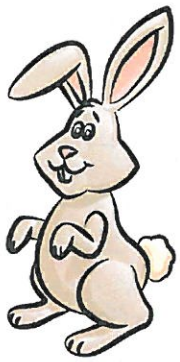
HIP 'OP



Timing of Surgical Intervention for Developmental Dysplasia of the Hip

Version 3.0
22-April-2015

SPONSOR: Southampton University Hospital NHS Foundation Trust

COORDINATING CENTRE: Southampton Clinical Trials Unit

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Protocol authorised by:

Name: **Professor NMP Clarke** ChM, DM, FRCS **Role:** **Chief Investigator**

Signature: N.M.C **Date:** 11-5-15

MAIN TRIAL CONTACT

Chief Investigator and Medical Expert: Professor NMP Clarke

University Orthopaedic Surgical Unit
Mail Point 817
Level C South Academic Block
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD

Tel: 02381 206140
Email: ortho@soton.ac.uk

COORDINATING CENTRE

For general trial and clinical queries e.g. patient queries, trial supplies, data collection, please contact in the first instance:

Hip 'Op Clinical Trial Coordinator – hipop@soton.ac.uk

Address: Southampton Clinical Trials Unit (SCTU)
Mail Point 131
Southampton General Hospital
Tremona Road
SOUTHAMPTON
SO16 6YD

Tel: 02381 205154
Fax: 0844 774 0621
Email: ctu@soton.ac.uk
Web: www.southampton.ac.uk/ctu

Randomisation: will be done via the Tenalea website and training will be given to all relevant staff

SAE Reporting

Email: ctu@soton.ac.uk
Fax: 0844 774 0621

SPONSOR

University Hospital Southampton NHS Foundation Trust is the research sponsor for this trial. For further information regarding sponsorship conditions, please contact the Director of Research and Development at:

Address: R&D Department
University Hospital Southampton NHS Foundation Trust
Southampton General Hospital, Level E, Laboratory & Pathology Block, SCBR, MP 138
Tremona Road
SOUTHAMPTON
SO16 6YD

Tel: 02381 204989
Fax: 02381 208678
Web: www.uhs.nhs.uk

FUNDER: This trial is funded by the NIHR Health Technology Assessment (HTA) programme.

Protocol Information

This protocol describes the Hip 'Op trial and provides information about procedures for entering patients. The protocol should not be used as a guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering patients for the first time are advised to contact Southampton Clinical Trials Unit or visit: www.southampton.ac.uk/ctu to confirm they have the most recent version.

Compliance

This trial will adhere to the principles of GCP. It will be conducted in compliance with the protocol, the Data Protection Act and all other regulatory requirements, as appropriate.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AP	Anterior Posterior
AVN	Avascular Necrosis
CarerQol	Care Related Quality of Life Questionnaire
CDH	Congenital Dislocation of the Hip
CRF	Case Report Form
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
DDH	Developmental Dysplasia of the Hip
DT	Delayed Treatment
ET	Early Treatment
GCP	Good Clinical Practice
HUI	Health Utility Index
HTA	Health Technology Assessment
ICF	Informed Consent Form
ITT	Intention To Treat
NHS	National Health Service
NIHR	National Institute for Health and Research
ON	Ossific Nucleus
PedsQL	(Measurent model for the) Paediatric Quality of Life Inventory
PI	Principal Investigator
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
TMG	Trial Management Group
TSC	Trial Steering Committee
SCTU	Southampton Clinical Trials Unit

KEYWORDS

Hip Dysplasia
Splintage
Avascular Necrosis (AVN)
Outcome
Closed/Open Reduction

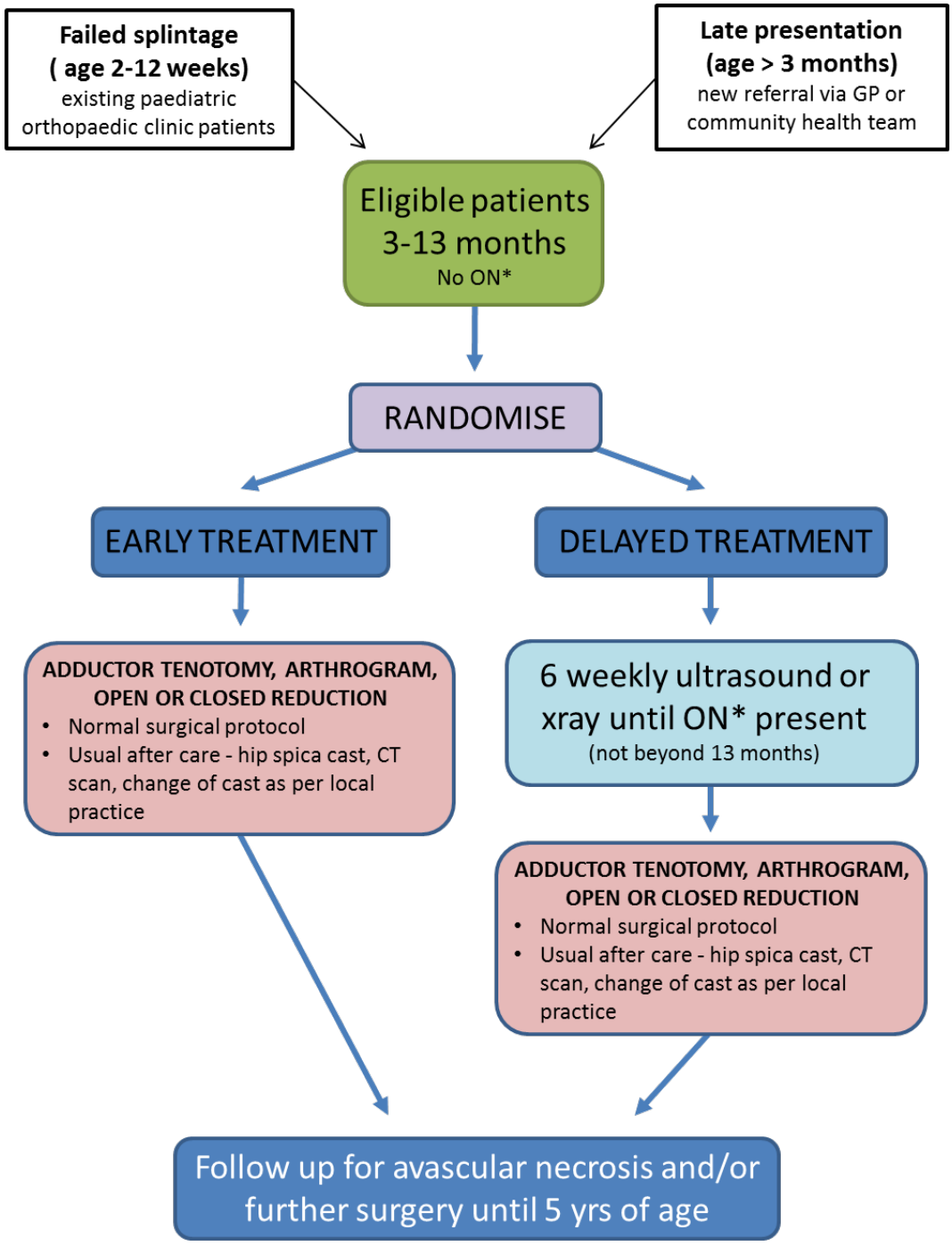
TRIAL SYNOPSIS

Title:	Hip 'Op - Timing of surgical intervention for Developmental Dysplasia of the Hip
Sponsor:	University Hospital Southampton NHS Foundation Trust (UHS)
Sponsor Ref Number:	RHM CHI-0716
Funder:	The National Institute for Health and Research (NIHR) Health Technology Assessment (HTA) are funding this trial
Trial Phase:	Phase III
Indication:	Developmental Dysplasia of the Hip
Primary Objective:	To assess the effect of timing of surgical intervention on the occurrence of Avascular Necrosis (AVN)
Secondary Objective:	To assess: ▪ The need for secondary surgery (for subluxation/dysplasia/AVN) ▪ Presence or absence of ossific nucleus (ON) at time of primary treatment for dysplasia ▪ Quality of life for the main carer ▪ Quality of life for the child ▪ Health Economics ▪ Qualitative analysis of the impact of early versus intentionally delayed surgery for developmental dysplasia of the hip on the family
Health Economic measures	We will conduct a detailed analysis of the cost and cost-effectiveness of early versus intentionally delayed treatment for children with developmental dysplasia of the hip (DDH). Our analysis will conform to accepted economic evaluation methods. We will estimate cost and cost-effectiveness for the 'within-trial' period (5 years) and over the expected lifetime of participants Health-related quality of life will be measured using the following validated instruments: CarerQol, Oucher and PedsQL. We will also measure NHS resource use and family costs. Utilities will be derived using HUI-3
Qualitative Measures	At 3 or 4 months post-surgery all participants in the RCT will be surveyed to determine the acceptability of the intervention and their experiences. Pilot work will be conducted with 20 families (10 in each group) and, based on these responses, 30 further families will be purposively sampled i.e. 15 more in each group, (this number is consistent with qualitative approaches and will involve sampling to cover a range of experiences for both intervention groups). They will be asked to take part in a telephone-based interview, which will take place around 6 months post-surgery and again with the same families at age 5 years, to establish parents' experiences beyond the rehabilitation phase.

Rationale:	To determine whether children between the ages of 12 weeks 13 months with DDH benefit from early or intentionally delayed surgery as related to the incidence of AVN
Trial Design:	Phase III randomised controlled trial
Sample size :	A total of 636 patients will be recruited (318 patients in each treatment arm)
Inclusion Criteria:	▪ Children aged 12 weeks - 13 months with either: - A new diagnosis of DDH - Failed splintage before 12 weeks of age ▪ Children born at ≥30-weeks gestation can be included ▪ Children who require surgical reduction of the hip (open or closed) ▪ Children who are fit for surgery – the decision to include in the study will be entirely at the discretion of the operating surgeon ▪ Parent or guardian able and willing to provide informed consent
Exclusion Criteria:	▪ Children older than 13 months ▪ Children with neurological or syndromic teratologic dislocation of the hip: if in doubt we will not include such infants ▪ Children born at <30-weeks gestation ▪ Children who have had any previous surgical treatment for hip dysplasia (closed reduction, open reduction or any form of tenotomy) ▪ Children with existing AVN ▪ Children with an existing ON
Primary Trial Endpoints:	Incidence of AVN at 5yrs of age - AVN will be classified radiologically according to the Kalamchi and MacEwen grading as part of routine assessment (grade II to IV). A subset will also be classified by an independant panel of radiologists/surgeons blinded to treatment arm
Secondary Trial Endpoints:	▪ The need for secondary surgery (for subluxation/dysplasia/AVN) will be recorded from review of medical records during follow-up visits ▪ Presence or absence of ON at time of primary treatment for dysplasia ▪ Quality of life for main carer ▪ Quality of life for child ▪ Health Economics ▪ Qualitative analysis of the impact of early versus intentionally delayed surgery for DDH on the family
Number of Sites :	At least 12 sites
Statistical Methods:	Presence of AVN will be analysed by logistic regression with centre as a random effect and the randomisation stratification factors as fixed effects

Pilot Phase	A pilot study will ascertain accrual during the first 18 months of recruitment. If the following success criteria are not achieved a closedown plan will be initiated if necessary: ▪ At least 10 centres actively recruiting patients ▪ At least 120 patients recruited ▪ Sufficient mean recruitment (based on the period since the 10th centre started to recruit) to expect to reach 636 patients by the end of month 56

TRIAL FLOW DIAGRAM



* ON = ossific nucleus

SCHEDULE OF OBSERVATIONS AND PROCEDURES

Table 1		SCHEDULE OF EVENTS													
	Pre-Study	Clinic Visit/ Consent	Pre-Surgery	Surgery	6wk	3mths	4mths	6mths	9mths	1yr	2yrs	3yrs	4yrs	5yrs
					These timepoints are ***post-surgery***						These timepoints are at ***age*** 2 – 5yrs			
Confirm eligibility for trial	X	X												
Provide Patient Information Sheet	X													
Written Informed Consent		X												
Randomisation		X												
Surgical reduction of the hip (open or closed)				X										
Imaging [1]	X		X[2]	X	X	X		X	X	X	X	X	X	X[3]
Adverse Events			X	X	X	X		X	X	X	X	X	X	X
Secondary Care Resource Use[4]			X	X	X	X		X	X	X	X	X	X	X
Parental Cost Diary (Early)**[6]		X[5]			X	X		X	X					
Parental Cost Diary (Late)*** [6]										X	X	X	X	X
CarerQol (one parent)* [6]		X[5]				X		X	X	X	X	X	X	X
Oucher*											X	X	X	X
PedsQL* [6, 7]		X[5]				X		X	X	X	X	X	X	X
HUI-3*														X
Demographic Questionnaire****[6]							X							
Qualitative Interview*****								X						X

[1] Modality and frequency as per standard care (crosses indicate where imaging may take place)

[2] In delayed arm (DT), 6-weekly (where possible) until ON appears

[3] An x-ray must be performed at 5yrs of age in order to assess AVN which is the primary endpoint

[4] Data will be collected for each interval between the collection time points indicated, by site staff, from the patients medical records

[5] These should be distributed on the day of consent

[6] In the event that the *post-surgery visits* overlap with *age specific-visits* (e.g. if the child reaches 1 year of age before all post-surgery visits are completed) please follow the ***post-surgery*** schedule as normal; e.g. if the child is already 1 year of age at entry into the trial, please complete all post-surgery visits (i.e. 6 weeks, 3, 6, 9 months and 1 year as per table above), then visits related to the child's ***age*** may be continued as appropriate

[7] Please ensure that the PedsQL appropriate to the child's age is distributed

* Will be completed by parents/guardians (or child in the case of the Oucher) and collected by site staff before the family leaves clinic at the visits indicated in the table

** Parental Diary – Early - during the first year post-surgery a parental diary will be used to collect data on primary care contacts and medications and will be distributed at each visit and collected from parents at their next clinic visit, recording contacts between visits. In the delayed group, the parents must be supplied with or sent further copies to ensure collection of data until the date of surgery. The last questionnaire will be given out at the 9 month visit and collected in at the 1yr visit

*** Parental Diary – Late - See table 2 below

**** Demographic Questionnaire – will be given to parents to complete on the day in clinic – site staff collect and send immediately to the SCTU. Can be done at 3 months if no 4 month visit planned

*****50 families (20 in internal pilot and 30 in main trial). Inteviews will be carried out by a Qualitative Research Fellow based on information provided on the Demographic Questionnaires

Table 2	**DATA COLLECTION SCHEDULE FOR COST DIARY (LATE)**							
Year 1	**Year 1-2**				**Year 2-3**	**Year 3-4**	**Year4-5**	
M12	**M15**	**M18**	**M21**	**M24**				**Y5**
Blank late diary (1) to be handed out in clinic	Phone call by Site to remind parent to complete data for past 3 months	Phone call by Site to remind parent to complete data for past 3 months	Phone call by Site to remind parent to complete data for past 3 months	Phone call by Site to remind parent to complete data for past 3 months	Hand out new blank diary (2) out in clinic. 3 monthly reminder phone calls	Hand out new blank diary (3) out in clinic . 3 monthly reminder phone calls	Hand out new blank diary (4) out in clinic . 3 monthly reminder phone calls	Final Diary (4) will be collected in clinic.
Parent is asked to diarize all costs as they occur	Parent continues using diary (1) as needed	Parent continues using diary (1) as needed	Parent continues using diary (1) as needed	Parent brings diary (1) they have kept over past year to clinic appointment.	Parent is asked to diarize all costs as they occur in new blank diary (2).	Parent is asked to diarize all costs as they occur in new blank diary (3).	Parent is asked to diarize all costs as they occur in new blank diary (4).	End.

1. INTRODUCTION

1.1 BACKGROUND

In the UK, hip instability at birth occurs with an incidence of 15-20 per 1000 live births. In many cases the instability resolves spontaneously. Early treatment with a splint is effective in 85% of cases, if treatment commences in the first 6-8 weeks of life. However, despite clinical and ultrasound screening programmes late presenting cases (over 3 months of age) persist. Such cases are synonymous with the need for surgery.

The hip dislocation may require an open (formal surgical) reduction or a closed reduction after adductor tenotomy. Reduction is confirmed as concentric by hip arthrography. Both types of intervention may be complicated by the development of avascular necrosis (AVN), which occurs as a consequence of partial, temporary or complete interruption of the blood supply to the femoral head and is entirely iatrogenic.

Prior to 8-10 months of age the femoral head is a chondroepiphysis and the blood supply is endarteriolar. With the development of the bony epiphysis (which may be delayed in DDH) the blood supply is anastomotic. It has been hypothesised that the anastomotic circulation renders the femoral head less vulnerable to compression and therefore vascular injury. Accordingly some surgeons delay surgical intervention until after the bony epiphysis has appeared, which can be monitored by ultrasound. However, delay also allows the dysplasia to progress and therefore surgery is not usually intentionally delayed beyond the age of 12 or 13 months; although by this time an epiphysis will have appeared in most cases.

The incidence of AVN is variously reported as occurring in 10-50% of cases and adversely affects outcome because of proximal femoral deformity, eccentric growth and poor femoral head containment, and leg length discrepancy. An early closed reduction requires more plaster changes and the majority of cases will require a secondary procedure to address residual acetabular dysplasia. Delayed open reduction is usually definitive treatment because acetabular dysplasia can be addressed at the primary procedure. There is no international consensus and the only meta-analysis carried out (Roposch 2009) was not conclusive in respect of either strategy.

The proposed research will address the clinical and cost effectiveness of intentionally delayed versus early surgical intervention in established congenital dislocation of the hip (CDH). There is no international evidence based consensus in relation to either strategy.

1.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

Proponents of intentional delay hypothesize that the appearance of the bony ossific nucleus (ON) within the femoral head confirms mechanical resistance to compression and hence the risk of avascular necrosis (iatrogenic ischaemic injury). Prior to the appearance of the ON, the chondroepiphysis is more vulnerable and secondary surgical procedures are more likely. The cost effectiveness will be interrogated by health economic studies. A preliminary feasibility study has addressed stakeholder and consumer willingness to take part, likelihood of recruitment and approximate recruitment rate.

2. TRIAL OBJECTIVES

Aims and objectives

The objective of the trial is to determine, in children aged 3-13 months, if delayed treatment of a dislocated hip in the absence of the proximal femoral ON can reduce the incidence of AVN in children at age 5 years. The main clinical outcome measures will be the incidence of AVN and the need for subsequent secondary surgical procedure during five year follow-up. We will also qualitatively assess parental satisfaction with the adopted strategy, and also NHS and societal costs to undertake a health economic analysis.

Health technologies being assessed:

The trial is assessing the timing (early or delayed) of surgical reduction of the hip (whether open or closed). The two strategies being compared are surgery soon after diagnosis (before the appearance of the ON) and delayed surgery after the appearance of the ON. The actual procedures carried out will be as decided by the treating clinician and will not be determined by the randomisation or specified in the protocol.

3. TRIAL DESIGN

This is a phase III, randomised controlled trial (RCT) incorporating internal pilot, qualitative and health economics analyses. Patients will be randomised between early or intentionally delayed reduction of a dislocated hip with a 1:1 allocation ratio.

The internal pilot will assess ability to recruit and likely generalisability of findings.

A total of 636 children aged 3-13 months with a dislocated hip in the absence of the proximal femoral ON will be recruited (318 each arm). They will be stratified at randomisation by failed splintage and age at diagnosis (≤10 months or >10 months).

3.1 TRIAL ENDPOINTS

Primary Trial Endpoints

Incidence of AVN at 5yrs of age - AVN will be classified radiologically according to the Kalamchi and MacEwen grading as part of routine assessment (grade II to IV). A subset will also be classified by an independent panel of radiologists/surgeons who will be blinded to treatment arm (see section 7.1).

Secondary Trial Endpoints

- The need for secondary surgery (for subluxation/dysplasia/AVN) will be recorded from review of medical records during follow-up visits
- Presence or absence of ON at time of primary treatment for dysplasia. We will use radiographs taken within 24 hours of the index reduction to ascertain this variable (intra-operative images should be used if no radiograph is available)
- Quality of life for main carer (CarerQol)
- Quality of life for child (Oucher, PedsQL, HUI-3)
- Health Economic Evaluation
- Qualitative analysis

4. SELECTION AND ENROLMENT OF PATIENTS

Target population

The target population for the trial is children aged 12 weeks -13 months with newly diagnosed developmental dysplasia of the hip (DDH) or who have had failed splintage, and who require surgery.

4.1 SCREENING AND PRE- RANDOMISATION EVALUATIONS

No trial-specific assessments are required. Evaluation for eligibility will be made by the treating clinician based on routine imaging and tests.

4.2 INFORMED CONSENT

The authorised representative (parent or guardian) of the child where possible will have a minimum of 24 hours after their initial invitation to participate in the trial and been given the Parent Information Sheet (PIS), before being asked to sign the main trial Informed Consent Form (ICF). The parent/guardian will be given the opportunity to ask questions and will also be able to view a trial-specific informative video to help them make their decision.

Verbal consent will be sought from the parent/guardian at the initial clinic visit to allow trial staff to contact them after 24hrs. Contact will be made by email, telephone or text to ask if they wish to participate in the trial. Documentation of reasons for non-participation is essential and where appropriate, if parents/guardian are uncertain about whether to take part, further information can be provided.

Written informed consent must have been given freely before any trial-related procedures can be conducted. Investigators will be provided with an ICF and PIS to be used with this protocol. These documents will be used to explain in, simple terms, the risks and benefits to the child before they are enrolled into the trial. The ICF contains a statement that the consent is freely given, and that the parent/guardian is aware of the risks and benefits of entering their child into the trial. Also that the parent/guardian is free to withdraw their child from the trial at any time. *(Please see withdrawal section 5.3)*

4.3 INCLUSION CRITERIA

- Children aged 12 weeks – 13 months with either:
  - a new diagnosis of developmental displacement of the hip
  - failed splintage up to 12 weeks of age
- Children born at ≥30-weeks gestation can be included
- Children who require surgical reduction of the hip (open or closed)
- Children who are fit for surgery - the decision to include in the study will be entirely at the discretion of the operating surgeon
- Parent or guardian willing to give consent to treatment, complete questionnaires and follow-up

4.4 EXCLUSION CRITERIA

- Children older than 13 months
- Children with neurological or syndromic teratologic dislocation of the hip: if in doubt we will not include such infants

- Children born at <30-weeks gestation
- Children who have had any previous surgical treatment for hip dysplasia (closed reduction, open reduction or any form of tenotomy).
- Children with existing AVN
- Children with existing ON

4.5 RANDOMISATION PROCEDURE

Once eligibility for the trial is confirmed, randomisation will be via an independent web-based system (TENALEA) and will be stratified by failed splintage and age at diagnosis (≤10 months or >10 months). The Principal Investigator (PI) or designee will log into the randomisation system and randomise the patient to the trial.

NB: Eligible premature babies should not be randomised until they reach 12 weeks of age as calculated using their corrected date of birth. However, the actual date of birth of such children should be entered into the TENALEA system for randomisation.

Due to the nature of the trial, neither parents or investigators/surgeons will be blinded to the treatment allocation.

4.6 PRE-SURGERY

The following will take place **pre-surgery**:

- Confirmation of patient eligibility for the trial
- Provide parents/guardians with the Parental Information Sheet
- Take written informed consent
- Randomisation of patient via Tenalea
- Distribution and collection of Parental Cost Diary (Early), CarerQol and PedsQL questionnaires. They will be provided to parents at the consent visit and collected immediately wherever possible. (see table 1 for detailed information)
- Collection of Secondary Care Resource Use data. This data will be collected immediately pre-surgery *and at every visit thereafter* ***except*** *at 4 months post-surgery*. The information will be collected by site staff from the patients medical records. (see table 1 for detailed information)
- Adverse events will be collected at all visits *after* the date of informed consent

5. TREATMENTS

Please Note: ***All treatment will be carried out according to standard local practice and is not mandated by this study protocol. Normal clinical and orthopaedic assessment will be carried out pre-surgery as noted above.***

5.1 TREATMENT ARMS

Arm A (ET) - Early Treatment
Arm B (DT) – (Intentionally) Delayed Treatment

5.2 TREATMENT REGIMENS

Arm A – EARLY TREATMENT

As per local practice – i.e. adductor/psoas tenotomy, arthrogram (or other definitive imaging), open or closed reduction, pre-operative traction

- Normal surgical protocol
- Timeframe for performing surgery is as per standard practice
- Usual after care – hip spica cast, imaging, change of cast **as per local practice**

Arm B – DELAYED TREAMENT

6-weekly ultrasound (or x-ray – as per local practice) until ON present, then:

As per local practice – i.e. adductor/psoas tenotomy, arthrogram (or other definitive imaging), open or closed reduction, pre-operative traction

- Normal surgical protocol
- Surgery should take place within 2-4 weeks of the appearance of the ON (unless exceptional circumstances require it to be delayed further)
- Usual after care – hip spica cast, imaging, change of cast **as per local practice**

5.3 PATIENT WITHDRAWAL

It is not envisaged that many withdrawals will take place. However, parents or guardians can withdraw their child from the trial at any time. It should be ascertained and documented as to whether they wish to withdraw from the trial completely and are therefore unwilling to provide further data. All data held at date of withdrawal will be included in any analysis unless expressly requested otherwise.

6. SAFETY

6.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with trial treatment or participation.

Serious Adverse Event (SAE) any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

6.2 CAUSALITY

The assignment of the causality to trial treatment of any serious event should be made by the investigator responsible for the care of the patient using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the SCTU, who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the Ethics Committee will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after treatment). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

6.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the SCTU in the first instance.

6.3.1 SIGNIFICANT MEDICAL HISTORY AND EXPECTED COMPLICATIONS

Significant medical conditions reported at the start of the trial should not be reported as AEs unless the condition worsens by at least one Common Terminology Criteria for Adverse Event (CTCAE) grade during the trial. The condition, however, must be reported in the pre-treatment section of the electronic Case Report Form (eCRF), if

symptomatic at the time of entry, or under concurrent medical conditions if asymptomatic.

The following are 'expected' complications of treatment for DDH and **should be reported as AEs not as SAEs**:

- Failed Location
- Wound Infection
- Re-dislocation
- Unscheduled Change of Plaster

6.3.2 NON-SERIOUS AEs

All AEs should be recorded in the AE electronic case report form within the requested time frame.

6.3.3 SERIOUS ADVERSE EVENTS (SAEs)

All SAEs should be reported within 24 hours of the local site becoming aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should assign the causality and expectedness of the event. Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

Reporting Details

An SAE form should be completed for all SAEs and faxed/emailed to the SCTU within 24 hours (or completed and sent via the electronic eCRF system if that is available).

Complete the SAE form & fax/email a copy of the form with as many details as possible to the SCTU together with anonymised relevant treatment forms and investigation reports.

Or

Contact the SCTU by phone for advice and then fax/email a copy of the completed SAE form.

SAE REPORTING CONTACT DETAILS

Please email or fax a copy of the SAE form to SCTU within 24 hours of becoming aware of the event

Fax: 0844 774 0621 or email: ctu@soton.ac.uk

SCTU will notify REC of related or unexpected SAEs occurring during the trial.

Local investigators should report any SAEs as required by their Research & Development Office.

6.3.4 FOLLOW-UP AND POST-TRIAL SAEs

The reporting requirement for SAEs affecting patients applies for all events occurring after surgery. All unresolved AEs should be followed by the investigator until resolved,

the patient is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's general practitioner, believes might reasonably be related to participation in this trial. The investigator should notify the trial sponsor of any death or AE occurring at any time after a patient has discontinued or terminated trial participation that may reasonably be related to this trial.

7. ASSESSMENT AND FOLLOW-UP OF PATIENTS

7.1 DATA COLLECTION

All patients will have the usual assessments needed as part of their standard treatment.

Screening logs recording the number of eligible patients seen, numbers randomised and reasons for patients not entering the trial will be collected from sites during the trial.

Clinical data from medical records will be collected for use in the trial and transcribed to eCRF. The following data is required as a minimum:

- **Baseline assessments** - confirmation of diagnosis and eligibility. Also the pre-operative radiological grade of dislocation and acetabular index measurements (where assessable from the type of imaging performed).

- **During the 'delay' period in the late treatment arm** - details of imaging used to determine appearance of the ON i.e. ultrasound/x-ray - *6-weekly x-ray or ultrasound is recommended (post-randomisation and as per standard care) until surgery to evaluate the appearance of ON.*

- **Treatment** - summary details of surgical intervention carried out and any complications.

- **Follow-up**

- Details of routine imaging carried out, grading of images, incidence of AVN and summary details of further treatment required.

  Patients will also be followed up at week 6, 3 months, 6 months, 9 months, 1yr post-surgery, and at 2yrs, 3yrs, 4yrs and 5yrs of age in order to carry out an economic evaluation. The exact timing of these visits may be earlier or later dependent on local clinical practice. It is not envisaged that extra visits to clinic will be required, however, if necessary, parents may be asked to bring their child to clinic for an interim visit.

- Data will be collected for each interval between the visits by site staff from the patients medical records

- **Secondary Care Resource Use** data will be collected immediately pre-surgery and at every visit except at 4 months post-surgery

- **Adverse events** will be collected at all visits after the date of informed consent

- **An x-ray must be performed at 5yrs of age in order to assess AVN which is the primary endpoint**

An independent panel of assessors will evaluate, in consensus, the 5-year anterior/posterior (AP) pelvis radiograph for the presence of AVN using the classification by Kalamachi and MacEwen.

Electronic copies of these radiographs will be sent to the SCTU by each hospital. The panel will evaluate these blinded to the intervention, nature of the treatment, site and patient details.

7.2 ECONOMIC EVALUATION: DESCRIPTION OF TOOLS AND DATA COLLECTION

Health care resource utilisation will be measured directly from patient records, and also using diaries completed by the parent.

Site staff will collect from hospital records resource use data on secondary care contacts. More specifically, we will collect the following information on secondary care contacts:

- Inpatient stays, length of stay (day cases), reason for admission
- Accident and Emergency Department attendances
- Outpatient visits, type of visit, reason for visit

Parental diaries will be used to collect data on primary care and community care resource use and costs borne by families. Through parental diaries the following information will be collected from the parents.

First, we will collect the following information on primary care and community care contacts:

- GP/nurse visits at practice or health centre
- GP/nurse visits at home
- GP/nurse telephone contacts

Second, we will ask parents to record other NHS contacts, listing the type of contact or the health care professional contacted, where the contact took place, the date of the contact, whether NHS or private, and also the money spent.

We will ask parents to record the medications taken, including the name of the medication, the dosage taken each time, the number of doses taken each day, the number of days the medication is taken, whether the medication was prescribed by a doctor or nurse, or bought over the counter, and also the money spent.

Third, we will also ask parents to record:

- whether they incurred other expenditures in relation to the child's hip condition;
- how they financed their health expenditures;
- the costs borne by them and their family, including whether the condition of their child has affected their work, private and social life;
- their childcare costs.

This information will be collected both in the first year post-surgery, and between ages 2-5 of the child. The diaries will be distributed at each visit and collected from the parents at their next clinic visit. The difference is that, since the visits are more frequent in the first year post-surgery, the information will be recorded at a weekly frequency in this period. The detailed timetable is shown in Tables 1 and 2.

Health-related quality of life will be measured using the following three validated instruments: CarerQol for the same parent/caregiver, Oucher and PedsQL.

The ***CarerQoL*** (Brouwer 2006) is aimed at measuring care-related quality of life in informal caregivers. This instrument combines the information density of a burden instrument (encompassing seven important burden dimensions) with a valuation component (a VAS scale for happiness).

The ***Oucher Pain Scale*** (Beyer 1992] is a poster-like instrument designed to help children provide self-reports of the intensity of their pain. We will use the 6-picture photographic scale.

The ***PedsQL®*** is a generic health related quality of life measure in children to be utilized across various pediatric chronic health conditions. We will use the PedsQL® Generic Core Scales for the specific age groups since baseline up to 5 years of age. These were designed to measure the core dimensions of health as delineated by the World Health Organisation, as well as role (school) functioning. The PedsQL Infant (1-12 months) has 5 subscales: Physical Functioning (6 items), Physical Symptoms (10 items), Emotional Functioning (12 items), Social Functioning (4 items) and Cognitive Functioning (4 items). The PedsQL Infant Scales (13-24 months) has 5 subscales: Physical Functioning (9 items), Physical Symptoms (10 items), Emotional Functioning (12 items), Social Functioning (5 items) and Cognitive Functioning (9 items). The PedsQL Parent Report for Toddlers (ages 2-4) has 4 subscales: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items)and School Functioning (3 items). The PedsQL Parent Report for Young Children (ages 5-7) has 4 subscales: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), Social Functioning (5 items) and School Functioning (5 items).

Except for the Oucher, all the instruments will be completed by parents, collected by site staff from parents at each visit according to the timetable detailed in Table 1 and returned to SCTU.

7.3 DATA COLLECTION - QUALITATIVE STUDY

As well as considering the outcome from early vs. intentionally delayed surgery, it is essential to determine the experiences of the families undergoing these procedures, to determine what it is like for the family managing with a child undergoing these procedures. For example, being able to inform future parents about the possible impact of the surgical approach on their child's mobility, personal care, sleep, family dynamics etc. would greatly enhance information available to parents.

At 3 or 4 months post-surgery all participants in the RCT will be surveyed to determine the acceptability of the intervention and their experiences. Pilot work will be conducted with 20 families (10 in each group) and, based on these responses, 30 further families will be purposively sampled i.e. 15 more in each group, (this number is consistent with qualitative approaches and will involve sampling to cover a range of experiences for both intervention groups). They will be asked to take part in a telephone-based interview, which will take place around 6 months post-surgery and again with the same families at age 5 years, to establish parents' experiences beyond the rehabilitation phase.

Interviews will be audio-recorded, transcribed verbatim and analysed thematically using a *Framework* approach.

Close collaboration with the PPI representative will assist with focussed coding and interpreting data. Further interviews will be conducted with the same families at age 5 years to establish parents' experiences beyond the rehabilitation phase.

This trial will generate original qualitative data from 100 interviews, providing a rich data-set on patient experience following DDH surgery. We will use this data to help interpret the quantitative data by considering patient experience alongside outcome, thereby considering the application of early and intentionally delayed surgery in the context of everyday life. This aspect of the trial will be particularly important if the results of the surgical endpoints end up being equivocal.

7.4 ECONOMIC EVALUATION AND QUALITATIVE DATA COLLECTION TIME POINTS

For details of time points for collection of parental and child measurements please see Tables 1 and 2.

7.5 LONG-TERM FOLLOW-UP

Parents will be asked for permission to follow-up their child beyond the trial period by collecting routine data from their medical records and Hospital Episode Statistics to determine the need for subsequent intervention (further surgery, hip replacement, diagnosis of arthritis, etc). We will re-consent participants to continue to this follow-up.

Long term follow-up will allow establishment of a cohort to understand the long-term consequences, if any, of these interventions.

Consent for long-term follow-up will only be sought after a parent has agreed to enter their child into the trial. Refusal will not affect the patient's participation in the main trial.

8. STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE

Allowing for 90% power to detect a 10% clinically meaningful difference between treatment arms in a 5% two-sided test indicates that 286 patients per arm will be required. This assumes proportions of AVN, defined as grade II-IV, of 20% (ON absent) versus 10% (ON present) or vice versa, i.e. to detect an odds ratio of 0.444. Allowing for 10% drop out during the 5 year follow-up period, the total number of patients required is 636 (318 per treatment arm). This sample size has been performed using nQuery Advisor version 7.0 (figure 3 Roposch 2009).

8.2 STATISTICAL PLAN

Main trial analysis

Presence of AVN will be analysed by logistic regression with centre as a random effect and the randomisation stratification factors as fixed effects, thus yielding an odds ratio with 95% confidence intervals for treatment effect (using ITT population).

Secondary analyses will explore the need for further surgery defined according to x-ray findings as well as further investigation on the grading of AVN between the treatment

arms. Presence or absence of ON at time of primary treatment for dysplasia will also be explored (determined by intra-operative imaging).

A pre-specified sub-group analysis will investigate the effect of failed splintage on the treatment effect (by including a treatment interaction in the regression model), although the study is not powered to detect such an effect.

A Statistical Analysis Plan (SAP) providing full details of the main trial analysis will be written for the study.

All results will be reported in accordance with the CONSORT statement (current statement was published in 2010 http://www.consort-statement.org/consort-statement/). The most up to date CONSORT statement available at the time of final Trial analysis will be used.

Data and all appropriate documentation will be stored until after each child reaches 18 years of age as children are being followed-up until this time.

8.3 HEALTH ECONOMIC ANALYSIS

We will conduct a detailed analysis of the cost and cost-effectiveness of early versus delayed treatment for infants with DDH using the data collected as described. Our analysis will conform to accepted economic evaluation methods. We will estimate cost and cost-effectiveness for the 'within-trial' period (5 years) and over the expected lifetime of participants.

In the primary economic analysis, costs will be assessed from the perspective of the NHS and personal social services. Cost components included in the analysis will consist of the costs of the intervention by type, diagnostic imaging, secondary operations by type, overall hospital length of stay, outpatient attendances, readmissions, all primary care contacts and all prescribed treatments. In a secondary economic analysis we will additionally include monetary costs borne by families.

As noted the volume of resource use for each cost component will be measured from NHS electronic records (for secondary care contacts) and from parental diaries and questionnaires (primary care contacts, costs borne by patients and families). Unit costs will be taken from standard published sources. Unit costs will be multiplied by mean resource use for each cost component to calculate mean costs per patient in each arm of the trial.

Cost-effectiveness measures in the 5 year endpoint will be the incremental cost per avascular necrosis averted and the incremental cost per quality-adjusted life year (QALY) gained. The number of cases of avascular necrosis averted will be based on trial outcomes.

8.3.1 HEALTH RELATED QUALITY OF LIFE AND UTILITIES

We will use the ***Health Utility Index®*** *(HUI-3)* collected at the last visit to derive utilities for children at the age of 5 years. HUI-3 is valid for children aged 5 years or over and has been used widely in this context [Furlong 2001]. Because HUI-3 has not been validated in children under the age of 5 years (utility measures for younger children do not exist), we will collect longitudinal data on health outcomes using *PedsQL* at baseline, 3, 6, 9 and 12 months, and at 2, 3, 4 and 5 years (PedsQL has been validated

for infants since 1 month), and *Oucher* in participants who are 2, 3, 4 and 5 years old (Oucher has been validated only for children from age 2 years onwards). Such longitudinally collected data will allow us to determine at 5 years the relationship between HUI-3 and PedsQL/Oucher. We will use regression analysis to model the relationship between HUI-3 (total score and the ambulation, pain, emotion and cognition attributes) using PedsQL/Oucher summary scores as the independent variables at 5 years, assuming the mapping is time-invariant. We will then use the estimated coefficients to predict HUI-3 scores since baseline. This will allow us to model QALYs for study participants for the entire duration of the trial.

In addition, we will determine the impact of a child's condition on the caregiver by measuring health-related quality of life of the same parent/carer using the *CarerQoL* periodically according to the timing detailed in Table 1.

Cost-effectiveness will be calculated as the mean cost difference between early versus delayed treatment divided by the mean difference in outcomes (occurrence of avascular necrosis/QALYs). This will give the incremental cost-effectiveness ratio and its confidence intervals will be estimated using bootstrapping techniques of the mean cost and outcomes differences [Briggs 1997]. The bootstrap replications will be used to construct a cost-effectiveness acceptability curve, which will show the probability that delayed surgery is cost-effective at 5 years for different values of the NHS' willingness to pay for an additional QALY. Deterministic sensitivity analysis will also be performed.

In the lifetime analysis, cost-effectiveness will be calculated in terms of the incremental cost per QALY gained. No previous analyses on the cost-effectiveness of differences in delayed/ immediate surgery for DDH exist. We will develop a de novo cost-effectiveness model based on pre-existing work [Roposch 2006; Roposch 2011]. Data from these studies and data collected in the trial will enable us to develop a new model taking into account long term outcomes, i.e. osteoarthritis of the hip and hip replacement surgery. Two HTA-funded studies on the cost-effectiveness of hip replacement surgery will provide further data in developing this model [Fitzpatrick 1998; de Verteuil 2008]. Given the clinical nature of DDH (operations may happen more than once; risk for osteoarthritis is continuous over time; timing of events is important) we will construct a Markov model. The health states in this model will reflect the various disease pathways (e.g., primary treatment of DDH; treatment for AVN; treatment for acetabular dysplasia; physical disability; onset of osteoarthritis; death). Following decisions about model structure, we will derive a list of parameter estimates required for the model. We will undertake deterministic and probabilistic sensitivity analysis [Briggs 2006] that will be used to construct cost-effectiveness acceptability curves.

9. REGULATORY ISSUES

This trial does not involve the testing of any Investigational Medicinal Products (IMPs) and therefore approval from the Medicines and Healthcare products Regulatory Agency is not required.

9.1 ETHICS APPROVAL

The trial protocol has received the favourable opinion of a Research Ethics Committee (REC no: 14/NS/0089).

The trial will be conducted in accordance with the recommendations for physicians involved in research on human patients adopted by the 18th World Medical Assembly,

Helsinki 1964 as revised and recognised by governing laws and EU Directives. Consent to participate in the trial should be obtained from the parent or guardian of each patient after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the parent to refuse to participate in the trial without giving reasons must be respected.

After the patient has entered the trial, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the patient. However, reasons for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the parent or guardian of each patient remains free to withdraw at any time from protocol treatment and trial follow-up without giving reasons and without prejudicing the child's further treatment.

The investigator must ensure that patient's anonymity will be maintained and that their identities are protected from unauthorised parties. Patients will not be identified by their names on CRFs, but by an identification code. The investigator should keep a patient enrolment log showing codes, names and addresses.

9.2 CONSENT

Consent to enter the trial must be sought from each parent/guardian only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed parental/guardian consent should be obtained. The right of the parent to refuse to allow their child to participate without giving reasons must be respected.

9.3 CONFIDENTIALITY

The SCTU will preserve the confidentiality of patients taking part in the trial.

9.4 INDEMNITY

The sponsor of the trial is University Hospital Southampton NHS Foundation Trust. For NHS sponsored research HSG (96) 48 reference no.2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

9.5 SPONSOR

University Hospital Southampton NHS Foundation Trust is acting as the Sponsor for this trial. The SCTU has been delegated duties by the Sponsor relating to: submissions to regulatory authorities and GCP. Other delegated duties will be assigned to the NHS Trusts or others taking part in this trial by means of the site clinical trial agreement.

9.6 FUNDING

The National Institute for Health and Research (NIHR) Health Technology Assessment (HTA) are funding this trial.

9.7 DEVIATIONS AND SERIOUS BREACHES

Any trial protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the local R&D Office immediately. The SCTU will then advise of and/or undertake any corrective and preventative actions as required.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and/or the trial protocol will immediately be reported to the regulatory authorities and other organisations, as appropriate.

9.8 AUDITS AND INSPECTIONS

The trial may be subject to inspection and audit by University Hospital Southampton NHS Foundation Trust, under their remit as sponsor, the SCTU as the Sponsor's delegate and other regulatory bodies to ensure adherence to GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

10. TRIAL CLOSURE

10.1 DEFINITION OF END OF TRIAL

The end of trial will be either:

1. The pilot study has ascertained that accrual during the first 18 months of recruitment has been unsuccessful and a closedown plan has been initiated.

2. Patients have completed study treatment and the five year follow-up phase and all study related data has been collected and analysed for reporting purposes.

10.2 EARLY DISCONTINUATION OF TRIAL

A pilot study will ascertain accrual during the first 18 months of recruitment. If the following success criteria are not achieved a closedown plan will be initiated if necessary:

- At least 10 centres actively recruiting patients
- At least 120 patients recruited
- Sufficient mean recruitment (based on the period since the 10th centre started to recruit) to expect to reach 636 patients by the end of month 56

10.3 CLOSEDOWN PLAN

Initiation

This plan will be initiated on the instruction of the HTA programme director, should it become apparent that continuation with the trial is futile due to an inability to recruit. That inability may be due to a lack of involvement by clinical centres, lack of eligible patients in recruiting centres, or unwillingness of either clinicians or parents to enter children into the trial.

Timeframe

HTA programme funded activities will stop within 6 months of a decision to close down.

Activities during the closedown period

1. All participating study centres will be notified of the decision to close the trial, and asked to stop recruiting patients.

2. All recruited patients will be notified of the closing of the trial, via their responsible consultant. Patients will be invited to discuss any concerns they have with their consultant. If necessary the CI will provide support to these conversations, but given the volume of patients involved is unlikely to be available in person, but is more likely to provide telephone support to local investigators.

3. Further HTA funded trial data collection will cease.

4. We will discuss with the TSC and DMEC what analyses can plausibly and sensibly be made on the data collected, and propose an analysis plan. In the first couple of years of the study it is unlikely that much exploitation can be made of the clinical data, as there will be a large imbalance between the two arms of the number of children who have actually received surgery. There will be more scope to exploit the qualitative and economic data.

5. The SCTU employed staff will be redeployed where possible within the SCTU when the contract ends. Other staff specifically employed for this project will enter their employer's redundancy procedures.

Care of patients already recruited

If the trial is closed decisions on care of patients already recruited will revert to their treating consultant. Consultants will not be expected to adhere to the assigned randomisation, but will be encouraged to in order to allow long term data collection (see below – 'Longer Term Follow-Up') and analysis based on routine data as follows:

- Most patients assigned to early intervention will have received their surgery should the study be closed down. Clinicians should treat these patients as they normally would.

- Many patients assigned to late intervention will not have received their surgery at the time of a closedown. While it may be useful to maintain treatment allocation in order to follow-up these patients with a routine record review and through routine data such as HES such follow-up is unlikely to be sufficiently powered to detect a difference between the two arms. Therefore consultants will be encouraged to continue with the allocated treatment, but will be free to switch to early surgery if they and the patient's parents feel this is the best option for this patient.

  This data may also inform a future meta-analysis should a similar study be undertaken elsewhere.

Longer term follow-up

The investigators will attempt to undertake some longer term follow-up through clinical note review and routine data (such as HES). We will not look to HTA to fund this work, and if successful will publish elsewhere.

11. TRIAL MANAGEMENT

The Trial Management Group (TMG) is responsible for overseeing progress of the trial. The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Steering Committee (TSC) and the Data Monitoring and Ethics Committee (DMEC).

12. PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the TMG. The first publication of the trial results will be in the name of the TMG, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator and his designate, Statistician and Trial Manager/Coordinator. SCTU as the management organisation, members of the TMG and the DMEC will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the TMG will be according to the individuals involved in the project but must acknowledge the contribution of SCTU and the TMG.

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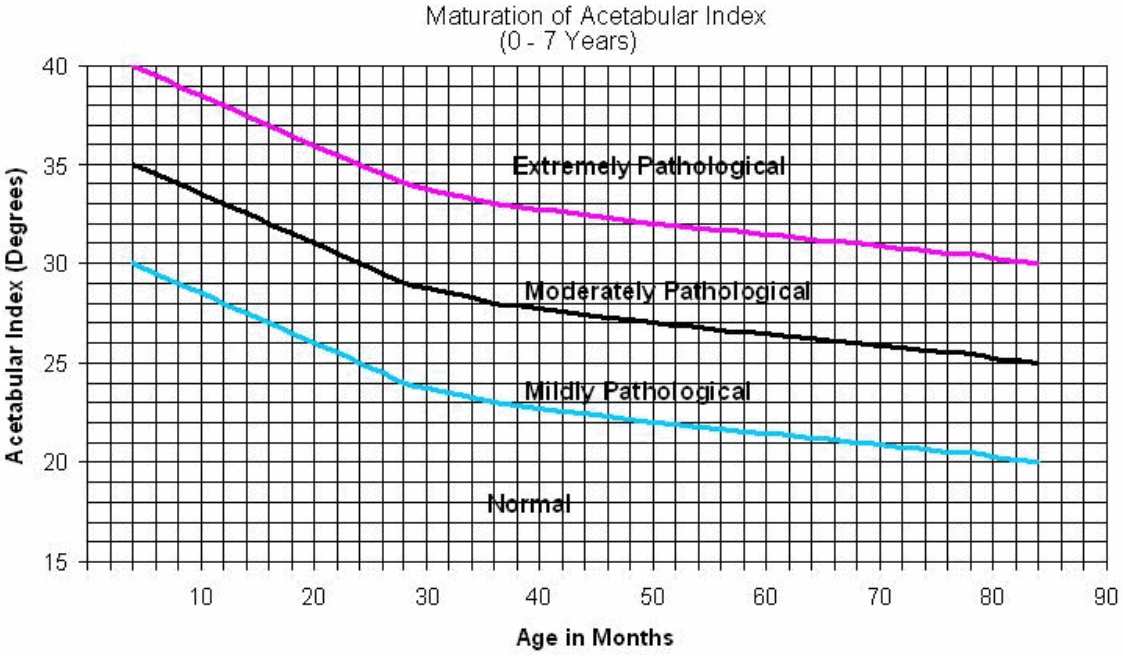
APPENDICES

APPENDIX 1 – ACETABULAR INDEX

Acetabular Index: The angle formed by drawing a horizontal line at the bottom of the pelvis and an angled line from the bottom of the pelvis to the outer edge of the socket. By 4 months of age, a normal child will have an index of 30 degrees or less with the index decreasing until it reaches 20 degrees or less. An index above 30 degrees should prompt the doctor to begin treatment, with the treatment being more aggressive the higher the index.



APPENDIX 2 - IMAGES SHOWING THE DEVELOPMENT OF THE CIRCULATION AND BONY OSSIFIC NUCLEUS WITHIN THE HIP

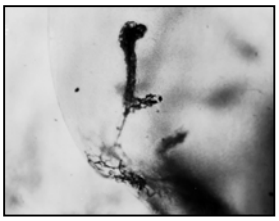


Figure 1. Injected specimen showing end arteriolar cartilage canal, which is vulnerable to compression and therefore ischemia.

This figure shows the fragile blood supply of the hip before development of the ossific nucleus. Any pressure on the joint can result in damage to the slender stalk so cutting off the blood supply resulting in tissue death (AVN) within the hip.

Figure 2. Anastamotic vascular pattern after formation of ossific nucleus, less vulnerable to compression.

After the ossific nucleus is formed a more robust blood circulation develops within the hip which much less vulnerable to compression. This picture shows the anastomotic circulation has developed within the hip.

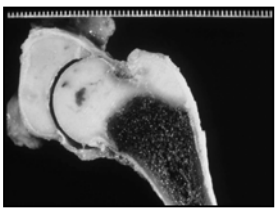


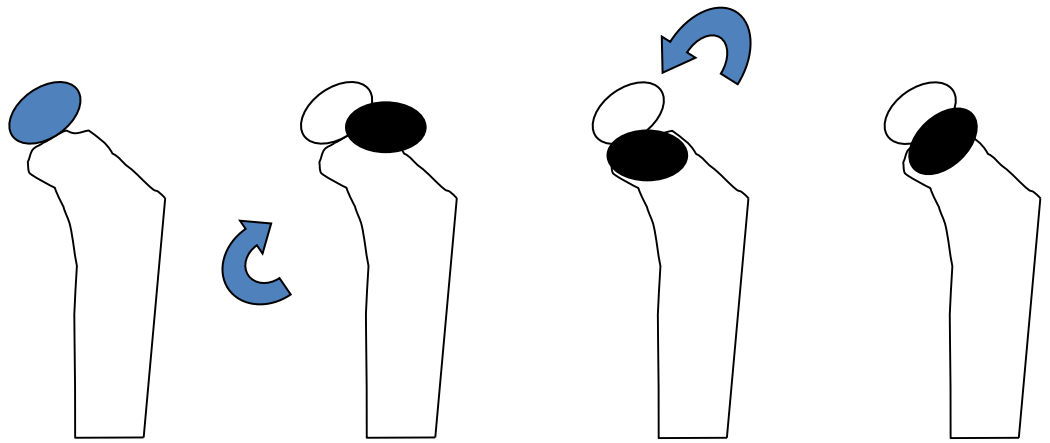
Figure 3. Corresponding specimen showing bony ossific nucleus present within the cartilaginous femoral head.

The bony ossific nucleus is visible by xray and ultrasound and so imaging can be used to detect that the more robust blood supply has developed.

APPENDIX 3 - KALAMCHI AND MACEWEN'S CLASSIFICATION OF AVASCULAR NECROSIS OF THE HIP

Kalamchi A and MacEwen GD Avascular necrosis following treatment of congenital dislocation of the hip. J Bone Joint Surg Am 1980;62:876-888.

Group I	Failure of appearance of the ossific nucleus during the first year after reduction Broadening of the femoral neck during the year after reduction Increased radiographic density followed by fragmentation Residual deformity after re-ossification is complete Present of persistent stiffness after cast removal even without radiological criteria may be the earliest sign of ischaemic necrosis
Group II	Damage of the lateral aspect of the growth plate is the principal characteristic of this group. Radiographs show lateral physeal bridging, and a lateral metaphyseal notch or defect. Patients in this group develop subcapital coxa valga, with a tendency to have poor acetabular coverage
Group III	Damage of the physis with a large central defect. Commonly, patients develop a short femoral neck without varus or valgus. Relative 'overgrowth' of the greater trochanter and limb-length discrepancy are the principal problem
Group IV	Damage to the entire femoral head and physis are characteristic of this group. Irregular femoral head with varus, flattening, and coxa magna. 'Overgrowth' of the greater trochanter, limb-length inequality, and subsequent early arthritis are the principal complications



I II III IV

APPENDIX 4 – RADIOLOGICAL GRADE OF DISLOCATION (IHDI) [25]