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

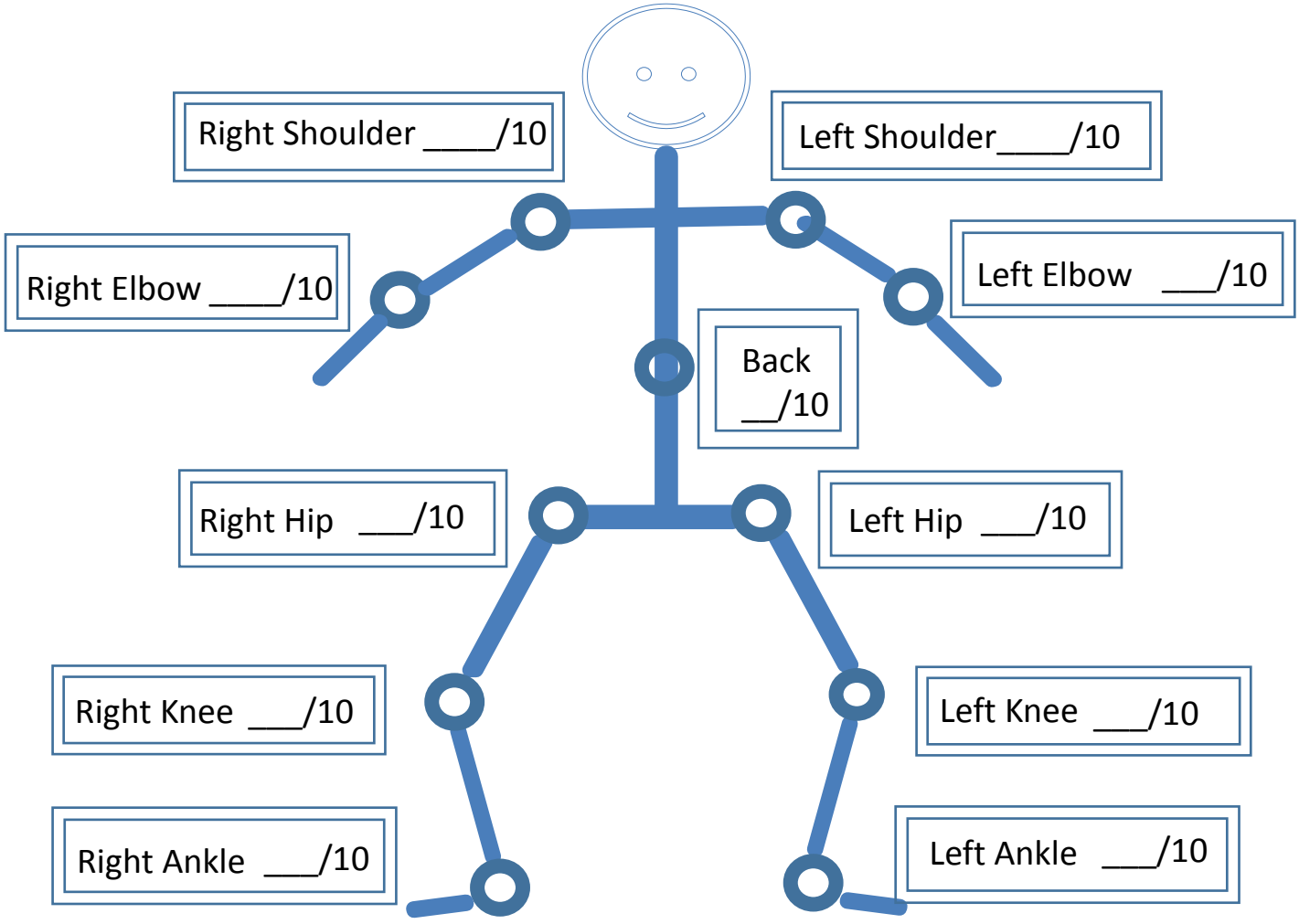
If you use a walking aid, how long have you been using it for?.....

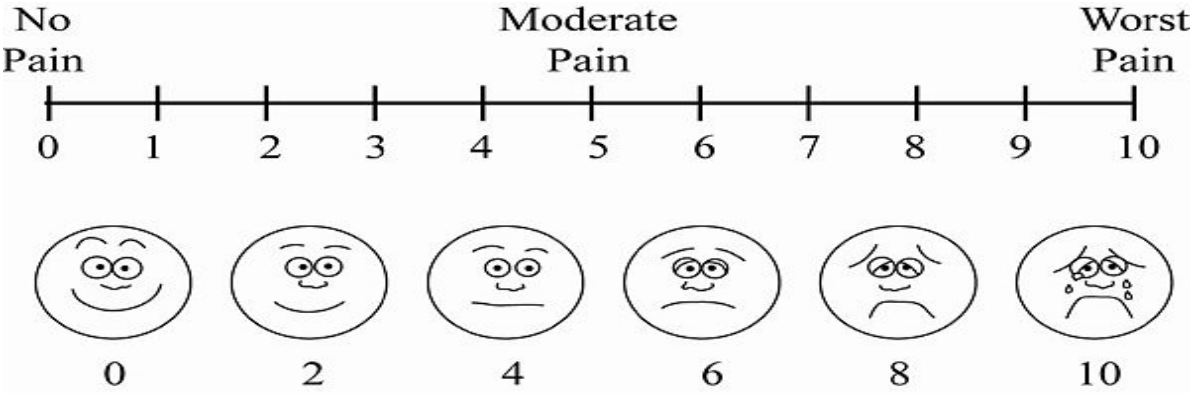
If you use a wheelchair, when going out, how often do you use it? Always/ Usually/ Occassionally/ Rarely/ Never?

Pain/Discomfort

Pain Scale:

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




No Pain
Moderate Pain
Worst Pain
0 1 2 3 4 5 6 7 8 9 10
0 2 4 6 8 10

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?	☐	☐	☐	☐	☐

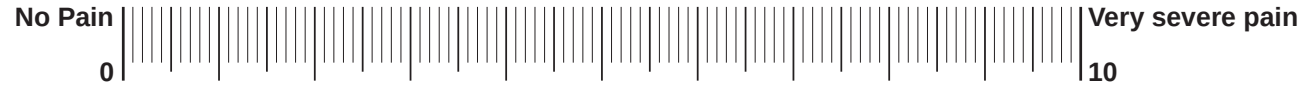
Please tick any AIDS or DEVICES that are usually needed for the following activities:

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

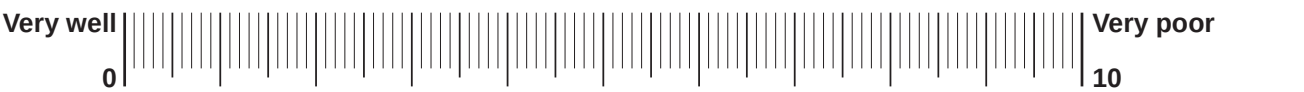
Please tick any categories for which help is usually needed from another person BECAUSE OF PAIN OR ILLNESS:

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



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.



Any concerns or questions you would like to discuss?

IRAS Project ID: **185365**

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.

References

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