ClinicalTrials.gov Document Cover Page

Official Title:	Time To Radiographic Union In Displaced Pediatric Diaphyseal Forearm Fractures Treated With Bioabsorbable Versus Titanium Intramedullary Nails: A Single-Center, Randomized, Blinded, Parallel-Group, Non-Inferiority Trial (FOREST Trial)
Short title:	Time to healing in displaced pediatric diaphyseal forearm fractures treated with bioabsorbable compared to titanium intramedullary nails
Very short title:	Time to healing in pediatric diaphyseal forearm fractures
Trial acronym:	FOREST Trial - **Fo**rearm **R**andomized **S**tudy of **ES**IN **T**echnique – Bioabsorbable versus Titanium Implants
NCT Number:	NCT07536581
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This document is submitted in accordance with ClinicalTrials.gov requirements. The above information identifies the study and document version for regulatory and public record purposes.

Forearm Randomized study of Elastic Stable intramedullary nailing Technique - bioabsorbable versus titanium implants

Full title

Time To Radiographic Union In Displaced Pediatric Diaphyseal Forearm Fractures Treated With Bioabsorbable Versus Titanium Intramedullary Nails: A Single-Center, Randomized, Blinded, Parallel-Group, Non-Inferiority Trial

Clinical Investigation Plan

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Version	Date	Author	Description of Changes	Approved by
1.0	2026-02-05	MJA	Initial version	MJA
1.1	2026-03-31	MJA	Minor revisions based on EC review	MJA
1.2	2026-04-17	MJA	Added ClinicalTrials.gov ID	MJA

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Content

Abbreviations/glossary

AE/SAE	Adverse Event(s)/Serious Adverse Event(s)
ADE/SADE	Adverse Device Event(s)/Serious Adverse Device Event(s)
BIN	Bioabsorbable Intramedullary Nails (PLGA)
CIP	Clinical Investigation Plan
CRF	Case Report Form
DICOM	Digital Imaging and Communications in Medicine
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESIN	Elastic Stable Intramedullary Nails (metal)
FDA	Food and Drug Administration
FSR	Final Study Report
FU(s)	Follow-up(s), eg follow-up visit(s), follow-up procedure(s)
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medical Device
ISF	Investigator Site File
ISO	International Organization for Standardization
ITT	Intention to treat
LOR	Loss of (fracture) reduction
PI	Principal Investigator
PP	Per Protocol
PDFF	Pediatric Diaphyseal Forearm Fracture
SAP	Statistical Analysis Plan
SC	Study Coordinator
SD	Standard Deviation
SOP	Standard Operating Procedure
U(S)ADE	Unanticipated (Serious) Adverse Device Effect
WHO	World Health Organization

Definitions

Baseline	Status post injury but pretreatment
Discharge	Discharge from pediatric department
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)
Parents	For readability, the term “parents” will be used throughout this protocol to refer to the participant’s parent(s) and/or legal guardian(s), unless otherwise specified
Pre-injury	Status before the injury (retrospectively assessed data)
Treatment day	"Day 0"; day of operation/reduction
Written informed consent	Legally binding signature on the informed consent form (ICF) (by the legally authorized representative), whereas the person who signs the ICF can understand the content of the patient information has signed and dated the EC approved written informed consent

1 Synopsis

Official title	Time to healing in displaced pediatric diaphyseal forearm fractures treated with bioabsorbable compared to titanium intramedullary nails: a single-center, multi-blinded, randomized parallel-group, non-inferiority study
Short title	Time to healing in displaced pediatric diaphyseal forearm fractures treated with bioabsorbable compared to titanium intramedullary nails
Very short title	Time to healing in pediatric diaphyseal forearm fractures
Trial acronym	FOREST Trial - **Fo**rearm **R**andomized Study of **ES**IN **T**echnique – Bioabsorbable versus Titanium Implants
Trial logo	
Sponsor	Department of Orthopedic Surgery Copenhagen University Hospital – Herlev and Gentofte Borgmester Ib Juuls Vej 1 2730 Herlev Denmark
Registration	The Danish Data Protection Agency ID: **P-2022-315** The Danish National Committee On Health Research Ethics ID: **16-0302-99** Clinicaltrials.gov: **NCT ID not yet assigned – pending review**
Background and purpose	Pediatric forearm fractures are the most common fractures in children and are a leading cause of orthopedic healthcare contact. Displaced diaphyseal forearm fractures requiring operative stabilization are most treated with titanium elastic nails (TEN). Although this fixation works well, routine implant removal after about 6–12 months is often recommended, requiring an additional operation that—while usually low risk—still places a significant burden on the child and family and uses healthcare resources. Bioabsorbable intramedullary nails (BIN) have been developed for similar indications and may eliminate the need for elective implant removal, thereby reducing reoperations and associated costs. Clinical experience and early studies indicate that BIN are safe and feasible; however, BIN are more flexible than titanium implants, which may theoretically increase the risk of delayed union. The purpose of this trial is to determine whether time to radiographic healing after fixation with BIN is non-inferior to that achieved with TEN. As no prior studies have directly compared time to healing between these implant types using a standardized radiographic healing metric, establishing non-inferior healing is essential before broader implementation of BIN as standard treatment.

Condition	Displaced Pediatric Diaphyseal Forearm Fractures (PDFF)
Investigational Medical Device	Activa IM-Nail™ (Bioretec Ltd., Tampere, Finland)
Comparator	Titanium Elastic Nail System (Synthes GmbH, Oberdorf, Switzerland)
Study type	Interventional
Study design	Single-center, randomized (1:1), parallel-group, blinded, non-inferiority clinical investigation comparing bioabsorbable intramedullary nails (BIN) versus titanium elastic nails (TEN).
Primary objective	To demonstrate that time to radiographic healing is non-inferior after BIN compared with TEN.
Secondary objective(s)	To compare the two groups with respect to: • Pain and discomfort • Return to physical and recreational activities • Emotional and psychosocial wellbeing • Complications from the injury and its treatment • Return to baseline activities daily living • Participation in learning • Appearance and deformity • Recovery of manual dexterity (for upper limb fracture) • Cost to family • Ability to sleep • Range of motion • The cost of treatment • Child satisfaction
Hypothesis	Time to radiographic healing after BIN is non-inferior to that after TEN.
Primary outcome measure	Time to radiographic healing, defined as time from surgery/randomization to achieving mRUS ≥ 11. Healing is assessed on plain anteroposterior (AP) and mediolateral (ML) radiographs and objectively quantified using the modified Radiographic Union Score (mRUS).
Secondary outcome measure(s)	• Range of motion (degrees) measured by goniometer • Grip strength measured by dynamometer • Faces Pain Scale – Revised (FPS-R) • Questions from the Nationwide Survey of Patient Experiences • Complications, reoperations, and adverse events (AEs) related to the procedure and/or implants • Pediatric and Danish version of EQ-5D (EQ-5D-Y) • Motor function assessment: Movement Assessment Battery for Children – Third Edition (MABC-3), Manual Dexterity domain

<table>
<tr><td>Statistical considerations and estimated enrollment</td><td>A statistician from the University of Copenhagen contributed to the trial design, including selection of statistical methods and the sample size/power calculations.

This is a randomized, parallel-group, non-inferiority study with equal allocation (1:1). The primary endpoint is time to healing, defined as the time from surgery to achieving mRUS ≥ 11.

The non-inferiority margin was selected based on clinical judgement and available evidence and was further contextualized by parent input from the pilot cohort regarding the maximum acceptable additional weeks of activity restriction (beyond the usual 6 weeks) in exchange for avoiding a second implant removal operation. We set the non-inferiority margin $\Delta = 3$ weeks.

With a non-inferiority margin $\Delta = 3$ weeks, the hypotheses are:
$H_0: \theta \geq \Delta$ (BIN is inferior to TEN by ≥ 3.0 weeks)
$H_1: \theta < \Delta$ (BIN is non-inferior to TEN)

<table><tr><th colspan="2">Sample size</th></tr><tr><td>Significance level</td><td>0.025</td></tr><tr><td>Power (1-β)</td><td>0.9</td></tr><tr><td>Ratio of sample size</td><td>1:1</td></tr><tr><td>Standard deviation (SD)</td><td>3 weeks</td></tr><tr><td>Non-inferiority margin (Δ)</td><td>3 weeks</td></tr><tr><td>Loss to follow-up/withdrawal (%)</td><td>5</td></tr><tr><td>Intercurrent events (%)</td><td>5</td></tr><tr><td>Result</td><td></td></tr><tr><td>Sample size per group</td><td>22</td></tr><tr><td>Sample size per group incl. attrition</td><td>25</td></tr><tr><td>Total sample size incl. attrition</td><td>50</td></tr></table>
The required sample size is 25 per group; to ensure operational robustness we will enroll 30 per group (total 60).</td></tr>
<tr><td>Start of enrollment</td><td>May 2026 (estimated)</td></tr>
<tr><td>Last patient/last visit</td><td>May 2029 (estimated) / May 2031 (estimated)</td></tr>
</table>

Eligibility inclusion criteria	• Children aged 3–13 years with open physes • Diagnosis of a traumatic diaphyseal forearm fracture of the radius, ulna, or both • Operative fixation required. Fractures must be: – complete (not unicortical or greenstick) AND – displaced >50% of bone width (after attempted closed reduction) AND/OR – angulated >10° in any plane (after attempted closed reduction) • Informed consent obtained, i.e.: – Willingness and ability to participate in the clinical investigation according to the Clinical Investigation Plan (CIP) – Parents able to understand the content of the patient information and informed consent form – Signed and dated EC-approved electronic informed consent form
Eligibility exclusion criteria	**Preoperative exclusion criteria** • Contraindication – Conditions where internal fixation is contraindicated (e.g. active or potential infection) – Grossly open fractures (Gustilo Anderson grade > 2) • Exclusion criteria – Fracture occurred more than 2 weeks prior – Fractures that are well managed conservatively (undisplaced or minimally displaced) – Previous ipsilateral forearm fracture (risk of closed medullary canal) – Fractures unsuited for intramedullary nailing (e.g. multifragmentary, metaphyseal or epiphyseal) – Concurrent ipsilateral wrist or elbow involvement (e.g. Monteggia or Galeazzi variants) – Unable to participate in follow-up – Existing bone pathology (e.g. tumor, osteogenesis imperfecta, degenerative disease) • Participation in any other medical device or medicinal product study within the previous month that could influence in opinion of the PI the results of the present study **Intraoperative exclusion criteria** • Fractures suitable for closed reduction and casting (see 6.3.9) • Indication for treatment 1 (BIN) only • Indication for treatment 2 (ESIN) only • Intraoperative decision to use implants other than the devices under investigation – E.g. plate fixation or external fixation

Study site	Department of Orthopedic Surgery Copenhagen University Hospital – Herlev and Gentofte Copenhagen, Denmark
Health authority	The Danish National Committee On Health Research Ethics
Imaging review	All masked radiographs will be assessed by independent blinded radiologists and orthopedic surgeons during the study.

2 Rationale and purpose of the study

Bioabsorbable intramedullary nails (BIN) are a feasible and seemingly safe option for the surgical treatment of displaced pediatric diaphyseal forearm fractures (PDFF). The key potential advantage of BIN compared with titanium elastic intramedullary nails (TEN) is the avoidance of routine secondary surgery for implant removal.

The operative technique for BIN and TEN is largely similar and is expected to entail a comparable perioperative risk profile. However, BIN are more flexible than titanium implants and may, in theory, provide less mechanical stability, which could increase the risk of delayed union. To date, no comparative studies have evaluated time to bone union between BIN and TEN in this population.

The primary aim of this study is to compare time to bone union in PDFF treated surgically with BIN versus TEN.

A single-center, randomized, parallel-group, non-inferiority design with blinding of relevant parties has been chosen. Given the clinically meaningful benefit of BIN in avoiding a second operation, the study is designed to determine whether BIN results in an acceptable (non-inferior) time to union compared with TEN, allowing for a limited delay in union if balanced by the avoidance of implant removal surgery.

All interventions are performed according to standard of care and within the approved indications for each device.

3 General information/responsibilities

The responsibilities of the sponsor and investigators are defined in accordance with the International Council for Harmonisation Good Clinical Practice (ICH-GCP) and ISO 14155. Study-specific requirements, including approvals from the responsible ethics committee (EC), are described elsewhere in this Clinical Investigation Plan (CIP). The study site undertakes to ensure the correct and timely conduct of the study, including accurate documentation and secure transmission of study data.

Prior to initiation of participant enrollment, the Principal Investigator (PI) and the research team will be instructed and trained in the conduct of the study to confirm their capability to meet the required quality standards and to comply with applicable standard operating procedures (SOPs).

The study site will ensure completion of study documentation for all enrolled participants. “Complete documentation” means that all scheduled follow-up (FU) visits have been performed, that assessments are recorded in the electronic case report forms (eCRFs) developed for this study, and that required radiological investigations have been obtained at the FU visits.

3.1 Responsibilities

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3.2 Study site

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4 Background and literature review

Forearm fractures are the most common fractures in children and the most frequent reason for orthopedic assessment. For most pediatric fractures, casting remains the standard of care because children's bones have a substantial capacity to remodel after union, allowing acceptable healing with greater angulation or displacement than would be tolerated in adults without long-term functional consequences. When forearm fractures exceed remodeling potential, early closed reduction by manipulation is generally the preferred treatment. Fractures that are not amenable to closed management, cannot be reduced closed, or re-displace during follow-up will often require operative stabilization [1,2].

Forearm fractures requiring surgical stabilization are commonly treated with elastic stable intramedullary nailing technique (ESIN), typically using titanium elastic intramedullary nails (TEN) [3]. Removal of TEN after 6–12 months is generally advocated [3–5]. Although implant removal is usually associated with few complications, it represents a substantial burden for the child and family and consumes healthcare resources [6]. Bioabsorbable intramedullary nails (BIN) have been developed for similar indications. Because bioabsorbable implants dissolve, they spare the child a second operation and potentially reduce overall healthcare costs [7].

4.1 Definition and epidemiology

Fractures constitute 10–25% of all pediatric injuries. During childhood, at least 50% of boys and 30% of girls will sustain a fracture. Fracture type, pattern, and mechanism vary between countries [8]. Pediatric diaphyseal forearm fractures (PDFF) of the radius and/or ulna are among the most common reasons for orthopedic care in children [9]. With an incidence of 6.8 per 10,000 children (8.3 for boys and 5.2 for

girls), this injury accounts for approximately 3–6% of all pediatric fractures [8,9] and occurs primarily between the ages of 5 and 14 years (median 8.5 years) [10].

Over the past three decades, the incidence of these fractures has increased markedly; however, the precise cause remains unknown [8,11]. Proposed explanations include physical inactivity, obesity, and vitamin D deficiency, potentially contributing to lower bone mineral density and an increasing number of pediatric fractures [12].

4.2 Fracture repair

A fracture disrupts the structural continuity of the cortical bone. The biology of fracture repair and bone healing is complex and not fully understood, but it aims to restore the injured bone to its pre-injury structure and composition. Following a complete fracture, secondary bone healing typically occurs through the stages summarized in Figure 1.

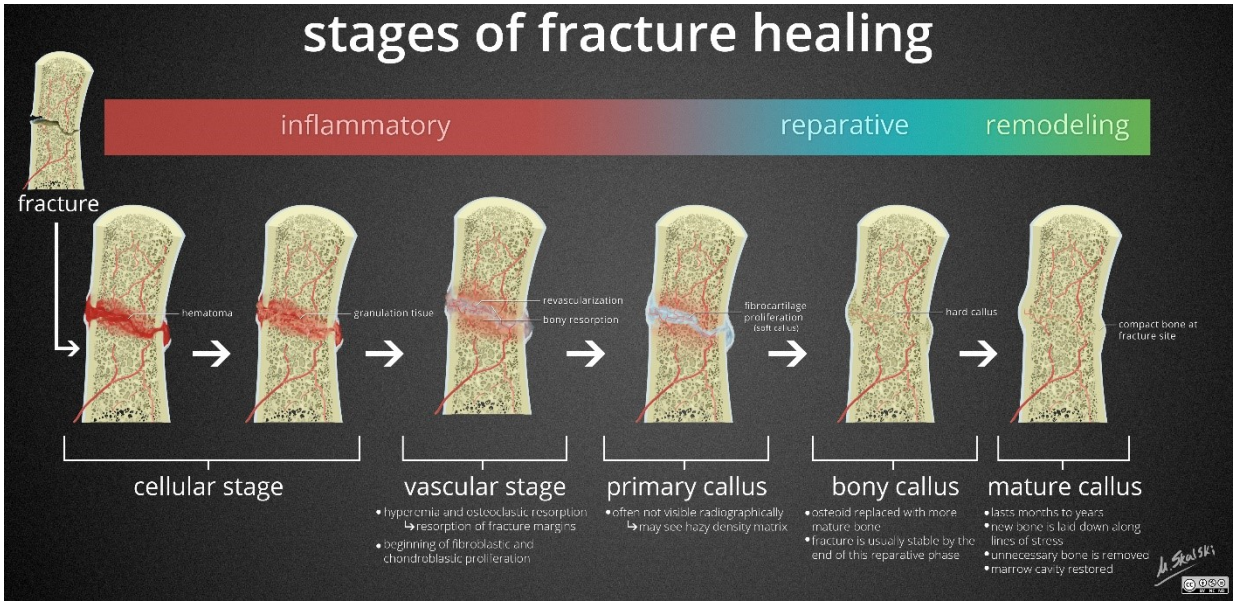


Figure 1 - Stages of fracture healing. Hematoma formation, immediately following fracture. Granulation tissue formation, within two weeks of fracture. Bony callus formation, within two to four weeks in children. Bone remodeling, continues for months to years after clinical union. Case courtesy of Matt Skalski, Radiopaedia.org, rID: 57418

4.3 Treatment options

Because of the complex functional relationship between the radius and ulna, prognosis depends on fracture healing without excessive shortening, rotational deformity, or angulation. Minimally displaced PDFF can be managed successfully with closed reduction and casting [13]. However, over the past two decades there has been a significant increase in the proportion of operatively managed fractures [14]. Non-operative management is generally considered acceptable when angulation is <10°, rotational deformity is <30°, and translation is <100%. Re-displacement in a cast occurs in approximately 10% of cases and may necessitate re-reduction or surgical fixation [13,15].

As for many fracture types, expectations for outcomes have increased over the past two decades, particularly with respect to motion of the elbow, forearm, and wrist. In 1981, a functional range of motion was described as elbow flexion/extension of 30–130 degrees and forearm rotation of 50 degrees of pronation and 50 degrees of supination [16]; however, that study did not include children. More recent

studies suggest that contemporary activities such as using a mobile phone, tablet, or computer keyboard may require additional range of motion [17,18]. Increasing functional demands, together with parental expectations and socioeconomic factors, may therefore expand the indications for surgical stabilization of PDFF.

The most common methods for treating unstable PDFF include closed or open reduction with elastic stable intramedullary nailing (ESIN) technique using titanium or steel nails, or open reduction and internal fixation (ORIF) using plates and screws [15]. ORIF provides excellent reduction and stable fixation but requires greater soft-tissue dissection and is often followed by implant removal. There is no conclusive evidence favoring one surgical method over another; however, with the introduction of minimally invasive ESIN, the use of this technique has increased substantially and it is now widely regarded as the preferred operative approach [11,14,15,19].

4.3.1 Closed reduction and casting

Slightly angulated or minimally displaced PDFF should be treated non-operatively. Fractures that exceed the acceptable limits of angulation, rotation, or displacement (as described above) should be managed with attempted closed manipulation/reduction followed by a well-molded circumferential above-elbow cast for 6-8 weeks. This approach yields good to excellent results in approximately 80% of cases, while the remainder require re-reduction or surgical fixation [20].

4.3.2 Metal Elastic Stable Intramedullary Nailing (ESIN)

Elastic stable intramedullary nailing (ESIN) technique was introduced in the 1970s, initially using Kirschner wires. In the 1990s, implants specifically designed for ESIN became widely available. Since then, ESIN has been shown to produce excellent results with relatively few complications [4,21]. Advantages include possible closed fracture reduction, minimal soft-tissue dissection, early mobilization, maintenance of reduction, and straightforward implant removal. Complications are uncommon but include soft-tissue irritation, superficial radial nerve injury, extensor pollicis longus tendon rupture, delayed union, malunion, refracture, and infection [3,15,22,23].

Several metallic alloys have been used for ESIN implants. The most widely used are titanium and steel which has favorable elastic properties [4].

4.3.3 Bioabsorbable implants

It is important to use a consistent and unified nomenclature within this research field. Liu et al. [24] suggest that implants or biomaterials that are ultimately absorbed by the body should be labeled “absorbable” or use the prefix “bio-”. The term “absorbable” emphasizes host metabolism of the degradation products of the implanted material. In this study protocol and the final manuscript, we will use the term “bioabsorbable” throughout.

Bioabsorbable implants have been used since the 1970s, and numerous materials have been investigated over time. Their use is increasing and has been shown to be a safe and feasible method for stabilizing fractures in the growing skeleton [25–27]. By using bioabsorbable implants, the need for routine implant removal is avoided, and the risks of late tissue reactions, stress shielding, and infection may be reduced [28].

Implants manufactured from oriented poly(lactic-co-glycolic acid) (PLGA) copolymers are sufficiently strong to support fractured bone. PLGA is composed of lactic acid and glycolic acid monomers, which

are part of normal human metabolism. PLGA implants undergo controlled degradation by hydrolysis into lactic acid and glycolic acid, which are subsequently metabolized to carbon dioxide and water. The implant retains strength and dimensions for at least eight weeks, and complete absorption typically occurs over approximately two to six years [29,30].

4.4 Metal implant removal in children

In children, implant removal, including removal of metal nails, is routinely performed and represents standard practice in Denmark, sanctioned by the Danish Health Authority. Implant removal is undertaken due to concerns about potential interference with skeletal growth, late tissue reactions, difficulty of delayed removal, stress shielding related to implant stiffness, interference with future orthopedic procedures, and corrosion [31]. Removal of ESIN is associated with a low complication rate of approximately 3% [32]. In some countries it is standard to leave metal implants, even in children.

4.5 The burden of surgery

As noted above, surgical implant removal is generally associated with few complications; however, it represents a substantial burden for the child and family and consumes healthcare and societal resources.

4.5.1 Operative anxiety in children

It has been shown that 50–70% of children experience significant anxiety and stress prior to surgery [33–35]. There is also evidence suggesting an association between preoperative anxiety and adverse postoperative outcomes, including emergence delirium, increased analgesic requirements, and negative behavioral changes [36]. In general, fear in children may be related to several factors, including separation from parents, an unfamiliar and potentially threatening hospital environment, painful procedures, the operation itself, and anesthesia. Operative anxiety in children should be prevented not only for humanitarian reasons, but also to reduce anxiety-related psychological distress and potential longer-term negative effects.

4.5.2 Economic burden and time away

The cost of one Activa IM-Nail™ (approximately $400) is about four times higher than that of a traditional titanium elastic nail (TEN; approximately $100). However, the cost of implant removal is approximately $1,900 [6,37], and the additional implant cost may therefore be offset. In a cost analysis that included both direct medical costs and indirect costs related to lost work time, the average cost saved per patient by using absorbable implants ranged from $410 to $903 [37].

Removal surgery is not only a socioeconomic concern. Parents typically need time off work for outpatient visits related to surgical planning, on the day of surgery, and potentially for days after treatment. This may create financial strain and, in some cases, concerns regarding job security. Similarly, the child will require time away from school.

4.5.3 Operation room burden

Because most implants in children are routinely removed, implant removal procedures consume substantial operating room capacity. Use of bioabsorbable implants may reduce the need for elective removal surgery, thereby freeing capacity for other procedures.

4.6 Current status of research in this area

To assess feasibility and safety, we conducted a prospective preliminary study including 18 children with forearm fractures treated with bioabsorbable intramedullary nails (BIN). No serious adverse events

or serious adverse device effects were observed. All fractures healed, and all children regained normal arm function within 3 months.

An international multicenter study of 76 children treated with the Activa IM-Nail reported few complications. In two cases, a small implant fragment was sheared off by the sharp fracture edge, necessitating secondary surgery for fragment removal. The Activa IM-Nail Technique Guide has subsequently been revised to emphasize additional caution when advancing the nail across the fracture site and to recommend only light hammer blows [38].

In Finland, the Activa IM-Nail has been investigated since 2011 in a randomized controlled trial comparing BIN with TEN. Both short- and long-term follow-up demonstrated similarly good outcomes [7,30].

To date, no studies have evaluated differences in time to bone union when comparing BIN with TEN. Furthermore, time to healing in PDFF has not been rigorously investigated in a prospective setting.

5 Primary and secondary objectives

5.1 Primary objective

- To investigate time to bone healing (weeks) in PDFF treated with bioabsorbable intramedullary nails (BIN) versus titanium elastic intramedullary nails (TEN).

5.2 Secondary objective(s)

- To investigate and describe
  - Functional outcome
  - Pain and discomfort
  - Refracture rate
  - Surgical complications
  - Implant-related complications
  - Patient-reported outcomes
  - Costs related to surgery
- To investigate time to bone healing (weeks) in PDFF treated non-operatively

5.3 Hypothesis

We hypothesize that time to bone healing with BIN is non-inferior to time to bone healing with TEN in the treatment of PDFF.

6 Study design

Given the potential advantages of bioabsorbable intramedullary nails (BIN), it is clinically acceptable for BIN to have a limited delay in healing compared with TEN, provided overall outcomes remain acceptable. Therefore, this study is designed as a non-inferiority trial.

A single-center, randomized, parallel-group, non-inferiority design with blinding of relevant parties has been selected, with stratification by age. The study design will follow CONSORT guidance for reporting non-inferiority trials [39].

6.1 Study population and patient enrollment

The study will be conducted at Copenhagen University Hospital – Herlev and Gentofte, Capital Region of Denmark. The hospital has a catchment area of approximately 600,000 inhabitants, including about 80,000 children aged 3–13 years.

This study investigates the treatment of pediatric forearm fractures and therefore cannot be conducted in consenting adults. Forearm fractures occur across all pediatric age groups, and it is not feasible to restrict inclusion to older children only. The study is expected to have potential direct benefit for participating patients and to generate knowledge that may improve care for future patients with the same condition.

Initial assessment in the emergency department will follow standard of care and will be independent of subsequent treatment allocation. The assessment includes medical history, physical examination, and radiographs in anteroposterior (AP) and mediolateral (ML) projections.

All operations will be performed at Herlev Hospital by orthopedic trauma surgeons.

6.1.1 Inclusion criteria

The inclusion criteria are aligned with the existing literature for the comparator (TEN).

Inclusion criteria

- Children aged 3 to 13 years with open physes
- Acute traumatic pediatric diaphyseal forearm fracture (PDFF) of the radius, ulna, or both
- Fracture characteristics:
  - Complete fracture (not unicortical or greenstick)
  - Displacement >50% of bone width, and/or angulation >10° in any plane
- Written informed consent obtained, including:
  - Ability of the parent(s) to understand the patient information and informed consent form (eICF)
  - Signed and dated ethics committee (EC)-approved eICF

6.1.2 Preoperative exclusion criteria

- **Contraindications**
  - Any condition in which internal fixation is contraindicated (e.g., active or suspected infection)
  - Grossly open fractures (Gustilo–Anderson grade > II)

- **Exclusion criteria**
  - Fracture occurred more than 2 weeks prior
  - Previous ipsilateral forearm fracture (risk of an obliterated/closed medullary canal)
  - Fractures not suitable for intramedullary nailing (e.g., multifragmentary, metaphyseal, or epiphyseal fractures)
  - Concurrent ipsilateral wrist or elbow involvement (e.g., Monteggia or Galeazzi variants)
  - Inability to participate in follow-up (e.g., no Danish CPR number/contact information, plans to move away within 3 months, or inability to attend visits despite offered scheduling flexibility)
  - Pre-existing bone pathology (e.g., tumor, osteogenesis imperfecta, or other bone disease affecting bone quality/healing)
  - Participation in another medical device or medicinal product study within the previous month that, in the opinion of the Principal Investigator (PI), could influence the results of the present study

6.1.3 Intraoperative exclusion criteria

- Intraoperative findings indicating that only Treatment 1 (BIN) is appropriate
- Intraoperative findings indicating that only Treatment 2 (TEN) is appropriate
- Intraoperative decision to use implants other than the investigational devices (e.g., plate fixation or external fixation)

6.1.4 Enrollment of participants

The study site will identify all eligible patients, defined as those who meet all inclusion criteria and none of the exclusion criteria.

6.1.4.1 Identification/prescreening

Potential participants may present to the Emergency Department (ED), the outpatient clinic (OC), or be referred from local clinics or other hospitals. Identification of eligible patients will occur during direct clinical contact in the ED or OC and/or through the routine daily review of radiographs obtained in the ED and OC or by referral.

6.1.4.2 Minimal screening log

A minimal screening log will be maintained to document the identification and flow of potentially eligible patients and to support transparency in recruitment (e.g., reasons for non-enrollment). The screening log will contain only the minimum necessary information to fulfil this purpose and will be kept separately from the study database.

For each prescreened patient, the log will include:

- a unique screening ID (assigned at prescreening)
- date of prescreening and the clinical point of identification (e.g., ED / outpatient review)
- eligibility status (eligible / not eligible / pending)
- primary reason for non-enrollment (e.g., not meeting inclusion/exclusion criteria, declined participation, logistical reasons)
- whether informed consent was obtained (yes/no) and, if yes, date of consent

The screening log will not include study outcomes or detailed clinical research data. To prevent duplicate entries and enable follow-up of pending cases, linkage to the medical record is required; this will be limited to a single linkage element (CPR number) and stored in an access-restricted manner. Access to the screening log will be limited to authorized study personnel (PI and delegated research staff) and it will be stored in a secure system (REDCap) with appropriate technical and organizational safeguards.

No study-specific data extraction beyond the minimal screening variables will occur prior to informed consent. Screening log data will be retained in accordance with applicable regulatory and institutional requirements and will be deleted or anonymized when no longer required.

6.1.4.3 Assessment of eligibility

If a patient appears to be a candidate for enrollment, and in accordance with ethics committee (EC) approval, the study team may contact the parents in person (in the ED or OC) to assess interest and confirm the child’s eligibility for participation. This initial contact will include a brief prescreening to verify key eligibility criteria and a concise description of the study, and the responsibilities associated with participation.

- Eligible patients/parents will be offered a scheduled study visit as soon as possible.
- Parents will be informed that they may bring an accompanying person (e.g., a support person) to the visit.

6.1.4.4 Study information

If the parents express interest in participation, a member of the research team will conduct the informed consent process face-to-face. The consent discussion will stress that any participation is completely voluntary and will cover the purpose of the study, study procedures, potential risks and benefits, alternatives to participation, and data protection.

- Parents will receive both oral and written information.
- All parents will sign an electronic or written Informed Consent Form (eICF/wICF), as applicable.
- The signed e/wICF will be filed in the Investigator Site File (ISF), and a copy will be provided electronically or written to all signatory.

6.1.4.5 Place of recruitment

Participants will be recruited at Copenhagen University Hospital – Herlev and Gentofte by delegated members of the research team.

6.1.4.6 Informed consent

A more detailed description of the informed consent process is provided in Section 10.

- All participants for whom written informed consent has been obtained will be assigned a unique trial participant number.
- The date of informed consent and recruitment details will be recorded in the study database.
- Participants who commence any study treatment are considered enrolled.
- All enrolled participants will be followed within the study unless participation is terminated prematurely for reasons specified in Section 6.2.17.

6.1.4.7 Recruitment period

The recruitment period is estimated to be 36 months, based on the number of eligible patients managed at our institution over the past 5 years. If recruitment targets are not met by 24 months, the recruitment period will be extended by an additional 12 months.

6.2 Study procedures

The schedule of all follow-up (FU) visits, including imaging procedures, and the data to be collected at each visit are presented in Table 1.

Table 1: Study schedule

Assessment parameters		**Pre- intra- and postoperative visits**													
				Day 0		**Visit X****	**Visit 1**	**Visit 2**	**Visit 3**	**Visit Y*****	**Visit Z*****	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
	Injury	**Screening**	**Pre-treatment visit**	**Intraoperative**	**Post-operative / reduction**	**1 week**	**2 weeks**	**4 weeks**	**6 weeks**	**8 weeks**	**10 weeks**	**12 weeks**	**6 months**	**1 year**	**2 years**
Screening/invitation		X													
Eligibility			X												
Patient information and consent			X												
Demographics			X												
Radiographs	X			X*	X	X	X	X	X	X	X	X	X	X	X
Bone age radiograph												X			
Cast removal for ESIN group							X								
Cast removal for BIN group								X							
Cast removal for non-operative group									X						
Clinical exam	X				X	X	X	X	X	X	X	X	X	X	X
Patient Reported Outcome			X			X	X	X	X	X	X	X	X	X	X
Test of Motor Proficiency												X			

All postoperative visits with the defined time windows are calculated from the day of surgery/randomization or reduction (Day 0).

* Fluoroscopy

** For non-operative group only

*** Visit only completed if all fractures are not healed sufficiently at previous visit.

6.2.1 Injury

On the day of injury, the patient is treated according to standard of care. The diagnosis is established on standard forearm radiographs (anteroposterior and lateral views). An above-elbow splint is applied to stabilize the fracture.

6.2.2 Screening

The screening and inclusion process is described in detail in 6.1.

6.2.3 Preoperative visit

The enrollment and informed consent process is described in Section 6.1.4 and Section 10, as well as in the corresponding SOP.

- All patients prescreened against the inclusion and exclusion criteria will be recorded in the Screening Log described in Section 6.1.4.2.
- Screening and baseline data will be entered into the eCRF.

6.2.4 Intraoperative (day 0)

- Confirmation of the indication for treatment and assessment of any contraindications that may have arisen since the preoperative visit
- Verification of intraoperative exclusion criteria
- Assessment for any adverse events (AEs) since the preoperative visit, including documentation and reporting as applicable
- Treatment as described in Section 6.3
- Randomization as described in Section 6.3.6
- Documentation of surgical details
- Source data verification and entry into the eCRF

6.2.5 Postoperative/discharge

- Postoperative ward rounds
- Discharge according to the treatment protocol described in Section 6.3.8 and related SOP
- Documentation of discharge details
- Source data verification and entry into the eCRF

6.2.6 Visit 1 (2 weeks)

- Assessment for any adverse events (AEs) since the previous visit, including documentation and reporting as applicable
- Radiographs
- Cast removal for the titanium elastic nail (TEN) group, if applicable
- Clinical examination and outcome assessments as described in Section 7
- Source data verification and entry into the eCRF
- Scheduling of the next visit
- Appointment for the next visit

6.2.7 Visit 2 (4 weeks)

- Assessment for any adverse events (AEs) since the previous visit, including documentation and reporting as applicable
- Radiographs

- Cast removal for the bioabsorbable intramedullary nail (BIN) group, if applicable
- Clinical examination and outcome assessments as described in Section 7
- Source data verification and entry into the eCRF
- Scheduling of the next visit
- Appointment for the next visit

6.2.8 Visit 3 (6 weeks)

- Assessment for any adverse events (AEs) since the previous visit, including documentation and reporting as applicable
- Radiographs
- Clinical examination and outcome assessments as described in Section 7
- Source data verification and entry into the eCRF
- Scheduling of the next visit:
  - If bone healing is not sufficient, defined as an mRUS < 11 in any fractured bone, a follow-up visit will be scheduled at 8 weeks postoperatively.
  - If bone healing is sufficient (mRUS ≥ 11 in all fractured bones), the next visit will be scheduled at 3 months postoperatively.

6.2.9 Visit X (8 weeks)

This visit is only performed if bone healing was not sufficient at Visit 3 (6 weeks), defined as mRUS < 11 in any fractured bone.

- Assessment for any adverse events (AEs) since the previous visit, including documentation and reporting as applicable
- Radiographs
- Clinical examination and outcome assessments as described in Section 7
- Source data verification and entry into the eCRF
- Scheduling of the next visit:
  - If bone healing is not sufficient, defined as mRUS < 11 in any fractured bone, a follow-up visit will be scheduled at 10 weeks postoperatively.
  - If bone healing is sufficient (mRUS ≥ 11 in all fractured bones), the next visit will be scheduled at 3 months postoperatively.

6.2.10 Visit Y (10 weeks)

This visit is only performed if bone healing was not sufficient at Visit X (8 weeks), defined as mRUS < 11 in any fractured bone.

- Assessment for any adverse events (AEs) since the previous visit, including documentation and reporting as applicable
- Radiographs
- Clinical examination and outcome assessments as described in Section 7
- Source data verification and entry into the eCRF
- Scheduling of the next visit

6.2.11 Visit 6 (12 weeks)

- Assessment for any adverse events (AEs) since the previous visit, including documentation and reporting as applicable

- Radiographs
- Clinical examination and outcome assessments as described in Section 7
- Test of Motor Proficiency administered by an occupational therapist
- Source data verification and entry into the eCRF
- Scheduling of the next visit

6.2.12 Visit 7 (24 weeks ± 2 weeks)

- Assessment for any adverse events (AEs) since the previous visit, including documentation and reporting as applicable
- Radiographs
- Clinical examination and outcome assessments as described in Section 7
- Test of Motor Proficiency administered by an occupational therapist
- Disclosure of treatment allocation (unblinding)
- For the titanium elastic nail (TEN) group, implant removal surgery will be planned in accordance with standard of care
- Source data verification and entry into the eCRF
- Scheduling of the next visit

6.2.13 Visit 8 (52 weeks ± 4 weeks)

- Assessment for any adverse events (AEs) since the previous visit, including documentation and reporting as applicable
- Radiographs
- Clinical examination and outcome assessments as described in Section 7
- Source data verification and entry into the eCRF
- Scheduling of the next visit

6.2.14 TEN removal surgery

Implant removal in the titanium elastic nail (TEN) group will be performed according to standard of care, 6–12 months after implantation.

6.2.15 Visit 9 (104 weeks ± 4 weeks)

- Assessment for any adverse events (AEs) since the previous visit, including documentation and reporting as applicable
- Radiographs
- Clinical examination and outcome assessments as described in Section 7
- Source data verification and entry into the eCRF
- End of study participation

6.2.16 Unscheduled visits

Unscheduled visits may occur at any time during the study if a medical concern arises or if deemed necessary by the investigator for patient care.

All unscheduled visits or unplanned patient contacts related to the injury, treatment, or study device will be documented in the patient's medical record as part of standard care.

For study purposes, unscheduled visits will be captured in a dedicated Unscheduled Visit form in the eCRF, as described in the corresponding SOP. The form will document the date, reason for contact,

and whether the contact resulted in an adverse event, additional treatment, or a change to the follow-up schedule.

Treatment-related adverse events will be recorded and reported in accordance with Section 11 and the corresponding SOP.

Data obtained during unscheduled visits will be reviewed and, where relevant, incorporated into the study database at the next scheduled study visit.

6.2.17 Premature study termination

A participant's involvement in the study may end prematurely (discontinuation of study participation) and/or the participant may discontinue the allocated treatment while remaining in study follow-up. Reasons may include, but are not limited to:

- Withdrawal of informed consent (for study participation and/or use of data)
- Protocol deviation/violation with potential impact on participant safety or data integrity
- Refracture and/or reoperation (e.g., infection, implant-related complication)
- Investigator's decision (e.g., noncompliance with study procedures, safety concerns)
- Sponsor's decision (e.g., early study termination, safety signal, or regulatory request)
- Lost to follow-up
- Death

6.2.17.1 Procedures and documentation

For all premature terminations/discontinuations, the Investigator will document the primary reason and relevant details in the eCRF (dropout/discontinuation form). Where appropriate, the case will be discussed with the Sponsor. If feasible, and if the participant and parents agree, an early termination visit will be performed to capture key outcome assessments and to collect information on adverse events/serious adverse events up to the time of discontinuation.

6.2.17.2 Handling of data and missing assessments (interval-censored primary endpoint)

Data collected prior to discontinuation will be retained and used in analyses in accordance with applicable law and the scope of consent. If consent for use of data is withdrawn, previously collected data will be handled in accordance with regulatory requirements (e.g., retention of essential safety data where required) and the participant's stated wishes.

The primary endpoint (time to radiographic healing) will be analyzed as an interval-censored time-to-event outcome. For participants with radiographs demonstrating "not healed" followed by "healed," the event time will be considered to occur within the interval between the date of the last radiograph showing "not healed" and the date of the first radiograph showing "healed."

If a participant has no radiograph demonstrating healing, the observation will be right-censored at the date of the last evaluable radiograph/assessment.

If a participant undergoes reoperation, experiences refracture, or otherwise has a clinical course that precludes further valid assessment of healing, follow-up will be censored at the date of the last evaluable radiograph prior to that event, unless the event is pre-specified as a competing event in the Statistical Analysis Plan.

Assumptions and handling of missing radiographs (including sensitivity analyses for potentially informative missingness) will be pre-specified in the Statistical Analysis Plan.

6.3 Study treatments

All study treatments are provided according to standard of care and in accordance with the applicable Technique Guide for each implant system. Treatments are considered as standardized treatment packages consisting of either:

- surgical treatment with bioabsorbable intramedullary nails (BIN) and casting for 4 weeks, or
- surgical treatment with titanium elastic intramedullary nails (TEN) and casting for 2 weeks.

This is a randomized controlled study. Randomization procedures are described below.

6.3.1 Device under investigation

The investigational medical device (IMD) in this study is the Activa IM-Nail™ (Bioretec Ltd., Tampere, Finland), a sterile, single-use, bioabsorbable intramedullary nail intended for intramedullary fixation of pediatric diaphyseal forearm fractures (radius and/or ulna) in the presence of appropriate immobilization.

6.3.1.1 Device identification (IMD)

- Device name / brand: Activa IM-Nail™
- Size range: diameters 2.0–3.2 mm; lengths 200–400 mm
- Key material characteristics (high-level): bioabsorbable polymer-based nail with a radiopaque marker (as described in the Investigator's Brochure/IFU).
- Degradation (high-level): biodegrades in a controlled manner within approximately two years.

6.3.1.2 Regulatory status and conformity (high-level)

- The device is CE-marked; design examination certification for Activa IM-Nail is issued by DEKRA Certification B.V. (Notified Body 0344), certificate 2094913DE05.
- The manufacturer's Declaration of Conformity and applicable quality system certification references are provided as appendices.
- Continued placing on the market and putting into service under the MDR transitional provisions is documented by the manufacturer (including applicability to Activa IM-Nail and stated end of transition period for bioabsorbable implants).

6.3.1.3 Use in this clinical investigation

The Activa IM-Nail™ will be used within its intended purpose and according to the manufacturer's instructions (Technique Guide/IFU). No modifications to the device or deviations from its intended purpose are planned.

6.3.1.4 Traceability and device accountability

To ensure traceability, the following will be recorded in the eCRF (and/or device accountability log): device name, catalogue/reference number (REF), and batch/lot number (LOT). Device labeling and essential regulatory documentation are retained in the Investigator Site File (ISF).

Supporting documentation (submitted as EC appendices; not repeated in the protocol text)

Detailed device description, intended purpose, contraindications/warnings, technical characteristics, pre-clinical and clinical evidence summaries, and conformity documentation are provided in:

- Investigator's Brochure (Activa IM-Nail™ Product Group)
- EC Design-Examination Certificate (DEKRA) 2094913DE05
- Declaration of Conformity (Class III devices)
- Manufacturer's Declaration regarding MDR transitional provisions (EU 2023/607)
- Essential Requirements Checklist

6.3.2 Comparator

The comparator device in this study is the Titanium Elastic Nail (TEN™) System (DePuy Synthes). The TEN™ system is a commercially available, CE-marked orthopedic trauma implant system used to perform elastic stable intramedullary nailing (ESIN) for stabilization of pediatric long-bone fractures, including pediatric diaphyseal forearm fractures. The TEN™ system is not investigational in the context of this clinical investigation and will be used within its approved intended use/indications and according to the manufacturer's Instructions for Use (IFU) and Surgical Technique.

The TEN™ system consists of flexible titanium alloy intramedullary nails supported by dedicated instrumentation for implantation and extraction. The nails are available in multiple diameters and lengths suitable for pediatric forearm fracture fixation (e.g., 1.5 mm × 300 mm and 2.0–4.0 mm × 440 mm).

Device traceability will be ensured by recording the device name and relevant identifiers (e.g., article number, and where applicable sterile/non-sterile designation and packaging identifiers) in source documentation and the eCRF/device accountability documentation, in accordance with local procedures. Detailed technical specifications, labeling, indications/contraindications, warnings, and handling instructions are provided in the appended TEN™ documentation (IFU/Surgical Technique/Investigator's Brochure) submitted to the Ethics Committee.

6.3.3 Constancy and assay sensitivity of the reference treatment (TEN)

Noninferiority inference in this trial relies on the assumption of constancy (assay sensitivity), i.e., that the active control intervention (TEN) would be expected to achieve its established effectiveness under the conditions of the present study.

The trial is therefore designed to maintain close similarity to the evidence base supporting TEN for pediatric diaphyseal forearm fractures with respect to (1) the enrolled population (age range, fracture location and pattern, displacement, and operative indication), (2) the conduct of the reference intervention (TEN performed according to manufacturer guidance and local standard practice by appropriately experienced surgeons, with standardized key perioperative and postoperative care pathways), and (3) outcome definitions and follow-up schedule (radiographic healing assessed using prespecified, operational criteria and prespecified time points).

Any clinically relevant differences from the studies underpinning TEN effectiveness (e.g., case-mix, perioperative regimen, immobilization practice, or outcome timing/definition) will be described and justified in the final trial report, and adherence to the planned delivery of TEN and follow-up will be monitored to support assay sensitivity.

6.3.4 Treatment, surgical technique and postoperative care

All operative and non-operative management is performed according to standard of care and in accordance with the manufacturer's Technique Guide/IFU for the relevant implant. Operational details are described in the corresponding site SOPs.

Procedures are performed under general anesthesia (GA) with the patient in the supine position and the injured arm positioned on a radiolucent arm table. GA may be supplemented with a peripheral nerve block (PNB) in accordance with local standard practice [40].

6.3.4.1 Closed reduction pathway (prior to randomization)

Where applicable, an attempt at closed reduction is performed before skin incision.

- If closed reduction is achieved and the fracture no longer meets criteria for surgical stabilization, a circumferential above-elbow cast is applied, and alignment is confirmed with intraoperative radiographs. If alignment is satisfactory, surgery is cancelled, and the participant is managed as part of the non-operative cohort (Section 6.3.8).
- If closed reduction is not applicable, unsuccessful, or the fracture remains irreducible and/or unstable, the participant proceeds to randomization (Section 6.3.5).

6.3.4.2 Operative pathway (randomized treatment packages)

Participants randomized to surgical treatment will undergo intramedullary fixation using either:

- BIN package: bioabsorbable intramedullary nail fixation with casting for 4 weeks, or
- TEN package: titanium elastic intramedullary nail fixation with casting for 2 weeks.

The operative technique for the two interventions is largely identical, with implant-specific steps performed according to the relevant Technique Guide. In brief, intramedullary canal access is established and the nail is advanced under fluoroscopic guidance; fracture reduction is performed closed where feasible, with open reduction permitted if required. Postoperative radiographs are obtained.

Antibiotic prophylaxis will be administered according to local standard practice (weight-based dosing). In case of penicillin allergy, an appropriate alternative will be used per local guidelines.

6.3.4.3 Postoperative care and discharge

Wounds are closed and dressed according to standard practice. A circumferential above-elbow cast is applied for the duration specified by the randomized treatment package. Discharge occurs when the child is clinically well and postoperative pain is controlled, typically on the same day or the day after surgery, in accordance with local routines. No formalized physiotherapy is routinely prescribed; participants and parents receive oral and written instructions regarding mobilization and home exercises.

Follow-up assessments are conducted according to the schedule described in Section 6.2.

6.3.5 Allocation to study groups

Allocation will be 1:1 between the investigational (BIN) and comparator (TEN) groups, stratified by age.

6.3.6 Randomization process

- The participant must meet all inclusion criteria and none of the exclusion criteria, and written informed consent from parents must be obtained.
- Randomization will be performed in the operating room (OR) with the participant under general anesthesia (GA) if closed reduction is not applicable or is unsuccessful (i.e., the fracture remains irreducible and/or unstable and surgical stabilization is indicated).
- A delegated member of the research team will randomize the participant to treatment with either BIN or TEN.
- Randomization will be conducted using the REDCap Randomization module with age stratification.
- Contingency plan: If REDCap is temporarily unavailable, randomization will be performed using a predefined, access-restricted backup procedure (e.g., sealed opaque envelopes or a pre-generated randomization list) as described in the corresponding SOP, and the allocation will be entered into REDCap as soon as system access is restored.

6.3.7 Blinding

Blinding is implemented to minimize performance and assessment bias [41–43]. Due to the nature of the interventions, the operating surgeon and operating room staff cannot be blinded to implant type.

Allocation is concealed from participants, parents, postoperative clinical staff, outcome assessors, and the statistician. A limited number of designated study personnel (e.g., PI and trial coordinator) are unblinded to facilitate device logistics and, when relevant, planning of elective titanium nail removal; these personnel will have no role in postoperative assessments, radiographic outcome evaluation, or data analysis.

Participant and parent unblinding will occur only after completion of the 6-month follow-up assessment, primarily to enable planning of elective removal of titanium nails in accordance with standard practice. All outcome assessors and the statistician will remain blinded until database lock and completion of the primary analysis, unless unblinding is required for patient safety.

6.3.7.1 Blinded postoperative documentation

To maintain blinding of participants, parents, and routine postoperative caregivers, a standardized “blinded” postoperative documentation pathway will be used in the electronic health record (EHR). The purpose is to prevent inadvertent disclosure of treatment allocation through operative notes, discharge documentation, or follow-up scheduling, while ensuring that complete and legally compliant source documentation is retained and remains available to authorized clinical staff when needed.

Immediately after surgery, documentation will be split into:

- Blinded postoperative note (visible to routine postoperative care and to families via patient-facing portals, where applicable): A standardized template will be used stating that the participant “underwent intramedullary fixation with one of the two study nails according to randomization,” without naming implant type. The note will include study information (including emergency contact information), non-allocating clinical essentials (diagnosis, reduction status, approach, complications, cast applied, neurovascular status, activity restrictions, analgesia plan, and safety advice).

- Additional operative record (restricted access): An additional operative record containing the implant type, sizes, lot/batch identifiers, and any implant-specific technical details will be completed and

retained as source documentation with access restricted to authorized staff (e.g., operating surgeon, delegated unblinded study personnel, and clinicians requiring access for safety). Implant traceability information (REF/LOT, sizes) will also be recorded in the device accountability log/eCRF as prespecified.

6.3.7.2 Maintaining blinding despite imaging and clinical routines

For research outcome assessment, postoperative radiographs will be exported as de-identified copies and edited to conceal implant-specific radiopaque features as described in Section 7.1. Clinical care will continue to rely on unedited radiographs in the medical record. Study staff involved in follow-up assessments will avoid disclosure of allocation, and participants and parents will be asked not to seek information on implant type until after the 6-month visit.

6.3.7.3 Emergency unblinding

Unblinding may be performed only when knowledge of the allocated implant is deemed necessary for urgent clinical management. Emergency unblinding will be performed by the PI, documented in the eCRF (date, reason, person unblinded, and who was informed), and reported to the sponsor.

6.3.7.4 Blinded groups

The following parties will be blinded to treatment allocation:

- Participants and parents will be blinded to implant type. Families will be informed preoperatively that postoperative immobilization duration may vary between 2–4 weeks based on radiographic assessment, and they will not be informed that immobilization duration differs systematically between the randomized interventions. As the implant is not externally visible after cast removal and implant-specific radiographic features are concealed for research assessments (Section 7.1), there is no direct method for participants and parents to identify allocation during follow-up.

- Postoperative ward/clinic caregivers and staff involved in routine care.

- Outcome assessors and data collectors, including:
  - Clinicians performing follow-up assessments
  - Radiologists and orthopedic surgeons reviewing radiographs (using edited, de-identified images; Section 7.1)
  - Occupational therapists / hand therapists performing functional assessments

- Statistician/data analyst, who will receive a dataset with groups coded (e.g., Group A/B) and will remain blinded until database lock and completion of the prespecified primary analysis.

6.3.7.5 Preventing inadvertent unblinding

To reduce inadvertent disclosure, the study team will implement the following safeguards:

- Use of standardized note templates for postoperative notes and discharge summaries.
- Clear instruction to staff not to document implant type in routine follow-up notes that are accessible to blinded parties.
- If implant type must be referenced for clinical reasons before planned unblinding, it will be documented and handled according to the emergency unblinding procedure.

6.3.7.6 Assessment of blinding success

Blinding success will be assessed immediately prior to participant/parent unblinding at the 6-month follow-up visit. Participants/parents will be asked to guess the allocation ("bioabsorbable", "titanium", or "don't know") and if they specify an implant, they will be asked why they chose that implant. The proportion of correct guesses and reasons (and proportion choosing "don't know") will be summarized by randomized group.

6.3.8 Postoperative care

Following surgery, a circumferential above-elbow cast is applied. The patient will be observed and/or admitted to the pediatric ward as clinically indicated until the effect of the peripheral nerve block (PNB) has subsided and discharge criteria are met. The patient is encouraged to mobilize the shoulder and fingers as soon as possible and to keep the arm elevated for the first few days. Daily activities may be resumed as tolerated. Return to sports will be discussed individually at the 3-month follow-up visit in accordance with standard of care.

Before discharge, a standardized discharge and follow-up plan will be provided.

In the investigational group (BIN), all patients will remain in a cast for 4 weeks. In the comparator group (TEN), cast removal is planned at the 2-week follow-up visit.

Any postoperative care not specifically described in this protocol will be provided according to standard of care at the study site and described in a specific SOP.

6.3.9 Non-operative treatment

If the fracture is successfully reduced by closed manipulation prior to skin incision and is considered eligible for non-operative management, the patient will be included in an exploratory prospective non-operative cohort. Based on our pilot experience, the proportion of successful closed reductions is anticipated to be approximately 15%.

6.3.9.1 Eligibility for non-operative management

Fractures are considered eligible for non-operative treatment when, after reduction, the fracture is:

- not displaced by more than 50% of the bone width, and
- not angulated by more than 10° in any plane.

The decision to manage the fracture non-operatively is at the treating surgeon's discretion and follows standard of care.

6.3.9.2 Follow-up and conversion to surgery

Participants in the non-operative cohort will have a radiographic follow-up at 1 week. Thereafter, they will follow the same follow-up schedule and outcome assessments as the randomized groups (Section 6.2). Fracture healing is typically sufficient to allow cast removal after 6–8 weeks.

If, during subsequent follow-up no later than 14 days after injury (e.g., at the planned 1-week non-operative control), loss of reduction occurs such that the fracture again meets the study's operative indication criteria, the participant remains eligible for the randomized comparison. In this situation, the participant will follow the standard pathway and be randomized in the operating room immediately prior to surgery, using the trial's randomization procedure (Section 6.3.5).

The period of initial non-operative management and the indication for conversion to surgery will be documented.

Any subsequent re-intervention or conversion to surgery occurring later than 14 days after injury will be recorded and analyzed descriptively.

7 Definitions of outcome measures and study variables

This study adheres to the CORE-Kids core set of outcome domains described by Marson et al. [44].

7.1 Primary outcome

Time to fracture healing (weeks), defined as the time from surgery/randomization (Day 0) to the first postoperative radiographic assessment meeting the prespecified healing criterion in all fractured bones as described in 7.1.2.3.

7.1.1 Time to fracture healing

As described in Section 4.2, fracture repair is a complex biological process and objective assessment in clinical trials is challenging [45]. Healing based on plain radiographs has historically been largely subjective. Whelan et al. developed the Radiographic Union Score (RUS) to quantify healing in tibial fractures based on callus formation and visibility of the fracture line [46]. RUS has since been shown to be reliable and repeatable, including anatomical sites beyond the tibia [47–49], and to correlate with biomechanical properties of healing [50]. To improve clarity and reduce ambiguity in scoring, a modified RUS (mRUS) has been proposed, defining callus as bridging versus non-bridging [51].

7.1.1.1 Definition of time-to-healing (primary time origin)

Time-to-healing will be defined as the time from the date of surgery/randomization (Day 0) to the first postoperative radiographic assessment meeting the pre-specified healing threshold in all fractured bones. For patients with fractures of both radius and ulna, the endpoint is met when the healing threshold is achieved for both bones; for isolated single-bone fractures, the endpoint is met when the fractured bone reaches the threshold. Injury date will be recorded for all participants. As sensitivity analyses, time-to-healing will also be calculated from the date of injury, and analyses may adjust for the injury-to-surgery interval to assess robustness.

7.1.1.2 Radiographic assessment method (mRUS)

Healing will be assessed on standard plain anteroposterior (AP) and lateral radiographs. For each fractured bone, four cortices are scored (1–4) and summed to yield an mRUS from 4 (not healed) to 16 (fully healed). Scoring of each cortex is defined as follows:

- visible fracture line and no callus — is scored 1 (Figure 2.1)
- non-bridging callus with visible fracture line — is scored 2 (Figure 2.2)
- bridging callus with visible fracture line — is scored 3 (Figure 2.3)
- bridging callus with no visible fracture line — is scored 4 (Figure 2.4)

The sum of the four cortices constitutes the mRUS for that bone. Based on prior work, a threshold of mRUS ≥ 11 is considered consistent with radiographic union and mRUS ≥ 13 with definite union [51].

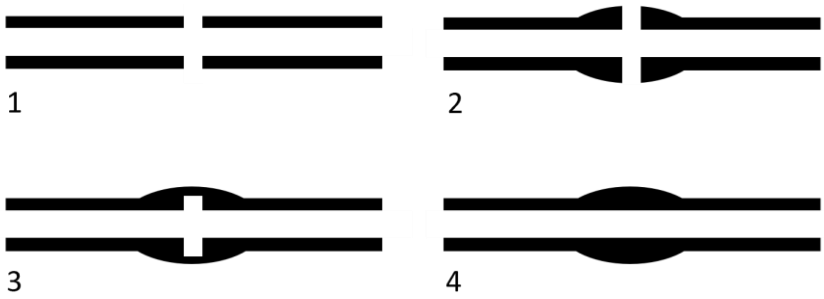


Figure 2 - Calculation of mRUS. A cortex with visible fracture line and no callus is scored one (1), with non-bridging callus and a visible fracture line is scored two (2), with bridging callus and a fracture line is scored three (3) and with bridging callus and no visible fracture line is scored four (4). The sum of the four scores gives the mRUS.

7.1.1.3 Radiographic healing threshold (primary endpoint)

Healing will be defined as mRUS ≥ 11 for the fractured bone with bridging callus (cortex score ≥3) present in at least three of four cortices, and no cortex with score of 1. For combined radius and ulna fractures, the endpoint is met when both bones meet the healing threshold on the same radiographic assessment.

This threshold operationalizes union as bridging callus in ≥3 cortices (consistent with established radiographic union definitions) while limiting premature classification by requiring absence of cortices with no callus.

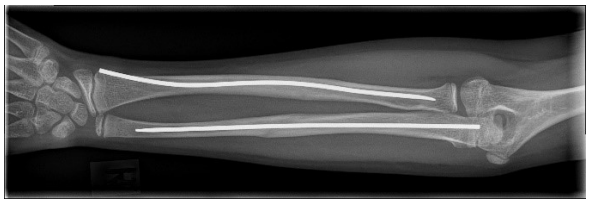
Definite union (supportive threshold). As a supportive radiographic definition, definite union will be defined as mRUS ≥ 13 for the fractured bone, which corresponds to bridging callus in all four cortices with at least one cortex demonstrating absence of a visible fracture line (cortex score 4). This more stringent threshold is expected to occur later in the healing trajectory and will therefore be used for pre-specified sensitivity analyses of the primary time-to-healing endpoint and for descriptive comparison of healing profiles between groups, rather than as the primary event definition.

7.1.1.4 Blinding of radiographs via standardized image masking

Bioabsorbable intramedullary nails are largely radiolucent, with only a radiopaque tricalcium phosphate tip, whereas titanium nails are inherently radiopaque. To ensure blinded radiographic outcome assessment across treatment groups, all postoperative radiographs will be de-identified and digitally masked prior to review. Using image-editing software, visible radiopaque implant components will be concealed, while preserving full visibility of the fracture region, cortical outlines, and callus formation (Figure 3). All patient identifiers and acquisition metadata will be removed, and images will be assigned a study-specific ID and a non-revealing time point label only.

Image manipulation will be performed by a member of the research team who is not involved in postoperative clinical assessment, outcome evaluation, or statistical analysis, and who will have no role in adjudication of radiographic endpoints. Masking procedures will be documented to ensure consistency. All manipulated images are stored outside PACS. All original unaltered radiographs are stored in the hospital's PACS.

Original follow-up radiograph



Edited radiograph with implant concealed

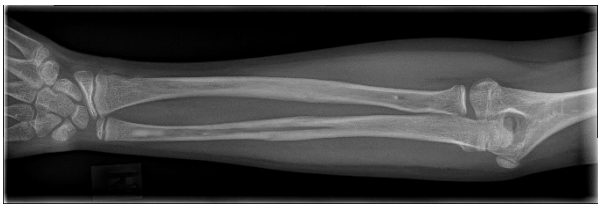


Figure 3 – Example of original and edited radiograph to blind the assessor to the implant.

7.1.1.5 Independent review, adjudication, and reliability (quality assurance)

All masked radiographs will be assessed independently by two blinded reviewers (musculoskeletal radiologist and orthopedic surgeon) using a pre-specified scoring manual. Reviewers will undergo a brief calibration exercise prior to study readings. Images will be presented in random order and without access to clinical data or treatment allocation.

Inter-rater reliability for mRUS will be quantified using appropriate agreement statistics (e.g., ICC for total mRUS and weighted kappa for ordinal cortex scores), and intra-rater reliability will be assessed by repeat scoring of a randomly selected subset of examinations after a washout period (e.g., 2–4 weeks), with re-randomization of the re-read set. Discrepant assessments of healing status relevant to the primary endpoint will be resolved by consensus; if consensus is not achieved, a third blinded reviewer will adjudicate. Reliability estimates will be reported with confidence intervals as part of study quality assurance.

7.2 Secondary outcomes

7.2.1 CORE-Kids outcomes

Marson et al. has developed the CORE-Kids core set of outcome domains for studies of childhood limb fractures [44]. These core outcomes are suggested to be included in all trials on childhood limb fractures to improve the consistency of research that can be combined for more meaningful meta-analyses and policy development.

The CORE-Kids outcome domains were agreed to include:

- Pain and discomfort
- Return to physical and recreational activities
- Emotional and psychosocial wellbeing
- Complications from the injury and its treatment
- Return to baseline activities daily living
- Participation in learning
- Appearance and deformity
- **Time to union – primary outcome**
- Recovery of mobility (for lower limb fracture)
- Recovery of manual dexterity (for upper limb fracture)

Another 5 outcomes were close to the consensus threshold:

- Cost to family

- Ability to sleep
- Range of motion
- The cost of treatment
- Child satisfaction

7.2.2 EQ-5D-Y - Patient reported outcome

To select an appropriate patient-reported outcome measure (PROM), we followed the recommendations of Marson et al. [52]. We selected the EQ-5D-Y questionnaire due to its ease of use, validated Danish translation, broad availability, use in prior research, and alignment with the intended secondary outcomes.

The questionnaire consists of the EQ-5D-Y descriptive system (index) and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions:

- Mobility
- Looking After Myself
- Doing Usual Activities
- Having Pain or Discomfort
- Feeling Worried, Sad or Unhappy

Each dimension has three response levels: no problems/no pain/not worried, some problems/some pain/a bit worried, and a lot of problems/a lot of pain/very worried. Respondents indicate their health state by selecting the most appropriate response level for each dimension.

The EQ VAS is a 0–100 scale on which respondents rate their overall health on the day of questionnaire completion. It is conceptually different from the EQ-5D-Y index, which represents a value assigned to an EQ-5D-Y health profile using a set of weights reflecting population preferences for different health states. The EQ VAS reflects the respondent's perspective, whereas most value sets reflect a societal perspective.

For children aged 4–7 years, the proxy version will be used. A parent will complete the questionnaire based on their impression of the child's health status on the day of administration. For children aged 8 years and older, the self-reported version will be used.

The EQ-5D-Y has an official Danish translation and has been evaluated. Data will be collected using the REDCap self-report and proxy versions (Version 2.0). Administration and scoring will follow the EQ-5D-Y User Guide, Version 2.0 (September 2020).

The original English and Danish versions are provided as appendices.

7.2.3 Pain and discomfort

At each FU visit, pain and discomfort and use of medication is evaluated and documented.

7.2.3.1 Faces Pain Scale – Revised (FPS-R)

To measure the outcome of pain in children we use the Faces Pain Scale – Revised (FPS-R) [53]. It is a self-report measure of pain intensity developed for children. It was adapted from the Faces Pain Scale [54] to make it possible to score the sensation of pain on the widely accepted 0-to-10 metric. The scale shows a close linear relationship with numerical rating scales (NRS). It is easy to administer and

requires no equipment except for the photocopied faces (Figure 4). 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, where 0 equals no pain and 10 equals very much pain.

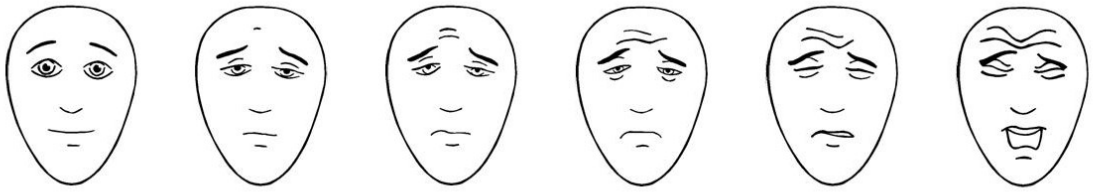


Figure 4 - Faces of the FPS-R. The child is instructed to point to the face that shows how much pain the child is in at that moment. Faces are scored 0, 2, 4, 6, 8 or 10 from left to right.

7.2.3.2 Discomfort

Pain and discomfort are domains in the EQ-5D-Y and is reported at each FU visit.

7.2.3.3 Pain medication

At each FU visit any use of pain medicine will be recorded.

7.2.4 Return to physical and recreational activities

Return to physical and recreational activity is described in the EQ-5D-Y. Return to sports will be documented in the eCRF.

7.2.5 Emotional and psychosocial wellbeing

Described by the domains of the EQ-5D-Y and the EQ VAS.

7.2.6 Complications from the injury and its treatment (adverse events)

This section describes all anticipated AEs, SAEs, ADEs, and SADEs. Further definition and description, see section 11.

7.2.6.1 Re-fracture, re-displacement, or re-angulation

At each FU the radiographs are reviewed for occurrence of re-fracture, re-displacement, or re-angulation. If changes are below the boundaries described in the inclusion criteria in 6.1.1 no additional treatment is necessary. If the boundaries are exceeded the PI and the surgeon will discuss the need for additional treatment.

7.2.6.2 Infection

Any surgery caries the risk of infection, however previous studies have shown very subtle infection risk [3,55] with the TEN procedure. We anticipate a risk of infection at 0.5%.

7.2.6.3 Nerve complications

Studies have shown a 5% risk of nerve injury [55], however all cases had spontaneous recovery of nerve function.

7.2.6.4 Re-operation

Re-operation risk is anticipated at 0.1-0.5% due for any reason following the procedure.

7.2.6.5 Discomforts/risks from casting

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

7.2.6.6 Adverse Device Effects and Device deficiency

ADE and DD are defined in 11.1. Two cases of breakage of the Activa IM-Nail™ have been described. Steps to avoid ADE and DD have already been taken with revision of the Technique Guide. With the completion of our pilot study, we have gained valuable knowledge of the Activa IM-Nail™ procedure.

7.2.7 Return to baseline activities daily living

Described by the domains of the EQ-5D-Y.

7.2.8 Participation in learning

Partially described by the domains of the EQ-5D-Y and the EQ VAS. Return to school is entered in the eCRF.

7.2.9 Appearance and deformity

At each FU visit clinical adverse appearance or deformity is noted in the eCRF.

7.2.10 Recovery of manual dexterity / Range of motion

At each visit, sensory and motor nerve function is examined, and any irregularities are recorded in the eCRF.

Grip strength and bilateral elbow and forearm range of motion (ROM) is measured in degrees by goniometer and dynamometer, respectively.

7.2.10.1 Motor function assessment (MABC-3)

Motor function will be assessed using the Movement Assessment Battery for Children – Third Edition (MABC-3). MABC-3 is a standardized, age-normed performance-based test of motor coordination validated for children aged 3–16 years .

In this study, the Manual Dexterity domain will be used as an objective measure of upper-limb motor performance. The domain consists of age-appropriate, timed tasks assessing fine motor control, coordination, and precision of hand use. Tasks are selected according to predefined age bands (3–6, 7–10, and 11–16 years) and administered according to the standardized test manual.

Assessments will be performed by trained personnel at 12 weeks post-injury. Raw scores will be converted to age-adjusted standard scores and percentiles using normative reference data. The primary MABC-3 outcome will be the Manual Dexterity standard score, analyzed as a continuous variable.

MABC-3 was chosen to provide an objective, developmentally appropriate measure of functional motor recovery that complements radiographic healing, range of motion, grip strength, and patient-reported outcomes.

7.2.11 Cost to family

Days off work and days off school are recorded in the eCRF.

7.2.12 Ability to sleep

Any problems with sleep are addressed in the eCRF.

7.2.13 The cost of treatment

Treatment costs are discussed in 4.5.2. We intend to produce a cost-effectiveness analysis of the procedures involved.

7.2.14 Child satisfaction

Satisfaction of the child and parents are recorded using a questionnaire from the Danish Nationwide Survey of Patient Experiences (Landsdækkende Undersøgelse af Patientoplevelser - LUP) during the FU visit after 2 years. A copy (in Danish) is amended to the EC application.

7.3 Required diagnostic procedures

For diagnostic and follow-up purposes, plain radiographs of the forearm will be obtained at the following time points:

- At injury / preoperatively
- Intraoperatively (fluoroscopy)
- Postoperatively
- At follow-up (FU) visits until healing is established, but at a minimum at the 2-, 4-, and 6-week visits and possibly 8 and 10 weeks
- At FU visits after 12 weeks, 6 months, 1 year, and 2 years

8 Statistical planning

The statistical methodology for this clinical investigation—including definition of the primary estimand and analysis approach, justification of the non-inferiority margin, and the assumptions underlying the sample size and power calculations—was developed in collaboration with an independent statistician from the University of Copenhagen. The statistician contributed to the planning and validation of the statistical measures and will provide continued methodological support as needed during conduct and reporting of the study.

- Baseline characteristics and outcomes collected at scheduled follow-up assessments will be described using descriptive summary statistics.
- Categorical variables will be summarized as counts and percentages for each category.
- Continuous variables will be summarized using the mean, standard deviation (SD), median, interquartile range (IQR), and minimum and maximum values.
- When both baseline and follow-up measurements are available, continuous variables will additionally be summarized as within-patient change from baseline to follow-up.
- EQ-5D-Y results will be reported in accordance with the EQ-5D-Y user guide/manual.
- Adverse events (AEs) considered related to the study intervention will be summarized at the patient level. For summaries by severity, action taken, or outcome, patients experiencing more than one event of the same type will be classified according to the maximum severity and/or worst outcome observed.
- Analyses will be performed using validated statistical software (e.g., R/Stata/SAS and/or SPSS for descriptive analyses), as specified in the SAP.

When designing this non-inferiority study, we have considered the risk of "technocreep," whereby successive non-inferiority trials may gradually erode the reference standard through incremental acceptance of smaller differences. For the present study, the non-inferiority margin is not derived from prior non-inferiority studies of the same implant type, thereby reducing the risk that margin selection is influenced by accumulated non-inferiority assumptions.

8.1 Non-inferiority hypotheses (primary estimand)

Let T denote time from surgery/randomization (Day 0) to radiographic union. Let θ denote the treatment effect expressed as the difference in time to union (BIN − TEN), in weeks. With a non-inferiority margin $\Delta = 3$ weeks, the hypotheses are:

$H_0: \theta \geq \Delta$ (BIN is inferior to TEN by ≥ 3.0 weeks)

$H_1: \theta < \Delta$ (BIN is non-inferior to TEN)

8.2 Sample size considerations

Sample size was calculated for a parallel-group, randomized (1:1), non-inferiority comparison of time to radiographic healing, defined as time from surgery/randomization to the first radiograph with mRUS ≥ 11.

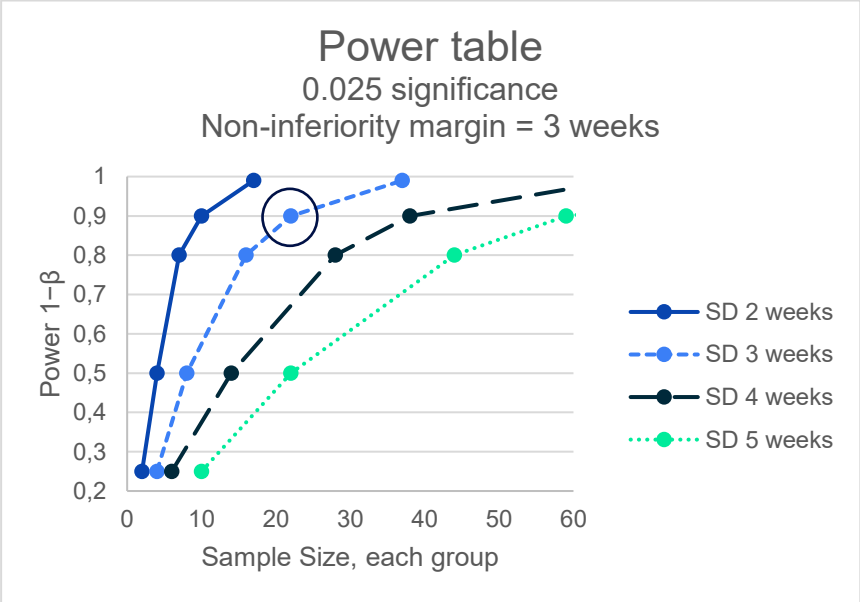


Figure 5 – Power table. To better appreciate the effects on sample size four standard deviations (SD) are plotted for five different power levels. The chosen SD and power are circled.

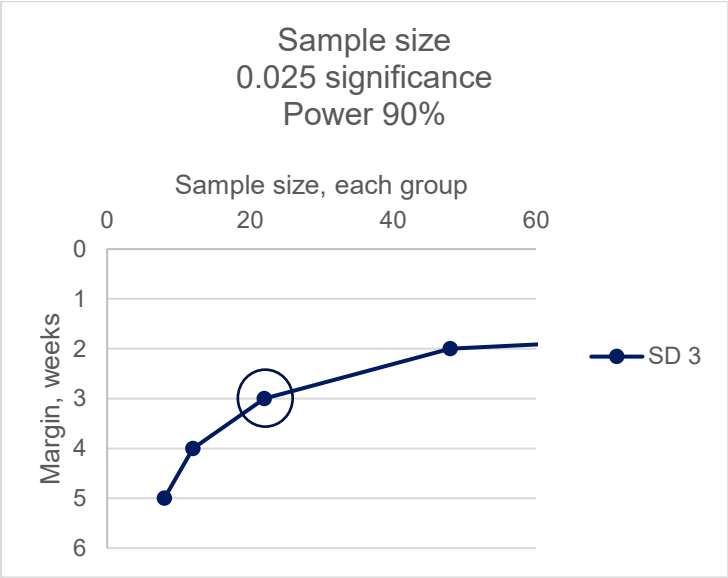


Figure 6 – Table to show sample size at 3 SD for 4 different non-inferior margins. The chosen margin and sample size are circled.

8.2.1 Power

To ensure a more reliable result, the power (1-β) is set to 90%.

8.2.2 Standard deviation

Due to limited evidence on the exact healing times of forearm fractures in children, the values are based on our pilot study, available literature [14,56] and our clinical expertise. In our pilot study of 18 fractures median time to healing with an mRUS of at least 11, was 8 weeks. We estimate that fractures heal to an mRUS of ≥ 11 at an average of 8 weeks with a SD of 3 weeks.

8.2.3 Significance level

Because a non-inferiority design is primarily investigating only one bound (lower or upper) of the confidence interval, we set a significance level (α) of 0.025 so that our one-sided test and upper confidence limit is comparable to results in two-sided superiority trials.

8.2.4 Non-inferiority margin

The primary objective is to demonstrate that bioabsorbable intramedullary nailing (BIN) is non-inferior to titanium elastic stable intramedullary nailing (TEN) with respect to time to radiographic union.

To support the choice of a clinically acceptable non-inferiority margin, we incorporated parent input from the pilot cohort. Parents were asked an acceptability question regarding the maximum additional weeks beyond the usual 6-week restriction for return to higher-risk activities (e.g., trampoline/contact sports) they would accept if their child could avoid a second operation for implant removal with bioabsorbable intramedullary nails. Responses were used to contextualize what families consider an acceptable trade-off and to ensure the non-inferiority margin is aligned with patient-relevant priorities, in addition to clinical judgement and the existing literature.

The non-inferiority margin is set at $\Delta = 3.0$ weeks, representing the largest clinically and parent acceptable delay in union for BIN compared with TEN.

8.2.5 Treatment effect (primary estimand)

The treatment effect will be expressed as the difference in time to union (in weeks):

$$\theta = T_{BIN} - T_{TEN}$$

where T denotes time from surgery date to radiographic union.

8.2.6 Drop rate / sample size inflation

In our pilot study, 1/18 (≈5%) participants were lost to follow-up. For the present RCT we apply a total inflation of 10%, comprising ~5% loss to follow-up/withdrawal and ~5% intercurrent events affecting the primary endpoint (e.g., healing-related reoperation). Although intercurrent events will be handled in the primary estimand strategy (see Section 8.3), they reduce the number of informative observations for time-to-union and are therefore accounted for in the sample size inflation.

8.2.7 Sample size estimation

Sample size	
Significance level	0.025
Power (1-beta)	0.9
Ratio of sample size	1:1
Standard deviation	3 weeks
Non-inferiority margin	3 weeks
Loss to follow-up/withdrawal (%)	5
Intercurrent events (%)	5
Result	
Sample size per group	22
Sample size per group incl. attrition	25
Total sample size incl. attrition	50

Table 1. Results of sample size estimation.

To further strengthen robustness against uncertainty in the SD estimate, potential deviations from the assumed distributional model, and the possibility that a greater proportion of participants than anticipated may have non-informative primary endpoint data (e.g., due to intercurrent events), the study will enroll 30 participants per group (total N = 60). This provides additional precision for estimating the between-group difference in time to healing and ensures that the trial maintains at least the planned statistical power under plausible departures from the planning assumptions.

8.3 Statistical analysis

A detailed Statistical Analysis Plan (SAP) will be prepared for this study before the final analysis. An overview is presented in the following sections.

8.3.1 Non-inferiority hypotheses test

Non-inferiority will be tested using a one-sided type I error of 2.5% (equivalently a two-sided 95% confidence interval [CI]):

$$H0: \theta \geq \Delta \ \ vs. \ \ H1: \theta < \Delta$$

Non-inferiority will be concluded if the upper bound of the two-sided 95% CI for θ is strictly less than Δ (3.0 weeks).

8.3.2 Analysis populations

In non-inferiority trials, intention-to-treat (ITT) analyses may be biased toward non-inferiority due to treatment cross-over and non-adherence. We intend to analyze both the per-protocol (PP) and ITT populations. The primary non-inferiority analysis will be performed in the PP population. A supportive analysis will be performed in the ITT population. Non-inferiority will be considered robust if conclusions are consistent in both PP and ITT analyses. We suspect very few cases will cross over. We suspect to find similar results in both groups and a discrepancy would warrant close examination of the results.

8.3.3 Per-Protocol (PP) population

Per-Protocol (PP) population will include all randomized participants who

- (i) received the allocated surgical intervention (BIN or TEN) as randomized
- (ii) had no major protocol deviations expected to materially affect fracture healing assessment
- (iii) contributed sufficient radiographic follow-up to define interval-censored time to union.

8.3.3.1 Major protocol deviations

Major protocol deviations resulting in exclusion from the PP population will include:
(1) implantation of a non-allocated device or cross-over to the alternate trial implant
(2) failure to undergo intramedullary fixation after randomization
(3) major deviations in post-operative immobilization that alter the treatment package (e.g., cast duration differing by more than ±7 days from the planned duration, unless medically indicated and documented)
(4) healing-related reoperation prior to reaching the radiographic healing threshold (e.g., revision fixation for loss of reduction or refracture)
(5) missing radiographic assessments such that the healing interval cannot be determined (e.g., absence of any post-operative radiograph beyond the initial post-operative imaging or missing consecutive assessments preventing interval definition).

8.3.3.2 Minor protocol deviations

Minor deviations (e.g., visit timing deviations within predefined windows) will not lead to PP exclusion and will be handled analytically through the interval-censored time-to-event framework.

8.3.4 Intention-to-Treat (ITT) population

Intention-to-Treat (ITT) population will include all randomized participants analyzed according to their randomized treatment allocation, regardless of the treatment actually received, protocol deviations, or subsequent withdrawal from the assigned intervention. Participants will contribute all available follow-up data collected until withdrawal of consent or study end. The ITT population will be used for supportive analyses of the primary endpoint and for key secondary outcomes, complementing the primary Per-Protocol analysis in this non-inferiority trial.

8.3.5 Testing for superiority

If non-inferiority is established, superiority of BIN versus TEN will be assessed using the same confidence interval framework. Superiority will be concluded if the upper bound of the 95% CI for (BIN − TEN) is < 0 weeks.

8.3.6 Interval-censored union times

Because union is assessed only at scheduled radiographic visits (every 2 weeks), the true time to union is interval-censored (occurring between the last assessment without union and the first assessment with union). The primary analysis will use an interval-censored time-to-event model. A parametric

accelerated failure time model (Weibull) will be used to estimate the treatment effect and its confidence interval on the pre-specified estimand scale (e.g., time ratio/acceleration factor, and/or model-based difference in median time to union in weeks). Sensitivity analyses will repeat the primary analysis using alternative parametric distributions (e.g., log-normal/log-logistic) to assess robustness.

8.3.7 Protocol violations

Any protocol violations will be logged and reported to the sponsor within 10 working days. Violations generally increase risk or decrease benefit, affect the subject's rights, safety, or welfare, or the integrity of the data.

8.3.8 Intercurrent events

Healing-related reoperation (e.g., for refracture, deep infection requiring implant removal, or nonunion) will be treated as an intercurrent event for the primary endpoint. In the primary analysis, participants will be censored at the last radiographic assessment prior to the intercurrent event. Sensitivity analyses will assess robustness using conservative assumptions, including classifying healing-related reoperation as not united within the follow-up window.

8.3.9 Patient discontinuation

All premature discontinuations are registered in the eCRF.

8.3.10 Missing data

To avoid missing data all required fields in the eCRF are mandatory and the researcher is informed of missing or wrong input during the entry phase. All data is sought to be put into the eCRF during the follow-up visit or immediately after and no later than 10 days after the visit. In this way participants can be contacted in due time in case of missing information. The reason for any missing data will be investigated and reported.
Because the primary endpoint is assessed at discrete radiographic time points, time to union will be analyzed using an interval-censored time-to-event framework. Therefore, no imputation of union time will be performed. Missed radiographs will widen the censoring interval where subsequent images are available; participants without radiographic confirmation of union will be treated as right-censored at their last evaluable radiograph. Missing data for secondary outcomes will be handled as specified in the SAP.

9 Risk analysis

A risk–benefit analysis of the study and the devices has been performed in accordance with ISO 14971 and ISO 14155.

9.1 Treatment-related risks

The risks in this study are associated with (1) the general risks of operative treatment for pediatric diaphyseal forearm fractures and (2) study-related procedures.

Anticipated adverse events (AEs) that may occur as a direct result of the treatment, general anesthesia, and the devices are identified and listed in Section 7.2.6. These risks are inherent to the standard management of fractures requiring surgical stabilization and would be present irrespective of study participation.

Standard treatment using titanium elastic intramedullary nails (TEN) typically includes forearm radiographs at:

- Preoperative / injury
- Intraoperative – using fluoroscopy
- Postoperative
- At FU-visits after 2 and 6 weeks and before implant removal (6-12 months).

9.2 Study disadvantages

Participation in the study involves additional outpatient follow-up visits. Participants will attend approximately 7–9 follow-up (FU) visits, which is 3–5 more visits than typically required with standard care. This increased visit burden may be considered a disadvantage. However, in our pilot study, parents demonstrated high adherence and were willing to attend all scheduled visits.

A potential disadvantage is a longer time to radiographic union and/or a longer restriction from higher-risk activities. Parent acceptability of a potential delay was explored in the pilot cohort by asking the maximum additional weeks beyond the usual 6-week restriction they would accept to avoid a second implant removal operation, and this perspective informed how we frame and communicate the study trade-off.

9.3 Study-related risks

Based on previous studies of the Activa IM-Nail™ [7,38], we anticipate that the risk of complications with bioabsorbable intramedullary nails (BIN) is comparable to, or potentially lower than, that observed with titanium elastic intramedullary nails (TEN).

9.3.1 Radiation

During follow-up, AP and lateral radiographs of the forearm will be obtained to assess fracture alignment and to evaluate the study's primary outcome. Compared with standard care, an additional 3–5 two-view forearm radiographic examinations are expected during follow-up.

Radiation exposure from extremity radiography is very low. A typical effective dose is approximately 0.001 mSv per projection; thus, a two-view examination (AP + lateral) is approximately 0.002 mSv. The cumulative additional effective dose is therefore estimated to be approximately 0.006–0.010 mSv. For context, The Danish Health Authority (Sundhedsstyrelsen) states that the average person in Denmark receives about 4 mSv per year from ionising radiation from all sources, most of it from natural background radiation. The additional study-related dose therefore constitutes only a very small fraction of annual background exposure and remains well below 0.1 mSv.

All imaging will be performed using pediatric low-dose protocols in accordance with the ALARA (As Low As Reasonably Achievable) principle, with collimation and shielding as appropriate. No CT imaging is required for study purposes.

9.3.2 Breakage of Activa IM-nail

Two cases have been reported worldwide in which a small fragment of the implant was sheared off by the sharp edge of the fracture, necessitating secondary surgery for fragment removal [38]. The Technique Guide for the Activa IM-Nail™ has subsequently been revised to emphasize additional caution when advancing the nail across the fracture site and to recommend only light hammer blows.

9.3.3 Fracture re-angulation

There may be an increased risk of fracture re-angulation when using BIN due to the greater flexibility of the implant. This risk is mitigated by immobilization in a circumferential above-elbow cast for 4 weeks, in accordance with the Technique Guide for the Activa IM-Nail™.

9.4 Loss of privacy

There is a risk that participants' private and confidential medical information could be disclosed, resulting in a breach of confidentiality. Measures to minimize this risk are described in Section 9.5.

9.5 Actions to minimize increased risks

- General treatment-related risks are present regardless of study participation and will be managed according to standard of care at the study site.

- The potential risk of fracture re-angulation with BIN is mitigated by immobilization in a circumferential above-elbow cast for 4 weeks, in accordance with the Technique Guide for the Activa IM-Nail™.

- The risk of loss of privacy and confidentiality will be minimized through strict adherence to data protection, safety, and security procedures described elsewhere in this CIP and in applicable SOPs.

- The study will be conducted in accordance with applicable national and international standards and guidelines, including ICH-GCP and ISO 14155. The ethical framework is based on the Declaration of Helsinki, supporting the protection of participant rights, safety, and well-being.

10 Informed consent process

10.1 Where? When? By whom?

All patients and parents will be informed at Herlev Hospital by a delegated member of the research team. Study information will be provided during a preoperative visit as soon as possible after the injury, typically within 3 days. The parents are informed about the option of bringing a support person.

10.2 How?

The information will be provided in an undisturbed setting, allowing sufficient time for discussion and questions. Study information will be provided using plain and understandable language and may be supported by age-appropriate materials (e.g., short videos and toys) to facilitate communication with the child and the parents. The nature of the study, its purpose, the procedures involved, the expected duration, potential risks and benefits, and any discomfort associated with participation will be explained.

In this pediatric study, the parents will receive face-to-face study information and provide written informed consent using the study-specific participant information and electronic informed consent form (eICF). The child will also be informed orally in an age-appropriate manner. Assent will be obtained from any child considered capable of understanding the basic information provided.

The parents will be informed that their child's medical records and radiographs will be accessed by authorized individuals involved in the study (see Section 12). Written informed consent will be obtained from the parents before any study-specific procedures or assessments are performed.

The parents will be provided with the study-specific participant information and eICF, as well as the general information on participation in health research issued by the Danish National Committee on Health Research Ethics, to support an informed decision regarding study participation.

10.3 Patient and Public Involvement - Involvement of children and parents from the pilot study

To improve feasibility and participant understanding before study start, children and parents who participated in the pilot study was invited to provide structured feedback on the randomized trial design and participant-facing materials. This activity was intended as user-testing/advisory input to refine procedures and communication; no clinical outcomes data was collected.

Pilot parents helped inform the clinically acceptable non-inferiority margin by responding to a short acceptability question on the maximum additional waiting time to resume higher-risk activities (beyond the typical 6 weeks for metal implants) that they would accept in exchange for avoiding a second implant removal operation.

Feedback also focused on (1) clarity and readability of the parent information sheet and age-adapted child assent materials, (2) acceptability and understanding of the randomized design, including the rationale for random and equal allocation between treatments, and (3) understanding and acceptability of the proposed blinding procedures and how these are explained to families.

Input was collected via an online questionnaire and optional short semi-structured interviews over phone. Findings was used to revise materials and, where relevant, inclusion procedures. Participation was voluntary and will not affect current or future care; feedback is handled confidentially and reported in aggregated form.

Secondary outcomes are based on the CORE-Kids core outcome set for childhood limb fractures by Marson et al. [44], which was developed using a Delphi consensus process with active involvement of children and parents to ensure the selected outcome domains reflect patient- and family-priorities.

10.4 Voluntariness

Parents and children will be informed that participation in the study is entirely voluntary. They may withdraw from the study at any time without providing a reason, and withdrawal of consent will not affect the child’s subsequent medical care or treatment.

10.5 Assessor

When inviting the family to the preoperative visit, the parents will be informed that they may bring an accompanying person (e.g., a support person) to the visit.

10.6 Consideration time

Unstable or displaced diaphyseal forearm fractures typically do not require emergency surgery; however, timely treatment is generally preferred. Surgical planning also requires time for the treating team to prepare for the specific procedure. Therefore, parents will be asked to provide informed consent as soon as possible and no later than the day before surgery.

In most cases, parents will have at least 24 hours to consider participation. In cases where surgery is indicated and can be performed promptly (e.g., due to clinical urgency or available operating room capacity), consideration time may be shorter, but not less than 2 hours whenever feasible. Treatment

will not be delayed for study purposes; if the family declines or is unable to decide within the available timeframe, the child will be treated per standard care and not enrolled.

10.7 Electronic Informed consent form (eICF)

Parents will indicate their willingness to allow their child to participate in the study by signing and dating an ethics committee (EC) approved electronic informed consent form (eICF). The eICF will be administered via REDCap-link sent to the parent's personal electronic mailbox (borger.dk) which requires identification login with secure "MitID". The consent form will automatically be signed and dated on behalf of the research team and retained as part of the study records.

The signed eICF will be filed, and a copy will be provided to the parents via secure electronic mail. A paper version of the informed consent form will be used if parents are unable to complete the eICF electronically.

11 Adverse event reporting

Sufficient safety data will be collected on adverse events (AEs) related to the injury, surgical procedure, implant use, and fracture healing, including information on implant revision and any required secondary surgery (i.e., complications). Detailed definitions of reportable AEs are provided in Section 7.2.6 of this CIP.

11.1 Definitions

In accordance with ISO 14155, adverse events (AEs), serious adverse events (SAEs), adverse device effects (ADEs), serious adverse device effects (SADEs), and device deficiencies are defined in the following sections. A flowchart illustrating AE categorization is provided in Figure 7.

11.1.1 Adverse event

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients.

11.1.2 Serious adverse event

A SAE is defined as any AE that:

- led to death
- led to a serious deterioration in health of the patient that either resulted in
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- inpatient or prolonged hospitalization, or
- a medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

Note: Planned hospitalization for a pre-existing condition or a procedure required by the CIP, without serious deterioration in health, is not considered as a SAE.
The definition of an AE does not imply that there is a relationship between the AE and the device or procedure under investigation.

11.1.3 Adverse device effect and serious adverse device effect

An ADE is defined as any AE related to the use of an investigational medical device.

Note 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device (see also section 11.1.5 for definition of device deficiency).

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
A SADE is defined as any ADE that results in any of the consequences characteristic of a SAE.

11.1.4 Unanticipated (serious) adverse device effect

An unanticipated (serious) ADE (U(S)ADE) is defined as a (S)ADE which by its nature, incidence, severity, or outcome has not been identified in 7.2.3.

11.1.5 Device deficiency

A device deficiency is defined as an inadequacy of the medical device under investigation with respect to its identity, quality, durability, safety, or performance.

Note 1: This includes malfunctions, use errors, and inadequate labeling.

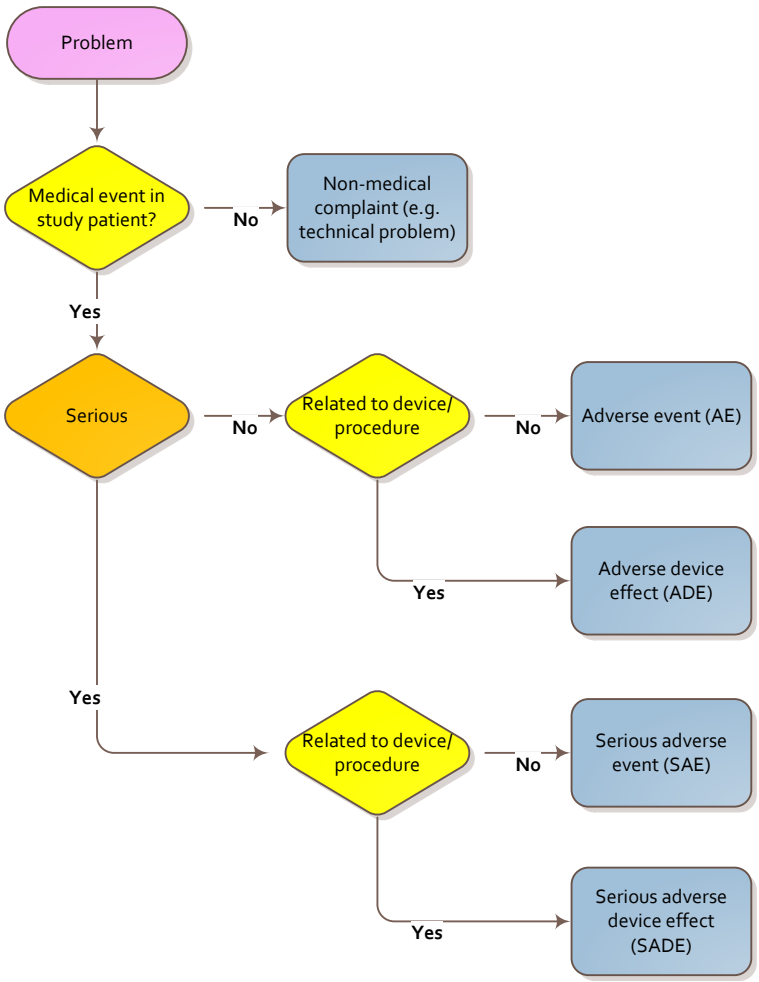


Figure 7: Schematic representation of AE categorization

11.2 Adverse event documentation

The following information is collected:

- Name and description of the event
- Start date of the event (if applicable)
- Actions taken due to the occurrence of the event
- Outcome of the event
- Date the patient has recovered from the event
- Relationship to device or treatment under investigation
- Severity of the event
- Seriousness of the event

If detailed information regarding an AE is not available at the time of initial reporting, completion of the AE form must be achieved at the next possible point in time.

The following steps need to be taken after a study patient has experienced an SAE:

- Initial SAE report: The investigator collects as much of the following information (see SAE form) as possible for reporting to the sponsor, EC and/or competent authorities:
  - Subject demographics
  - Date of occurrence of the event
  - Description of the event, including severity and relationship to device or procedure
  - Possible cause of SAE other than the investigational device
  - Relevant medical history
  - Relevant test/laboratory data
  - Concomitant medications
  - Name and contact details of the person who has reported the event.
- The investigator completes the SAE form and follows the SAE reporting instructions according to the local applicable regulations.
- FU of the event: The investigator collects all additional information to the event (e.g. discharge summary, autopsy reports) and sends these to the sponsor, if requested. The investigator is responsible for updating the SAE form.
- Documentation: The investigator ensures that the SAE is properly documented in the patient's chart, eCRF, SAE form, and that the appropriate forms are retained in the ISF.

11.3 Serious adverse event reporting

As soon as a research team member becomes aware of an SAE, this person will ensure that the following people will be notified:

- PI
- Sponsor: For regulated studies (e.g. investigational device exemption), the sponsor will also report this information to the appropriate regulatory body.
- EC
- The investigator is obliged to submit the SAE form within 24 hours after becoming aware of the event.
- Each SAE needs to be reported by the investigator to the EC according to their regulatory requirements.
- The timelines of AE reporting are specified in the local applicable regulations.

11.4 Follow-up of adverse events

Each AE will be followed up until resolved with or without persistent damage or until the end of the patient's study participation.

All patients experiencing an AE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed. The results of any additional diagnostic measure (not included in the CIP) that are obtained because of the occurrence of an AE or SAE should be attached to the eCRF highlighting the date on which these measurements were taken.

For any deaths occurring during the study, a postmortem report must be supplied by the investigator to the sponsor, whenever possible.

11.5 Adverse event review

All documented AEs will be reviewed by a medical expert for completeness, medical correctness of the data and the classification into AE, SAE, ADE, SADE, U(S)ADE according to ISO 14155 definitions, as described in the SOP "Adverse Event – Documentation and Reporting" according to the "Guidelines for adverse event reporting under directives 90/385/eec and 93/42/eec".

Furthermore, the medical expert performs the review according to the process defined by the manufacturer. In case of an ADE or SADE, the manufacturer's Complaint Handling Unit needs to be informed using the AE and SAE review form provided by the manufacturer (see flowchart added below). In addition, a device report form is sent to the clinic, containing the following questions:

- Patient's demographics
- Name and contact details of the surgeon and clinic
- Device related information (e.g. decontamination, article number)
- Liability and insurance related details

The manufacturer is in charge of supporting the study site in collecting this information.

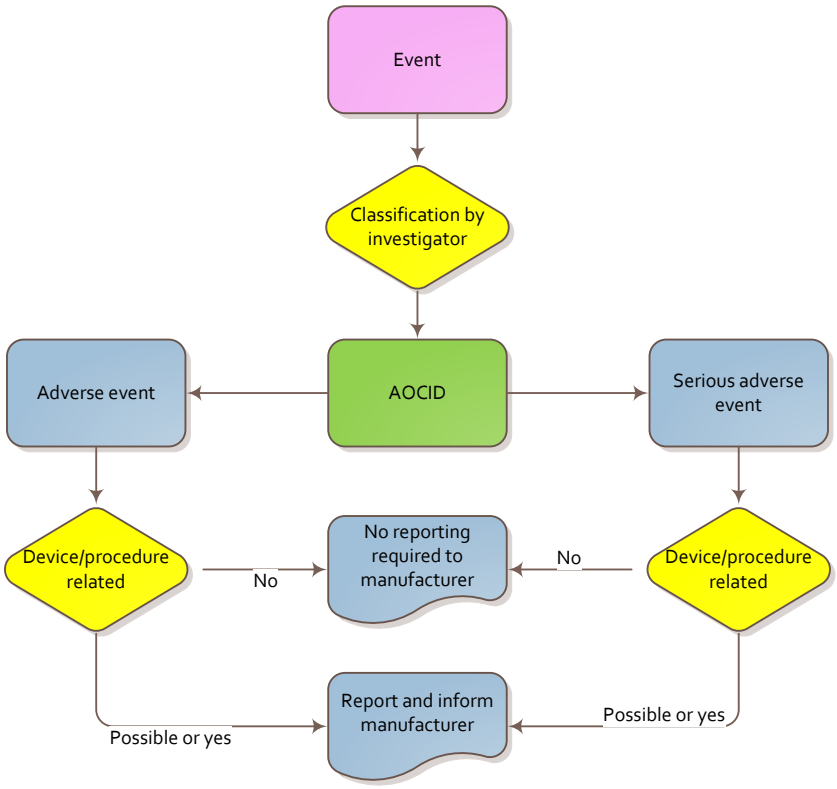


Figure 8: Adverse event review and reporting flowchart

11.6 Device deficiency reporting

The following information is collected by the investigator and reported to the sponsor:

- Specification of the deficient device
- Name and description of the deficiency
- Date of the start and resolution (occurrence) of the deficiency (if applicable)
- Actions taken due to the occurrence of the deficiency
- Consequence of the deficiency (i.e. if the deficiency may have led or led to an AE – if an AE occurred, this will be documented in the AE form)

The sponsor will analyze the information and must report only some deficiencies that could have led to a SADE. If detailed information regarding device deficiency is not available at the time of initial reporting, completion of the device deficiency form must be achieved at the next possible point in time.

11.7 Device deficiency review

In case of licensed medical device under investigation this is reported as per local law and not within the study. Additionally, if it is an investigational device, the sponsor will provide the procedures.

Furthermore, the medical expert performs the review according to the process defined by the manufacturer.

The manufacturer oversees supporting the study site in collecting this information as described in the SOP "Adverse Event – Documentation and Reporting".

12 Data management

12.1 Data collection, source data, storage, and archiving

Data management will be performed by the Principal Investigator (PI). Data handling and protection will be conducted in accordance with ISO 14155, ICH-GCP, and applicable national and institutional regulations.

The study complies with the EU General Data Protection Regulation (GDPR) and Danish data protection legislation (Databeskyttelsesloven and Databeskyttelsesforordningen).

The electronic case report form (eCRF) will capture all study data for each participant, as specified in this CIP. Any modification of the eCRF will be made only if necessary and in accordance with an approved amendment to the CIP.

A minimal screening log will be maintained separately from the study database, as described in Section 6.1.4.1.

12.1.1 Electronic Hospital records (EHR)

No study-related access to the patient's electronic hospital record (EHR) will occur before informed consent for study participation has been obtained.

Parents will be asked to consent to EHR access for the purposes of planning and conducting follow-up visits, admissions, and surgery, and for collection of relevant study data. This includes permission to:

- retrieve participant-related data and review clinical documentation related to outpatient visits, admissions, surgical procedures, and any adverse events (AEs);
- access and review radiographic imaging; and
- maintain EHR access until completion of the study.

By providing consent, parents authorize the Principal Investigator (PI) and relevant authorities to access information in the patient's medical record for the purpose of conducting the study and for oversight activities, including self-inspection, quality control, and monitoring, as required.

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

12.1.2 Electronic CRF

For this study, an electronic case report form (eCRF) has been designed to accommodate the specific features of the study design. Access to the eCRF is password protected and role-based, with functions assigned according to user responsibilities. The eCRF will be completed in a timely manner after each participant visit or other documentable event, typically within 7 days.

In general, data recorded in the hospital patient record are considered source data. Data collected through participant- and investigator-completed electronic questionnaires are also regarded as source data.
The eCRF is stored securely using Research Electronic Data Capture (REDCap; Vanderbilt University, USA), hosted by the Capital Region of Denmark.

12.2 Imaging data

Radiographs are stored securely in the hospital's Picture Archiving and Communication System (PACS). For the blinding process, radiographs provided for outcome assessment will be de-identified and will not contain patient-identifiable information. The images will be labeled only with the participant's numeric study identifier code.

12.3 Confidentiality

Participant privacy and confidentiality will be maintained throughout the study. The eCRF and all other study documents transferred to the sponsor will be de-identified and will contain only the participant's numeric study identifier code. The study site will maintain the linkage between the study identifier code and the participant's identity.

Fully identifiable information may be reviewed for the purpose of source data verification and confirmation of eCRF entries only at the study site. Such review may be performed by the sponsor or the sponsor's designee, regulatory authorities, or quality assurance personnel, in accordance with applicable site-specific regulations and procedures. Personal medical information will be treated as confidential at all times.

The informed consent materials will describe confidentiality safeguards and will include permission for authorized access to relevant medical information for study conduct and oversight purposes.

13 Study management and quality control

13.1 Contract Research Organization

No Contract Research Organization (CRO) will be engaged for this clinical investigation.

13.2 Training and organization at the study site

Prior to enrolling the first participant, Sub-Investigators (SIs) and study coordinator(s) (SCs) will receive study-specific training. Training will cover the CIP procedures, inclusion and exclusion criteria, eCRF completion, and relevant requirements under ISO 14155 and ICH-GCP. Training will be conducted by the Principal Investigator (PI). In the event of changes in study site personnel, new staff will undergo the same training prior to performing any study-related tasks.

The PI holds current GCP (or equivalent) training/certification.

An Investigator Site File (ISF) will be maintained at the study site and will contain all essential study documents.

The PI is responsible for overall supervision of the study and will provide direction, oversight, and training to delegated research personnel as required.

14 Monitoring and safety oversight

An independent monitor will be appointed before enrolment of the first participant. The monitor will be independent of both the research group and the Department of Orthopedic Surgery and may be based in another department at Copenhagen University Hospital - Herlev and Gentofte, or in another appropriate hospital unit. The monitor will have no role in recruitment, informed consent discussions,

treatment allocation, postoperative outcome assessment, radiographic endpoint evaluation, or statistical analysis.

Monitoring will be performed according to a written monitoring plan and will focus on trial-critical processes and data, including informed consent documentation, eligibility, randomization, device traceability/accountability, source data verification for the primary endpoint, protocol deviations, and the completeness and timeliness of SAE/SADE reporting. Monitoring findings will be documented in written monitoring reports, and any corrective and preventive actions will be followed to resolution by the Principal Investigator and sponsor.

Clinical safety oversight remains the responsibility of the Principal Investigator and sponsor as described in Sections 11 and 19. Any monitoring finding considered relevant to participant safety or data integrity will be communicated without undue delay to the sponsor and Principal Investigator.

15 Regulatory affairs

The Clinical Investigation Plan (CIP), associated documents, investigator financial disclosures, and the participant information and informed consent forms (ICFs) will be submitted to the relevant ethics committee (EC) for review and approval. The EC will be kept informed of study progress and relevant events in accordance with its regulations and procedures.

If additional regulatory approvals are required, the study will commence only after all necessary approvals have been obtained from the appropriate authorities.

16 Ethics

As described in Section 9, the risks associated with surgical treatment of pediatric diaphyseal forearm fractures are inherent to standard clinical care. Participation in this study is not expected to materially increase treatment-related risk. The incremental burdens of participation are primarily additional follow-up visits and radiographs; the additional radiation exposure is minimal, and follow-up procedures are designed to support both patient safety and robust outcome assessment.

The study addresses a clinically relevant question: whether bioabsorbable intramedullary nails (BIN) provide an acceptable (non-inferior) time to radiographic healing compared with titanium elastic intramedullary nails (TEN).

The ethical balance of this trial includes a patient-relevant trade-off: potential avoidance of a second implant removal operation versus the possibility of delayed healing and/or delayed return to higher-risk activities. To ensure this trade-off is communicated transparently and reflects family priorities, parents from the pilot cohort reviewed the information materials and contributed acceptability input on the maximum additional weeks of activity restriction they would consider acceptable.

The study will be conducted in accordance with the principles of the Declaration of Helsinki and applicable requirements under ICH-GCP and ISO 14155. Participation is voluntary. Parents and children will be informed that they may withdraw consent at any time without consequences for the child’s current or future medical care. Children will be informed in an age-appropriate manner, and

assent will be obtained when appropriate. Participant confidentiality and data protection will be ensured as described in Section 12.

We acknowledge that longer-term registry-based follow-up could provide valuable supplementary information on later healthcare utilization and complications related to the two treatment strategies, including implant removal procedures, reoperations, refracture, and other late healthcare contacts. An approximately 5-year registry-based follow-up is therefore considered scientifically relevant. However, such follow-up is not part of the present active study period and will only be undertaken following a separate protocol amendment and any required ethics, data protection, and registry approvals.

17 Patient insurance

As with all treatment provided within the Danish healthcare system, all participants are covered by the Danish Patient Compensation Association (Patienterstatningen).

18 Study report and publication policy

18.1 Final Study Report

The results of the statistical analyses will be summarized in a statistical report, which will form the basis for the comprehensive Final Study Report (FSR). The comprehensive FSR will serve as the primary source document for subsequent publications.

18.2 Publication

The publication strategy will be agreed between the sponsor and the Principal Investigator (PI), and any other relevant parties.

This Clinical Investigation Plan (CIP) may be submitted for publication in a peer-reviewed international journal.

The study will be reported to the European database on medical devices (EUDAMED) in accordance with the Medical Device Regulation (EU) 2017/745, as applicable.

The final study results—including positive, negative, and inconclusive findings—will be submitted for publication in a peer-reviewed international orthopedic journal and may also be presented at national and international scientific meetings.
If publication in a peer-reviewed journal is not achieved within a reasonable period after completion of the Final Study Report, the results will instead be made publicly available through an alternative publicly accessible channel, such as a preprint server and/or an institutional or sponsor repository

19 Termination criteria

Study progress, including recruitment and safety aspects, will be closely monitored in collaboration with the sponsor. The sponsor may decide to terminate the study for reasons defined in Section 19.1. In the event of early study termination, all participants already enrolled will, where feasible, continue follow-up until the final follow-up visit as defined in this CIP.

19.1 Stopping rules

To identify potential safety signals or unexpected complications, an interim safety review will be performed after approximately 50% of the planned randomized participants have reached the 12-week follow-up visit (or have achieved radiographic healing, whichever occurs first).

The interim safety review will be conducted by the PI in collaboration with the sponsor and will include review of adverse events (AEs), adverse device effects (ADEs), serious adverse events (SAEs), serious adverse device effects (SADEs), and key clinical outcomes (refracture, deep infection, reoperation, loss of reduction, delayed union). If predefined stopping criteria are met, recruitment will be temporarily paused while the events are reviewed and appropriate actions are taken (including notification of the ethics committee, as applicable).

This interim review is for **safety monitoring only** (AEs/ADEs/SAEs/SADEs and prespecified healing-related safety signals including refracture and delayed healing) and is not a formal interim analysis of the primary noninferiority hypothesis; no early stopping for noninferiority/superiority efficacy is planned, and no alpha-spending adjustment will be applied based on this safety review.

Recruitment will be put on hold for safety reasons if at least one of the following incidents occurs and is assessed as possibly related to the investigational device (BIN):

- Refracture: An absolute refracture rate >25% (within the study follow-up period) will not be tolerated and will constitute a criterion for pausing recruitment.
- Delayed healing: An observed mean time to radiographic healing >12 weeks in the investigational (BIN) group will constitute a criterion for pausing recruitment.

After review, the sponsor and PI will decide whether recruitment can resume unchanged, resume with protocol modifications/risk-mitigation measures, or whether the study should be terminated.

20 Disclosures and economy

The initiative for this study has been taken solely by the authors.

The authors and affiliated colleagues have not received financial payments or other benefits from any commercial entity related to the subject of this study. The authors declare that they have no conflicts of interest.

Participants will not receive any financial compensation, gifts, or other economic benefits for participation in this study.

21 Deviations from the Clinical Investigation Plan

Deviations from the procedures described in this CIP, or changes to the CIP without following the defined process, are not permitted.

A CIP deviation is any non-adherence to the protocol that does not involve eligibility (inclusion/exclusion criteria), the primary endpoint, or compliance with GCP/ISO 14155 requirements. Deviations are

considered minor and are not expected to have a major impact on participant safety or data integrity. Deviations will be documented and reported to the sponsor within 10 working days.

A CIP violation is any significant divergence from the protocol by the participant, investigator, sponsor, or other responsible party that may affect, for example, eligibility (inclusion/exclusion criteria), the primary endpoint, or compliance with GCP/ISO 14155 requirements. The sponsor must be notified within 5 working days of becoming aware of the violation. Violations will be documented at the study site and recorded in the eCRF.

22 Amendments to the Clinical Investigation Plan

No changes to the approved CIP are permitted except where necessary to eliminate an immediate hazard to participant safety or where changes are purely administrative or logistical and do not affect participant safety or the scientific validity of the study. Any urgent change implemented to protect the life, health, or well-being of enrolled participants will be reported to the relevant bodies in accordance with applicable requirements, and no later than 5 days after implementation.

If changes to this CIP become necessary during study conduct, a formal amendment will be prepared, issued, and submitted for approval and/or notification to the relevant ethics committee and other required authorities, as applicable, prior to implementation.

23 Time schedule

Ethics Committee approvals	2.2026	to	05.2026
First patient/first visit			05.2026
Last patient/first visit			05.2029
Last patient/last visit			05.2031
Data analysis	06.2031	to	12.2031
Final Study Report	01.2032	to	03.2032

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CIP approval signatures

Name	Function	Date	Signature
Morten Jon Andersen	Principal Coordinating Investigator		

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Appendix 1 - CIP approval

Study site	Department of Orthopedic Surgery Copenhagen University Hospital – Herlev and Gentofte Borgmester Ib Juuls Vej 1 | 2730 Herlev | Denmark

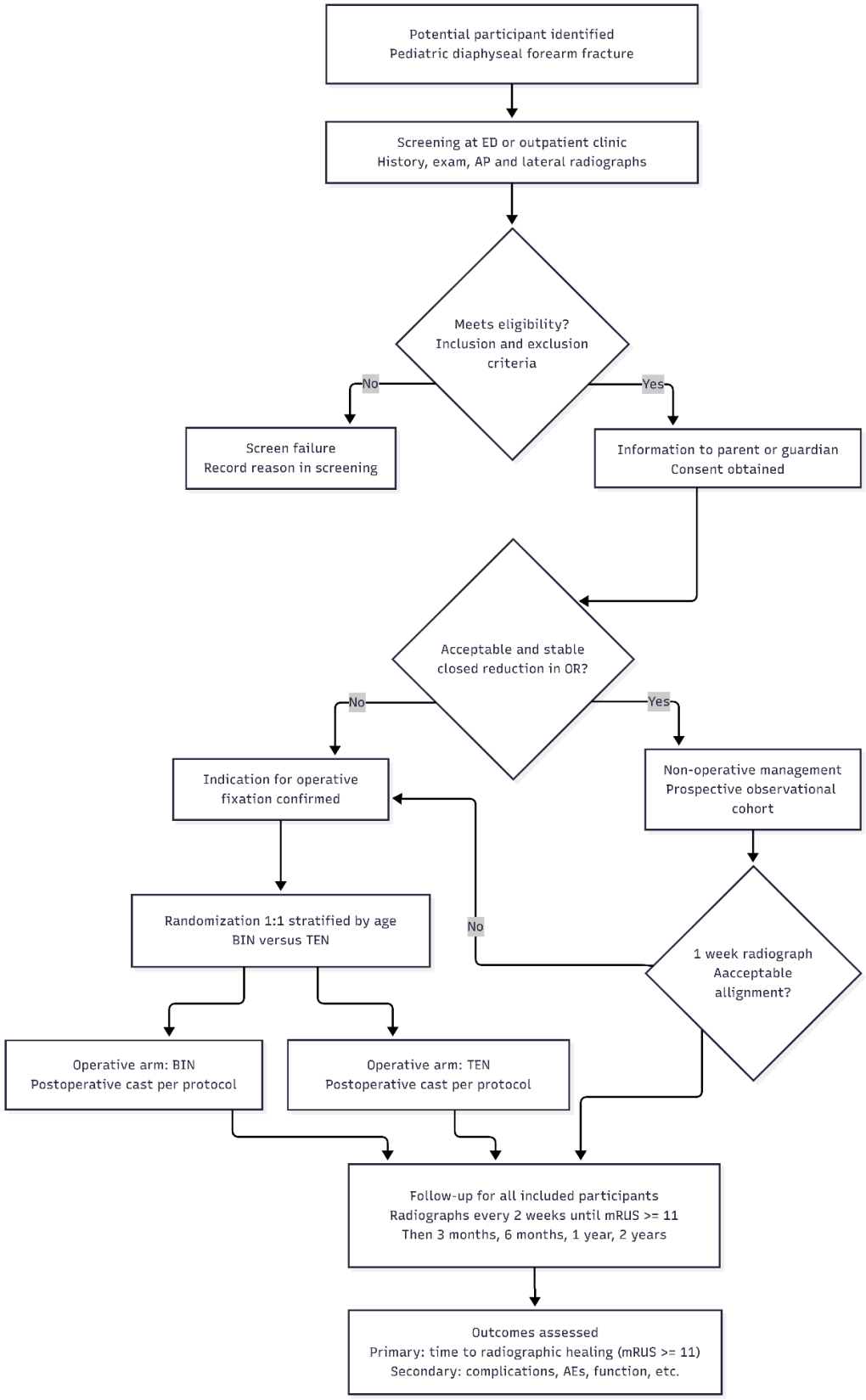
CIP approval signature of Principal Investigator

Name	Position	Date	Signature
Morten Jon Andersen	MD, PI		

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 from 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 all aspects of ICH-GCP and all applicable regulatory requirements.

Appendix 2 - Study flowchart and allocation



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Appendix 3 - Device table (Investigational device and comparator)

	Investigational device (BIN)	Comparator device (TEN)
Device role in study	Investigational device	Comparator device
Product type / generic name	PLGA bioabsorbable intramedullary nail	Titanium Elastic Intramedullary Nail
Trade name	Activa IM-Nail™	Titanium Elastic Nail (TEN™) System
Manufacturer	Bioretec Ltd., Tampere, Finland	Synthes GmbH, Oberdorf, Switzerland
Specific model(s) used in trial	B-ANIM-27400 Activa IM-Nail™ 2.7 x 400 mm B-ANIM-32400 Activa IM-Nail™ 3.2 x 400 mm	475.9xxS (xx=mm diameter) (sterile “S” variants)
Sizes / range relevant to study	2.0–3.2 mm x 200–400 mm	1.5 mm × 300 mm 2.0–3.0 mm × 440 mm
CE-marked	Yes	Yes
Device class (MDR)	Class III	Class III
Notified Body	DEKRA Certification B.V. (NB 0344)	TÜV SÜD (NB 0123)
Sterile	Yes	Yes
Measuring function	No	No
Reusable surgical device	No	No
Invasive / implantable	Yes / Yes	Yes / Yes
Incorporates medicinal substance / blood derivative	No	No
Incorporates non-viable tissues/cells (human/animal)	No	No
Intended use (high-level)	Intramedullary fixation of pediatric forearm diaphyseal fractures	Bone fixation nails are intended for temporary fixation, correction and stabilization of bones

Target population (IFU)	Pediatric	Recommended for skeletally immature patients
Key contraindications (headline)	• Multifragmentary fractures • Metaphyseal or epiphyseal fractures General contraindications to internal fixation / use: • Active or suspected infection	
Key potential adverse events / residual risks	Infection, malunion/non-union, neurovascular damage, implant migration/loosening/breakage, compartment syndrome, etc.	
Accessories / related components used	BIN system instruments (awl, dilator, inserter, cutter, impactor, etc.)	TEN system instruments (awl, inserter, cutter, impactor, extraction pliers, etc.)
Sterilization / reprocessing notes	Device is delivered in a sterile state and re-sterilization by any method is restricted in the labelling.	Sterile devices: irradiated; single-use devices not to be reused
MRI information	MRI safe	MRI Conditional: non-clinical 3T testing described in IFU
Implant removal	No	Routine removal after bone healing

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