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The British OsteoNEcrosis Study (BONES): A prospective cohort study to examine the natural history of osteonecrosis in older children, teenagers and young adults with acute lymphoblastic leukaemia and lymphoblastic lymphoma

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Title: The **B**ritish **O**steo**NE**crosis **S**tudy (BONES): A prospective cohort study to examine the natural history of osteonecrosis in older children, teenagers and young adults with acute lymphoblastic leukaemia and lymphoblastic lymphoma

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Abstract:

Introduction

Osteonecrosis is a well-recognised treatment related morbidity risk in patients diagnosed with acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL), with a high rate of affected patients requiring surgical intervention. In this population osteonecrosis is most common in patients aged 10 to 20 years at diagnosis, but few other risk factors have been universally identified. Patients may have asymptomatic changes on imaging studies that spontaneously regress, and little is known about the natural history of osteonecrotic changes seen. The main aim of the British OsteoNEcrosis Study (BONES) is to determine:

- The incidence of symptomatic and asymptomatic osteonecrosis in survivors of ALL diagnosed aged 10-24 years or LBL in the UK at different time points in their treatment
- Risk factors for progression and the development of symptomatic osteonecrosis in this population
- Specific radiological features that predict for either progression or regression in those with asymptomatic osteonecrosis

Methods and analysis

BONES is a prospective, longitudinal cohort study based at Principal Treatment Centres around the UK. Participants are patients diagnosed aged 10- 24 years with ALL or LBL under standard criteria. Assessment for osteonecrosis will be within 4 weeks of diagnosis, at the end of delayed intensification, and 1, 2 and 3 years after start of maintenance therapy. Assessment will consist of magnetic resonance imaging (MRI) scans of the lower limbs and physiotherapy assessment. Clinical and biochemical data will be collected at each of the time-points. Bone mineral density data (lumbar spine, total body less head) and vertebral fracture assessment using dual energy X-ray absorptiometry (DXA) of patients will be collected at diagnosis and annually for 3 years after diagnosis of malignancy.

Ethics

Ethical approval has been obtained through the Yorkshire and Humber Sheffield Research Ethics Committee (REC reference number: 16/YH/0206).

Trial registration number: NCT02598401

Date of registration: 05/11/2015

Article summary

Osteonecrosis is a potentially debilitating complication of treatment for ALL and LBL. This paper describes the protocol for a novel study to investigate how potential osteonecrotic changes on imaging

evolve during treatment, and risk factors for their evolution. The results of this study will be essential in informing future studies regarding potential interventions for patients at highest risk.

Strengths and limitations of this study

- This study will be the first UK prospective study to obtain MR imaging within 4 weeks of diagnosis of ALL, with sequential imaging at 4 further time-points to assess progression or regression of osteonecrotic lesions.
- This study targets the most vulnerable patient population, those aged 10-24, who are at highest risk of development of symptomatic osteonecrosis. A greater understanding of the pathophysiology in this specific patient group should enable future targeting of specific therapies for patients who develop osteonecrosis.
- It will simultaneously assess multiple domains (radiological information, clinical data, information from a physiotherapy assessment and biochemical results) to correlate physical signs, symptoms and biological markers with MRI changes.
- The results of this study will contribute to identification of factors that may explain the differences in progression of osteonecrotic lesions in a cohort of patients during and after treatment for ALL or LBL.
- A limitation of this study is the anticipated small sample size, which is due to the rarity of ALL and LBL in patients over 10 years of age

Introduction:

Survival from acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL) has steadily increased over the last 40 years so that the expected cure rate is now greater than 90% in children and young people presenting with ALL[1]. This progress shifts the entire treatment paradigm so that the goal moves beyond cure to returning the young person to a normal life. The biggest barrier to this is the burden of treatment associated toxicity, and attention internationally is now beginning to focus on this issue. Osteonecrosis (previously also referred to as avascular necrosis, ischaemic necrosis and aseptic necrosis) can be a devastating complication of treatment in older children and teenagers treated for ALL, and can cause significant long term morbidity[2].

However, despite increasing concern about osteonecrosis, our understanding is limited. Historically, information about osteonecrosis has not been well captured in previous studies of ALL, which partly reflects lack of good definitions and piecemeal retrospective reporting.

Osteonecrosis occurs when there is bone ischaemia and infarction caused by temporary or permanent disruption to the blood supply and in ALL typically affects the femoral head, humeral head, knee, shoulder and ankles[2]. It is mostly an iatrogenic complication that has been attributed to increased use of glucocorticoids in treatment of ALL[3] , although asparaginase[4], high dose methotrexate[5] and cyclophosphamide[6] have also been implicated. The cumulative dose of received glucocorticoids in patients with ALL has been shown to correlate with the risk of osteonecrosis[7], but there is no clear increase in osteonecrotic risk with the administration of either prednisolone or dexamethasone[7-10]. Development of osteonecrosis appears to be multifactorial, but is seen more commonly in patients as survival improves and high dose steroids have become embedded in treatment regimens.

Glucocorticoids predispose to the development of osteonecrosis in a number of ways, with proposed aetiologies including:

- Creation of a hypercoagulable state with endothelial cell apoptosis and development of microthrombi;
- Suppression of osteoblasts and apoptosis of osteocytes impairing the bone repair process;
- Stimulation of intramedullary lipocyte proliferation and hypertrophy resulting in increased intraosseous pressure.

These factors combine to compromise blood circulation to the bone leading to cell death in a self-perpetuating cycle[11].

Interosseous fat emboli with intravascular coagulation and osteonecrosis has been described[12], with an overload of subchondral fat emboli, hypercoagulability, stasis and endothelial damage by free fatty acids hypothesised to cause end organ damage. Glucocorticoids causing dyslipidaemia may promote the formation of fat emboli, although fat emboli are also found in healthy bones which do not go on to develop osteonecrosis. The role of hypercoagulability is unclear. Some studies have shown procoagulant abnormalities in patients with osteonecrosis[13], but the common thrombophilias have not been identified as risk factors for osteonecrosis, indicating the multifactorial nature of the condition.

In one of the largest studies with prospective MRI screening to assess both symptomatic and asymptomatic ON, the cumulative incidence of ON involving the epiphysis or metaphysis of at least one hip was 17.1% ±1.8% after early screening (1 year) and 21.7%±1.9% after completion of therapy (4 years)[14]. By the end of therapy, extensive femoral head ON affecting ≥30% of the epiphyseal surface had developed in 6.5%±1.1% of all patients, and 24%±4.4% of those aged over 10 years[14].

There are many more reports which rely on proactive reporting to the study centre, with no prospective screening for asymptomatic osteonecrosis, and as expected these tend to give a far lower prevalence of ON, ranging from 0.67% [8] to 15% [15].

Age has consistently been identified as the most significant risk factor for development of symptomatic osteonecrosis, with the greatest incidence of osteonecrosis in patients between 10 and 20 years of age [2, 15-19] at diagnosis of ALL, a time of rapid skeletal growth. Other risk factors such as sex and ethnicity have not been consistently replicated.

Various genetic risk factors for the development of osteonecrosis have been identified. Genome-wide association studies indicate the glutamate receptor pathway to be of crucial importance, and single nucleotide polymorphisms (SNPs) in adipogenesis pathways and in enhancers active in mesenchymal stem cells were also significantly associated with osteonecrosis development[20, 21]. Glucocorticoid receptor binding sites have also been implicated in development of osteonecrosis[22].

It is recognised that a significant percentage of changes on imaging studies identified as osteonecrosis may regress[16], although the reasons for this are not understood. It is possible that some radiological changes interpreted as representing steroid associated osteonecrosis are in fact changes which have been present at diagnosis and which are a consequence of the original leukaemia.

The current most widely used radiological classifications use a multi-modal approach combining scores for x-ray, magnetic resonance imaging (MRI) and in some cases bone scan findings. They were

developed specifically for changes in the femoral head, over 20 years ago and in an entirely different patient population. Further classifications systems have been developed with no prognostic validation. This study will provide the data needed to develop and provide prognostic validation of a radiological classification system which correlates with clinical status, as well as provide greater understanding of the natural history of bone lesions in patients being treated for ALL or LBL. Only once this is done can meaningful intervention studies be initiated.

Current treatment for patients with ALL or lymphoblastic lymphoma

The majority of young people currently diagnosed with ALL or LBL consent to be part of the national trial, UKALL2011 (ISRCTN64515327, Eudract 2010-020924-22), and current treatment for patients aged between 10 and 25 at diagnosis of ALL or LBL is described in figure 1. A list of all chemotherapeutic agents are available in supplementary file 1. If patients do not consent to participate in UKALL2011 they will receive the same treatment as those on the trial, and at the point of randomisation they will receive standard interim or Capizzi interim maintenance, depending on their risk stratification. At the next randomisation point they will receive maintenance therapy with vincristine/dexamethasone pulses and intrathecal methotrexate.

Post induction treatment is determined by minimal residual disease (MRD) in ALL patients, or tumour volume assessment in patients with LBL. Patients with no MRD results are assessed by morphology (% of blasts at day 8 of induction).

If a patient has been randomised to high dose methotrexate therapy, they will have no subsequent intrathecal methotrexate in maintenance but can be randomised to either pulses or no pulses. An exception to this is that patients with T-cell ALL with white cell count >100 x 10^9 cells/l at diagnosis have an additional 6 doses of intrathecal methotrexate in maintenance. Pulses consist of vincristine and dexamethasone. If they have been randomised to either standard or Capizzi interim maintenance they will be randomised to maintenance therapy with or without pulses, and all patients will receive intrathecal methotrexate.

Treatment will last 2 years from the start of interim maintenance for female patients, and 3 years from the start of interim maintenance for male patients. There are some treatment modifications for patients with Down's syndrome to reduce toxicity.

Objectives

The objective is to establish a prospective, multi-centre study for older children, teenagers and young adults which can address the following questions:

- What is the incidence of symptomatic and asymptomatic osteonecrosis in older children, teenagers and young adults being treated for ALL or LBL in the UK at different time points in their treatment?
- What are the risk factors for progression and the development of symptomatic osteonecrosis in this population?

- Are there specific radiological features that predict for either progression or regression in those with asymptomatic osteonecrosis?

The study also aims to

- Evaluate functional ability as measured by the childhood Health Assessment Questionnaire (c-HAQ) and physiotherapy assessment and explore the correlation of this with MRI findings, to start to establish validity of use in patients with osteonecrosis.

- Evaluate changes in bone mineral density and vertebral fracture incidence during treatment for ALL or LBL

Methods and analysis

The SPIRIT checklist was used as a basis for structuring this report[23]. Details of the protocol, data collection forms, consent forms and patient information leaflets are available at http://childhealth.leeds.ac.uk/bones.html.

Study design

Multi-centre prospective longitudinal cohort study

Patient and public involvement

Patients and families undergoing treatment or who had completed treatment for ALL or LBL were involved in the study design and in literature developed for patient information by use of semi-structured interviews. Patients were not involved in the recruitment to and conduct of the study. Results will be disseminated to study participants via the BONES website.

Study setting

The BONES (British OsteNEcrosis Study) is conducted in Principal Treatment Centres and teenage and young adult centres for patients with cancer within the UK. It is currently open in Leeds Children's Hospital; St James's Hospital, Leeds; Birmingham Children's Hospital; and Southampton Children's Hospital. Additional centres, including Children's Hospital for Wales are in the research and development process.

Dates of study

The first site opened to recruitment on 10/04/2017. The most recent centre to join opened to recruitment on 22/03/2018. Additional sites are still in the process of opening the study. Recruitment is for a period of 2 years, or until a total of 50 patients are recruited.

Study population

Inclusion criteria: Children, teenagers or young adults between the age of 10 and 24 years 364 days (at the time of diagnosis) with a first diagnosis of ALL or LBL (TNHL or SmIg negative precursor B-NHL) diagnosed under standard criteria are eligible for BONES.

Exclusion criteria: Inability to have MRI scans of lower limbs

Recruitment target.

The recruitment target is 50 patients over a 2 year period, which is based on an anticipated participation of 75% of eligible cases. This is an observational study and there is therefore no relevant power calculation.

Study outcomes

Primary Outcome:

- Cumulative incidence of symptomatic and asymptomatic osteonecrosis in patients aged between 10 and < 25 years being treated for ALL or LBL in the UK at multiple time points in their treatment

Key Secondary Outcomes:

- Risk factors for progression and development of symptomatic osteonecrosis
- Specific radiological features that predict for either progression or regression in those with osteonecrosis
- Evaluation of functional ability as measured by Childhood Health Assessment Questionnaire (c-HAQ) and physiotherapy assessment and exploration of correlation of with radiological findings.
- Bone mineral density changes as measured by dual-energy X-ray absorptiometry (DXA) during treatment for ALL or LBL
- Prevalence and risk factors for development of vertebral fractures during treatment for ALL or LBL

Patient assessment

Irrespective of symptoms patients will be screened for osteonecrosis via prospective MRI of the hips, knees and ankles at the following time-points:

- Within 4 weeks of diagnosis
- At the end of delayed intensification (typically 6 to 8 months after start of ALL treatment)
- One year after the start of maintenance
- Two years after the start of maintenance
- Three years after the start of maintenance

Patients will also have a physiotherapy assessment at each of these time points, including subjective and objective assessments, with collection of clinical and biochemical data.

Where facilities exist, DXA scans and vertebral fracture assessment will be performed at diagnosis and annually for 3 years after diagnosis.

MRI imaging

MRI of the lower limbs including hips, knees and ankles comprises of unenhanced coronal T1 weighted and STIR (short tau inversion recovery) images of 5mm (or less) slice thickness as a minimum protocol. Scanning parameters may vary slightly depending on available MR scanners in each participating centre.

Clinical and demographic data collection

Baseline demographic data collection includes the child's age, sex, ethnic background (White British; Asian; Black; Mixed; Other) postcode, height and weight at diagnosis. Clinical data are provided by the treating clinicians via a dedicated clinical report form, which includes information on pubertal status, highest white cell count prior to treatment, immunophenotype, cytogenetics and molecular results, along with presence or absence of hepatomegaly, splenomegaly, lymphadenopathy and bone pain at diagnosis.

At each of the time-points outlined above details regarding treatment regime, height, weight, phase of puberty, and diagnosis and management of symptomatic osteonecrosis is collected. Data on results of routine blood tests, including lipid profile, albumin, bone profile, PTH and vitamin D levels is also collected. Clinicians collecting these details are blinded to the study MRI reports.

Physiotherapy evaluation

The physiotherapy assessment consists of a paper questionnaire for completion by the participant, which includes information about activity levels, mobility, pain and the c-HAQ, alongside a physical assessment evaluating gait, range of movement and muscle power[24]. The c-HAQ assesses 3 outcome dimensions: disability, discomfort and pain, and is completed by self-report, requiring approximately 10-15 minutes to complete. It is most commonly used to assess health status and physical function in children with juvenile arthritis, for whom it is validated[24], but is also validated for use in children with chronic musculoskeletal pain[25], dermatomyositis[26] and systemic lupus erythematosus[27].

Bone mineral density and vertebral fracture assessment

Patients undergo DXA scans with vertebral fracture assessment with collection of the following measurements: posterior-anterior lumbar spine (L1-4) and total body less head (TBLH) areal bone mineral density (BMAD), and thoracic and lumbar vertebral fracture incidence.

A schema with BONES study procedures is presented in figure 2.

Data analysis plan

The report of this study will be prepared in accordance to guidelines set by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies[28]. Data will be collected and analysed in clinically relevant categories, whilst Chi-squared tests and multivariable logistic regression models will be used to determine differences between groups adjusting for a relevant set of confounders identified using causal inference methods[29]. Potential confounders that will be assessed include age, sex, ethnic group, socioeconomic status (Index of Multiple Deprivation, IMD), treatment arm, highest white cell count, immunophenotype, cytogenetics, phase of puberty, body mass index, lipids, albumin, presence of vertebral fractures, bone mineral density, bone ALP, PTH and vitamin D status. There will be descriptive analysis of MR imaging to determine imaging changes in relation to clinical symptoms and patterns of presentation.

A central review panel consisting of Paediatric Radiologists with an interest in paediatric musculoskeletal imaging will review each MRI. The grade of osteonecrosis will be assessed using a modified scoring system by reference using a study radiology *proforma*. DXA and vertebral fracture assessment results will also be reviewed centrally, with adjustments to bone mineral density using bone mineral adjusted density (BMAD) for the spine, and the height Z-score for TBLH[30]. The thoracic and lumbar vertebra are assessed (T4-L4 where possible), using the Genant semi-quantitative method[31].

Descriptive analysis will allow assessment of correlation of physiotherapy assessment with radiological results.

Missing observations

If data on some subjects are missing at some time points the entire subject history will not simply be excluded from analysis. The main patient characteristics will be described in terms of variable completeness by summarising the proportion of missing values. If numbers allow, levels of missing-ness will also be examined according to each recruiting centre. If the data are missing at rates higher than the expected attrition rate the following steps will be taken:

- If data regarding independent variables are missing but data for the corresponding dependent variables are present, we will do multiple imputations for the missing values
- If some data associated with a dependent variable are missing, such as some follow-up data, and the underlying mechanism is random, only the missing observations will be excluded.
- If some dependent variable data are missing and the underlying mechanism is non-random, we will estimate group effects according to methods proposed by Wu and Bailey[32] and Milliken and Johnson[33].

Violations of the missing-at-random assumption will be investigated by following established precedents in paediatric oncology studies.

Data management

All patients enrolled in the study are given a unique identifier. A Microsoft Access database has been developed to record and link all the socio-demographic and clinical data for a study participant with information from their radiology assessments. Data protection regulations at each centre will be complied with. Data will be submitted centrally via a secure NHS email address with all patient identifiers removed. At each hospital site local clinicians and physiotherapists will complete the relevant forms at each time-point, with forms anonymized locally prior to being returned to the central trial unit. Images of MRI scans are to be anonymised locally and placed onto CDs which are to be sent to the central trial unit. DXA scan images and reports are to be anonymised locally and sent to the central trial unit.

At present data is not published in a data repository.

The full protocol is available in supplementary file 2. Sample consent forms and patient information sheets are available as supplementary file 3.

Protocol amendments

All substantial protocol amendments will be agreed with the protocol contributors and require Research Ethics Committee approval. Modifications will be communicated to the relevant parties via the website, newsletters and e-mail.

Ethics and dissemination:

Ethical approval has been obtained through the Yorkshire and Humber Sheffield Research Ethics Committee (REC reference number: 16/YH/0206). NHS code of confidentiality and data protection will be adhered to. All data acquisition, storage and transmission will comply with the Data Protection Act 1998. The local clinical team will identify and provide age appropriate patient information sheets to potential participants. Written patient consent or assent will be obtained by the local clinical team, with parental consent obtained for patients under 16 years of age. The protocol document and data collection tools are available online (http://childhealth.leeds.ac.uk/bones.html). All substantial protocol contributors will be granted authorship of the final study report. There are no plans to use professional medical writers.

Collective results of the study will be published on the website, in peer-reviewed journals and presented at relevant conferences and via social media.

Trial registration number: NCT02598401. Date of registration: 04/11/2015

Acknowledgements: We thank the research teams involved in setting up the studies in all participating centres, and patients and families who helped develop the study protocol.

Figure legends:

Figure 1. UKALL 2011 trial schema for patients over the age of 10 (excluding patients with Down's Syndrome)

MRD: Minimal residual disease
BFM: Berlin-Frankfurt-Munich
SER: Slow early response (≥25% blasts at day 8 of induction)
RER: Rapid early response (<25% blasts at day 8 of induction)

Figure 2. Schema of BONES study procedures

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Authors' contributions:
NA, SK, BJ, RF, JK, EW and MV all contributed to develop the protocol, helped to write and review the manuscript and made the decision to submit the manuscript for publication.

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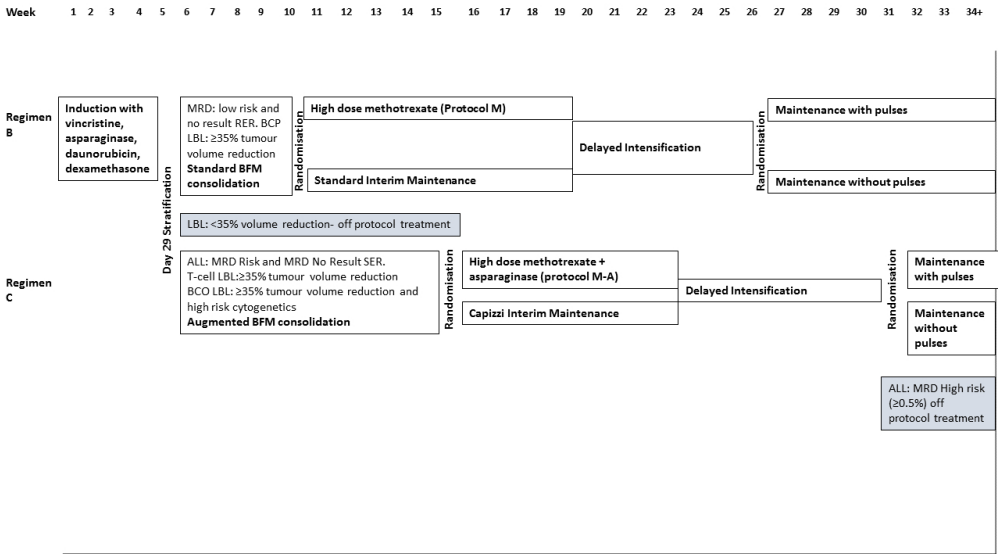

108x60mm (300 x 300 DPI)

	Within 4 weeks of diagnosis	Week 1-4	End of induction	End of delayed intensification	One year after diagnosis	One year after start of maintenance	Two years after diagnosis	Two years after start of maintenance	Three years after diagnosis	Three years after start of maintenance
Consent	◊									
MRI scan lower limbs		◊		◊		◊		◊		◊
Routine blood tests (LFTs, calcium, phosphate, cholesterol, triglycerides, HDL, LDL Vitamin D, PTH		◊	◊	◊		◊		◊		◊
Physiotherapy assessment including c-HAQ		◊		◊		◊		◊		◊
DXA scan with vertebral fracture assessment		◊			◊		◊		◊	
Clinician assessment		◊		◊		◊		◊		◊
End of induction form			◊							

108x60mm (300 x 300 DPI)

Chemotherapy agents used during treatment:

Induction:

- dexamethasone 6mg/m2/day orally for 28 days (maximum single dose 10mg/day)
- vincristine 1.5mg/m2 IV weekly for 2 weeks, starting on day 2 (maximum single dose 2mg)
- daunorubicin 25mg/m2 IV on days 2, 9, 16, 23
- pegaspargase 1000iu/m2 IM day 4 and 18
- methotrexate 12mg intrathecal on days 1, 8, 29
- mercaptopurine 60mg/m2/day orally from day 29 to day 28 of consolidation.

Standard BFM consolidation:

- cyclophosphamide 1000mg/m2 IV days 1 and 15
- cytarabine 75mg/m2/day IV or subcutaneous. 4 consecutive days in weeks 6,7,8,9
- mercaptopurine 60mg/m2/day orally until day 28 of consolidation
- methotrexate 12mg intrathecal days 1, 8, 15

Augmented BFM consolidation:

- cyclophosphamide 1000mg/m2 IV days 1, 29
- cytarabine 75mg/m2 IV or subcutaneous. 4 consecutive days in weeks 6,7,10 and 11
- mercaptopurine 60mg/m2/day for 21 days starting week 5 of induction, and again for 14 days on days 29-42
- vincristine 1.5mg/m2 IV days 16, 23, 44, 51 (maximum single dose 2mg)
- pegaspargase 1000 units/m2 intramuscular days 16, 44
- methotrexate 12mg intrathecal days 1, 8, 22

Standard interim maintenance:

- dexamethasone 6mg/m2/day orally days 1-5 and days 29-33
- vincristine 1.5mg/m2 IV day 1, 29 (maximum single dose 2mg)
- mercaptopurine 75mg/m2/day orally days 1056
- methotrexate 20mg/m2 orally once/week on week 11, 12, 14, 15, 16, 18, 19
- methotrexate 12mg intrathecal days 15, 43

Protocol M

- mercaptopurine 25mg/m2/day orally days 1-56
- methotrexate 5g/m2 IV days 8, 22, 36, 50
- folinic acid 15mg/m2 IV 42,48 and 54 hours after start of methotrexate infusion
- methotrexate 12mg intrathecal days 8, 22, 36, 50

Capizzi interim maintenance:

- vincristine 1.5mg/m2 IV days 2, 12, 22, 32, 42 (maximum single dose 2mg)
- methotrexate 100mg/m2 IV day 2. Escalating subsequent doses as tolerated on days 12, 22, 32, 42
- pegasparagase 1000 units/m2 IM days 3, 23
- methotrexate 12mg intrathecal day 1, 31

Protocol M-A:

- mercaptopurine 25mg/m2/day orally days 1-49
- methotrexate 5g/m2 IV days 1, 15, 29, 43
- folinic acid 15mg/m2 IV 42,48 and 54 hours after start of methotrexate infusion
- methotrexate 12mg intrathecal days 1, 15, 29, 43
- pegaspargase 1000 units/m2 IM days 2, 23

Delayed intensification:

- dexamethasone 10mg/m2/day orally for 7 days week 20 and 22
- vincristine 1.5mg/m2 IV days 2,9,16 (maximum single dose 2mg)
- doxorubicin 25mg/m2 IV days 2,9,16
- pegaspargase 1000iu/m2 IM day 4
- methotrexate 12mg intrathecal day 1
- cyclophosphamide 1000mg/m2 IV day 29
- mercaptopurine 60mg/m2/day orally day 29-42
- cytarabine 75mg/m2/day IV or subcutaneous. 4 consecutive days weeks 24,25

If delayed intensification is in regimen C the dexamethasone is given days 2-5 and 16-22, cytarabine is given in weeks 28 and 29, and vincristine given on days 2, 9, 16, 43 and 50. Intrathecal methotrexate is also given on days 29 and 36, and pegaspargase is also given on day 43.

Maintenance:

- mercaptopurine 75mg/m2/day orally throughout maintenance
- methotrexate 20mg/m2 orally days 1, 8, 22, 29, 36, 43, 50, 57, 64, 71, 78

If a patient has been randomised to pulses during maintenance they also receive:

- dexamethasone 6mg/m2/day orally days 1-5, 29-33, 57-61
- vincristine 1.5mg/m2 IV days 1, 29 and 57 (maximum single dose 2mg)

If patient was randomised to standard or Capizzi interim maintenance they will also receive 12mg of intrathecal methotrexate on day 15 of each cycle, as will T-ALL patients presenting with a white cell count of >$100x10^9$/L.

All patients are also to receive co-trimoxazole prophylaxis for PCP throughout treatment (except during protocol M and M-A) with dose depending on body surface area.

Will my participation in this study be kept confidential?

During this study your identity will be protected as defined under the Data Protection Act 1998. When you are first registered onto this study you will be given a study number. This study number, along with your initials and date of birth will be used to identify the data we collect.

Only information needed for this study will be collected. All information will be strictly confidential. By taking part in the trial you will be agreeing to allow research staff to look at the trial records, including your medical records and scan images. Your medical records and all data obtained from this study will be made available to representatives of the study Sponsor and regulatory authorities. This is to make sure the information collected is an accurate reflection of the study.

The information collected will be stored on a secure database for analysis at the University of Leeds, and will only be accessed by authorised people, who have a duty of confidentiality to you. Your GP will also be informed so they understand why you will be having some extra tests. You will not be able to be identified in any report, presentation or publication arising from this trial.

What will happen to the results of the trial?

Results may be published in medical and scientific journals, and presented at international conferences, but your name will not be used in any publications. If you would like to obtain a copy of the published results, please ask your doctor or nurse.

Who has reviewed the trial?

This trial has been reviewed by the an independent Research Ethics Committee. Research Ethics Committees review all research to protect the safety, rights, well being and dignity of patients.

What will happen if I don't want to carry on with the study?

You are free to withdraw from this trial at any time without giving a reason and this will not affect your future treatment. If you decide to withdraw you will be asked to allow the continued collection of follow-up data (you will not need to attend more clinic appointments for this than normal for your condition).

Who is organising and funding the research?

This study is funded by Candlelighters charitable foundation and sponsored by the University of Leeds. No-one will receive payment for taking part in this study.

What if there is a problem?

Any concern or complaint about the way you have been dealt with during the trial or any possible harm you might suffer will be addressed. If you wish to complain or are unhappy about any aspect of the way you have been approached or treated during the course of the study, in the first instance please contact your consultant or a member of the research team- you can use the contact numbers at the end of this sheet. If you are still unhappy you can complain through the hospital complaints department.

Local contact for further information

If you require any further information please contact:

Fighting children's cancer Candle Lighters in Yorkshire

UNIVERSITY OF LEEDS

BONES

British OsteoNEcrosis Study

Patient information sheet for patients aged 16+ years

We would like to invite you to take part in a clinical trial run by the University of Leeds called BONES (British Osteonecrosis Study), which is part of a postgraduate research project. Before you decide whether you want to take part in the study we would like you to understand why the study is being done and what it would involve.

Please take the time to read the following information carefully and discuss it with friends, relatives, doctors and nurses if you wish. Ask us if there is anything that is not clear, or if you would like more information.

You can also visit our website: http://childhealth.leeds.ac.uk/bones.html

What is the purpose of the study?

You have been diagnosed with Acute Lymphoblastic Leukaemia (ALL) or lymphoblastic lymphoma. The treatment is usually very successful and we are now trying to improve treatment further by investigating the side-effects that can occur during and after treatment, in order to reduce these. One of the side effects that can occur in parts of bone is called osteonecrosis. This happens when there is an interruption to the blood supply to the bone which causes changes in the bone itself, and happens most often in the hips, knees, and ankles. If osteonecrosis is severe patients need surgery. However, in many cases where it is less severe the patient may recover fully.

We know that osteonecrosis occurs more commonly in patients over 10 years of age but we don't know why some people develop it and others do not. With this study we hope to learn more about:

- What makes a person more likely to develop osteonecrosis
- When osteonecrosis develops
- What happens to patients when they develop osteonecrosis

Why have I been invited?

You have been invited because you have been diagnosed with ALL or lymphoblastic lymphoma and are aged between 10 years and 25 years. Over the next 2 years a number of hospitals in the UK will be inviting children and young people diagnosed with ALL or lymphoblastic lymphoma to take part in this trial.

Do I have to take part?

No, taking part is entirely voluntary. It is up to you to decide whether or not you want to take part. You can withdraw at any time, without giving a reason. This would not affect the rest of the care that you receive.

Will anyone else know I'm taking part?

The only people who will know that you are taking part in this study will be the team of doctors, nurses and researchers looking after you.

What will happen if I take part?

Being in the study involves scans, a physiotherapy assessment and a questionnaire. We will also look at your medical records to see the results of some of the tests you are having routinely.

We will look for signs of osteonecrosis by taking pictures of your legs and hips with a special scanner. These are called magnetic resonance imaging (MRI) scans. There will be five scans in total. The first scan will be in the next few weeks. The next scans will be at six months, then one year, two years and three years after you start maintenance treatment. For the scan you will be asked to lie on a table and the table will move through the scanner. It doesn't hurt, and will take around half an hour.

You will also have an appointment with a physiotherapist at roughly the same times as the scan, which will take around 30 minutes. Physiotherapists look at how patients are moving, and they will help us recognise if there are any problems developing with your arms or legs. They will also ask you to complete a questionnaire to see if there seem to be any problems developing.

MRI Scanner

In some centres there will be extra imaging of bones by dual energy X-ray absorptiometry (DXA), which measures bone mineral density and assesses fracture risk . These are routinely performed in some centres, but there is not currently a national standard. We would like to look at the results of these scans, which will be performed at diagnosis and annually, to a total of 4 scans. DXA scans are very safe and painless. You would be required to lie on your side on an X-ray table as a scanner passes over you.

If you agree to take part in this study you will be asked to sign a consent form. You will be a given a copy of it, and this information sheet to keep.

We can reimburse reasonable travel expenses (public transport or car mileage) which are due to being part of this study.

Are there any disadvantages or risks involved in taking part in this study?

If you decide to take part in this trial the leukaemia treatment you receive will be the same as if you choose not to participate.

MRI scans are painless and very safe. They do not involve radiation and there are no known side effects of an MRI scan. There are some cases where an MRI scan may not be recommended, because the strong magnets used during the scan can affect metal implants or fragments in the body. Please let your health care team know if you have any metal in your body. DXA scans use a very low dose of radiation (less than 2 days exposure to normal background radiation), which is much lower than standard X-ray examinations.

There is a possibility we might find something unexpected in your images. If this happens, we will notify you first and you will be referred to the appropriate specialist for further investigation.

Before any trial can start it has lots of safety checks before it can be approved. This study has undergone these checks and we hope that the trial will help improve the treatment for children and young adults with ALL and lymphoblastic lymphoma in the future.

What are the possible benefits of taking part?

The aim of the study is to gain information to improve how we look after young people with ALL or lymphoblastic lymphoma in the future. We are not expecting you to directly benefit from taking part. All the extra tests are only for the study and will not change how you are managed unless something unexpected is seen.

What happens when the trial stops?

At the end of the trial all of the data that has been gathered will be examined, and the results used in the future to help identify patients at highest risk of osteonecrosis, and consider how this risk can be reduced. Anonymised data will be kept for 10 years.

Informed Consent Form (Patient aged 16 years and over)

British OsteoNEcrosis Study

Site_____ **Principle Investigator**_____

Patient Trial Number _____**Trial Reference Number**_____

Please initial each box

1. I confirm that I have read and understood the Patient Information Sheet (version 7, 20/11/2017) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected. ☐
3. I give permission for a copy of this consent form to be sent to the research team based at the University of Leeds. ☐
4. I understand that relevant sections of my medical notes and data collected during the trial may be looked at by individuals from the research team, regulatory authorities, Sponsors and/or NHS bodies, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records and to collect, store, analyse and publish information from this research. I understand that my name will be kept confidential. ☐
5. If I withdraw from the study I agree to allow the continued collection of follow up data. ☐
6. I agree for my GP to be informed about my involvement in this study ☐
7. I agree to take part in the above study. ☐
8. I consent for data from this study to be used in future research projects ☐

Name of patient: _____Date:_____Signature:_____

Name of person taking consent: _____Date:_____Signature:_____

BONES: The British OsteoNEcrosis Study: A prospective multi-centre study to examine the natural history of osteonecrosis in older children, teenagers and young adults with acute lymphoblastic leukaemia

Aims

The aim of this research is to examine the natural history of osteonecrosis in older children, teenagers and young adults with acute lymphoblastic leukaemia within the UK.

Objectives

The objective is to establish a prospective, multi-centre study for older children, teenagers and young adults which can address the following questions:

- What is the incidence of osteonecrosis in older children, teenagers and young adults being treated for acute lymphoblastic leukaemia (ALL) in the UK at different time points in their treatment?
- What are the risk factors for progression and the development of symptomatic osteonecrosis in this population?
- Are there specific radiological features that predict for either progression or regression in those with asymptomatic osteonecrosis?

Background

Survival from acute lymphoblastic leukaemia (ALL) has steadily increased over the last 40 years so that we now expect to cure >90% children and young people presenting

with ALL. This progress shifts the entire treatment paradigm so that the goal moves beyond simply cure to returning the young person to a normal life. The biggest barrier to this is the burden of treatment associated toxicity and attention internationally is now turning to this. Osteonecrosis (previously also referred to as avascular necrosis, ischaemic necrosis and aseptic necrosis) is one of the most devastating complications seen in older children and teenagers treated for ALL, and can cause significant long term morbidity.

However, despite increasing concern about osteonecrosis, our understanding is limited. Historically, information about osteonecrosis has not been well captured in previous studies of ALL - either in the UK or in other countries. This partly reflects lack of good definitions and piecemeal reporting. These deficiencies have been acknowledged and there is now an international will to address them. The starting point for this is standardisation of definitions, for which we can use the The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4[1], which will allow future comparison (see appendix 1). It is imperative that we maximise the potential of the current UK study, UKALL 2011, to further understanding of osteonecrosis in this population.

Osteonecrosis is one of the most debilitating complications seen after or during treatment for ALL, and is mostly an iatrogenic complication that has been attributed mostly to increased use of glucocorticoids[2]; asparaginase, high dose methotrexate and cyclophosphamide have also been implicated. Development of osteonecrosis appears to be multifactorial, but is being seen more commonly in patients as survival improves and high dose steroids have become imbedded in treatment regimens. Osteonecrosis occurs when there is bone ischaemia and infarction caused by temporary or permanent disruption to the blood supply and in ALL typically affects the femoral head, humeral head, knee, shoulder and ankles. Glucocorticoids predispose to the development of osteonecrosis in a number of ways, with proposed aetiologies including:

- Creation of a hypercoagulable state with endothelial cell apoptosis and development of microthrombi;
- Suppression of osteoblasts and apoptosis of osteocytes impairing the bone repair process;
- Stimulation of intramedullary lipocyte proliferation and hypertrophy resulting in increased intraosseous pressure.

These factors combine to compromise blood circulation to the bone leading to cell death in a self-perpetuating cycle[3].

The most comprehensive prospective study to examine osteonecrosis in children with ALL examined 364 patients and reported a cumulative incidence of 72%, of which 18% had symptomatic osteonecrosis [4]. Symptomatic osteonecrosis was associated with a low serum albumin and high serum cholesterol, both of which were also associated with ACP1 polymorphisms. Severe osteonecrosis was associated with poor dexamethasone clearance. There are many more reports which rely on proactive reporting to the study centre, with no identification of asymptomatic osteonecrosis, and as expected these tend to give far lower incidences. These range from 0.67% [5] to 15% [6].The UK data suggests that 4% had symptomatic osteonecrosis in UKALL 2003 [7], but it is recognised anecdotally that many patients with symptomatic osteonecrosis were not reported by clinicians in UKALL 2003.

Despite the variation in the reported incidence across the different study protocols, there is striking agreement in some of the risk factors for the development of osteonecrosis, with significant controversy in others. Age has consistently been associated with increased risk with symptomatic necrosis, with patients aged <10 years at diagnosis at much lower risk of development of osteonecrosis[4]. The significance of female sex as a risk factor for development of osteonecrosis is less clear. A number of studies found it

was a risk factor , while it appeared to be non-significant in other studies , even when similar treatment regimens were used [8]. Even in groups with highest rates of osteonecrosis there are disparate results - the CCG study reported the disorder more frequently in females [8], whilst no gender difference were found in the DFCI ALL consortium [9] and studies at SJCRH [10]. In the study by Mattano in 2000 [11] the gender difference was greatest in the 10-15 year age group, with 3 year rates of 19.2% for females and 9.8% for males.

Ethnicity is notoriously difficult to capture. White race was found to be a risk factor in a number of studies, but not in others[8, 10, 12] .

A number of candidate genes have been proposed. In the prospective study by Kawedia et al [13]single nucleotide polymorphism (SNP) genotyping was performed. After adjustment for age and treatment arm 423 SNPs were associated with symptomatic osteonecrosis, of which 27 were associated with low albumin or high cholesterol. The top 4 SNPs were in the SH3YL1-ACP1 gene locus. ACP1 is associated with serum cholesterol and triglyceride levels [10], and regulates osteoblast differentiation [4]. Higher serum cholesterol and lower serum albumin have been associated with grade 2-4 osteonecrosis, suggesting that ACP1 may act via multiple mechanisms to affect bone homeostasis.

Dexamethasone, which is now the steroid of choice in the UK protocols, in view of its superiority over prednisolone in reducing central nervous system relapse, may be associated with an increase in osteonecrosis compared with prednisolone.

Mattano et al [8] reported higher incidence of osteonecrosis in paediatric patients with ALL treated with dexamethasone during induction phase than in those treated with prednisone (11.6% and 8.7%, respectively). This difference between these types of corticosteroids was observed only in patients' age 13 years or older, suggesting that older children may be more vulnerable to the effect of dexamethasone. Similarly, 11% of children treated with dexamethasone developed osteonecrosis in one UK report compared with only 3.5% those on prednisolone [4]. However, a much larger

prospective study analysing results from UKALL97 and UKALL97/99 [14] found no excess of ON in the dexamethasone arm of the trial, but only assessed NCI grade 3 or 4 toxicity, so the impact of dexamethasone versus prednisolone in development of osteonecrosis remains unclear.

In the current UKALL 2011 study there is an upfront randomisation to standard versus short course dexamethasone. Standard dexamethasone consists of 4 weeks of dexamethasone 6mg/m2 with a further weaning week. Short course dexamethasone consists of two weeks of dexamethasone 10mg/m2. This is given for the first two weeks consecutively in children <10 years old, or split so that it is given for weeks 1 and 3 in older children and those with Down syndrome. The CCG1961 trial evaluated components of therapeutic intensification in high-risk patients (white cell count ≥50x10^9 and/or age ≥10 years). It was found that use of alternate week rather than continuous dexamethasone during delayed intensification in high risk ALL patients results in a 2-fold reduction in the relative risk of symptomatic osteonecrosis among rapid responders aged ≥10years, and particularly those over the age of 16 years. There was a four-fold reduction among those randomised to intensified therapy, despite those with alternate week dexamethasone having a higher total dexamethasone exposure. The incidence of ON was lower among slow responders age ≥ 10 years assigned to double delayed intensification with alternate-week dexamethasone when compared to a similar cohort on the CCG1882 trial [15] who were assigned to two delayed intensification phases with continuous dexamethasone (11.8% versus 23.2%), and could indicate that in this particular patient population dosing manner supersedes cumulative exposure. UKALL 2011 offers the first opportunity in the UK to examine the effects on osteonecrosis toxicity of short compared with standard dexamethasone.

It is recognised that osteonecrosis may regress, although the reasons for this are not understood. It is possible that some radiological changes interpreted as representing steroid associated osteonecrosis are in fact changes which have been present at

diagnosis and which are a consequence of the original leukaemia. In the prospective study of 364 children[16], 39% had osteonecrosis changes on their initial MRI, but were asymptomatic. The majority of this group, 74%, did not go on to develop symptomatic osteonecrosis. The current radiological classifications use a multi-modal approach combining scores for clinical, x-ray, MRI and in some cases bone scan findings. They were developed specifically for changes in the femoral head, over 20 years ago and in an entirely different patient population.

In addition to using internationally agreed standard definitions for osteonecrosis (appendix 1), this study will provide the data needed to develop a radiological classification which correlates with clinical status.

Given the very significant morbidity associated with osteonecrosis it is imperative that the opportunity afforded by the UKALL study to examine this is maximised. Only once this is done can meaningful intervention studies to try to reduce the burden of osteonecrosis be initiated. Osteonecrosis should not be a price that young people pay for cure.

Method

Participants

Children, teenagers or young adults between the age of 10 (including the day of the 10th birthday) and 24 years 364 days (at the time of diagnosis) with a first diagnosis of acute lymphoblastic leukaemia or lymphoblastic lymphoma (T-NHL or SmIg negative precursor B-NHL) diagnosed under standard criteria are eligible for BONES. Written informed consent is required for all patients.

Recruitment

Patients will be recruited locally by the primary treatment centre.

Target recruitment

The recruitment target is 50 patients over a 2 year period, which is based on an anticipated ascertainment target of 75%. This is an observational study and there is therefore no relevant power calculation.

Data collection

Information will be collected on basic demographics, presenting features and diagnosis at initial recruitment (see appendix 2). Further data will be collected at 4 subsequent time-points detailed below to ascertain treatment and response, along with results of relevant investigations performed (see appendix 3). The clinician completing the form will access investigation results from the patient's medical records. Clinical information collected in clinic/ hospital will include height, weight and phase of puberty. At each time point (5 in total) further data will be collected, including MR imaging of lower limbs, physiotherapy assessment using a structured assessment tool, and routine clinical and biochemical information(see appendices 4, 5 and 6). Bone mineral density and lateral vertebra assessment will be assessed at diagnosis and annually to a total of 4 assessments.

Investigations

The results of the following investigations will be collected:

The following are usually performed as part of the routine assessment:

At diagnosis /earliest results obtained during induction)- highest white cell count, immunophenotype, cytogenetics, molecular results; albumin; lipid profile; vitamin D level, bone profile (calcium, phosphate, PTH, ALP)

At the end of induction (results nearest to day 29) - MRD result, flow cytometry from end of induction bone marrow; albumin; lipid profile

DXA scans results (performed at diagnosis and annually) – lumbar spine bone mineral apparent density (measured in AP direction L1-4) Z-scores, and total body less head Z-scores. Vertebral fractures would be assessed with DXA lateral vertebral assessment of thoracic and lumbar vertebra (T4-L4 if possible), using the Genant semi-quantitative

method. If DXA VFA is not available, lateral thoracolumbar spine radiographs can be used instead and assessed using the same method.

Pelvic X-rays and full joint assessment via MRI which are performed if significant problems are identified by the clinical team, according to orthopaedic opinion.

Investigations specific to patients recruited into the study:

At the following time-points, patients recruited into the study will have additional assessment:

Within 4 weeks of diagnosis

At the end of delayed intensification

One year after the start of maintenance

Two years after the start of maintenance

Three years after the start of maintenance

The additional assessment will include:

MRI of the hips, knees and ankles. These should comprise of unenhanced coronal T1 and STIR images as a minimum protocol. Knees and ankles can be imaged together. Where further information of a specific joint is needed pre-treatment additional sequences in different planes could be performed at the discretion of the participating centre.

Physiotherapy assessment, including completion of patient questionnaire.

In centres where annual DXA and lateral vertebral assessment is not standard of care, additional annual assessments will be requested where facilities exist.

The MRI images obtained are not routine MRI scans, as they are being done according to a study protocol developed for BONES, and are not for local interpretation. Local reports should simply say that images are for trial purposes only. If a significant abnormality (not osteonecrosis) is found when images are centrally reviewed, information will be fed back to the local centre. In the event of the development of symptomatic osteonecrosis, which is diagnosed locally, the patient should be managed

according to local protocols and at the discretion of their own consultant (see appendix 7). Information on treatment and outcomes will be collected.

Radiological review

A central review panel consisting of Paediatric Radiologists with an interest in paediatric haematology will review each MRI in order to agree the grade of osteonecrosis and noting specific features according to the study radiology *proforma*.

There will also be retrospective central analysis of DXA and lateral vertebral assessment results. Vertebral fracture prevalence will be assessed on lateral vertebral assessment using the Genant semi-quantitative method.

Data management

Information will be collected centrally at the University of Leeds.

Local data management:

Local clinician to complete forms at each time point.

Local physiotherapist to collect questionnaire data, and complete physiotherapy assessment form.

Both forms to be anonymised locally, with only trial number, initials and date of birth (in form of month/year) available on forms.

PI at local centres to be custodians of local data, and to have research file at site of personal data.

Trial centre to send separate encrypted spreadsheet of trial number, date of birth and sex to CI.

Forms and spreadsheet to be sent by secure e-mail. Consent forms to be sent to CI.

Personal data relating to study to be destroyed by PI at end of storage period (10 years).

Radiographic data:

Anonymised images of MRI scans to be put onto CD, (only trial number on disk).

Anonymised DXA scans and lateral vertebral assessment images to be put onto CD (only trial number on disk)

Both sent to CI

Central data management:

MRI and DXA CDs, forms and consent forms to be secured in locked filing cabinet in University of Leeds, in secure room. Only CI and members of research team to have access to this filing cabinet.

Electronic database to be created with trial numbers, date of birth (mm/yy), sex and of investigations/questionnaires.

Database to be stored on CI University M drive, a secure, password protected, University of Leeds server. A copy will be held by one of the MD research supervisors (Dr Feltbower) on their secure password protected University of Leeds server, and only available to relevant members of the research team. They will also provide the long term storage of data, after completion of student research time.

CI to be responsible for deleting data from database at end of storage period.

Statistical analysis

Epidemiology Unit located within the University of Leeds.

Participant reimbursement of expenses

Patients or their parents will be reimbursed for excess travel expenses. This will be reimbursement of public transport expenses, or car mileage (24p/mile) to a maximum of £20/ journey. Patients can claim travel expenses through petty cash arranged locally or equivalent local arrangements.

Appendix 1. Definition of osteonecrosis

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 defines ON as 'a disorder characterised by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, necrotic changes result in the collapse and the destruction of the bone structure'.

Grade	
1	Asymptomatic; clinical or diagnostic observations only, intervention not indicated.
2	Symptomatic; limiting instrumental ADL
3	Severe symptoms; limiting self care ADL; elective operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated

CTCAE v 4.0 definition and grading of osteonecrosis

Appendix 2. Form to be completed at initial recruitment

Initials _____

Date of birth _____

Trial Number _____ Sex male/female/prefer not to say

Date of initiation of therapy _____ Ethnicity_____

Recruiting centre _____

Patient postcode _____

Highest white cell count _____ x 10^9/l date _____

Immunophenotype _____

Cytogenetics _____

Molecular results _____

Height (cm) _____ Weight (kg) _____

Pubertal Status: Pre-pubertal/in puberty/completing puberty

V5. 02/10/2017

IRAS Project ID: **185365**

	Pre-puberty (Tanner stage 1)	In Puberty (Tanner stage 2-3)	Completing Puberty (Tanner stage 4-5)
Girls	If all of the following: No signs of pubertal development	If any of the following: Any breast enlargement pubic or axillary hair	If all of the following Started periods with signs of pubertal development
Boys	If all of the following: High voice and No signs of pubertal development	If any of the following: Slight deepening of the voice Early pubic or axillary hair growth Enlargement of testes or penis	If any of the following: Voice fully broken Facial hair Adult size of penis with pubic and axillary hair

Hepatomegaly yes / no

Splenomegaly yes / no

Palpable lymphadenopathy yes / no

Duration of symptoms before diagnosis _____

Was bone pain present at diagnosis? yes / no

Please document units for all available blood test results:

Serum albumin _____date_____

Lipid profile:

V5. 02/10/2017

IRAS Project ID: **185365**

- HDL _____date_____
- LDL _____date_____
- Cholesterol _____date_____
- Triglycerides _____date_____

25-Hydroxyvitamin D _____date_____

PTH _____date_____

Alkaline phosphatase _____date_____

Calcium _____date_____

Phosphate _____date_____

Completed by : _____date_____

V5. 02/10/2017

IRAS Project ID: **185365**

Appendix 3. Form to be completed at day 29 of induction

Trial number _____ Patient initials_____

Date of day 29 of induction _____

Recruiting centre_____

Treatment regimen for induction A / B

Treatment regimen for consolidation A / B / C

If changed, why was this? _____

flow cytometry results at end of induction _____

MRD status at end of induction low / high / not able to be assessed

Please document units for all available blood test results as close to day 29 as possible:

Serum albumin _____date_____

Lipid profile:

V5. 02/10/2017

IRAS Project ID: **185365**

[Type here]

- HDL _____date_____
- LDL _____date_____
- Cholesterol _____date_____
- Triglycerides _____date_____

25-Hydroxyvitamin D _____date_____

PTH _____date_____

Alkaline phosphatase _____date_____

Calcium _____date_____

Phosphate _____date_____

Completed by : _____date_____

If vitamin D was low, has this been treated? yes / no

If yes, please document treatment_____

Date of induction MRI _____

Completed by : _____ date _____

V5. 02/10/2017

IRAS Project ID: **185365**

[Type here]

Please also send anonymised MRI images on disk to Chief Investigator

Appendix 4. Form to be completed and sent with relevant images at the end of delayed intensification, 1 year after start of maintenance, 2 years after start of maintenance, 3 years after start of maintenance

Trial number_____ Patient initials_____

Recruiting centre_____

Timepoint (please circle and date)

Timepoint	Date
end of delayed intensification	
1 year after start of maintenance	
2 years after start of maintenance	
3 years after start of maintenance	

Treatment regimen for interim maintenance A standard interim maintenance

A high dose methotrexate

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B standard interim maintenance

B high dose methotrexate

C Capizzi

C high dose methotrexate

Treatment regimen for maintenance vincristine/dexamethasone pulses

no pulses

Have there been any treatment modifications yes / no

If yes, please provide further details _____

Please document units for all available blood test results:

Serum albumin _____date_____

Lipid profile:

- HDL _____date_____
- LDL _____date_____

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- Cholesterol _____date_____
- Triglycerides _____date_____

25-Hydroxyvitamin D _____date_____

PTH _____date_____

Alkaline phosphatase _____date_____

Calcium _____date_____

Phosphate _____date_____

At the time of each scan:

Height _____ Weight _____

Pubertal status: Pre-pubertal/in puberty/completing puberty

	Pre-puberty (Tanner stage 1)	In Puberty (Tanner stage 2-3)	Completing Puberty (Tanner stage 4-5)
Girls	If all of the following: No signs of pubertal development	If any of the following: Any breast enlargement pubic or axillary hair	If all of the following Started periods with signs of pubertal

			development
Boys	If all of the following: High voice and No signs of pubertal development	If any of the following: Slight deepening of the voice Early pubic or axillary hair growth Enlargement of testes or penis	If any of the following: Voice fully broken Facial hair Adult size of penis with pubic and axillary hair

Has there been a diagnosis of osteonecrosis since the last report? yes / no

If yes, when was this? date_____

Which joints are affected? _____

Which of the following have occurred: steroids stopped yes / no

mobility problems yes / no

core decompression yes / no

joint replacement yes / no

Has a DXA/ lateral vertebral assessment been performed in the last year?

yes / no

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If yes, please attach report and send anonymised images.

Have bisphosphonates been used? yes / no

If yes, then please give details regarding start date, type, dose and frequency of treatment

_____

Completed by : _____ date _____

Please also attach physiotherapy assessment and send anonymised MRI images on disk to

Chief Investigator

Appendix 5. Physiotherapy Assessment

At physiotherapy assessment:

For completion by physiotherapist:

Trial number:	Patient initials:

Recruiting centre: Date:

For completion by participant

BONES

British OsteoNEcrosis Study

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Activity Levels

On a typical day, on average how many hours of the day are you active for e.g. walking, playing, exercising …….hours

Mobility

Since you were last seen (if relevant), were you told to continue to fully/ partially or not weight bear? Full/Partial/None

If you use a walking aid, what hand do you use it in? Right/Left/Both

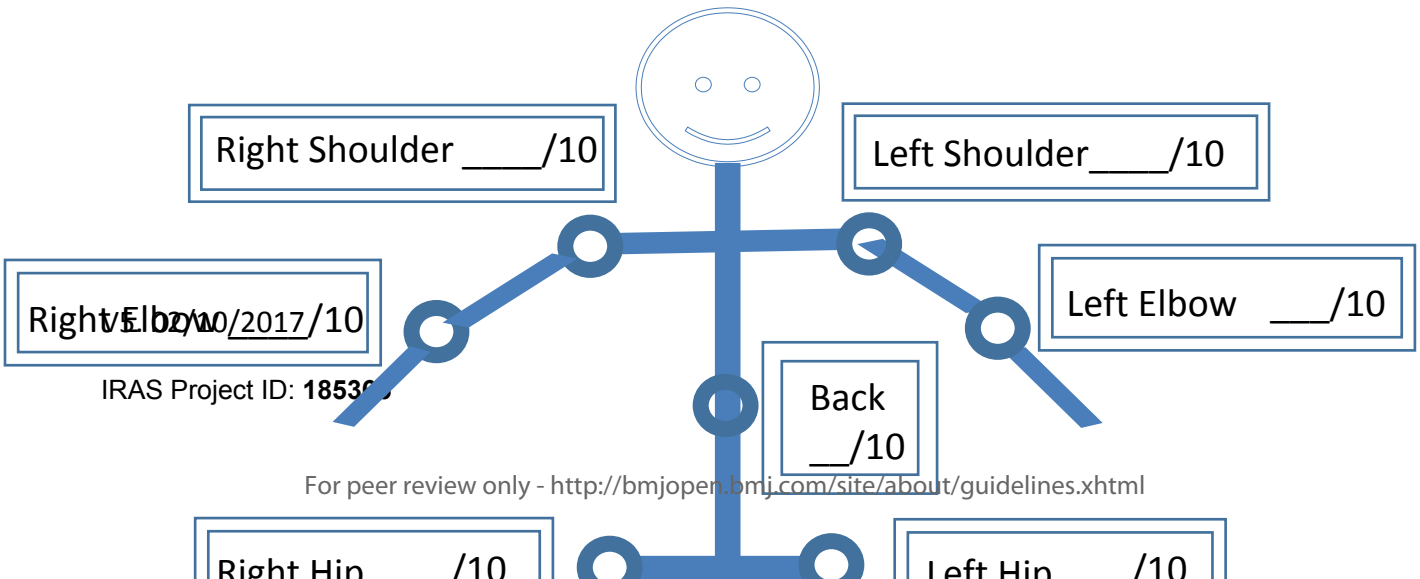
If you use a walking aid, how long have you been using it for?.....

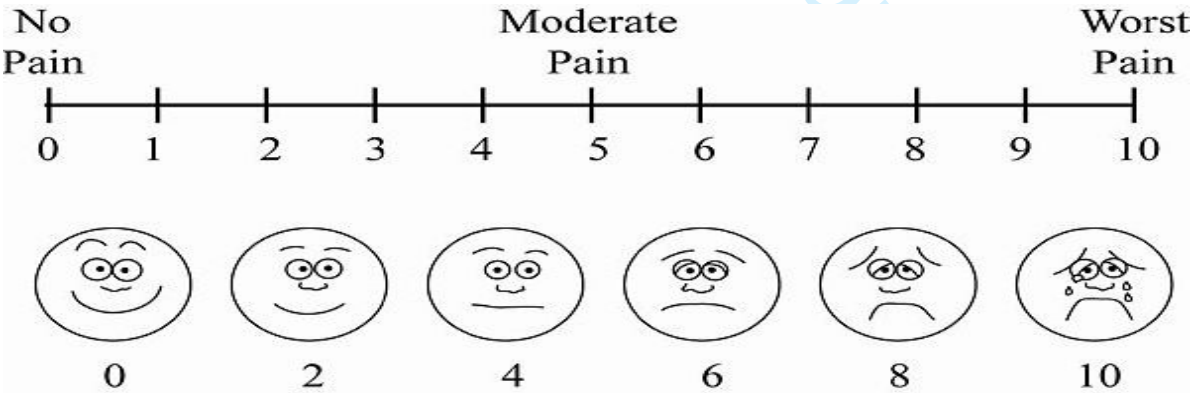
If you use a wheelchair, when going out, how often do you use it? Always/ Usually/ Occassionally/ Rarely/ Never?

Pain/Discomfort

Pain Scale:

Please score pain in each joint out of 10, using the scale below the diagram:





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C.H.A.Q.

Childhood health assessment questionnaire

We are interested in learning how a child or young person's long term illness affects his / her ability to function in daily life. This will help the assessment in clinic.

This form can be completed by the child / young person themself or their parent or carer

For the following questions, please tick one response which best describes the young person's / child's function **OVER THE LAST WEEK**

- Please note that there are **2 pages** and that for very young children the answer to many questions will be 'Not Applicable'

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	Not Applicable
DRESSING & PERSONAL CARE					
- Dress, including tying shoelaces and doing buttons?	☐	☐	☐	☐	☐
- Remove socks?	☐	☐	☐	☐	☐
- Cut fingernails?	☐	☐	☐	☐	☐
GETTING UP					
- Stand up from a low chair or floor?	☐	☐	☐	☐	☐
- Get in and out of bed or stand up in a cot?	☐	☐	☐	☐	☐
EATING					
- Cut own meat?	☐	☐	☐	☐	☐
- Lift a cup or glass to mouth?	☐	☐	☐	☐	☐
- Open a new cereal box?	☐	☐	☐	☐	☐
WALKING					
- Walk outside on flat ground?	☐	☐	☐	☐	☐
- Climb up five steps?	☐	☐	☐	☐	☐
- Run errands and shop?	☐	☐	☐	☐	☐
- Get in and out of a car or toy car or school bus?	☐	☐	☐	☐	☐
- Ride bike or tricycle?	☐	☐	☐	☐	☐
- Do household chores (e.g. wash dishes, take out rubbish, hoovering, gardening, make bed, clean room)?	☐	☐	☐	☐	☐
- Run and play?	☐	☐	☐	☐	☐
HYGIENE					
- Wash and dry entire body?	☐	☐	☐	☐	☐
- Take a bath, get in and get out?	☐	☐	☐	☐	☐
- Get on and off the toilet or potty?	☐	☐	☐	☐	☐
- Brush teeth?	☐	☐	☐	☐	☐
- Comb / brush hair?	☐	☐	☐	☐	☐
REACH					
- Reach and get down a heavy object such as a large game or books from above?	☐	☐	☐	☐	☐
- Bend down to pick up clothing or a piece of paper from the floor?	☐	☐	☐	☐	☐
- Pull on a jumper over head?	☐	☐	☐	☐	☐
- Turn neck to look back over shoulder?	☐	☐	☐	☐	☐
GRIP					
- Write or scribble with a pen or pencil?	☐	☐	☐	☐	☐
- Open car doors?	☐	☐	☐	☐	☐
- Open jars which have been previously opened?	☐	☐	☐	☐	☐
- Turn taps on and off?	☐	☐	☐	☐	☐
- Push open a door when need to turn a door knob?	☐	☐	☐	☐	☐

Please tick any AIDS or DEVICES that are usually needed for the following activities:

Raised toilet seat	☐	Bath rail	☐
Bath seat	☐	Long-handled appliances for reach	☐
Jar opener (for jars previously opened)	☐	Long-handled appliances in bathroom	☐

Please tick any categories for which help is usually needed from another person BECAUSE OF PAIN OR ILLNESS:

Hygiene	☐	Gripping and opening things	☐
Reach	☐	Errands and chores	☐

Please tick any AIDS or DEVICES that are usually needed for any of the above activities:

PAIN: How much pain has been experienced IN THE PAST WEEK? Place a mark on the line below, to indicate the severity of the pain

No Pain 0 ——— **Very severe pain** 10

Walking Frame	☐	Build up pencil or special utensils	☐
Crutches	☐	Special or built up chair	☐

GENERAL EVALUATION: Considering all the ways affected by pain or illness, rate how the patient is doing by placing a single mark on the line below.

Very well 0 ——— **Very poor** 10

Please tick any categories for help is usually needed from another person BECAUSE OF PAIN OR ILLNESS:

Dressing and personal care	☐	Eating	☐
Getting up	☐	Walking	☐

Any concerns or questions you would like to discuss?

.....

Appendix 6: Physiotherapy assessment

For completion by physiotherapist:

Trial number:	Patient initials:

Recruiting centre: Date:

Gait Analysis

……

……

……..

ROM and Muscle power

	Muscle power (0-5)	Full range of movement	If limited range of movement, please enter degree and plane of movement that is restricted
Right hip		Yes/No	
Left hip		Yes/No	

Right knee		Yes/No	
Left knee		Yes/No	
Right ankle		Yes/No	
Left ankle		Yes/No	
Right Shoulder		Yes/No	
Left Shoulder		Yes/No	

If joints are limited please comment on why below e.g pain/stiffness

……

……

……

……

Assessment completed by Print ……

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Signed …….

Date …….

Appendix 7. Management of osteonecrosis

Whilst this is an observational study, it is recognised from previous experience, that management advice may be sought when a young person develops osteonecrosis. The guidelines below represent the usual practice of the clinicians involved in designing the study and are in no way mandated.

Recommendations

1. **Asymptomatic ON detected coincidentally.**

No evidence to suggest discontinuation of dexamethasone is routinely indicated in asymptomatic cases.

Monitor closely and early repeat MRI if symptomatic

Consider orthopaedic referral. The risk of collapse of the femoral head is affected by the location and extent of the necrotic lesion. All femoral head lesions which are either large or extend to the edge of the epiphysis should be referred to orthopaedic team for consideration of core decompression in order to prevent femoral head collapse. Using MRI images in both coronal and sagittal planes the Kerboul combined necrotic angle is a good MRI-based method to assess risk of hip collapse.

2. Symptomatic ON.

Confirm and document duration of symptoms in affected joint/joints. Review all other joints.

Organise physiotherapy assessment.

Review vitamin D and bone profile results.

Consider continuation of dexamethasone and 6 monthly MRI screening to detect progression of ON.

For persistent/worsening symptoms or MRI progression, reduction/discontinuation of dexamethasone will need to be considered. If in doubt contact trial coordinators in these cases.

Consider orthopaedic referral (see 1c above)

Routine use of bisphosphonates can ONLY be recommended in patients with coexisting osteoporosis, defined by reduced bone mineral density and presence of low-impact fractures (ISCD Criteria) or as part of a clinical trial.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	9

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	See note 1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial,	n/a

		if applicable (see Item 21a for data monitoring committee)	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	5-6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6

Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	n/a
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7,8

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8, 9
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other	8-9

		details of the statistical analysis plan can be found, if not in the protocol	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 3
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or	n/a

molecular analysis in the current trial and for future use in ancillary studies, if applicable

Author notes

1. 1, 2, 5, 9,11

BMJ Open

The British OsteoNEcrosis Study (BONES) protocol: A prospective cohort study to examine the natural history of osteonecrosis in older children, teenagers and young adults with acute lymphoblastic leukaemia and lymphoblastic lymphoma

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-027204.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Feb-2019
Complete List of Authors:	Amin, Nadia; University of Leeds, Leeds Institute of Cancer and Pathology Kinsey, Sally; University of Leeds; Leeds Children's Hospital, Paediatric Haematology Feltbower, Richard; University of Leeds, Epidemiology Kraft, Jeannette; Leeds Teaching Hospital NHS Trust, Radiology Whitehead, Elizabeth; Leeds Children's Hospital, Physiotherapy Velangi, Mark; Birmingham Women's and Children's NHS Foundation Trust James, Beki; Leeds Children's Hospital
Primary Subject Heading:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Paediatrics, Oncology, Radiology and imaging, Research methods
Keywords:	Calcium & bone < DIABETES & ENDOCRINOLOGY, Leukaemia < HAEMATOLOGY, Lymphoma < HAEMATOLOGY, PAEDIATRICS, STATISTICS & RESEARCH METHODS

Title: The **B**ritish **O**steo**NE**crosis **S**tudy (BONES) protocol: A prospective cohort study to examine the natural history of osteonecrosis in older children, teenagers and young adults with acute lymphoblastic leukaemia and lymphoblastic lymphoma

Corresponding author: Dr Nadia Amin

Corresponding author e-mail address: nadia@cantab.net

Address: Room 9.86, Level 9, Worsley Building, University of Leeds, Leeds, LS2 9NL

Telephone: 0113 3932596

Country of recruitment: United Kingdom

Health condition studied: Osteonecrosis in patients with acute lymphoblastic leukaemia and lymphoblastic lymphoma

Study Type: observational

Date of first enrolment: August 2017

Target Sample Size: 50

Recruitment Status: Recruiting

Contact information for trial sponsor:

Name: Clare Skinner

Email address: governance-ethics@leeds.ac.uk

Protocol Version: Version 5. 02/10/2017

Protocol contributors:

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Dr Mark Velangi, Birmingham Women's and Children's NHS Foundation, Consultant Paediatric Haematologist

Dr Beki James, Leeds Children's Hospital, Consultant Paediatric Haematologist

Abstract:

Introduction

Osteonecrosis is a well-recognised treatment related morbidity risk in patients diagnosed with acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL), with a high rate of affected patients requiring surgical intervention. Patients may have asymptomatic changes on imaging studies that spontaneously regress, and little is known about the natural history of osteonecrotic changes seen. The main aim of the British OsteoNEcrosis Study (BONES) is to determine the incidence of symptomatic and asymptomatic osteonecrosis in the lower extremities of survivors of ALL or LBL diagnosed aged 10-24 years in the UK at different time points in their treatment. This study also aims to identify risk factors for progression and the development of symptomatic osteonecrosis in this population, as well as specific radiological features that predict for progression or regression in those with asymptomatic osteonecrosis

Methods and analysis

BONES is a prospective, longitudinal cohort study based at Principal Treatment Centres around the UK. Participants are patients aged 10- 24 years diagnosed with ALL or LBL under standard criteria. Assessment for osteonecrosis will be within 4 weeks of diagnosis, at the end of delayed intensification, and 1, 2 and 3 years after the start of maintenance therapy. Assessment will consist of magnetic resonance imaging (MRI) scans of the lower limbs and physiotherapy assessment. Clinical and biochemical data will be collected at each of the time-points. Bone mineral density data and vertebral fracture assessment using dual energy X-ray absorptiometry (DXA) will be collected at diagnosis and annually for 3 years after diagnosis of malignancy.

Ethics and dissemination

Ethical approval has been obtained through the Yorkshire and Humber Sheffield Research Ethics Committee (REC reference number: 16/YH/0206). Study results will be published on the study website, in peer-reviewed journals and presented at relevant conferences and via social media.

Trial registration number: NCT02598401

Date of registration: 05/11/2015

Strengths and limitations of this study

- This study will be the first UK prospective study to obtain MR imaging within 4 weeks of diagnosis of ALL, with sequential imaging at 4 further time-points to assess progression or regression of osteonecrotic lesions.
- This study targets the most vulnerable patient population, those aged 10-24, who are at highest risk of development of symptomatic osteonecrosis.
- It will simultaneously assess multiple domains to correlate physical signs, symptoms and biological markers with MRI changes.
- This study is limited by the anticipated small sample size, which is due to the rarity of ALL and LBL in patients over 10 years of age, and prospective imaging of lower extremities only.

Introduction:

Survival from acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL) has steadily increased over the last 40 years so that the expected cure rate is now greater than 90% in children and young people presenting with ALL[1]. This progress shifts the entire treatment paradigm so that the goal moves beyond cure to returning the young person to a normal life. The biggest barrier to this is the burden of treatment associated toxicity, and attention internationally is now beginning to focus on this issue. Osteonecrosis (previously also referred to as avascular necrosis, ischaemic necrosis and aseptic necrosis) can be a devastating complication of treatment in older children and teenagers treated for ALL, and can cause significant long term morbidity[2]. However, despite increasing concern about osteonecrosis, our understanding of it in the context of ALL or LBL is limited. Historically, information about osteonecrosis has not been well captured in previous studies of ALL, which partly reflects lack of good definitions and incomplete retrospective reporting.

Osteonecrosis occurs when there is bone ischaemia and infarction caused by temporary or permanent disruption to the blood supply and in ALL typically affects the femoral head, humeral head, knee, shoulder and ankles[2]. It is mostly an iatrogenic complication that has been attributed to increased use of glucocorticoids in treatment of ALL[3]. The role of other agents, such as high dose methotrexate[4] and asparaginase[5, 6] are uncertain. It has been reported that asparaginase reduces dexamethasone clearance and could potentiate the osteonecrotic effect of glucocorticoids[6, 7]. The cumulative dose of received glucocorticoids in patients with ALL has been shown to correlate with the risk of osteonecrosis[8], but there is no clear increase in osteonecrotic risk with the administration of either prednisolone or dexamethasone[8-11]. Development of osteonecrosis appears to be multifactorial, but is seen more commonly in patients as survival improves and high dose steroids have become embedded in treatment regimens.

Glucocorticoids predispose to the development of osteonecrosis in a number of ways, with proposed aetiologies including:

- Creation of a hypercoagulable state with endothelial cell apoptosis and development of microthrombi;
- Suppression of osteoblasts and apoptosis of osteocytes impairing the bone repair process;
- Stimulation of intramedullary lipocyte proliferation and hypertrophy resulting in increased intraosseous pressure.

These factors combine to compromise blood circulation to the bone leading to cell death in a self-perpetuating cycle[12].

Interosseous fat emboli with intravascular coagulation and osteonecrosis has been described[13], with an overload of subchondral fat emboli, hypercoagulability, stasis and endothelial damage by free fatty acids hypothesised to cause end organ damage. Glucocorticoids causing dyslipidaemia may promote the formation of fat emboli, although fat emboli are also found in healthy bones which do not go on to develop osteonecrosis. The role of hypercoagulability is unclear. Some studies have shown pro-coagulant abnormalities in patients with osteonecrosis[14], but the common thrombophilias have not been identified as risk factors for osteonecrosis, highlighting the multifactorial nature of the condition.

In one of the largest studies with prospective MRI screening to assess both symptomatic and asymptomatic osteonecrosis, the cumulative incidence of osteonecrosis involving the epiphysis or metaphysis of at least one hip was 17.1% ±1.8% after early screening (1 year) and 21.7%±1.9% after completion of therapy (4 years)[15]. By the end of therapy, extensive femoral head osteonecrosis

affecting ≥30% of the epiphyseal surface had developed in 6.5%±1.1% of all patients, and 24%±4.4% of those aged over 10 years[15]. The first findings of the OPAL trial where MRI screening was at a median of 12.5 days, found leukaemic infiltrate at diagnosis was not associated with osteonecrotic lesions [16] but the point at which asymptomatic lesions develop remains unclear.

There are many more reports which rely on proactive reporting to the study centre, with no prospective screening for asymptomatic osteonecrosis, and as expected these tend to give a far lower prevalence of osteonecrosis, ranging from 0.67% to 15%[17-23].

Age has consistently been identified as the most significant risk factor for development of symptomatic osteonecrosis, with the greatest incidence of osteonecrosis occurring in patients between 10 and 20 years of age at diagnosis of ALL [2, 22, 24-28], a time of rapid skeletal growth. The pathogenesis that puts this group at highest risk of development of osteonecrosis is uncertain, although factors such as hormonal changes, skeletal maturation, osseous blood vessel supply, dexamethasone clearance and changes in concentrations of coagulation factors may all play a role[7, 29].

There is no clear consensus on risk differences with sex of the patient, with variation in study findings [10, 15, 17, 18, 22, 30-42]. Inconsistent results have also been reported regarding the influence of increased BMI as a risk factor for development of osteonecrosis [15, 33, 35, 41, 42], and it is possible that varying thresholds used for statistical analysis effect likelihood of BMI being found as a risk factor. One prospective study has reported a higher cumulative incidence of osteonecrosis in patients with higher increases in total cholesterol and triglycerides during therapy[43]. White race was found to be a risk factor in a number of studies [25, 34, 36], but again this was inconsistent [15, 24]. Ethnicity as a risk factor is a difficult area to study due to a number of confounding factors, variation in terminology and differences in how ethnic groups are categorised.

Various genetic risk factors for the development of osteonecrosis have been identified. Genome-wide association studies indicate the glutamate receptor pathway to be of crucial importance, and single nucleotide polymorphisms (SNPs) in adipogenesis pathways and in enhancers active in mesenchymal stem cells were also significantly associated with osteonecrosis development[36, 44]. Glucocorticoid receptor binding sites have also been implicated in development of osteonecrosis[45].

It is recognised that a significant percentage of changes on imaging studies identified as osteonecrosis may regress[24], although the reasons for this are not understood. It is possible that some radiological changes interpreted as representing steroid associated osteonecrosis are in fact changes which have been present at diagnosis and which are a consequence of the original leukaemia.

Currently the most widely used radiological classification systems, such as the modified Ficat and Arlet[46], use a multi-modal approach combining scores for x-ray, magnetic resonance imaging (MRI) and in some cases bone scan findings. Most widely used classification systems were developed specifically for changes in the femoral head, in some cases over 20 years ago and in an entirely different patient population [46-50]. Further classifications systems have been developed more specifically for our patient population, but as yet with no prognostic validation[51]. This study will provide the data needed to develop and provide prognostic validation of a radiological classification system which correlates with clinical status, as well as provide greater understanding of the natural history of bone lesions in patients being treated for ALL or LBL. Only once this is done can meaningful intervention studies be initiated.

Treatment for UK patients with ALL or lymphoblastic lymphoma

The majority of young people diagnosed with ALL or LBL between 26/04/2012 and 31/12/2018 consented to be part of the national trial, UKALL2011 (ISRCTN64515327, Eudract 2010-020924-22), and treatment for patients aged between 10 and 25 at diagnosis of ALL or LBL is described in figure 1. A list of all chemotherapeutic agents are available in supplementary file 1. Patients who did not consent to participate in UKALL2011, or who are diagnosed after the study closure, will receive the same treatment as those on the trial, and at the point of randomisation receive standard interim or Capizzi interim maintenance, depending on their risk stratification. At the next randomisation point they receive maintenance therapy with vincristine/dexamethasone pulses and intrathecal methotrexate.

Post induction treatment is determined by minimal residual disease (MRD) in ALL patients, or tumour volume assessment in patients with LBL. Patients with no MRD results are assessed by morphology (% of blasts at day 8 of induction).

If a patient has been randomised to high dose methotrexate therapy, they will have no subsequent intrathecal methotrexate in maintenance but can be randomised to either pulses or no pulses. An exception to this is that patients with T-cell ALL with white cell count >100 x 10^9 cells/l at diagnosis who have an additional 6 doses of intrathecal methotrexate in maintenance. Pulses consist of vincristine and dexamethasone. If they have been randomised to either standard or Capizzi interim maintenance they will be randomised to maintenance therapy with or without pulses, and all patients will receive intrathecal methotrexate.

Treatment will last 2 years from the start of interim maintenance for female patients, and 3 years from the start of interim maintenance for male patients. There are some treatment modifications for patients with Down's syndrome to reduce toxicity.

Objectives

The objective is to establish a prospective, multi-centre study for older children, teenagers and young adults which can address the following questions:

- What is the incidence of symptomatic and asymptomatic osteonecrosis in older children, teenagers and young adults being treated for ALL or LBL in the UK at different time points in their treatment?
- What are the risk factors for progression and the development of symptomatic osteonecrosis in this population?
- Are there specific radiological features that predict for either progression or regression in those with asymptomatic osteonecrosis?

The study also aims to

- Evaluate functional ability as measured by the childhood Health Assessment Questionnaire (CHAQ) and physiotherapy assessment and explore the correlation of this with MRI findings, to start to establish validity of use in patients with osteonecrosis.

- Evaluate changes in bone mineral density and vertebral fracture incidence during treatment for ALL or LBL

Methods and analysis

Details of the protocol, data collection forms, consent forms and patient information leaflets are available at http://childhealth.leeds.ac.uk/bones.html.

Study design

Multi-centre prospective longitudinal cohort study

Patient and public involvement

Patients and families undergoing treatment or who had completed treatment for ALL or LBL were involved in the study design and in literature developed for patient information by use of semi-structured interviews. Patients were not involved in the recruitment to and conduct of the study. Results will be disseminated to study participants via the BONES website.

Study setting

The BONES (British OsteNEcrosis Study) is conducted in Principal Treatment Centres and teenage and young adult centres for patients with cancer within the UK. It is currently open in Leeds Children's Hospital; St James's Hospital, Leeds; Birmingham Children's Hospital; and Southampton Children's Hospital. Additional centres, including Children's Hospital for Wales are in the research and development process.

Dates of study

The first site opened to recruitment on 10/04/2017. The most recent centre to join opened to recruitment on 22/03/2018. Additional sites are still in the process of opening the study. Recruitment is for a period of 2 years from site opening, or until a total of 50 patients are recruited.

Study population

Inclusion criteria: Children, teenagers or young adults between the age of 10 and 24 years 364 days (at the time of diagnosis) with a first diagnosis of ALL or LBL (TNHL or SmIg negative precursor B-NHL) diagnosed under standard criteria are eligible for BONES.

Exclusion criteria: Inability to have MRI scans of lower limbs

Recruitment target.

The recruitment target is 50 patients over a 2 year period, which is based on an anticipated participation of 75% of eligible cases. Given the observational nature of the study, and the wide number of potential predictors of interest, a power calculation is of limited relevance, and is difficult to calculate given the current lack of data. However, taking pubertal status as an example, assuming 60% of patients will be in puberty, the study would detect a risk ratio of 3 with 82% power with a 5% level of significance.

Study outcomes

Primary Outcome:

- Cumulative incidence of symptomatic and asymptomatic osteonecrosis in patients aged between 10 and < 25 years being treated for ALL or LBL in the UK at multiple time points in their treatment

Key Secondary Outcomes:

- Risk factors for progression and development of symptomatic osteonecrosis
- Specific radiological features that predict for either progression or regression in those with osteonecrosis
- Evaluation of functional ability as measured by Childhood Health Assessment Questionnaire (CHAQ) and physiotherapy assessment, with exploration of correlation with radiological findings.
- Bone mineral density changes as measured by dual-energy X-ray absorptiometry (DXA) during treatment for ALL or LBL
- Prevalence and risk factors for development of vertebral fractures during treatment for ALL or LBL

Patient assessment

Irrespective of symptoms patients will be screened for osteonecrosis via prospective MRI of the hips, knees and ankles at the following time-points:

- Within 4 weeks of diagnosis
- At the end of delayed intensification (typically 6 to 8 months after start of ALL treatment)
- One year after the start of maintenance
- Two years after the start of maintenance
- Three years after the start of maintenance

Patients will also have a physiotherapy assessment at each of these time points, including subjective and objective assessments, with collection of clinical and biochemical data.

Where facilities exist, DXA scans and vertebral fracture assessment will be performed at diagnosis and annually for 3 years after diagnosis.

MRI imaging

MRI of the lower limbs including hips, knees and ankles comprises of unenhanced coronal T1 weighted and STIR (short tau inversion recovery) images of 5mm (or less) slice thickness as a minimum protocol. Scanning parameters may vary slightly depending on available MR scanners in each participating centre.

It can be difficult to differentiate osteonecrosis from other abnormalities affecting the bone such as marrow oedema, punctate foci of altered signal, haematopoietic marrow changes in children and, as we are imaging children with ALL, early leukaemic marrow infiltration[52]. Osteonecrosis is defined as an area of yellow marrow surrounded by a low signal intensity rim on all pulse sequences or a double line rim comprising of a low signal line and an adjacent high signal line on fluid sensitive sequences. The area of osteonecrosis may be complex in shape with serpentine, crescentic, band-like or undulating outline or represented as multiple small lesions [53-55]. The presence of non-classical abnormalities will also be recorded if encountered, including haemorrhagic or cystic change as well as non-specific marrow changes and marrow oedema as these have been previously described and may represent significant prognostic factors [53-55].

Clinical and demographic data collection

Baseline demographic data collection includes the child's age, sex, ethnic background (White British; Asian; Black; Mixed; Other) postcode, height and weight at diagnosis. Clinical data are provided by the treating clinicians via a dedicated clinical report form, which includes information on pubertal status, highest white cell count prior to treatment, immunophenotype, cytogenetics and molecular results, along with presence or absence of hepatomegaly, splenomegaly, lymphadenopathy and bone pain at diagnosis.

At each of the time-points outlined above, details regarding treatment regime, height, weight, phase of puberty, and diagnosis and management of symptomatic osteonecrosis is collected. Data on results of routine blood tests, including lipid profile, albumin, bone profile, PTH and vitamin D levels is also collected. Clinicians collecting these details are blinded to the study MRI reports.

If a patient develops symptomatic osteonecrosis of upper or lower limbs they will be managed as per local policy, but imaging results and clinical data will be collated.

Physiotherapy evaluation

The physiotherapy assessment consists of a paper questionnaire for completion by the participant, which includes information about activity levels, mobility, pain and the CHAQ, alongside a physical assessment evaluating gait, range of movement and muscle power[56]. The CHAQ assesses 3 outcome dimensions: disability, discomfort and pain, and is completed by self-report, requiring approximately 10-15 minutes to complete. It is most commonly used to assess health status and physical function in children with juvenile arthritis, for whom it is validated[56], but is also validated for use in children with chronic musculoskeletal pain[57], dermatomyositis[58] and systemic lupus erythematosus[59].

Bone mineral density and vertebral fracture assessment

Patients will undergo DXA scans with vertebral fracture assessment with collection of the following measurements: posterior-anterior lumbar spine (L1-4) and total body less head (TBLH) areal bone mineral density (BMAD), and thoracic and lumbar vertebral fracture incidence.

A schema with BONES study procedures is presented in figure 2.

Data analysis plan

The report of this study will be prepared in accordance to guidelines set by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies[60].

A central review panel consisting of Paediatric Radiologists with an interest in paediatric musculoskeletal imaging will review each MRI. The grade of osteonecrosis will be assessed using a modified scoring system by reference using a study radiology *proforma*.

We will be using the classification system published by Niinimäki et al to assess osteonecrosis in the lower legs [51]. As this system is not joint specific it can be used to assess hips, knees and ankles in the same way. Our study radiology proforma will also separately record osteonecrosis seen within the metaphysis and diaphysis of long bones. If different scores are seen for two bones comprising a joint (e.g. tibial and femoral epiphysis as part of the knee) both scores will be captured before giving

the overall score for the knee according to Niinimäki, with the aim to assess the overall burden of osteonecrosis in the limb.

DXA and vertebral fracture assessment results will also be reviewed centrally, with adjustments to bone mineral density using bone mineral adjusted density (BMAD) for the spine, and the height Z-score for TBLH [61]. The thoracic and lumbar vertebra will be assessed (T4-L4 where possible), using the Genant semi-quantitative method [62].

The information from the CHAQ will be numerically coded using the disability index, global evaluation and pain assessment. The physiotherapy assessment will also be numerically coded to score muscle power and range of movement for each individual joint. Qualitative statements will be recorded and coded at the end of the study.

Data will be collected and analysed in clinically relevant categories, whilst Chi-squared tests and multivariable logistic regression models will be used to determine differences between groups adjusting for a relevant set of confounders identified using causal inference methods[63]. Potential confounders that will be assessed include age, sex, ethnic group, socioeconomic status (using the Index of Multiple Deprivation rank [64]), treatment arm, highest white cell count, immunophenotype, cytogenetics (categorised into risk groups as per the UKALL2011 protocol), phase of puberty, body mass index Z-score, lipids, albumin, presence of vertebral fractures, bone mineral density, bone ALP, PTH and vitamin D status. Odds ratios will be used to describe size of observed associations with 95% confidence intervals. If numbers are sufficiently robust a more sophisticated ordered logistic regression analysis will be carried out using an ordered categorical outcome variable for severity of osteonecrosis, and risk of developing osteonecrosis will be assessed using Poisson regression, using the same set of confounders and the risk estimates, quantified by incidence rate ratios and 95% confidence intervals.

Data completeness and validity

We will carry out range checks on the variables listed:

- Albumin
- HDL
- LDL
- Cholesterol
- Triglycerides
- PTH
- Vitamin D
- ALP
- Calcium
- Phosphate

If data on some subjects are missing at some time points the entire subject history will not simply be excluded from analysis. The main patient characteristics will be described in terms of variable completeness by summarising the proportion of missing values. If numbers allow, levels of missing-ness will also be examined according to each recruiting centre. If the data are missing at rates higher than the expected attrition rate the following steps will be taken:

- If data regarding independent variables are missing but data for the corresponding dependent variables are present, we will do multiple imputations for the missing values

- If some data associated with a dependent variable are missing, such as some follow-up data, and the underlying mechanism is random, only the missing observations will be excluded.
- If some dependent variable data are missing and the underlying mechanism is non-random, we will estimate group effects according to methods proposed by Wu and Bailey[65] and Milliken and Johnson[66].

Violations of the missing-at-random assumption will be investigated by following established precedents in paediatric oncology studies.

Data management

All patients enrolled in the study are given a unique identifier. A Microsoft Access database has been developed to record and link all the socio-demographic and clinical data for a study participant with information from their radiology assessments. Data protection regulations at each centre will be complied with. Data will be submitted centrally via a secure NHS email address with all patient identifiers removed. At each hospital site local clinicians and physiotherapists will complete the relevant forms at each time-point, with forms anonymized locally prior to being returned to the central trial unit. Images of MRI scans are to be anonymised locally and placed onto CDs which are to be sent to the central trial unit. DXA scan images and reports are to be anonymised locally and sent to the central trial unit.

At present data is not published in a data repository.

The full protocol is available in supplementary file 2. Sample consent forms and patient information sheets are available as supplementary file 3.

Protocol amendments

All substantial protocol amendments will be agreed with the protocol contributors and require Research Ethics Committee approval. Modifications will be communicated to the relevant parties via the website, newsletters and e-mail.

Ethics and dissemination:

Ethical approval has been obtained through the Yorkshire and Humber Sheffield Research Ethics Committee (REC reference number: 16/YH/0206). NHS code of confidentiality and data protection will be adhered to. All data acquisition, storage and transmission will comply with the Data Protection Act 1998. The local clinical team will identify and provide age appropriate patient information sheets to potential participants. Written patient consent or assent will be obtained by the local clinical team, with parental consent obtained for patients under 16 years of age. The protocol document and data collection tools are available online (http://childhealth.leeds.ac.uk/bones.html). All substantial protocol contributors will be granted authorship of the final study report. There are no plans to use professional medical writers.

Collective results of the study will be published on the website, in peer-reviewed journals and presented at relevant conferences and via social media.

Trial registration number: NCT02598401. Date of registration: 04/11/2015

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Figure legends:

Figure 1. UKALL 2011 trial schema for patients over the age of 10 (excluding patients with Down's Syndrome)

MRD: Minimal residual disease
BFM: Berlin-Frankfurt-Munich
SER: Slow early response (≥25% blasts at day 8 of induction)
RER: Rapid early response (<25% blasts at day 8 of induction)

Figure 2. Schema of BONES study procedures

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Authors' contributions:

NA, SK, BJ, RF, JK, EW and MV all contributed to develop the protocol, helped to write and review the manuscript and made the decision to submit the manuscript for publication.

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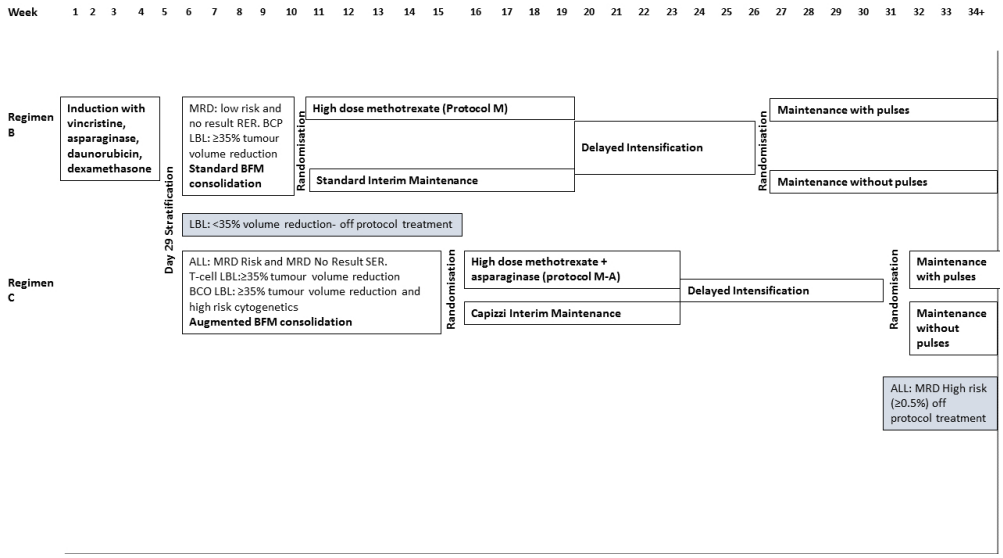

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	Within 4 weeks of diagnosis	Week 1-4	End of induction	End of delayed intensification	One year after diagnosis	One year after start of maintenance	Two years after diagnosis	Two years after start of maintenance	Three years after diagnosis	Three years after start of maintenance
Consent	◊									
MRI scan lower limbs		◊		◊		◊		◊		◊
Routine blood tests (LFTs, calcium, phosphate, cholesterol, triglycerides, HDL, LDL Vitamin D, PTH		◊	◊	◊		◊		◊		◊
Physiotherapy assessment including c-HAQ		◊		◊		◊		◊		◊
DXA scan with vertebral fracture assessment		◊			◊		◊		◊	
Clinician assessment		◊		◊		◊		◊		◊
End of induction form			◊							

108x60mm (300 x 300 DPI)

Chemotherapy agents used during treatment:

Induction:

- dexamethasone 6mg/m2/day orally for 28 days (maximum single dose 10mg/day)
- vincristine 1.5mg/m2 IV weekly for 2 weeks, starting on day 2 (maximum single dose 2mg)
- daunorubicin 25mg/m2 IV on days 2, 9, 16, 23
- pegaspargase 1000iu/m2 IM day 4 and 18
- methotrexate 12mg intrathecal on days 1, 8, 29
- mercaptopurine 60mg/m2/day orally from day 29 to day 28 of consolidation.

Standard BFM consolidation:

- cyclophosphamide 1000mg/m2 IV days 1 and 15
- cytarabine 75mg/m2/day IV or subcutaneous. 4 consecutive days in weeks 6,7,8,9
- mercaptopurine 60mg/m2/day orally until day 28 of consolidation
- methotrexate 12mg intrathecal days 1, 8, 15

Augmented BFM consolidation:

- cyclophosphamide 1000mg/m2 IV days 1, 29
- cytarabine 75mg/m2 IV or subcutaneous. 4 consecutive days in weeks 6,7,10 and 11
- mercaptopurine 60mg/m2/day for 21 days starting week 5 of induction, and again for 14 days on days 29-42
- vincristine 1.5mg/m2 IV days 16, 23, 44, 51 (maximum single dose 2mg)
- pegaspargase 1000 units/m2 intramuscular days 16, 44
- methotrexate 12mg intrathecal days 1, 8, 22

Standard interim maintenance:

- dexamethasone 6mg/m2/day orally days 1-5 and days 29-33
- vincristine 1.5mg/m2 IV day 1, 29 (maximum single dose 2mg)
- mercaptopurine 75mg/m2/day orally days 1056
- methotrexate 20mg/m2 orally once/week on week 11, 12, 14, 15, 16, 18, 19
- methotrexate 12mg intrathecal days 15, 43

Protocol M

- mercaptopurine 25mg/m2/day orally days 1-56
- methotrexate 5g/m2 IV days 8, 22, 36, 50
- folinic acid 15mg/m2 IV 42,48 and 54 hours after start of methotrexate infusion
- methotrexate 12mg intrathecal days 8, 22, 36, 50

Capizzi interim maintenance:

- vincristine 1.5mg/m2 IV days 2, 12, 22, 32, 42 (maximum single dose 2mg)
- methotrexate 100mg/m2 IV day 2. Escalating subsequent doses as tolerated on days 12, 22, 32, 42
- pegasparagase 1000 units/m2 IM days 3, 23
- methotrexate 12mg intrathecal day 1, 31

Protocol M-A:

- mercaptopurine 25mg/m2/day orally days 1-49
- methotrexate 5g/m2 IV days 1, 15, 29, 43

- folinic acid 15mg/m2 IV 42,48 and 54 hours after start of methotrexate infusion
- methotrexate 12mg intrathecal days 1, 15, 29, 43
- pegaspargase 1000 units/m2 IM days 2, 23

Delayed intensification:

- dexamethasone 10mg/m2/day orally for 7 days week 20 and 22
- vincristine 1.5mg/m2 IV days 2,9,16 (maximum single dose 2mg)
- doxorubicin 25mg/m2 IV days 2,9,16
- pegaspargase 1000iu/m2 IM day 4
- methotrexate 12mg intrathecal day 1
- cyclophosphamide 1000mg/m2 IV day 29
- mercaptopurine 60mg/m2/day orally day 29-42
- cytarabine 75mg/m2/day IV or subcutaneous. 4 consecutive days weeks 24,25

If delayed intensification is in regimen C the dexamethasone is given days 2-5 and 16-22, cytarabine is given in weeks 28 and 29, and vincristine given on days 2, 9, 16, 43 and 50. Intrathecal methotrexate is also given on days 29 and 36, and pegaspargase is also given on day 43.

Maintenance:

- mercaptopurine 75mg/m2/day orally throughout maintenance
- methotrexate 20mg/m2 orally days 1, 8, 22, 29, 36, 43, 50, 57, 64, 71, 78

If a patient has been randomised to pulses during maintenance they also receive:

- dexamethasone 6mg/m2/day orally days 1-5, 29-33, 57-61
- vincristine 1.5mg/m2 IV days 1, 29 and 57 (maximum single dose 2mg)

If patient was randomised to standard or Capizzi interim maintenance they will also receive 12mg of intrathecal methotrexate on day 15 of each cycle, as will T-ALL patients presenting with a white cell count of $>100x10^9/L$.

All patients are also to receive co-trimoxazole prophylaxis for PCP throughout treatment (except during protocol M and M-A) with dose depending on body surface area.

Will my participation in this study be kept confidential?

During this study your identity will be protected as defined under the Data Protection Act 1998. When you are first registered onto this study you will be given a study number. This study number, along with your initials and date of birth will be used to identify the data we collect.

Only information needed for this study will be collected. All information will be strictly confidential. By taking part in the trial you will be agreeing to allow research staff to look at the trial records, including your medical records and scan images. Your medical records and all data obtained from this study will be made available to representatives of the study Sponsor and regulatory authorities. This is to make sure the information collected is an accurate reflection of the study.

The information collected will be stored on a secure database for analysis at the University of Leeds, and will only be accessed by authorised people, who have a duty of confidentiality to you. Your GP will also be informed so they understand why you will be having some extra tests. You will not be able to be identified in any report, presentation or publication arising from this trial.

What will happen to the results of the trial?

Results may be published in medical and scientific journals, and presented at international conferences, but your name will not be used in any publications. If you would like to obtain a copy of the published results, please ask your doctor or nurse.

Who has reviewed the trial?

This trial has been reviewed by the an independent Research Ethics Committee. Research Ethics Committees review all research to protect the safety, rights, well being and dignity of patients.

What will happen if I don't want to carry on with the study?

You are free to withdraw from this trial at any time without giving a reason and this will not affect your future treatment. If you decide to withdraw you will be asked to allow the continued collection of follow-up data (you will not need to attend more clinic appointments for this than normal for your condition).

Who is organising and funding the research?

This study is funded by Candlelighters charitable foundation and sponsored by the University of Leeds. No-one will receive payment for taking part in this study.

What if there is a problem?

Any concern or complaint about the way you have been dealt with during the trial or any possible harm you might suffer will be addressed. If you wish to complain or are unhappy about any aspect of the way you have been approached or treated during the course of the study, in the first instance please contact your consultant or a member of the research team- you can use the contact numbers at the end of this sheet. If you are still unhappy you can complain through the hospital complaints department.

Local contact for further information

If you require any further information please contact:

Fighting children's cancer Candle Lighters in Yorkshire

UNIVERSITY OF LEEDS

BONES

British OsteoNEcrosis Study

Patient information sheet for patients aged 16+ years

We would like to invite you to take part in a clinical trial run by the University of Leeds called BONES (British Osteonecrosis Study), which is part of a postgraduate research project. Before you decide whether you want to take part in the study we would like you to understand why the study is being done and what it would involve.

Please take the time to read the following information carefully and discuss it with friends, relatives, doctors and nurses if you wish. Ask us if there is anything that is not clear, or if you would like more information.

You can also visit our website: http://childhealth.leeds.ac.uk/bones.html

What is the purpose of the study?

You have been diagnosed with Acute Lymphoblastic Leukaemia (ALL) or lymphoblastic lymphoma. The treatment is usually very successful and we are now trying to improve treatment further by investigating the side-effects that can occur during and after treatment, in order to reduce these. One of the side effects that can occur in parts of bone is called osteonecrosis. This happens when there is an interruption to the blood supply to the bone which causes changes in the bone itself, and happens most often in the hips, knees, and ankles. If osteonecrosis is severe patients need surgery. However, in many cases where it is less severe the patient may recover fully.

We know that osteonecrosis occurs more commonly in patients over 10 years of age but we don't know why some people develop it and others do not. With this study we hope to learn more about:

- What makes a person more likely to develop osteonecrosis
- When osteonecrosis develops
- What happens to patients when they develop osteonecrosis

Why have I been invited?

You have been invited because you have been diagnosed with ALL or lymphoblastic lymphoma and are aged between 10 years and 25 years. Over the next 2 years a number of hospitals in the UK will be inviting children and young people diagnosed with ALL or lymphoblastic lymphoma to take part in this trial.

Do I have to take part?

No, taking part is entirely voluntary. It is up to you to decide whether or not you want to take part. You can withdraw at any time, without giving a reason. This would not affect the rest of the care that you receive.

Will anyone else know I'm taking part?

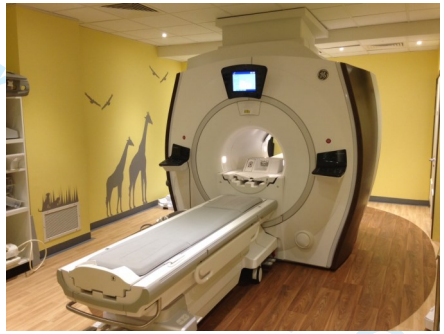
The only people who will know that you are taking part in this study will be the team of doctors, nurses and researchers looking after you.

What will happen if I take part?

Being in the study involves scans, a physiotherapy assessment and a questionnaire. We will also look at your medical records to see the results of some of the tests you are having routinely.

We will look for signs of osteonecrosis by taking pictures of your legs and hips with a special scanner. These are called magnetic resonance imaging (MRI) scans. There will be five scans in total. The first scan will be in the next few weeks. The next scans will be at six months, then one year, two years and three years after you start maintenance treatment. For the scan you will be asked to lie on a table and the table will move through the scanner. It doesn't hurt, and will take around half an hour.

You will also have an appointment with a physiotherapist at roughly the same times as the scan, which will take around 30 minutes. Physiotherapists look at how patients are moving, and they will help us recognise if there are any problems developing with your arms or legs. They will also ask you to complete a questionnaire to see if there seem to be any problems developing.



MRI Scanner

In some centres there will be extra imaging of bones by dual energy X-ray absorptiometry (DXA), which measures bone mineral density and assesses fracture risk . These are routinely performed in some centres, but there is not currently a national standard. We would like to look at the results of these scans, which will be performed at diagnosis and annually, to a total of 4 scans. DXA scans are very safe and painless. You would be required to lie on your side on an X-ray table as a scanner passes over you.

If you agree to take part in this study you will be asked to sign a consent form. You will be a given a copy of it, and this information sheet to keep.

We can reimburse reasonable travel expenses (public transport or car mileage) which are due to being part of this study.

Are there any disadvantages or risks involved in taking part in this study?

If you decide to take part in this trial the leukaemia treatment you receive will be the same as if you choose not to participate.

MRI scans are painless and very safe. They do not involve radiation and there are no known side effects of an MRI scan. There are some cases where an MRI scan may not be recommended, because the strong magnets used during the scan can affect metal implants or fragments in the body. Please let your health care team know if you have any metal in your body. DXA scans use a very low dose of radiation (less than 2 days exposure to normal background radiation), which is much lower than standard X-ray examinations.

There is a possibility we might find something unexpected in your images. If this happens, we will notify you first and you will be referred to the appropriate specialist for further investigation.

Before any trial can start it has lots of safety checks before it can be approved. This study has undergone these checks and we hope that the trial will help improve the treatment for children and young adults with ALL and lymphoblastic lymphoma in the future.

What are the possible benefits of taking part?

The aim of the study is to gain information to improve how we look after young people with ALL or lymphoblastic lymphoma in the future. We are not expecting you to directly benefit from taking part. All the extra tests are only for the study and will not change how you are managed unless something unexpected is seen.

What happens when the trial stops?

At the end of the trial all of the data that has been gathered will be examined, and the results used in the future to help identify patients at highest risk of osteonecrosis, and consider how this risk can be reduced. Anonymised data will be kept for 10 years.

Informed Consent Form (Patient aged 16 years and over)

British OsteoNEcrosis Study

Site_____ **Principle Investigator**_____

Patient Trial Number _____**Trial Reference Number**_____

Please initial each box

1. I confirm that I have read and understood the Patient Information Sheet (version 7, 20/11/2017) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected. ☐
3. I give permission for a copy of this consent form to be sent to the research team based at the University of Leeds. ☐
4. I understand that relevant sections of my medical notes and data collected during the trial may be looked at by individuals from the research team, regulatory authorities, Sponsors and/or NHS bodies, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records and to collect, store, analyse and publish information from this research. I understand that my name will be kept confidential. ☐
5. If I withdraw from the study I agree to allow the continued collection of follow up data. ☐
6. I agree for my GP to be informed about my involvement in this study ☐
7. I agree to take part in the above study. ☐
8. I consent for data from this study to be used in future research projects ☐

Name of patient: _____Date:_____Signature:_____

Name of person taking consent: _____Date:_____Signature:_____

BONES: The British OsteoNEcrosis Study: A prospective multi-centre study to examine the natural history of osteonecrosis in older children, teenagers and young adults with acute lymphoblastic leukaemia

Aims

The aim of this research is to examine the natural history of osteonecrosis in older children, teenagers and young adults with acute lymphoblastic leukaemia within the UK.

Objectives

The objective is to establish a prospective, multi-centre study for older children, teenagers and young adults which can address the following questions:

- What is the incidence of osteonecrosis in older children, teenagers and young adults being treated for acute lymphoblastic leukaemia (ALL) in the UK at different time points in their treatment?
- What are the risk factors for progression and the development of symptomatic osteonecrosis in this population?
- Are there specific radiological features that predict for either progression or regression in those with asymptomatic osteonecrosis?

Background

Survival from acute lymphoblastic leukaemia (ALL) has steadily increased over the last 40 years so that we now expect to cure >90% children and young people presenting with ALL. This progress shifts the entire treatment paradigm so that the goal moves beyond simply cure to returning the young person to a normal life. The biggest barrier to this is the burden of treatment associated toxicity and attention internationally is now turning to this. Osteonecrosis (previously also referred to as avascular necrosis, ischaemic necrosis and aseptic necrosis) is one of the most

devastating complications seen in older children and teenagers treated for ALL, and can cause significant long term morbidity.

However, despite increasing concern about osteonecrosis, our understanding is limited. Historically, information about osteonecrosis has not been well captured in previous studies of ALL - either in the UK or in other countries. This partly reflects lack of good definitions and piecemeal reporting. These deficiencies have been acknowledged and there is now an international will to address them. The starting point for this is standardisation of definitions, for which we can use the The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4[1], which will allow future comparison (see appendix 1). It is imperative that we maximise the potential of the current UK study, UKALL 2011, to further understanding of osteonecrosis in this population.

Osteonecrosis is one of the most debilitating complications seen after or during treatment for ALL, and is mostly an iatrogenic complication that has been attributed mostly to increased use of glucocorticoids[2]; asparaginase, high dose methotrexate and cyclophosphamide have also been implicated. Development of osteonecrosis appears to be multifactorial, but is being seen more commonly in patients as survival improves and high dose steroids have become imbedded in treatment regimens. Osteonecrosis occurs when there is bone ischaemia and infarction caused by temporary or permanent disruption to the blood supply and in ALL typically affects the femoral head, humeral head, knee, shoulder and ankles. Glucocorticoids predispose to the development of osteonecrosis in a number of ways, with proposed aetiologies including:

- Creation of a hypercoagulable state with endothelial cell apoptosis and development of microthrombi;
- Suppression of osteoblasts and apoptosis of osteocytes impairing the bone repair process;
- Stimulation of intramedullary lipocyte proliferation and hypertrophy resulting in increased intraosseous pressure.

These factors combine to compromise blood circulation to the bone leading to cell death in a self-perpetuating cycle[3].

The most comprehensive prospective study to examine osteonecrosis in children with ALL examined 364 patients and reported a cumulative incidence of 72%, of which 18% had symptomatic osteonecrosis [4]. Symptomatic osteonecrosis was associated with a low serum albumin and high serum cholesterol, both of which were also associated with ACP1 polymorphisms. Severe osteonecrosis was associated with poor dexamethasone clearance. There are many more reports which rely on proactive reporting to the study centre, with no identification of asymptomatic osteonecrosis, and as expected these tend to give far lower incidences. These range from 0.67% [5] to 15% [6].The UK data suggests that 4% had symptomatic osteonecrosis in UKALL 2003 [7], but it is recognised anecdotally that many patients with symptomatic osteonecrosis were not reported by clinicians in UKALL 2003.

Despite the variation in the reported incidence across the different study protocols, there is striking agreement in some of the risk factors for the development of osteonecrosis, with significant controversy in others. Age has consistently been associated with increased risk with symptomatic necrosis, with patients aged <10 years at diagnosis at much lower risk of development of osteonecrosis[4]. The significance of female sex as a risk factor for development of osteonecrosis is less clear. A number of studies found it was a risk factor , while it appeared to be non-significant in other studies , even when similar treatment regimens were used [8]. Even in groups with highest rates of osteonecrosis there are disparate results - the CCG study reported the disorder more frequently in females [8], whilst no gender difference were found in the DFCI ALL consortium [9] and studies at SJCRH [10]. In the study by Mattano in 2000 [11] the gender difference was greatest in the 10-15 year age group, with 3 year rates of 19.2% for females and 9.8% for males.

Ethnicity is notoriously difficult to capture. White race was found to be a risk factor in a number of studies, but not in others[8, 10, 12] .

A number of candidate genes have been proposed. In the prospective study by Kawedia et al [13]single nucleotide polymorphism (SNP) genotyping was performed. After adjustment for age and treatment arm 423 SNPs were associated with

symptomatic osteonecrosis, of which 27 were associated with low albumin or high cholesterol. The top 4 SNPs were in the SH3YL1-ACP1 gene locus. ACP1 is associated with serum cholesterol and triglyceride levels [10], and regulates osteoblast differentiation [4]. Higher serum cholesterol and lower serum albumin have been associated with grade 2-4 osteonecrosis, suggesting that ACP1 may act via multiple mechanisms to affect bone homeostasis.

Dexamethasone, which is now the steroid of choice in the UK protocols, in view of its superiority over prednisolone in reducing central nervous system relapse, may be associated with an increase in osteonecrosis compared with prednisolone.

Mattano et al [8] reported higher incidence of osteonecrosis in paediatric patients with ALL treated with dexamethasone during induction phase than in those treated with prednisone (11.6% and 8.7%, respectively). This difference between these types of corticosteroids was observed only in patients' age 13 years or older, suggesting that older children may be more vulnerable to the effect of dexamethasone. Similarly, 11% of children treated with dexamethasone developed osteonecrosis in one UK report compared with only 3.5% those on prednisolone [4]. However, a much larger prospective study analysing results from UKALL97 and UKALL97/99 [14] found no excess of ON in the dexamethasone arm of the trial, but only assessed NCI grade 3 or 4 toxicity, so the impact of dexamethasone versus prednisolone in development of osteonecrosis remains unclear.

In the current UKALL 2011 study there is an upfront randomisation to standard versus short course dexamethasone. Standard dexamethasone consists of 4 weeks of dexamethasone 6mg/m2 with a further weaning week. Short course dexamethasone consists of two weeks of dexamethasone 10mg/m2. This is given for the first two weeks consecutively in children <10 years old, or split so that it is given for weeks 1 and 3 in older children and those with Down syndrome. The CCG1961 trial evaluated components of therapeutic intensification in high-risk patients (white cell count ≥50x10^9 and/or age ≥10 years). It was found that use of alternate week rather than continuous dexamethasone during delayed intensification in high risk ALL patients results in a 2-fold reduction in the relative risk of symptomatic osteonecrosis among rapid responders aged ≥10years, and particularly

those over the age of 16 years. There was a four-fold reduction among those randomised to intensified therapy, despite those with alternate week dexamethasone having a higher total dexamethasone exposure. The incidence of ON was lower among slow responders age ≥ 10 years assigned to double delayed intensification with alternate-week dexamethasone when compared to a similar cohort on the CCG1882 trial [15] who were assigned to two delayed intensification phases with continuous dexamethasone (11.8% versus 23.2%), and could indicate that in this particular patient population dosing manner supersedes cumulative exposure. UKALL 2011 offers the first opportunity in the UK to examine the effects on osteonecrosis toxicity of short compared with standard dexamethasone.

It is recognised that osteonecrosis may regress, although the reasons for this are not understood. It is possible that some radiological changes interpreted as representing steroid associated osteonecrosis are in fact changes which have been present at diagnosis and which are a consequence of the original leukaemia. In the prospective study of 364 children[16], 39% had osteonecrosis changes on their initial MRI, but were asymptomatic. The majority of this group, 74%, did not go on to develop symptomatic osteonecrosis. The current radiological classifications use a multi-modal approach combining scores for clinical, x-ray, MRI and in some cases bone scan findings. They were developed specifically for changes in the femoral head, over 20 years ago and in an entirely different patient population.

In addition to using internationally agreed standard definitions for osteonecrosis (appendix 1), this study will provide the data needed to develop a radiological classification which correlates with clinical status.

Given the very significant morbidity associated with osteonecrosis it is imperative that the opportunity afforded by the UKALL study to examine this is maximised. Only once this is done can meaningful intervention studies to try to reduce the burden of osteonecrosis be initiated. Osteonecrosis should not be a price that young people pay for cure.

Method

Participants

Children, teenagers or young adults between the age of 10 (including the day of the 10th birthday) and 24 years 364 days (at the time of diagnosis) with a first diagnosis of acute lymphoblastic leukaemia or lymphoblastic lymphoma (T-NHL or SmIg negative precursor B-NHL) diagnosed under standard criteria are eligible for BONES. Written informed consent is required for all patients.

Recruitment

Patients will be recruited locally by the primary treatment centre.

Target recruitment

The recruitment target is 50 patients over a 2 year period, which is based on an anticipated ascertainment target of 75%. This is an observational study and there is therefore no relevant power calculation.

Data collection

Information will be collected on basic demographics, presenting features and diagnosis at initial recruitment (see appendix 2). Further data will be collected at 4 subsequent time-points detailed below to ascertain treatment and response, along with results of relevant investigations performed (see appendix 3). The clinician completing the form will access investigation results from the patient's medical records. Clinical information collected in clinic/ hospital will include height, weight and phase of puberty. At each time point (5 in total) further data will be collected, including MR imaging of lower limbs, physiotherapy assessment using a structured assessment tool, and routine clinical and biochemical information(see appendices 4, 5 and 6). Bone mineral density and lateral vertebra assessment will be assessed at diagnosis and annually to a total of 4 assessments.

Investigations

The results of the following investigations will be collected:

The following are usually performed as part of the routine assessment:

At diagnosis /earliest results obtained during induction)- highest white cell count, immunophenotype, cytogenetics, molecular results; albumin; lipid profile; vitamin D level, bone profile (calcium, phosphate, PTH, ALP)

At the end of induction (results nearest to day 29) - MRD result, flow cytometry from end of induction bone marrow; albumin; lipid profile

DXA scans results (performed at diagnosis and annually) – lumbar spine bone mineral apparent density (measured in AP direction L1-4) Z-scores, and total body less head Z-scores. Vertebral fractures would be assessed with DXA lateral vertebral assessment of thoracic and lumbar vertebra (T4-L4 if possible), using the Genant semi-quantitative method. If DXA VFA is not available, lateral thoracolumbar spine radiographs can be used instead and assessed using the same method.

Pelvic X-rays and full joint assessment via MRI which are performed if significant problems are identified by the clinical team, according to orthopaedic opinion.

Investigations specific to patients recruited into the study:

At the following time-points, patients recruited into the study will have additional assessment:

Within 4 weeks of diagnosis

At the end of delayed intensification

One year after the start of maintenance

Two years after the start of maintenance

Three years after the start of maintenance

The additional assessment will include:

MRI of the hips, knees and ankles. These should comprise of unenhanced coronal T1 and STIR images as a minimum protocol. Knees and ankles can be imaged together. Where further information of a specific joint is needed pre-treatment additional sequences in different planes could be performed at the discretion of the participating centre.

Physiotherapy assessment, including completion of patient questionnaire.

In centres where annual DXA and lateral vertebral assessment is not standard of care, additional annual assessments will be requested where facilities exist.

The MRI images obtained are not routine MRI scans, as they are being done according to a study protocol developed for BONES, and are not for local interpretation. Local reports should simply say that images are for trial purposes only. If a significant abnormality (not osteonecrosis) is found when images are centrally reviewed, information will be fed back to the local centre. In the event of the development of symptomatic osteonecrosis, which is diagnosed locally, the patient should be managed according to local protocols and at the discretion of their own consultant (see appendix 7). Information on treatment and outcomes will be collected.

Radiological review

A central review panel consisting of Paediatric Radiologists with an interest in paediatric haematology will review each MRI in order to agree the grade of osteonecrosis and noting specific features according to the study radiology *proforma*.

There will also be retrospective central analysis of DXA and lateral vertebral assessment results. Vertebral fracture prevalence will be assessed on lateral vertebral assessment using the Genant semi-quantitative method.

Data management

Information will be collected centrally at the University of Leeds.

Local data management:

Local clinician to complete forms at each time point.

Local physiotherapist to collect questionnaire data, and complete physiotherapy assessment form.

Both forms to be anonymised locally, with only trial number, initials and date of birth (in form of month/year) available on forms.

PI at local centres to be custodians of local data, and to have research file at site of personal data.

Trial centre to send separate encrypted spreadsheet of trial number, date of birth and sex to CI.

Forms and spreadsheet to be sent by secure e-mail. Consent forms to be sent to CI.

Personal data relating to study to be destroyed by PI at end of storage period (10 years).

Radiographic data:

Anonymised images of MRI scans to be put onto CD, (only trial number on disk).

Anonymised DXA scans and lateral vertebral assessment images to be put onto CD (only trial number on disk)

Both sent to CI

Central data management:

MRI and DXA CDs, forms and consent forms to be secured in locked filing cabinet in University of Leeds, in secure room. Only CI and members of research team to have access to this filing cabinet.

Electronic database to be created with trial numbers, date of birth (mm/yy), sex and of investigations/questionnaires.

Database to be stored on CI University M drive, a secure, password protected, University of Leeds server. A copy will be held by one of the MD research supervisors (Dr Feltbower) on their secure password protected University of Leeds server, and only available to relevant members of the research team. They will also provide the long term storage of data, after completion of student research time.

CI to be responsible for deleting data from database at end of storage period.

Statistical analysis

Epidemiology Unit located within the University of Leeds.

Participant reimbursement of expenses

Patients or their parents will be reimbursed for excess travel expenses. This will be reimbursement of public transport expenses, or car mileage (24p/mile) to a maximum of £20/ journey. Patients can claim travel expenses through petty cash arranged locally or equivalent local arrangements.

Appendix 1. Definition of osteonecrosis

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 defines ON as 'a disorder characterised by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, necrotic changes result in the collapse and the destruction of the bone structure'.

Grade	
1	Asymptomatic; clinical or diagnostic observations only, intervention not indicated.
2	Symptomatic; limiting instrumental ADL
3	Severe symptoms; limiting self care ADL; elective operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated

CTCAE v 4.0 definition and grading of osteonecrosis

Appendix 2. Form to be completed at initial recruitment

Initials _____

Date of birth _____

Trial Number _____ Sex male/female/prefer not to say

Date of initiation of therapy _____ Ethnicity_____

Recruiting centre _____

Patient postcode _____

Highest white cell count _____ x 10^9/l date _____

Immunophenotype _____

Cytogenetics _____

Molecular results _____

Height (cm) _____ Weight (kg) _____

Pubertal Status: Pre-pubertal/in puberty/completing puberty

	Pre-puberty (Tanner stage 1)	In Puberty (Tanner stage 2-3)	Completing Puberty (Tanner stage 4-5)
Girls	If all of the following: No signs of pubertal development	If any of the following: Any breast enlargement pubic or axillary hair	If all of the following Started periods with signs of pubertal development

Boys	If all of the following: High voice and No signs of pubertal development	If any of the following: Slight deepening of the voice Early pubic or axillary hair growth Enlargement of testes or penis	If any of the following: Voice fully broken Facial hair Adult size of penis with pubic and axillary hair

Hepatomegaly yes / no

Splenomegaly yes / no

Palpable lymphadenopathy yes / no

Duration of symptoms before diagnosis _____

Was bone pain present at diagnosis? yes / no

Please document units for all available blood test results:

Serum albumin _____date_____

Lipid profile:

- HDL _____date_____
- LDL _____date_____
- Cholesterol _____date_____
- Triglycerides _____date_____

25-Hydroxyvitamin D _____date_____

PTH _____date_____

Alkaline phosphatase _____date_____

Calcium _____date_____

Phosphate _____date_____

Completed by : _____date_____

Appendix 3. Form to be completed at day 29 of induction

Trial number _____ Patient initials_____

Date of day 29 of induction _____

Recruiting centre_____

Treatment regimen for induction A / B

Treatment regimen for consolidation A / B / C

If changed, why was this? _____

flow cytometry results at end of induction _____

MRD status at end of induction low / high / not able to be assessed

Please document units for all available blood test results as close to day 29 as possible:

Serum albumin _____date_____

Lipid profile:

- HDL _____date_____
- LDL _____date_____
- Cholesterol _____date_____
- Triglycerides _____date_____

25-Hydroxyvitamin D _____date_____

PTH _____date_____

Alkaline phosphatase _____date_____

Calcium _____date_____

Phosphate _____date_____

Completed by :

_____date_____

If vitamin D was low, has this been treated? yes / no

If yes, please document treatment_____

Date of induction MRI _____

Completed by : _____ date

_____

Please also send anonymised MRI images on disk to Chief Investigator

Appendix 4. Form to be completed and sent with relevant images at the end of delayed intensification, 1 year after start of maintenance, 2 years after start of maintenance, 3 years after start of maintenance

Trial number_____ Patient initials_____

Recruiting centre_____

Timepoint (please circle and date)

Timepoint	Date
end of delayed intensification	
1 year after start of maintenance	
2 years after start of maintenance	
3 years after start of maintenance	

Treatment regimen for interim maintenance A standard interim maintenance

A high dose methotrexate

B standard interim maintenance

B high dose methotrexate

C Capizzi

C high dose methotrexate

Treatment regimen for maintenance vincristine/dexamethasone pulses

no pulses

Have there been any treatment modifications yes / no

If yes, please provide further details _____

Please document units for all available blood test results:

Serum albumin _____date_____

Lipid profile:

- HDL _____date_____
- LDL _____date_____
- Cholesterol _____date_____
- Triglycerides _____date_____

25-Hydroxyvitamin D _____date_____

PTH _____date_____

Alkaline phosphatase _____date_____

Calcium _____date_____

Phosphate _____date_____

At the time of each scan:

Height _____ Weight _____

Pubertal status: Pre-pubertal/in puberty/completing puberty

	Pre-puberty (Tanner stage 1)	In Puberty (Tanner stage 2-3)	Completing Puberty (Tanner stage 4-5)

Girls	If all of the following: No signs of pubertal development	If any of the following: Any breast enlargement pubic or axillary hair	If all of the following Started periods with signs of pubertal development
Boys	If all of the following: High voice and No signs of pubertal development	If any of the following: Slight deepening of the voice Early pubic or axillary hair growth Enlargement of testes or penis	If any of the following: Voice fully broken Facial hair Adult size of penis with pubic and axillary hair

Has there been a diagnosis of osteonecrosis since the last report? yes / no

If yes, when was this? date_____

Which joints are affected? _____

Which of the following have occurred: steroids stopped yes / no

mobility problems yes / no

core decompression yes / no

joint replacement yes / no

Has a DXA/ lateral vertebral assessment been performed in the last year?

yes / no

If yes, please attach report and send anonymised images.

Have bisphosphonates been used? yes / no

If yes, then please give details regarding start date, type, dose and frequency of treatment

_____

Completed by : _____ date _____

Please also attach physiotherapy assessment and send anonymised MRI images on disk to Chief Investigator

Appendix 5. Physiotherapy Assessment

At physiotherapy assessment:

For completion by physiotherapist:

Trial number:	Patient initials:
Recruiting centre:	Date:

For completion by participant

BONES

British OsteoNEcrosis Study

Activity Levels

On a typical day, on average how many hours of the day are you active for e.g. walking, playing, exercising …….hours

Mobility

Since you were last seen (if relevant), were you told to continue to fully/ partially or not weight bear? Full/Partial/None

If you use a walking aid, what hand do you use it in? Right/Left/Both

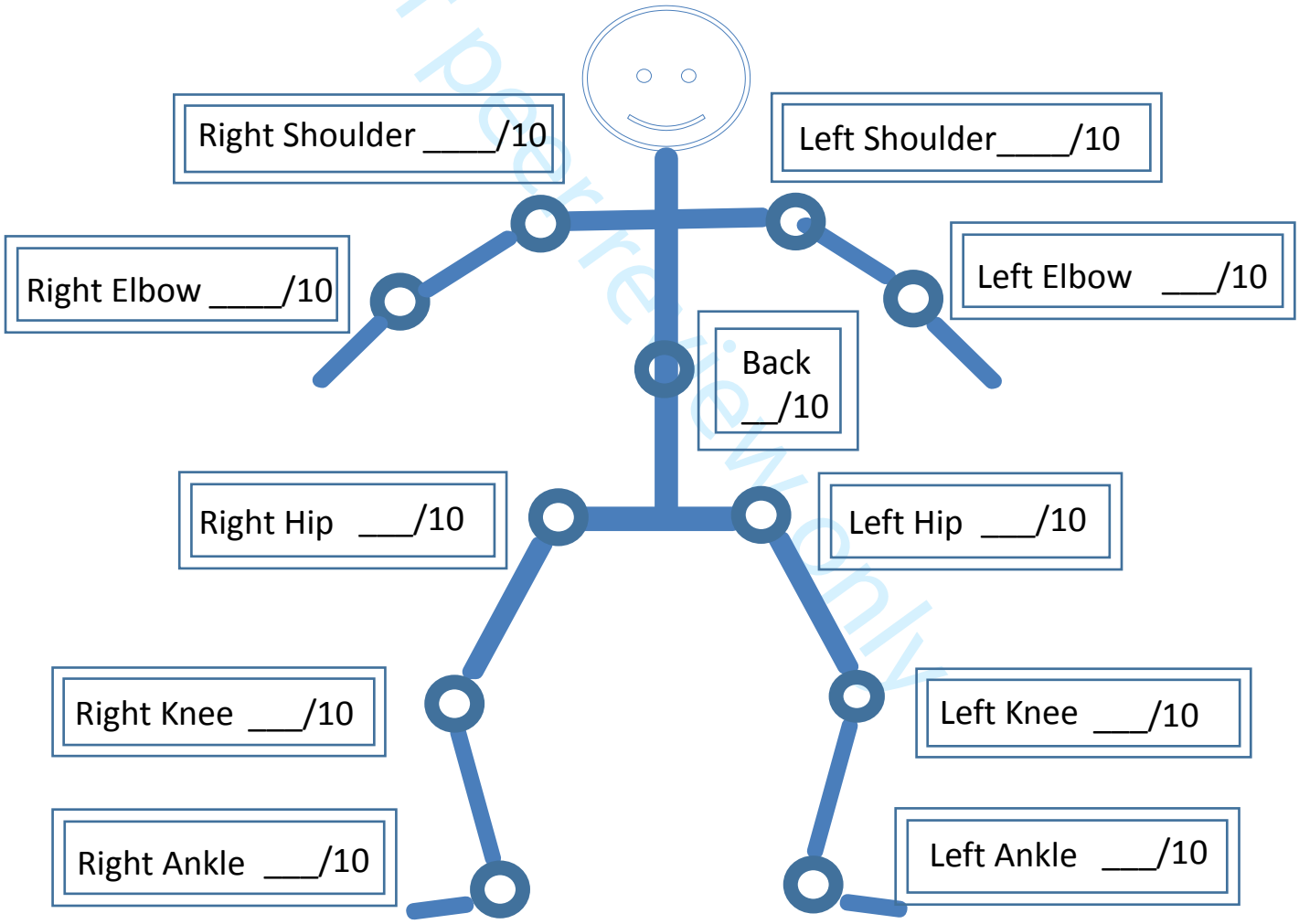
If you use a walking aid, how long have you been using it for?.....

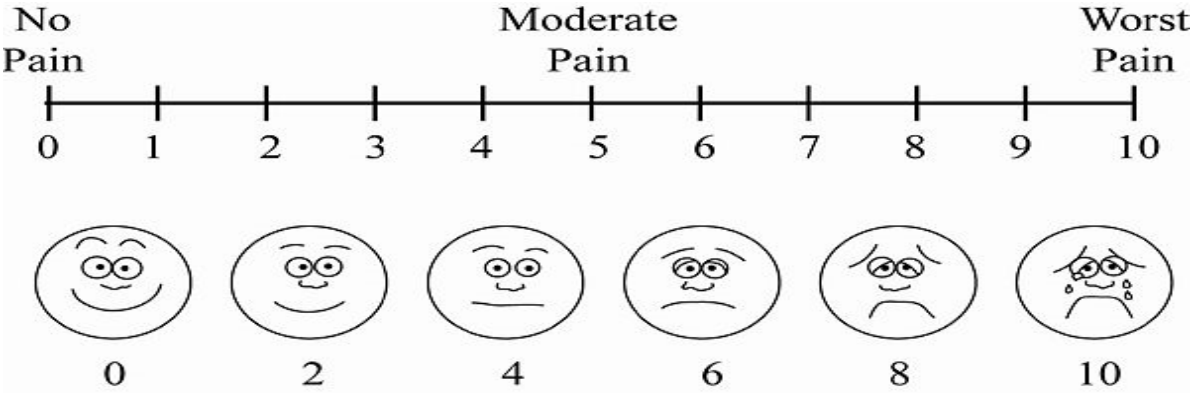
If you use a wheelchair, when going out, how often do you use it? Always/ Usually/ Occassionally/ Rarely/ Never?

Pain/Discomfort

Pain Scale:

Please score pain in each joint out of 10, using the scale below the diagram:





C.H.A.Q.

Childhood health assessment questionnaire

Trial Number:	DOB	Date:

- We are interested in learning how a child or young person's long term illness affects his / her ability to function in daily life. This will help the assessment in clinic.
  This form can be completed by the child / young person themself or their parent or carer
- For the following questions, please tick one response which best describes the young person's / child's function **OVER THE LAST WEEK**
- **PLEASE ONLY NOTE THOSE DIFFICULTIES WHICH ARE DUE TO THE LONG TERM ILLNESS**
- Please note that there are **2 pages** and that for very young children the answer to many questions will be 'Not Applicable'

DRESSING & PERSONAL CARE	**Without ANY Difficulty**	**With SOME Difficulty**	**With MUCH Difficulty**	**UNABLE To Do**	**Not Applicable**
- Dress, including tying shoelaces and doing buttons?	☐	☐	☐	☐	☐
- Shampoo hair?	☐	☐	☐	☐	☐
- Remove socks?	☐	☐	☐	☐	☐
- Cut fingernails?	☐	☐	☐	☐	☐
GETTING UP					
- Stand up from a low chair or floor?	☐	☐	☐	☐	☐
- Get in and out of bed or stand up in a cot?	☐	☐	☐	☐	☐
EATING					
- Cut own meat?	☐	☐	☐	☐	☐
- Lift a cup or glass to mouth?	☐	☐	☐	☐	☐
- Open a new cereal box?	☐	☐	☐	☐	☐
WALKING					
- Walk outside on flat ground?	☐	☐	☐	☐	☐
- Climb up five steps?	☐	☐	☐	☐	☐

Please tick any AIDS or DEVICES that are usually needed for any of the above activities:

Walking	☐	Devices used for dressing (button hook, zip pull, long-handled shoe horn, etc.)	☐
Walking Frame	☐	Build up pencil or special utensils	☐
Crutches	☐	Special or built up chair	☐
Wheechair	☐	Other (Specify: ……..)	☐

Please tick any categories for help is usually needed from another person BECAUSE OF PAIN OR ILLNESS:

Dressing and personal care	☐	Eating	☐
Getting up	☐	Walking	☐

HYGIENE	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	Not Applicable
- Wash and dry entire body?	☐	☐	☐	☐	☐
- Take a bath (get in and get out)?	☐	☐	☐	☐	☐
- Get on and off the toilet or potty?	☐	☐	☐	☐	☐
- Brush teeth?	☐	☐	☐	☐	☐
- Comb / brush hair?	☐	☐	☐	☐	☐
REACH					
- Reach and get down a heavy object such as a large game or books from above?	☐	☐	☐	☐	☐
- Bend down to pick up clothing or a piece of paper from the floor?	☐	☐	☐	☐	☐
- Pull on a jumper over head?	☐	☐	☐	☐	☐
- Turn neck to look back over shoulder?	☐	☐	☐	☐	☐
GRIP					
- Write or scribble with a pen or pencil?	☐	☐	☐	☐	☐
- Open car doors?	☐	☐	☐	☐	☐
- Open jars which have been previously opened?	☐	☐	☐	☐	☐
- Turn taps on and off?	☐	☐	☐	☐	☐
- Push open a door when need to turn a door knob?	☐	☐	☐	☐	☐
ACTIVITIES					
- Run errands and shop?	☐	☐	☐	☐	☐
- Get in and out of a car or toy car or school bus?	☐	☐	☐	☐	☐
- Ride bike or tricycle?	☐	☐	☐	☐	☐
- Do household chores (e.g. wash dishes, take out rubbish, hoovering, gardening, make bed, clean room)?	☐	☐	☐	☐	☐
- Run and play?	☐	☐	☐	☐	☐

Please tick any AIDS or DEVICES that are usually needed for the following activities:

Raised toilet seat	☐	Bath rail	☐
Bath seat	☐	Long-handled appliances for reach	☐
Jar opener (for jars previously opened)	☐	Long-handled appliances in bathroom	☐

Please tick any categories for which help is usually needed from another person BECAUSE OF PAIN OR ILLNESS:

Hygiene	☐	Gripping and opening things	☐
Reach	☐	Errands and chores	☐

PAIN: How much pain has been experienced IN THE PAST WEEK? Place a mark on the line below, to indicate the severity of the pain

No Pain — **Very severe pain**

0 — **10**

GENERAL EVALUATION: Considering all the ways affected by pain or illness, rate how the patient is doing by placing a single mark on the line below.

Very well — **Very poor**

0 — **10**

Any concerns / questions you would like to discuss?

.....

.....

Appendix 6: Physiotherapy assessment

For completion by physiotherapist:

Trial number:	Patient initials:
Recruiting centre:	Date:

Gait Analysis

……

……

……..

ROM and Muscle power

	Muscle power (0-5)	Full range of movement	If limited range of movement, please enter degree and plane of movement that is restricted
Right hip		Yes/No	
Left hip		Yes/No	
Right knee		Yes/No	
Left knee		Yes/No	
Right ankle		Yes/No	
Left ankle		Yes/No	
Right Shoulder		Yes/No	
Left Shoulder		Yes/No	

If joints are limited please comment on why below e.g pain/stiffness

……

……

……

……

Assessment completed by Print …….

Signed ……

Date ……

Appendix 7. Management of osteonecrosis

Whilst this is an observational study, it is recognised from previous experience, that management advice may be sought when a young person develops osteonecrosis. The guidelines below represent the usual practice of the clinicians involved in designing the study and are in no way mandated.

Recommendations

1. Asymptomatic ON detected coincidentally.

No evidence to suggest discontinuation of dexamethasone is routinely indicated in asymptomatic cases.

Monitor closely and early repeat MRI if symptomatic

Consider orthopaedic referral. The risk of collapse of the femoral head is affected by the location and extent of the necrotic lesion. All femoral head lesions which are either large or extend to the edge of the epiphysis should be referred to orthopaedic team for consideration of core decompression in order to prevent femoral head collapse. Using MRI images in both coronal and sagittal planes the Kerboul combined necrotic angle is a good MRI-based method to assess risk of hip collapse.

2. Symptomatic ON.

Confirm and document duration of symptoms in affected joint/joints. Review all other joints.

Organise physiotherapy assessment.

Review vitamin D and bone profile results.

Consider continuation of dexamethasone and 6 monthly MRI screening to detect progression of ON.

For persistent/worsening symptoms or MRI progression, reduction/discontinuation of dexamethasone will need to be considered. If in doubt contact trial coordinators in these cases.

Consider orthopaedic referral (see 1c above)

Routine use of bisphosphonates can ONLY be recommended in patients with coexisting osteoporosis, defined by reduced bone mineral density and presence of low-impact fractures (ISCD Criteria) or as part of a clinical trial.

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