Non-operative treatment of pediatric lateral humeral condyle fractures: a cohort study of 50 patients

Clinical Investigation Plan

File name: Study Protocol - Non-OP treatment of LHCF - H-21017621.pdf

Version and date: Version 3.0, 30 July 2021

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The Danish Data Protection Agency ID: P-2020-1197

The Danish National Committee On Health Research Ethics ID: H-21017621

Content

Abbreviations/glossary

AE/SAE	Adverse Event(s)/Serious Adverse Event(s)
ADE/SADE	Adverse Device Event(s)/Serious Adverse Device Event(s)
AO	Arbeitsgemeinschaft für Osteosynthesefragen = Association for the Study of Internal Fixation (ASIF)
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organization = Clinical Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FSR	Final Study Report
FU(s)	Follow-up(s), eg follow-up visit(s), follow-up procedure(s)
GA	General Anesthesia
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISF	Investigator Site File
ISO	International Organization for Standardization
LHCF	Lateral Humeral Condyle Fracture
MeSH	Medical Subject Heading
MRI	Magnetic Resonance Imaging
PCI	Principal Coordinating Investigator (= Principal Clinical Investigator)
PI	Principal Investigator
SD	Standard Deviation
U(S)ADE	Unanticipated (Serious) Adverse Device Effect

Definitions

Baseline	Status post injury but pretreatment
Enrolled	Patients with written informed consent who commenced treatment within the study
Follow-up visit	FU; visit at predefined times after the treatment day
Follow-up population	Patients intended to be followed-up (i.e. enrolled population)
Injury day	"Day 0"; day of injury
Written informed consent	Legally binding signature on the informed consent form (ICF) (i.e. the patient's parents or legal guardians)

1 Synopsis

Official title	Non-operative treatment of pediatric lateral humeral condyle fractures: a cohort study of 50 patients
Short title	Non-operative treatment of pediatric lateral humeral condyle fractures
Sponsor	Department of Orthopedic Surgery Copenhagen University Hospital – Herlev and Gentofte
Registration	The study will be registered with ClinicalTrials.gov
Background and purpose	The diagnosis of LHCF is complicated by radiographic inability to show the full extent of the injury into the chondral (unossified) epiphysis. MRI gives a perfect view of these fractures. The safety and feasibility of non-operative treatment based on MRI findings in children with elbow fractures has not been investigated in a Danish setting. If safe and feasible, the use of MRI could dramatically lower the need for surgery in children with LHCF.
Condition	Pediatric lateral humeral condyle fracture
Intervention/procedure investigated	Non-operative treatment of LHCF based on MRI findings
Comparison	None
Study type	Interventional
Study design	Prospective, Cohort, Single center
Short description	Cohort study of 50 patients aged 2-15 with acute LHCF. Intervention with non-operative treatment based on MRI performed without sedation or anesthesia. Objectives are to describe functional outcome, radiological healing, secondary fracture displacement and any complications after two years. Patients are seen for follow-up 1, 2 and 4 weeks and 3, 6, 12 and 24 months after injury. The investigators hypothesize that undisplaced and minimally displaced LHCF can be treated non-operatively based on MRI findings with good functional outcomes after two years.
Primary objective	Describe the functional outcome two years after non-operative treatment of undisplaced and minimally displaced LHCF in children.
Secondary objectives	• Describe the feasibility of performing a subacute MRI of the elbow in children with LHCF within 2-7 days after the injury without sedation or anesthesia • Report MRI findings and classify fractures according to Song classification based on MRI • Report the number and proportion of fractures that displace secondarily and their treatment • Report final treatment; non-operative or operative • Describe radiographic results and compare with MRI • Report any early or late complications

Hypothesis	Children with minimally displaced LHCF (Song stage 1, 2 and 3) can be treated non-operatively based on MRI findings with good functional outcome after two years.
Primary outcome measure	Mayo Elbow Performance Score (MEPS) two years after injury
Secondary outcome measures	• Pain • Radiographic results • MRI results • Alteration in treatment regime based on MRI • Number and proportion of fractures with secondary displacement • Any early or late complications
Statistical considerations and estimated enrollment	Sample size is estimated from previous studies which included less than 30 participants. The investigators of this study suspect that by enrolling 50 participants the age distribution and variation in fracture pattern will be representative of the background population. Baseline characteristics and outcomes recorded at scheduled FU assessments will be presented using simple summary statistics.
Start of enrollment	October 2021 (estimated)
Last patient/last visit	October 2025 (estimated)
Eligibility inclusion criteria	Inclusion criteria: • Children age 2-15 years • Diagnosis of acute LHCF (<5 days) with <5 mm of displacement on plain radiographs • Parental informed consent obtained
Eligibility exclusion criteria	Exclusion criteria: • Contraindication(s) to performing an MRI • Unable to participate in follow-up • Existing bone pathology • Previous ipsilateral elbow fracture
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Study site	Department of Orthopedic Surgery Copenhagen University Hospital – Herlev and Gentofte Copenhagen, Denmark
Health authority	The Danish Data Protection Agency The Danish National Committee On Health Research Ethics

Pubmed Medical Subject Heading [MeSH] terms and keywords	Child [MeSH] Casts, Surgical [MeSH] Fracture Fixation [MeSH] Humeral Fractures [MeSH]
Imaging review	All images collected will be analyzed by independent radiologists during the study

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2 Rationale and purpose of the study

The treatment of LHCF is most often surgical with open reduction and fixation [1]. The diagnosis of LHCF is complicated by radiographic inability to show the full extent of the injury into the unossified chondral epiphysis and therefore physicians often opt for open surgical treatment. MRI; however, gives a perfect view of these fractures [2–5]. This project investigates the safety and feasibility of non-operative treatment of LHCF based on MRI performed without sedation or anesthesia and seeks to dramatically lower the need for surgery. Objectives are to describe functional outcome, radiological healing, secondary fracture displacement and any complications after two years. The investigators hypothesize that undisplaced and minimally displaced LHCF can be treated non-operatively based on MRI findings with good functional outcomes after two years. A cohort study design is used to follow 50 children with LHCF.

3 General information/responsibilities

The International Conference on Harmonization for Good Clinical Practice (ICH-GCP) and ISO 14155 guidelines define the responsibilities of the sponsor and investigators in the context of the study. Specific topics, such as the permission from the responsible EC, are defined separately in the CIP. The study site undertakes to guarantee correct and prompt implementation, documentation, and transmission of the study data.

In the context of the study, the participating study site will return the completely documented cases. Completely documented means that all FU visits have been carried out for the cases included in the study and that these assessments are recorded on the electronic Case Report Forms (eCRFs) specially designed for this study. Furthermore, the necessary radiological investigations must be performed at the FU visits.

3.1 Responsibilities

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4 Background and literature review

4.1 Definition and epidemiology

Fractures of the distal humerus account for 5-10% of all pediatric fractures but constitute up to 30% in children aged 4-9 years of age [6–10]. Fractures of the lateral humeral condyle account for 10-20% of all elbow fractures in children making it the second most frequent after supracondylar fractures [3,11,12].

LHCF are usually the result of a fall on an outstretched arm with either the extensor-supinator mass pulling or the radial head pushing off the lateral condyle [13]. The diagnosis is suspected by the history of a fall, usually a swollen and painful elbow with tenderness over the lateral aspect. In more severe cases a hematoma can present early.

A LHCF is a Salter-Harris type II or IV physeal fracture which can appear as everything from a hairline fracture to grossly displaced intraarticular injuries.

4.2 Diagnosis

Fractures are usually diagnosed on plain radiographs with antero-posterior (AP), medial-lateral (ML) and internal oblique (IO) radiographs. Especially the IO is important in appreciating the amount of displacement [14]. The distal humerus, especially in younger children, is largely composed of cartilage and is termed the chondroepiphysis [7]. Four secondary ossification centers arise with growth at different ages making interpretation of elbow radiographs in children a challenge [15]. A study showed that emergency department (ED) physicians only made the right radiographic diagnosis in 53% (16/30) of cases concerning pediatric elbow injuries [16].

4.3 Outcome

Neglecting to treat displaced LHCF can lead to painful nonunion, malunion and growth disturbances e.g. fishtail deformity. Complications such as tardy ulnar nerve palsy and varus or valgus deformity can develop years after an untreated injury [13].

4.4 Current status of research in this area

Undisplaced and minimally displaced LHCF found on radiographs compose a specific challenge in choosing between non-operative or operative treatment [13]. The risk of secondary displacement of an initially undisplaced fracture varies from 4% to more than 40% depending on the initial stability and displacement [12].

Historically these fractures where classified according to Milch [17] however this system neither describes fracture stability nor focusses on fractures in children and has no prognostic value [1].

Song’s classification (figure 1) [18] discerns incomplete from complete and undisplaced from displaced fractures clearly describing fracture stability.

Song stage 1 fractures only involve the bony metaphysis. Stage 2 fractures pass into the chondroepiphysis, but not through, leaving the articular cartilage intact and functioning as a hinge [4].

Stage 1 and 2 fractures are considered stable and can be treated non-operatively. Stage 3 fractures are complete and traverse the entire course of the metaphysis, chondroepiphysis and the articular cartilage leaving the fragment without any attachment. These fractures can be undisplaced but are always considered unstable. Treatment controversy arises from the inability to distinguishing stage 1 and 2 from stage 3 on plain radiographs.

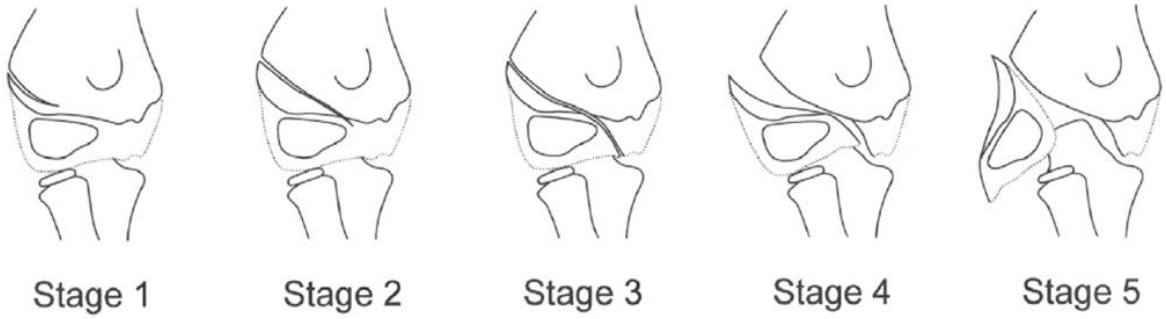

Figure 1 - Song classification.

Because of the risk of secondary displacement, operative treatment is often conducted with many surgeons choosing open reduction and fixation in all cases [19,20]. Operative fixation imposes the risk of minor complications such as superficial infection, ulcers and granulomas but also major complications such as deep infection, osteomyelitis, malunion, non-union, growth disturbance and osteonecrosis [21].

MRI with specific cartilage sequences (figure 2) can clearly show the chondroepiphysis and studies have shown that MRI is capable of precisely showing the fracture pattern [2,3,5,22]. Using simple techniques and advances in technology to prepare the child, MRI has been shown to be feasible in younger children without sedation or anesthesia in whom this was previously thought necessary [23–30].

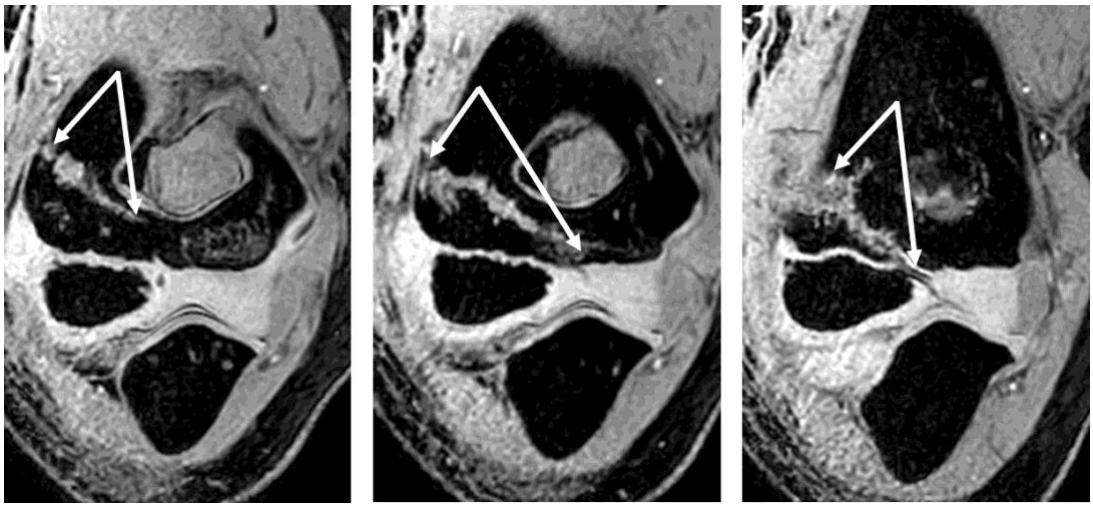

Figure 2 - MRI showing LHCF. Left: Stage 1, confined to metaphysis. Center: Stage 2, fracture line stops in the chondroepiphysis. Right: Stage 3, traverses the joint cartilage.

5 Primary and secondary objectives

5.1 Primary objective

To describe the functional outcome two years after non-operative treatment of undisplaced and minimally displaced LHCF in children.

5.2 Secondary objective(s)

- Describe the feasibility of performing a subacute MRI of the elbow in children with LHCF within 2-7 days after the injury without sedation or anesthesia
- Report MRI findings and classify fractures according to Song classification based on MRI
- Report the number and proportion of fractures that displace secondarily and their treatment
- Report final treatment; non-operative or operative
- Describe radiographic results and compare with MRI
- Report any early or late complications

5.3 Hypothesis

Children with minimally displaced LHCF (Song stage 1, 2 and 3) can be treated non-operatively based on MRI findings with good functional outcome after two years.

6 Study design

This project uses a cohort study design conformed to the STROBE Statement [31]. The investigators aim to prospectively and consecutively recruit all children with undisplaced or minimally displaced LHCF (cohort) which based on MRI are treated non-operatively (exposure). We report functional and radiological outcome two years after the injury (outcome). This study design is relevant in reporting the primary and secondary outcomes based on the exposure in our cohort.

6.1 Study population and patient enrollment

This study investigates the treatment of pediatric LHCF; therefore, this study cannot be conducted in consenting adults. LHCF occur predominantly in 4-9 year olds and thus it is not possible to select only older children for inclusion.

This study is believed to have great positive implications for the participants and successive patients with the same condition.

6.1.1 Setting

The study will be performed in the Capitol Region of Denmark. Patients in the catchment area of Copenhagen University Hospital – Herlev and Gentofte are eligible for recruitment (population 700.000 of which 80.000 are children).

6.1.2 Inclusion criteria

- Children aged 2-13 years
- Diagnosis of acute LHCF
  - Fracture <5 days old
  - Fracture with <5 mm of displacement on plain radiographs (AP, ML and IO views)

- Parental informed consent obtained:
  - Ability of all legal guardians to understand the content of the patient information and ICF
  - Willingness and ability to let the child participate in the clinical investigation according to the Clinical Investigation Plan (CIP)
  - Signed and dated EC-approved written parental informed consent sheet

6.1.3 Exclusion criteria

- Contraindication(s) to performing an MRI [32] without the use of sedation or anesthesia:
  - Ferromagnetic implants or foreign bodies
  - Pacemaker
  - Ear implant
  - Severe claustrophobia
- Unable to participate in follow-up
- Existing bone pathology
  - Tumor
  - Osteogenesis imperfecta
  - Degenerative disease
- Previous ipsilateral elbow fracture

6.1.4 Enrollment of participants

A member of the research team will identify all eligible patients (i.e., who meet all of the inclusion and none of the exclusion criteria).

The identification of eligible patients is done during the daily routine review of radiographs taken in the ED of Copenhagen University Hospital - Herlev and Gentofte.

Electronic letters for FU cannot be sent to minors; therefore all parents are routinely approached by phone. During this standard approach we ask permission from the EC to inquire the parents about their interest and their child's eligibility in participating in this study. This inquiry will include a short prescreening with questions to confirm eligibility as well as a short description of the study and responsibilities for participating. None of the data of the pre-screening process will be documented study specifically.

If interested in participating, the parents and the patient are invited to the outpatient clinic. Parents are informed of the possibility of bringing an assessor. At the visit, a member of the research team will go through the informed consent process, and explain the purpose of the study, the procedures, the risk/benefits, alternatives to participation, and data protection.

For each patient participating the parents will sign and date an ICF. A copy of the signed ICF will be placed into the ISF and one copy will be handed over to the parents. A more detailed description of the informed consent process is provided in section 12.

All patients with written informed consent will be allocated to a unique patient trial number. The date of informed consent and the recruitment information is entered in the study database.

The recruitment period will be up to 24 months, during which 50 patients are planned to be enrolled.

6.2 Study procedures

The schedule of all FU visits including imaging procedures as well as the data to be collected at each visit is shown in Table 1. All FU visits with the defined time windows are calculated from the day of injury (i.e. day 0).

All participants live in the catchment area of Herlev and Gentofte Hospital within short transportation time. Information about the time and place for the follow-up examination is sent physically by mail to the current address registered in the Civil Registration System and via the electronic health record (EHR) system. Parents are usually very keen to take their children for follow-up appointments making the risk of missing an appointment low. Any participants who miss an appointment will be contacted by phone to reschedule.

Table 1: Study schedule

Assessment parameters		**Out-patient clinic visits and imaging procedures ***										
		Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	
	Injury (day 0)	**Screening**	**Information visit**	**Enrollment and consent**	**5 (± 3) days**	**12 (± 3) days**	**4 weeks**	**3 months**	**6 months**	**12 months**	**24 months**	
Eligibility		X										
Patient information			X									
Consent				X								
Demographics				X								
MRI					X							
If applicable - Control-MRI						(X)						
Cast removal***							X					
Radiographs and clinical exam						X	X	X	X	X	X	

* All FU visits with the defined time windows are calculated from the day of injury (i.e. day 0).
** Telephone interview.
*** Casting may be prolonged two weeks in case of lack of callus formation at four weeks.

6.2.1 Visit 1: Screening (by phone)

- As described in section 6.1.4, the parents of potential study patients are informed about the study over telephone by the PI.

6.2.2 Visit 2: Information visit

- All inclusion and exclusion criteria are checked to decide if the patient can participate in the study.
- Specific procedures for enrollment of pediatric patients are undertaken. A more detailed description of the enrolment of participants and informed consent process is provided in section 6.1.4 and 10.
- Before any study-specific examinations are performed, the patient's parents give written informed consent to participate in the study according to the CIP.

6.2.3 Visit 3: Enrolment, consent and preparation for MRI

- Obtain baseline demographics
- Book MRI
- Prepare child for MRI using the Child Centered Care model described in section 6.3
- Data verification and entry into the eCRF

6.2.4 Visit 4: MRI (5 (± 3) days)

- The MRI is performed according to the Child Centered Care model described in section 6.3
- Results of the MRI are given to the parents by phone
- Any necessary adjustments to the treatment plan is made
- Entry into the eCRF

6.2.5 ONLY if applicable: Control-MRI (12 (± 3) days)

- If an unstable Song stage 3 fracture is diagnosed based on the initial MRI an additional control MRI is performed during this visit
- Results of the MRI are given to the parents by phone
- Any necessary adjustments to the treatment plan is made
- Entry into the eCRF

6.2.6 Visit 5: Radiographs and clinical examination (12 (± 3) days)

- Plain radiographs of injured elbow without cast (AP, ML and IO)
- Clinical examination
  - Cast condition
  - Assessment of pain and use of pain medication
  - Neurovascular status of the hand
- Entry into the eCRF

6.2.7 Visit 6, 7, 8, 9 and 10: Radiographs and clinical examination (4 weeks and 3, 6, 12 and 24 months).

- Plain radiographs of injured elbow without cast (AP, ML and IO)
- Clinical examination
  - Assessment of pain and use of pain medication
  - Neurovascular status of the hand
  - Bilateral elbow assessment according to Mayo Elbow Performance Score (MEPS)
  - Bilateral carrying angle of the elbow measured in degrees by goniometer
- Entry into the eCRF

6.2.8 Unscheduled visits

Unscheduled visits can take place at any time during the study if a need occurs or if the investigator considers this to be appropriate for patient care. Information collected between study visits are to be documented at the next regular study visit with the following exceptions:

- If a patient drops out of the study, a dropout form is completed at the time of dropout

6.2.9 Premature study termination

Patient participation in the study may end prematurely for one of the following reasons:

- Patient withdrew informed consent
- Protocol violation
- Investigator's discretion (e.g. patient noncompliance with CIP)
- Unknown/lost to FU

For each case of premature termination detailed information will be obtained explaining the circumstances leading to the termination. This will be recorded on a dropout form in the eCRF.

If patients are withdrawn from the study, any collected data will be censored. Censoring allows this collection of data to be accounted for in the analysis.

6.3 Study treatments

This study is not investigating any medical device. All devices in this study will be used per standard of care at the participating institutions.

6.3.1 Emergency treatment

All patients who sustain a LHCF are initially treated in the ED with an above elbow splint. Parents and, when applicable, the patient are informed of the injury, cast management and use of pain medicine.

6.3.2 MRI in children without sedation or anesthesia

Child Centered Care (CCC) (figure 3 and 4) consists of:

- Oral and written information about MRI together with a demonstration of the process using a toy scanner is given by a member of the research team to parents and patient.
- Movies from the hospital’s radiology department that prepare the child for the experience.
- An interactive app (Rumble in MRI, free in App Store and Google Play Store) that prepares and motivates the child. The troll character Rumble and 3D animations of rooms increase recognisability.
- A pediatric team of radiographers focus on the child feeling safe and secure.
- A child-friendly environment in the MRI room with lights and movies coordinated in themes known from the app projected on the wall (“Philips Ambient Experience”, Philips Electronics, Koninklijke, Netherlands).

Figure 3 - Left) Rumble in MRI app. Right) Toy scanner from Playmobil® used to show children the procedure.

To further better the child's experience, all MRIs are performed during daytime hours, preferably before noon. Parents are asked to give the child pain medicine according to age and weight before leaving home. Scans are performed with an above elbow splint on.

6.3.3 MRI protocol

MRI examination (figure 4) of the elbow is performed using Philips dStream S flex coils on 3 Tesla MRI scanners (Philips Ingenia Elition X 3T and Philips Ingenia 3T). Patients undergoing the examination will have a splint on with the elbow flexed to 90 degrees. The splinted elbow is lowered beside the patient, removing the respiratory artifact. The dStream S flex coils include two flexible coils which can obtain 10 cm coverage with a maximum of four channels. These coils are placed around the patients elbow parallel to each other, and perpendicular to the static magnetization field.

Figure 4 – A pediatric team of radiographers focus on the child feeling safe and secure.

The MRI protocol consists of three sequences with breaks in between; 3D WATS - 2 minutes and 32 seconds, T1 coronal – 2 minutes and 16 seconds and STIR coronal 3 minutes and 53 seconds. Total scan time is less than 9 minutes. The most important information comes from the 3D WATS sequence and in most cases the derived images will be sufficient to choose between non-operative or operative treatment.

In total, 45 minutes is set aside for receiving and briefing patient and parents, positioning the child and completing the scans. Parents are invited to sit next to the child during the scan. The radiographers involve the children by dialog and each child can choose the color of the room. The child holds the stop

button in his or her hand, so that they can press stop along the way. Communication with radiographers is possible throughout the procedure. The procedure is stopped at any request from the child or parents or if deemed necessary by the radiographers.

3D Water Selective Excitation (WATS)

3D WATS is a fast field echo T1 weighted pulse sequence [33]. 3D WATS utilizes the chemical shift artifact to differentiate between the frequencies of fat and water. The sequence applies a technique where the water protons are selectively excited to induce fat suppression in cartilage. WATS is a 3D imagery so it can be reconstructed with various slices in the computer after the scan. The 3D WATS sequence is usually used for evaluation of cartilage.

T1

T1 weighted images results from the differences in the T1 recovery times of the tissues. In T1 sequences, fat and degeneration has a high signal, where cortical bone, infection and cysts has a low signal. T1 weighted images are used to portray the anatomy.

Short Tau Inversion Recovery (STIR)

STIR is a pulse sequence that suppresses the signal from fat [34]. STIR is an important sequence in musculoskeletal imaging showing lesions inside of the bone. A normal bone contains fat bone marrow and STIR suppresses fat which shows lesions with bone marrow edema.

Table 2: Specific scan parameters and scan times

Parameter	3D WATS	T1 COR	STIR COR
TR	20	Range (450-750) 750	3536
TE	4.9	9	60
FA	15	90	*Inversion Recovery*: 220 msek. *Refocusing angle*: 90*
Scan mode	3D	2D	2D
Technique	FFE	SE (TSE)	IR (TSE)
Slice thickness	3 mm	3 mm	3 mm
Interslice gap	-1.5 mm	0.3 mm	0.3 mm
FOV	150 x 150	140 x 140	130 x 130
Voxel	0.493 x 0.493	0.5 x 0.53	0.6 x 0.74
Time	2.32 min	2.16 min	3.53 min

6.3.4 MRI results

The results of the MRI are reconstructed and read by senior MRI radiologists together with the PI. Patient and parents are informed of the MRI findings and the following treatment (operative or non-operative) by the PI.

6.3.5 Operative treatment

If the MRI cannot be completed for any reason, the images are insufficient in establishing fracture pattern or if the MRI shows an unstable fracture which is displaced more than 2 mm, we will suggest operative treatment with Kirschner wire fixation. Further participation in this project will be terminated.

6.3.6 Non-operative treatment

Patients with undisplaced and minimally displaced LHCF as seen on MRI will follow a non-operative treatment protocol (appendix 1). The treatment consists of an above elbow splint until radiographic union. Radiographic union usually occurs after four weeks; however, treatment will be continued until callus formation is seen at the cortex of the metaphysis.

Fractures that are not complete (e.g., do not traverse both metaphysis, physis, epiphysis and joint cartilage) are considered stable. Complete fractures displaced <2 mm are considered unstable but still eligible for non-operative treatment. All patients will be seen for FU as outlined in section 6.2.

Any patient with a fracture seen to displace more than 2 mm during FU will be suggested operative treatment.

7 Definitions of outcome measures and study variables

7.1 Primary outcome

7.1.1 Mayo Elbow Performance Score (MEPS)

MEPS consists of four domains; pain, elbow range of motion (ROM), stability and function [35]. We use a modified MEPS which omits the functional domain because it is not relevant in smaller children. The total score ranges from 0-100 with higher scores indicating better function (figure 5). If the total score ranges between 75 and 100, the result is good (satisfactory); 50–74, fair (acceptable); <50, poor (unsatisfactory) [36]. MEPS has been found to be accurate and reliable compared to other elbow scoring systems [37].

Criteria	No. of points
PAIN (max., 60 points)	
None	60
Mild to occasional, no medication	40
Moderate to occasional, activity limited, medication	20
Severe to incapacitating	0
MOTION (max. 30 points)	
Arc of extension/flexion:	
>90	30
60–89	20
30–59	10
<30	0
STABILITY (max., 10 points)	
Effect on function of the elbow	
None or mild (does not limit activity)	10
Moderate (impairs certain functions)	5
Severe (markedly limits activity)	0

Figure 5 - Modified Mayo Elbow Performance Score.

7.2 Secondary outcomes

7.2.1 MRI results

- Proportion of successful MRIs defined as a completed scan with an image quality that is useful for analysis by the radiologist.
- MRI findings.
- Song classification based on MRI.
- Scan length (minutes).
- Any discomforts for the child during the scan.

7.2.2 Radiographic results

Injury radiographs and subsequent radiographs during FU will be read and described by a senior orthopedic surgeon.

7.2.3 Secondary displacement

Any secondary displacement and amount of radiographic displacement (mm) is recorded.

7.2.4 Pain

To quantify pain in the patient, an age appropriate rating scale is applied:

- Age <5 years: Face, Legs, Activity, Cry, Consolability Scale (FLACC)
- Age >4 years: Faces Pain Scale – Revised (FPS-R)
- Age >8 years: Visual analogue scale

Face, Legs, Activity, Cry, Consolability Scale (FLACC)

To quantify pain behaviors in children who may not be able to verbalize the presence or severity of pain FLACC [38] provides a simple framework. The child is observed for at least 2-5 minutes. Legs and body are observed uncovered. Activity is observed and body is assessed for tenseness and tone.

Behavior	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jow
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams, sobs, frequent complaints
Consolability	Content, relaxed	Reassured by touching, hugging or being talked to, distractible	Difficult to console or comfort

Assessment of Behavioural Score:

- 0 = Relaxed and comfortable
- 1-3 = Mild discomfort
- 4-6 = Moderate pain
- 7-10 = Severe discomfort/pain

Faces Pain Scale – Revised (FPS-R)

The Faces Pain Scale – Revised (FPS-R) [39] is used to quantify pain in children above four years of age. It is a self-report measure of pain intensity developed for children. It was adapted from the Faces Pain Scale [40] to make it possible to score the sensation of pain on a 0-to-10 metric. The scale shows a close linear relationship with visual analog pain scales (VAS) across the age range of 4-16 years.

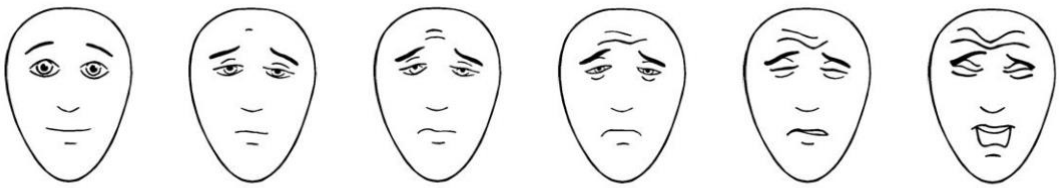

Figure 6 - Faces of the FPS-R. The child is instructed to point to the faces that shows how much pain the child is in at that moment. Faces are scored 0, 2, 4, 6, 8 or 10 from left to right.

FPS-R is easy to administer and requires no equipment except for the photocopied faces (figure 6). The child is asked to point to the face that shows how much pain the child is in at that moment. Faces are scored 0-10 so 0 equals no pain and 10 equals very much pain.

Visual analogue scale

A visual analogue scale (VAS) (Figure 7) is used to quantify pain in children age 8 and above. VAS has been extensively investigated in quantifying pain in older children [41,42]. The child is asked to put a mark on the line corresponding to the child's pain at that moment. A mark to the far left equals no pain and a mark to the far right equals worst possible pain. The line is 10 cm long and the child's mark is measured from left to right in cm with one decimal e.g., 3.4 cm equaling a VAS of 3.4. If the child cannot cooperate to using VAS, FPS-R is used instead.

Figure 7 - Visual analogue scale (VAS) for quantifying pain in children age 8 and above.

8 Statistical planning

8.1 Hypotheses

Minimally displaced LHCF (Song stage 1, 2 and 3) can be treated non-operatively based on MRI findings with good functional outcomes after two years.

8.2 Sample size considerations

Samples size is estimated from previous studies which included less than 30 participants [22,23]. The investigators of this study suspect that by enrolling 50 participants the age distribution and fracture pattern variation will be representative of the background population. By enrolling 50 patients the investigators suspect that any frequent and serious complications will be found.

8.3 Statistical analysis

Baseline characteristics and outcomes recorded at scheduled FU assessments will be presented using simple summary statistics.

- Categorical variables will be summarized using the frequency and percentage for each category.
- Continuous variables will be summarized using the mean, standard deviation (SD), median, inter-quartile range, and minimum and maximum values and, if appropriate, according to clinically relevant categories.

In general, continuous variables with both baseline and FU measurements available will also be summarized in terms of the individual patient-level changes between baseline and follow-up.

A p-value of <0.05 is regarded as being significant. Data will be analyzed using SPSS (SPSS, Chicago, IL, USA).

8.3.1 Patient discontinuation

If a participant chooses to discontinue the follow-up examinations for any reason, the date and reason for drop-out is recorded and the latest examination will be carried forward in the analysis. In case of drop-out before the first follow-up visit the participant will be excluded from the analysis. Participants are only removed from the study if they decline participation.

9 Bias

We strive to minimize bias in our study. Minimally displaced fractures of the elbow can go unnoticed and be missed by our project. However, Danish parents are usually not withholding in taking an injured child to the ED. A strict protocol for referrals for treatment are in place in Denmark. All eligible patients referred to Herlev and Gentofte University Hospital will be asked to participate in the study. We speculate that by enrolling 50 participants the cohort will be representative of the background population. We speculate that these efforts will limit selection bias. Efforts described in the follow-up section reduce the risk of loss to follow-up. Overall, we find a low risk of bias in our study for the chosen study design and size.

10 Benefits

Classifying lateral condyle fractures and establishing whether they are stable or not is the key to choosing the right treatment strategy. MRI is the only feasible image modality that can make that distinction.

LHCF is currently a fracture that requires open surgery in most cases due to the radiographic inability to distinguish stable injuries from unstable. This project seeks to use MRI without sedation or GA in order to distinguish fracture patterns. MRI has been shown to be feasible in all age groups without the need for sedation or GA [24].

Thévenin-Lemoine et.al. found that 25 of 27 children could successfully complete an MRI without sedation or GA [23]. Of the 25 children, 17 (68%) had incomplete stable fracture patterns and six (24%) had complete but minimally displaced fractures. In all, 23 (92%) children could be treated non-operatively. Two children had unstable and displaced fractures and underwent surgery.

If proven safe and feasible, non-operative treatment for undisplaced and minimally displaced LHCF would relieve the child of hospital admission, anesthesia and surgery and reduce parent's need for time off work and reduce overall healthcare costs.

The investigators suspect a significant decrease in the need for operative management based on the results of this project.

11 Risk analysis

The risks that occur in this study are associated with the general risks of non-operative treatment for LHCF.

11.1 Treatment-related risks

Discomforts/risks from casting:

- Heat injury
- Pressure sores and skin breakdown
- Dermatitis
- Joint stiffness

11.2 Study disadvantages

Extra visits to the outpatient clinic. We follow all patients with seven visits to the outpatient clinic. This is four more than with standard treatment and might be viewed as a disadvantage.

11.3 Study-related risks

11.3.1 Secondary displacement

During non-operative treatment of fractures, the risk of secondary displacement is well known. The risk of secondary displacement of an initially undisplaced LHCF varies from 4% to more than 40% depending on the initial stability and displacement [12]. As the initial stability in this study is evaluated by MRI the investigators suspect that the risk of secondary displacement will be close to 4%.

11.3.2 Radiation

In comparison with the standard follow up of LHCF there are four additional visits to the out-patient clinic with radiographs of the elbow in AP, ML and IO view. Collectively, the effective dosage is 0.004 mSv - far below 0.1 mSv and is considered insignificant.

11.3.3 Loss of privacy

Patients' private and confidential medical information may get disclosed and confidentiality broken.

11.4 Actions to minimize increased risks

General treatment-related risks will be present whether the patient participates in the study or not. Such risks will be managed by use of standards of treatment, i.e. casting by trained physicians and nurses.

Risk of unnoticed secondary displacement is lowered by an increased number of FUs with radiographs and MRI in case of unstable injury.

The risk of loss of privacy and confidentiality will be managed by strict adherence to data safety and security procedures explained elsewhere in this CIP.

The study will be implemented according to current valid international guidelines (ICH-GCP and ISO 14155). The ethical position is based on the Declaration of Helsinki, thus guaranteeing optimal protection of patient interests.

12 Informed consent process

12.1 Special considerations to consent pediatric patients

In this pediatric study, the parent(s) or legal guardian(s) are informed face-to-face about the study and provide informed consent using specific patient information and ICF. In any case, the child is informed orally in an adequate way.

Written informed consent needs to be obtained from the parent(s) or legal guardian(s). Assent is obtained from any child considered to be able to understand the basic information provided.

A member of the research team will, in an undisturbed environment, explain using a plain, understandable language, movies and toys to each participant and parents the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail.

Parents and children will be informed that the participation in the study is completely voluntary and that they may withdraw from the study at any time and that withdrawal of consent will not affect subsequent medical assistance and treatment.

The participant’s parents will be informed that their child’s medical records will be examined directly by authorized individuals involved in the study.

Consent will be obtained from every patient’s parents before any study-specific procedures or assessments take place.

Parents will be provided specific information and ICF describing the study and providing sufficient information for the parents to make an informed decision about their child's participation in the study together with general information about participating in a research project from the Danish National Committee on Health Research Ethics.

Parents will in most cases have at least 24 hours to consider enrollment however, there might be factors (e.g. late presentation to the ED) that dictate more emergent treatment requiring consent with less consideration time.

The parents will signify their willingness to let their child participate in the study by signing and dating a personal copy of the approved ICF. The consent form must also be signed and dated by a member of the research team and it will be retained as part of the study records. The investigator will keep the original ICF in the ISF and provide the patient's parents with a copy.

13 Adverse event reporting

In this clinical investigation no medical devices are used and based on the risk analyses, AEs or serious AEs (SAEs) according to ISO 14155 are not collected.

14 Data management

This project complies with the EU's General Data Protection Regulation (GDPR) according to the Danish law on data protection *Databeskyttelsesloven* and *Databeskyttelsesforordningen*.

In order to plan and conduct visits we ask that consent is given to access the patient's EHR. We ask permission to retrieve patient-related data and to read entries regarding visits. We ask permission to access radiographs and MRIs. We ask that access the patient's EHR is given until the conclusion of the project. No access to the patient's EHR regarding the study is made before informed consent to participate is given.

Consent gives the person responsible for the trial and the relevant authorities direct access to obtain information in the patient's medical records for the purpose of carrying out the project as well as for control purposes.

14.1 Data collection, source data, storage and archiving

Data management will be performed by the PI. Data handling and protection are conducted according to the ISO 14155 guidelines and ICH-GCP and applicable regulations.

The eCRF collects data from each participant. Specifically all data on each patient participating in the study are documented in the eCRF. The eCRF contains data items as specified in this CIP. Modification of the eCRF will be made only if deemed necessary and in accordance with any amendment to the CIP.

The patient's hospital records are stored securely in the hospital's EHR (Epic Systems Corporation, Verona, Wisconsin, USA).

14.1.1 Electronic CRF

For this study, an eCRF is designed to accommodate the specific features of the study design. Access to the eCRF is password protected. The project's eCRF is stored securely using Research Electronic Data Capture (RedCAP, Vanderbilt University, USA). The eCRF is to be completed in a timely manner after a patient's visit (i.e. 14 days after occurrence of a documentable event).

14.2 Imaging data

Radiographs and MRIs are stored securely in the hospital's Picture archiving and communication system (PACS).

14.3 Confidentiality

Privacy and confidentiality of the patient's medical data will be maintained through the study.

Fully identifiable information may be reviewed for the purpose of verifying data in the eCRF. This can be carried out by the PI. Personal medical information will be treated as confidential at all times. The informed consent document will contain information about the confidentiality of the medical information and approval for the access.

15 Regulatory affairs

The CIP, associated documents, investigator's financial disclosure, the patient information and ICFs will be sent to a respective EC for evaluation and approval. The relevant EC will be kept informed about the study progress and events according to their specific regulations and procedures.

16 Disclosures and economy

The initiative for this study has been taken solely by the investigators. The investigators and affiliated colleagues have not received any financial payments or other benefits from any commercial entity related to the subject of this project. The investigators declare that they have no conflict of interest.

Participants do not receive any economic benefits or gifts from the participation in this project.

All expenses are paid for by the sponsor.

17 Patient insurance

As with any treatment in the Danish healthcare system all patients are insured and covered by The Patient Compensation Association (Patienterstatningen).

18 Study report and publication policy

18.1 Final Study Report

The results of the statistical evaluation will be summarized in a report, which forms the basis for the comprehensive FSR. The comprehensive FSR forms the basis for all future publications.

18.2 Publication

The study protocol and the trial will be registered with Clinicaltrials.gov

The results, both positive, negative and inconclusive, will be sent for submission in a peer reviewed international orthopedic journal, and the results will be presented at national and international scientific meetings. Reporting will adhere to the STROBE guidelines for cohort studies [31].

19 Termination criteria

The progress of the study, in particular the enrollment and safety aspects, will be closely monitored together with the sponsor. The sponsor may decide to terminate the. In case of an early study termination, all patients already enrolled in the study will be followed up until the last FU visit as defined in the CIP.

19.1 Stopping rules

The recruitment will be put on hold for safety reason if:

- Secondary displacement of more than 2 mm during FU in > 75% of cases at interim analysis.

In such a case, the reported complication will be discussed with the sponsor. The sponsor will decide about the actions to be taken and if the study needs to be stopped or not.

20 Deviations from the Clinical Investigation Plan

Deviations from the procedures as described in this CIP or altering the CIP without following a defined process are not permitted.

A CIP deviation is any non-adherence to the protocol that does not involve the inclusion/exclusion criteria, primary efficacy variable, and GCP guidelines. CIP deviations are minor and do not impact the study in a major way. CIP deviations are to be reported to the sponsor within ten working days.

A CIP violation is any significant divergence from the protocol on the part of the patient, investigator, sponsor, or any other responsible party that affects e.g. the inclusion/exclusion criteria, primary efficacy variable, or GCP guidelines. Violations will be recorded at the study site and in the eCRF.

21 Amendments to the Clinical Investigation Plan

No changes to the approved CIP are allowed, except when the change removes immediate threats for the patient safety or is of a purely administrative or logistic nature.

Should there be any need during the performance of the study to change this CIP, an amendment will be developed, issued and approved by or notified to the required bodies.

22 Time schedule

Ethics Committee approvals	28.06.2021	to	01.09.2021
First patient/first visit	01.10.2021		
Last patient/first visit	01.10.2023		
Last patient/last visit	01.10.2025		
Data analysis	01.11.2025	to	01.03.2026
Final Study Report	01.03.2026	to	01.06.2026

23 Authors

CIP developed by

PCI	Department of Orthopedic Surgery Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark
Project Manager	Morten Jon Andersen
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CIP approval signatures

Name	Function	Date	Signature
Morten Jon Andersen	Principal Coordinating Investigator		

Name	Function	Date	Signature
Bo Sanderhoff Olsen	Director of institution		

With signing this statement, I agree and confirm:

- To have read and understood this CIP and to have informed and to have supervised the appropriate training of all research team members of this study site involved with the conduct of the study.
- To assume responsibility to conduct the study in compliance with this protocol and future amendments at this study site.
- To obtain written approval the independent EC before initiating the clinical investigation at this study site.
- To not implement any changes to the protocol or the corresponding procedures without written agreement from the sponsor and the EC, except where necessary to eliminate immediate risk to the study patients.
- That I and all team members involved in the conduct of this clinical investigation are aware and trained in aspects of ICH-GCP and all applicable regulatory requirements.

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879 # Appendix 1 - Diagnosis and Treatment Protocol