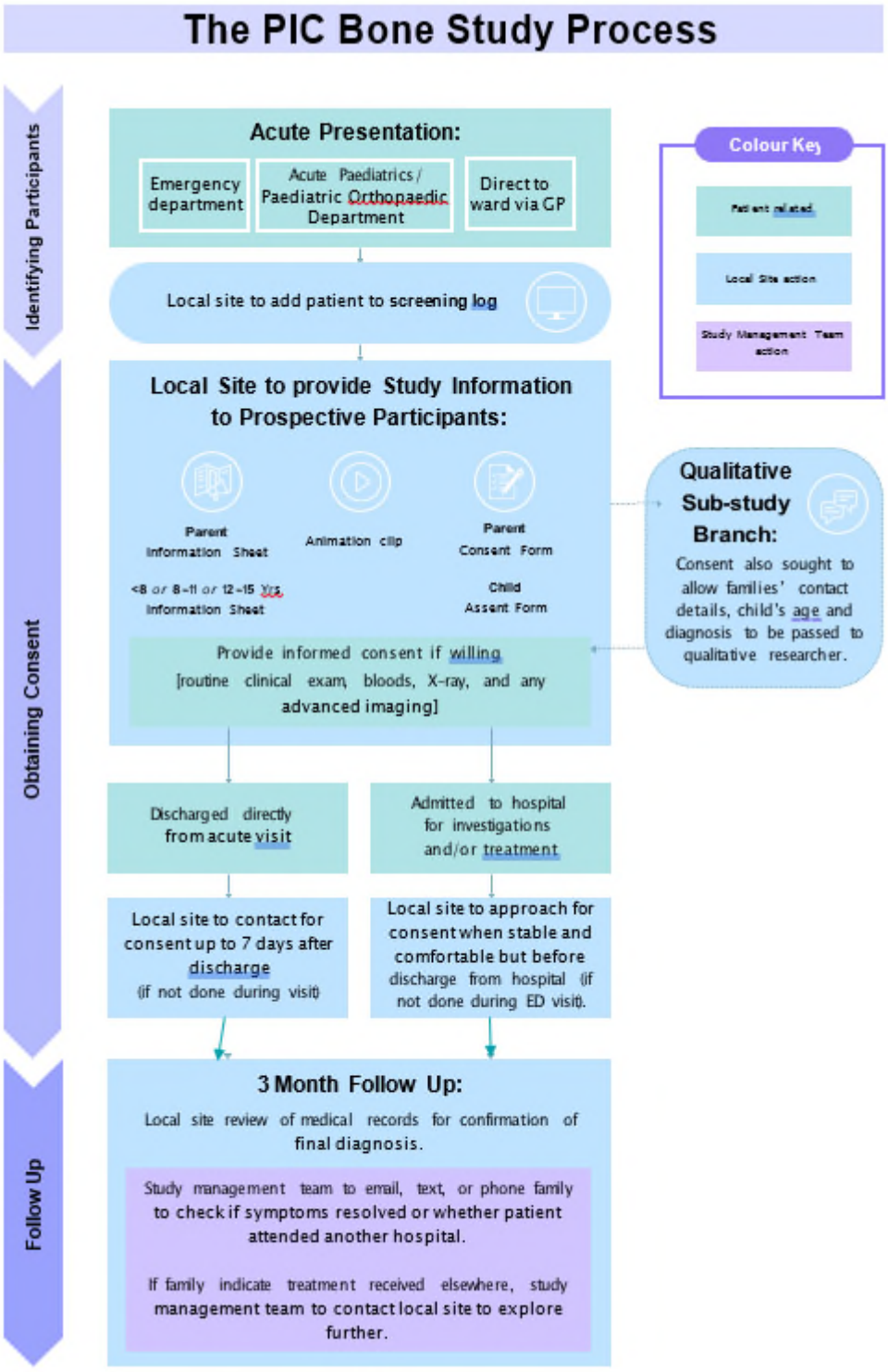
C. Definitive exclusion of BJI diagnosis:

Clinical resolution of symptoms without ANY antibiotic treatment by 3 months. Less than 24 hours of treatment dose antibiotics or the use of long-term prophylactic antibiotics will be considered as 'no' antibiotic use.

OR confirmation of an alternative diagnosis to explain symptoms subsequently established, even if treatment dose antibiotics were administered.

MRI and USS will be requested as per the usual practice of the treating clinician without any technical constraints. Timing of investigations will be recorded to determine where in the pathway the technologies are applied. The MRI and USS reports issued by the treating radiologist will be collected to document the suggested differential diagnoses based on the imaging. The radiologist's seniority will be recorded to assess any effect on diagnostic accuracy.

### 9.7 Flowchart (Prospective Study only)




## 9.8 Qualitative Study

The central research team (qualitative) at University of Liverpool will conduct semi-structured qualitative interviews with a purposive sample of approximately 20 families, sampling for diversity in terms of study site, child age, ethnicity, and socio-economic status. We will include families with lived experience of USS, MRI, or both. The sample will mainly comprise those diagnosed with BJI, but we will also interview a sub-set of patients/families who have undergone investigations for suspected BJI but received other diagnoses. The perspectives of these two groups may differ in important ways and it is important that clinical practice

is informed by both groups. Sampling of families will also be informed by the concept of information power (12) and the ongoing data analysis.

Interview topic-guides have been co-developed with our PPI co-investigator and panel and adapted so that these are suitable for use with children and parents. Initial discussions within the research team and with Generation-R and other stakeholders have suggested exploring families' experiences of: consulting and diagnosis from onset of symptoms; information and communication needs about investigations and the diagnostic pathway; management of pain and distress; use of sedation, anaesthesia and behavioural techniques during imaging and investigations; suggestions for improving the diagnostic process; preferences and trade-offs around choice of USS v MRI imaging. We will periodically review and revise topic guides over the course of interviewing and analysis to make sure important, yet previously unanticipated issues are explored.

Interviewing will be conducted by an experienced qualitative researcher who will ensure interviews are conversational and responsive to participants. The qualitative researcher will establish contact with the family, send participant information sheet(s), offer more information about doing an interview and provisionally arrange an interview.

Participatory techniques will be used so that interviews are engaging for participants, especially children and young people. We will ask families if we can hold interviews with young children in-person where possible, although families will always have the choice of being interviewed via video-conference (using Teams, with the voice recording made via dictaphone) or telephone if they prefer. Where children are aged 8-15 years, we will aim to interview the child as well as his/her parents. While our preference is usually to hold separate interviews with children/young people and parents (e.g. to avoid either party being inhibited by the other), we will discuss this with participants and interview children and parents together or separately, according to their preferences. As it can be challenging to engage young children in interviews even when participatory techniques are used (13), we will seek the advice of parents, particularly regarding interviewing 6-7 year olds; where children are aged 5 years or younger we will interview only the parents. We will aim to interview families within a maximum of 3 months of investigation for BJI (i.e. within 3 months of enrolment into the main study).

We will conduct focus group interviews with a purposive sample of approximately 12 health professionals (2 groups each with 6 participants), although we will aim to accommodate those who prefer to take part in individual interviews. In sampling health professionals, we will seek diversity in terms of study site and role (e.g. to include ED practitioners, radiologists, paediatricians, and orthopaedic surgeons). We will involve a wide range of health professionals, such as radiographers, ultrasonographers, nurses, play specialists and physiotherapists, whose views will be important to capture in the qualitative study. While topic guides for the health professionals' focus groups will also be co-developed with our PPI panel, we anticipate exploring their views and experiences of: the diagnostic pathway; communicating with families about clinical investigations and diagnosis; care of patients during imaging and investigations, including pain and behavioural management; ways to improve the diagnostic process and avoid 'pinch-points' and delays; preferences and trade-offs around choice of USS v MRI imaging. Focus groups will be conducted via video conference and facilitated by an experienced qualitative researcher and a member of the research team who has clinical experience.

Consent/assent for qualitative interviews with parents and children will be sought by the qualitative researcher prior to starting the interviews. For in-person interviews, families will be given the option of signing a paper consent and assent form or to consent online. To consent online, the qualitative researcher will request an email address for the parent / guardian to which an e-consent link will be sent. For telephone/video conference interviews, online consent and assent will be sought from families but, if this is not possible, consent/assent will be sought verbally. This will involve the researcher reading each aspect of a remote consent form to participants. When the participant provides verbal consent, the researcher will initial next to each box on the remote consent form, and will add the participant's name, their own name, date, and signature. The researcher will post/email a copy of the form to the family, posting via recorded delivery, marking the envelope as confidential. Consent/assent, transcripts, paper, and electronic records will be retained for auditing purposes and stored for up to 5 years at the University of Liverpool.

For focus groups with health professionals, the qualitative researcher will contact health professionals who express an interest in participating, send the relevant information sheet, offer more information about the focus groups, and provisionally arrange a time for the focus group discussion. The consent of health professionals will be sought prior to focus groups through an e-consent process.

### 9.9 Sample Handling

The study does not involve the collection of samples.

### 9.10 Early Discontinuation/Withdrawal of Participants

During the prospective cohort study a participant may choose to withdraw at any time. However, as the study will not affect the clinical pathway of the patients, we anticipate a high rate of recruitment and low attrition.

Potential reasons for withdrawal may include but are not limited to:

- Inability to comply with study procedures
- Participant decision

Participants may choose to withdraw from the study prior to the 3-month follow-up call but may remain on study follow-up based on the medical record.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely.

According to the design of the study, participants may have the following three options for withdrawal;

1) Participants may withdraw from active follow-up and further communication but allow the study team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care, i.e. medical records, medical imaging, laboratory results and disease progression data etc.

2) Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.

3) Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal, with the exception of data that has already been analysed/recordings that

have already been transcribed. All other data already collected would not be used in the final study analysis.

We will continue recruiting until we have the necessary numbers to achieve the objectives of the study.

### 9.11 Definition of End of Study

The end of study is defined as the point at which all the study data has been entered and queries resolved.

## 10 SAFETY REPORTING

The study does not involve an intervention and will not affect the clinical pathway of the patients; therefore safety reporting is not applicable.

## 11 STATISTICS AND ANALYSIS

### 11.1 Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be available from the time that the first participant is recruited. The SAP will be finalised before any analysis takes place.

### 11.2 Description of the Statistical Methods

For each index test (USS and MRI), the results will be compared to the reference standard in all patients with available data and cross tabulations reported (including indeterminate results). The sensitivity, specificity, negative predictive value, positive predictive value, likelihood ratio and diagnostic odds ratios will be reported (with 95% confidence intervals) overall, as well as separately for patients aged 5 years and older versus those 4 years and younger. This choice was based on our feasibility study finding that most children under the age of 5 years would require sedation or anaesthesia for MRI, whilst those 5 years of age and above would not.

<u>Clinical prediction model development:</u>

In the retrospective cohort, there will be 1440 children and 107 BJI events for children aged 4 years and younger (Model 1) and 4560 children with 348 events for children aged 5 years and older (Model 2). This is based on the estimate that 24% of children with confirmed BJI disease will be under 5 years old (NHS Digital 2017/18), To minimise the risk of overfitting and to precisely estimate the overall outcome risk, 10 predictors can be examined for inclusion in Model 1 and 32 predictors can be examined for inclusion in Model 2. This is based on a conservative estimate of the anticipated R2 of 0.15*max($R^2$) (max $R^2$=0.41 for an anticipated outcome prevalence of 0.074).

Both models will be fitted using logistic regression. Candidate predictors will be chosen based on clinical plausibility and from a review of the literature. We will select variables for inclusion in the model using least angle selection and shrinkage operator (LASSO) penalties. Continuous predictors will be examined for nonlinear relationship with confirmed BJI using fractional polynomials. Missing data will be inevitable with not all patients providing data on all predictors of interest. To avoid excluding patients when developing and validating our models, we will use multiple imputation to impute missing values, under a missing at random assumption. Identifying the true underlying missing data mechanism from the available

data is rarely possible. Assumptions need to be made on the plausible mechanism, and approaches needed to be used. Under a missing completely at random mechanism (MCAR), the missingness mechanism does not depend on unobserved (unseen) data. Carrying out a complete case analysis will produce unbiased estimates (but with a loss precision if full data are observed). Under the missing at random (MAR) assumption, the missingness after conditioning on the observed data does not depend on the unobserved (unseen) data. Under this approach, we can apply approaches such as multiple imputation, by fitting a joint model to the observed data and impute the missing data, taking account of the uncertainty in the estimated parameters of this joint model. We feel this, MAR, approach makes a less strong and more realistic assumption than the MCAR approach. The MAR imputation model will include all variables considered for the multivariable model building, the outcome, and any auxiliary variables (such as centre specific covariates) that will help explain the missingness. The assumption of a missing not at random (MNAR) approach, whilst not implausible, is considerably more complex to investigate – there is a dearth of research investigating MNAR in the context of prediction model research. We will nevertheless explore whether the MAR assumption holds by comparing the imputed values (after accounting for the observed values) and the missing values to identify if there are any systematic differences to suggest a MNAR assumption. We will further consider the mechanisms of missing data and perform sensitivity analysis if appropriate. Full details will be included in the statistical analysis plan and will be guided by recent work in this area.(15)

The internal validity of the final models will also be assessed using bootstrap resampling to adjust for over-optimism in the estimation of model performance. The internal validation will quantify and be used to adjust the performance measures for any optimism. Heterogeneity in model performance will be explored over different centres using internal-external cross-validation.

The performance of the prediction model will be characterised by assessing calibration and discrimination. Calibration, which reflects how close the predictions from the model are to the observed outcome frequencies will be assessed graphically, using a calibration plot, plotting observed outcomes against predictions using smoothing techniques. The plot will also be supplemented with results for individuals grouped by similar probabilities (tenths) comparing the mean predicted probability to the mean observed outcome. Calibration will also be quantified by calculating the calibration slope and intercept. The discrimination of the prediction models will be summarised with the concordance index (equivalent to the Area Under Receiver Operating Characteristic curve) with 95% confidence intervals.

Prospective external validation: the prospective cohort of 1500 children will provide approximately 111 confirmed BJI cases, which is more than the recommended 100 events (14) to evaluate the discrimination and the calibration of the developed model in an independent sample (external validation).

The performance of the two models will also be assessed in the prospective external validation cohort. Discrimination and calibration will be evaluated. Any miscalibration identified during this phase will be addressed by recalibrating the model (e.g., re-estimating the intercept or updating the regression coefficients by a common factor) (16). During the external validation the incremental value of adding USS and MRI to both models will be examined.

An important goal of a prediction model is to classify patients into risk groups. Both models will produce a risk score (probability) for each patient, based on their own predictor values. We will then identify a range

of cut-off values to decide when the risk is high (such that we predict poor outcome) and when it is low (such that we predict a good outcome). The cut-off value (or range of), will be examined using decision curve analysis, which calculates the net benefit of using the model (compared to not using the model). The net benefit of a model is the difference between the proportion of true positives and the proportion of false positives, weighted by the odds of the selected threshold for high-risk designation.

### 11.3 Sample Size Determination.

Retrospective study

For the primary objective, we propose to collect retrospective data for an estimated sample of 6000 children with suspected BJI. Based on our feasibility data, approximately 444 (7.4%) would have confirmed BJI and 5556 (92.6%) would be disease-free. This would provide data for approximately 351 (79%) MRI disease cases and 408 (92%) USS disease cases, allowing MRI sensitivity to be estimated to within 2.9 percentage points of 91.5% and USS sensitivity to be estimated to within 4.3 percentage points of 74.1% with 95% confidence. This would also provide 611 (11%) MRI and 1000 (18%) USS disease-free cases, allowing specificity to be estimated to within 3.7 percentage points of 67% for MRI and within 3.1 percentage points of 47% for USS with 95% confidence interval.

Prospective study

In an external validation study, it is recommended that there are at least 100 events (14) to evaluate the discrimination and the calibration of the developed model in an independent sample. The DINOSAUR study (2) recruited at least one child admitted with suspected BJI from each centre every month. We therefore plan to recruit 111 patients from at least 30 centres over 12 months.

### 11.4 Analysis populations

All eligible children enrolled in the study will be included in the analysis. Cases with uncertain diagnosis (expected as less than 5% on the basis of the feasibility study) will be excluded from the initial analysis and will be considered separately.

### 11.5 Decision points

Successful delivery of the study will depend on achieving the target sample size for both the retrospective and prospective components. The SMG (Study Management Group) will review monthly recruitment figures for both components and compare these against target figures to identify any appropriate intervention as early as possible. An independent Study Steering Committee (SSC) will also provide regular review and monitor progress against targets for the project.

### 11.6 Stopping rules

We have not pre-defined any stopping rules: we seek to recruit 111 children with confirmed BJI diagnosis from through the prospective study, which appears entirely feasible considering the numbers discussed above. As the study will not affect the clinical pathway of the patients, we anticipate a high rate of recruitment and low attrition.

### 11.7 The Level of Statistical Significance

Not applicable.

### 11.8 Procedure for Accounting for Missing, Unused, and Spurious Data.

Please refer to 11.2 above.

### 11.9 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Please see 11.2 above.

### 11.10 Qualitative data analysis

Interviews and focus groups will be audio-recorded, transcribed, checked and pseudonymised before being analysed. Analysis of transcripts will be informed by reflexive thematic approaches (15, 16) and by writings on quality in qualitative research (17). Coding of transcripts will be assisted by QSR NVivo software. The transcription agency used will be on the InfoSec third party register. A confidentiality agreement with the transcription agency will be in place and secure means will be used to transfer the recordings to the agency. The qualitative team will undertake the analysis, meeting regularly to review transcripts and compare coding and interpretations. The PPI panel, and the wider PIC Bone research team, will be involved in discussions of the developing analysis to ensure that data interpretation is informed by their perspectives. We will also link closely with the PPI panel and wider PIC Bone team in disseminating the qualitative findings to key stakeholders (including patients/families, clinicians, professional societies and the wider public). We will seek the advice of stakeholders to help make sure NHS clinical practice for the investigation and imaging of children with suspected BJI incorporates the perspectives of children/young people and their families.

### 11.11 Health Economics Analysis

The study will not include Health Economics.

## 12 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management/Monitoring Plan.

### 12.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and all relevant investigations described above will be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, radiology, correspondence and qualitative interview and focus group audio recording. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

### 12.2 Access to Data

Direct access will be granted to authorised representatives from the sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

### 12.3 Data Recording and Record Keeping

Clinical data will be entered into the database (REDCap) by the designated team members working in each recruitment site. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Staff in the central study office will work closely with local team members to ensure that the data are as complete and accurate as possible. Each site will maintain a master list of study code number assigned to patients against their identity in order to be able to resolve queries and check data quality. Extensive range and consistency checks will further enhance the quality of the data.

Any paper documents will be stored safely in confidential conditions (i.e., locked cabinets) both at local hospital sites and the central study office. Patients' data will be recorded on a secure online database called REDCap which is frequently utilised to capture data for clinical research. Direct access will be granted to authorised representatives from the sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations. Personal identifiable data will be kept for 12 months following the end of the study unless the parent/carer has consented to long term contact (up to 16 years) for future research (see clause 7 of consent form). Anonymised research data will be archived for 5 years following the end of the study.

During the prospective study we will seek consent from participants and their family for future contact. We will request the details of their preferred contact method, i.e. email address or telephone number. This, along with the patient and parent/guardian's name, date of birth and NHS number (where applicable). All data will be entered into REDCap and will be encrypted in transit between the client and server. All electronic patient-identifiable information, including electronic consent forms, will be held on a server located in an access-controlled server room at the University of Oxford. The data will be entered into a GCP compliant data collection system and stored in a database on the secure server, accessible only to members of the research team based on their role within the study. The database and server are backed up to a secure location on a regular basis. The consent form indicating the patient and parent/guardian's preferences will be retained at the local site. Consent for future contact will allow for assessment of any long-term effects of BJI on bone growth and degenerative arthritis. Any studies involving long-term follow-up will seek separate funding and ethical approval and will be reported at a later time-point, separate to the final report/monograph to the funder.

**Qualitative Research Study**

Accuro Transcription Solutions Ltd. (hence forth called 'Accuro') will transcribe audio recordings arising from the interviews with patients and their families, and from interviews and focus groups with health professionals. The audio recordings shared with Accuro will not contain any identifiable information; only a study code assigned by the Qualitative Research Team. Audio recordings are transferred by a secure online portal. This team have a Terms of Service document with Accuro, which serves as a Data Sharing Agreement. Accuro has been transcribing confidential recordings for over 20 years. Their software has been developed around the stringent encryption standards required by the NHS. They are certified to ISO27001, the internal standard governing data security. They are visited annually by external auditors who review every part of their transcription, operational, and technical processes. They are registered

with the Information Commissioner's Office and have an inhouse compliance team who are responsible for monitoring adherence to UK GDPR regulations.

Interview transcripts and anonymised data will be archived at the University of Oxford and the University of Liverpool jointly for 5 years from completion of the study. This data will be securely transferred between the Universities of Oxford and Liverpool using secure file-drop systems.

At the University of Liverpool, the only personal data that will be retained will be the contact details for each formally interviewed participant, child's age in whole years, together with their diagnosis (positive or negative for infection). Access will be managed by researcher carrying out the interviews and only named members of the research study team at the University of Liverpool will have access to these. This information will be encrypted and will be stored on the University of Liverpool's project specific Research FileStore allocation – on a secure drive.

Members of the research team at the University of Liverpool and the University of Oxford will have access to anonymised interview transcripts and other data such as documentation for analytical purposes. Quotations and recordings from interviews used in reports and papers will be anonymised by using study ID numbers.

**Use of SMS Works messaging service**

The parents/guardians of participants are to be contacted at 3-months post-presentation to complete a survey. One of the methods of contacting the parents/guardians is via SMS message. The PIC Bone study will use a 3rd party called 'The SMS Works' to send SMS messages on behalf of the study management team. They are a University of Oxford approved third party service provider to send text messages to parents of patients on our behalf. All our third-party service providers are based in the UK and are required to take appropriate security measures to protect your data in line with our policies and in line with GDPR. We do not allow them to use your data for their own purposes. We permit them to process your data only for specified purposes and in accordance with our instructions and we ask that they destroy your data no longer than 60 days after us providing it to them.

The SMS Works provides an email to SMS service which is used in this study. An email is automatically sent by the prospective clinical database to an SMS Works email address. This email is converted into an SMS message with a link to the survey and is sent to the parent/guardian. Email messages received by the SMS Works are deleted as soon as the SMS message is sent. Records of the SMS messages are retained by the SMS Works for 60 days in the form of delivery reports before being deleted. Personal data held by the SMS Works is the participant's name and parent/guardian's mobile phone number, as well as implied participation in the PIC Bone study.

The SMS Works Ltd uses cloud providers to host its data (MongoDb Atlas, backed by Amazon Web Services). Database records that match deletion criteria set by the PIC Bone team are deleted from live database storage volumes by application logic. The cloud backup policy ensures that when backups are deleted, that data becomes unrecoverable after 24 hours. AWS decommissions media using techniques detailed in NIST 800-88. As The SMS Works Ltd does not operate it's own physical media for customer data storage it does not have to adhere to any standards internally.

## 13 QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

### 13.1 Risk Assessment and Study monitoring

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study. Regular monitoring will be performed according to the study specific Data Management/Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Data Management/Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

### 13.2 Study Committees

The study will be supervised by the Study Management Group (SMG) comprising grant holders and representatives from the SITU Trial Office. The SMG will meet at least monthly within the first and last six months of the trial and every two months in between.

The Study Steering Committee (SSC) will be set up and run in accordance with their Charter. All members have to sign to agree to the conditions of the Charter before sitting on a committee.

## 14 PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

## 15 SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

## 16 ETHICAL AND REGULATORY CONSIDERATIONS

### 16.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

### 16.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

### 16.3 Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and associated advertising materials will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.
The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

## 16.4 Other Ethical Considerations

### 16.4.1 Consenting children and parents / guardians

This study will require the participation of children (aged 15 years and under). Consent will be obtained from the parents/legal guardians of the children for participation in the study. Information for parents/guardians will give guidance to ensure that they understand the nature of the study and what would be required of them and their children in terms of follow up. Whilst consent is not obtained from the children, age-appropriate information sheets will actively involve the children in the study process. We will seek assent from all children whom the clinical team believe is competent to understand the study process, which we imagine will be the majority of children from 8 years old. These include an information portal/sheet for those aged 7 and under, another for 8-11-year-olds and a third for 12-15-year-olds. The portal/sheet for aged 8 and under has modified wording regarding study withdrawal to ensure that patients don't refuse their standard clinical treatment. Parents/guardians will have a separate information portal/sheet.

If the child actively declines participation their wishes will be respected and we will not include them in the study.

### 16.4.2 Collection of anonymised routine clinical data

The retrospective cohort involves the collection of diagnostic and treatment data to inform an evaluation of current practices not a collection of data to assess individual diagnostic and treatment effects. UK Obstetric Surveillance System (UKOSS), British Paediatric Surveillance Unit (BPSU), British Orthopaedic Surveillance Study (BOSS), British Association of Paediatric Surgeons-Congenital Anomalies Surveillance System (BAPS-CASS) and Cerebral Palsy in the British Orthopaedic Surgery Surveillance Study (CPinBOSS) have employed similar methodology and obtained relevant approvals to allow data collection without individual patient consent. Seeking consent may reduce case ascertainment and introduce selection bias, i.e. certain groups or types of individuals might be more likely to refuse consent. To avoid bias, UKOSS surveillance studies, and those undertaken by the BPSU are undertaken without seeking individual consent and use limited identifiable data to protect confidentiality (18, 19).

The retrospective cohort within this project will collect anonymous data only. There are thus no individual participants, no potential for harm to participants, or incentives to participants. Inclusion of children's data in the study will not affect post-study access to interventions, care, or benefits. The harmonised arrangement for the governance of research ethics committees (GAfREC) has judged that the use of anonymised information in this way is acceptable without requiring patient consent (17). Studies using very similar methodology UKOSS and the BPSU have successfully sought ethical approval (18, 19).

No further study-specific ethical issues are anticipated. The Investigator will ensure that this study is conducted in accordance with relevant regulations and with the principles of the Declaration of Helsinki and Good Clinical Practice.

### 16.5 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, sponsor, and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

### 16.6 Transparency in Research

The study will be included on the ISRCTN (International Standard Randomised Controlled Trial Number) registry.

The study website will be updated with study findings and the URL/QR code for the website will be provided on the participant information sheets. When results become available, an email or text will also be sent to each participant with the URL to access the website.

### 16.7 Participant Confidentiality

The study will comply with the United Kingdom General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of patient details required to facilitate the three-month follow-up calls. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

### 16.8 Expenses and Benefits

The study does not involve any visits additional to normal care therefore reimbursement for additional travel will not be required.

## 17 FINANCE AND INSURANCE

### 17.1 Funding

The study is funded by the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) Programme (NIHR134125). The Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences at the University of Oxford will manage the finances and budget.

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

### 17.2 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

## 18 PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the

NIHR HTA programme. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

Contribution from team members who participate in the study at a site level will be considered the study management team to be members of the PIC Bone collaborative. They will be citable but not named authors.

## 19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable.

## 20 ARCHIVING

All anonymised data will be archived according to University of Oxford Clinical Trials and Research Governance Standard Operating Procedures and departmental contracts. These stipulate data related to the study will be archived for at least 5 years after the study has ended.

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18. UKOSS website: United Kingdom Obstetric Surveillance Study. University of Oxford.
19. BAPS-CASS: British Association of Paediatric Surgeons-Congenital Anomaly Surveillance System.

# 22 Appendix A:

## 22.1 Reference Standards for BJI

A. Definitive Diagnosis of BJI (at least any ONE of the following):

Positive histopathology sample indicative of infection from relevant tissue/fluid biopsy sample or surgical bone/joint specimen OR
Positive microbiology joint aspirate (bacterial growth indicating proven infection, positive Gram stain, pus cells combined with macroscopic appearance of pus) OR
Positive PCR joint aspirate with proven infection OR
Positive blood culture with no other source of infection AND subsequent localising signs on imaging OR
Joint aspirate >50,000 WBC OR
Evidence of osteomyelitis on two imaging modalities or confirmatory changes on follow-up imaging.

B. Uncertain Group

Children with negative or equivocal diagnostic investigations, who recovered following more than 24 hours of antibiotic treatment will be considered as a separate "uncertain" group. Less than 24 hours of treatment dose antibiotics or the use of long-term prophylactic antibiotics will be considered as 'no' antibiotic use, as neither could effectively treat an infection of bone or joint.

C. Definitive exclusion of BJI diagnosis:

Clinical resolution of symptoms without ANY antibiotic treatment by 3 months. Less than 24 hours of treatment dose antibiotics or the use of long-term prophylactic antibiotics will be considered as 'no' antibiotic use.
OR confirmation of an alternative diagnosis to explain symptoms subsequently established, even if treatment dose antibiotics were administered.

MRI and USS will be requested as per the usual practice of the treating clinician without any technical constraints. Timing of investigations will be recorded to determine where in the pathway the technologies are applied. The MRI and USS reports issued by the treating radiologist will be collected to document the suggested differential diagnoses based on the imaging. The radiologist's seniority will be recorded to assess any effect on diagnostic accuracy.

## 22.2 Imaging Report Classification

The diagnostic outcome of the imaging was determined from the respective radiologists reports and classified as normal, inconclusive, or abnormal (where abnormal was indicative of infection). Criteria detailed below:

1. For MRI
    a. Normal MRI – include normal anatomy and those MRIs which were diagnostic of another condition (i.e. not infective).
    b. Inconclusive MRI – some abnormal findings but not a definitive diagnosis of infection.
    c. Abnormal MRI – changes diagnostic of BJI.

2. For USS
    a. Normal USS – no abnormality detected or features of another condition
    b. Inconclusive USS – small effusion or no drainable-effusion
    c. Abnormal USS – effusions with a diagnostic aspirate (BJI confirmed)

## 23 APPENDIX D: AMENDMENT HISTORY

| Amendment No. | Protocol Version No. | Date issued | Author(s) of changes | Details of Changes made |
|---|---|---|---|---|
| Substantial amendment 1 | V2.0 | 06Feb2024 | Anjali Shah<br>Nicholas Magrane<br>Marie-Caroline Nogaro<br>Tim Theologis | Update Greg Firth's affiliation.<br>Update study dates given 4-month recruitment extension given by NIHR.<br>Clarification of inclusion and exclusion criteria to ensure inclusion of all children with BJI in their differential diagnosis, even if the suspicion of infection is remote.<br>In Section 9.1.1 add 'transient synovitis' to the list of key words for patients to be included.<br>In Section 9.1.2 add information on the new patient poster.<br>In Section 9.2 provide information on the counter-signed e-Consent form being emailed to the participant.<br>Amend Section 9.2 & 12.3 to say that age of child in whole years and diagnosis of BJI or not will be given to the qualitative research team.<br>Amend Section 9.3 to replace 'ED' with 'hospital.'<br>Amend Section 9.6 to specify dates for the Retrospective study.<br>In Section 9.6.3 & Appendix A clarify information needed from microscopy for positive diagnosis.<br>Amend Section 9.7 with updated flowchart.<br>In Section 12.3 provide information on SMS Works and Accuro Transcription Solutions Ltd. |