Complications on Lower Limb Lengthening with a Bone Lenghtening Nail

An Evaluation of the Frequency and Origin of Complications in the Literature and in Cohort

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BY
MARKUS WINTHER FROST

DISSERTATION SUBMITTED 2022

AALBORG UNIVERSITY
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PREFACE

The inspiration for this thesis stemmed from my orthopedic training at Aalborg University hospital, where I was introduced to the incredible effect of distraction osteogenesis by a leader in the Nordic field of bone lengthening, Knud Stenild Christensen, who regularly presented distraction osteogenesis cases of both the frame and nail. The prospect of studying distraction osteogenesis and improving treatment through the evidence-based work of a Ph.D. was, therefore, welcome.

The submission of this Ph.D. thesis is the termination of a four-year journey filled with detours, achievements, and unexpected challenges. At the outset of this Ph.D. journey, the course pointed toward a series of rabbit studies to restart the field of experimental animal orthopedic research at Aalborg University hospital. Skills from rabbit intubation to understanding strain gauge were acquired, but the project ran aground, as with many other Ph.D. projects. The focus, therefore, shifted to the epidemiological discipline, which required skills and knowledge related to database structuring and general linear models. Thus, this thesis provides the opportunity to present some of the many things that I have learned and investigated on this journey, which should enhance my future work as an orthopedic surgeon and researcher.

The work entailed in this Ph.D. thesis was conducted over the years 2018–2022. During this time of change for the world, I was employed in the Orthopedic Research Unit at Aalborg University hospital under the supervision of Professor Søren Kold and Professor Ole Rahbek. The two professors assembled the research unit and established their future research field while the world outside was fighting a COVID-19 virus pandemic in the winter of 2020 and 2021. The research was, therefore, at times performed at a dinner table while homeschooling, and international congress was moved from the auditorium to an online platform. In some ways, research and life during a viral pandemic are

similar, both requiring alterations in thought or action depending on the research problem or new pandemic restriction. Fortunately, for research and human survival, we have a high adaptive ability.

If the work of this Ph.D. thesis should change the field of bone lengthening, it would be the highest honor and work achievement for me. Yet, even if this work changes the outcome of bone lengthening for just one patient, it would make a world of difference for both the patient and me.

Markus Winther Frost

LIST OF PAPERS

This Ph.D. thesis is based on the following papers/manuscripts:

I. Systematic review of complications with externally controlled motorized intramedullary bone lengthening nails (FITBONE and PRECICE) in 983 segments.
   Markus W Frost; Ole Rahbek; Jens Traerup; Adriano A Ceccotti; Søren Kold
   (Published in Acta Orthopaedica 2021)

II. Complications and risk factors of externally controlled intramedullary bone lengthening: A retrospective multicenter cohort study of 314 FITBONE and PRECICE nails.
   Markus W Frost; Ole Rahbek; Christopher Iobst; Anirejuoritse Bafor; Molly Duncan; Søren Kold
   (unpublished)

III. Do surgeons agree on severity and origin of complications in bone lengthening nails? An inter-and intra-rater reliability study
   Markus Winther Frost; Ole Rahbek; Marie Fridberg; Mindaugas Mikužis; Søren Kold.
   (unpublished)

The papers will be referenced in-text by their Roman numerals (I–III)

This thesis is constructed based on the three manuscripts listed above, with the intension to fulfill the requirements of the Ph.D. degree.

ENGLISH SUMMARY

Twenty years ago, the established treatment for bone lengthening was external fixation, which had the major disadvantages of high complication rates and patient discomfort. Since then, the externally controlled bone lengthening nail was introduced to reduce complications and improve patient comfort. More than 14,000 FITBONE and PRECICE bone lengthening nails have been implanted worldwide and have become many reconstructive surgeons' first choice for lower limb lengthening. However, established evidence concerning the complications of bone lengthening nails remains lacking in the published literature, which mostly consists of small retrospective cohort studies without consistent complication reporting. Complications related to the use of externally controlled bone lengthening nails were, therefore, the primary aim of this Ph.D. investigation. The frequency of complications combined with their origin and severity was mapped. Patient- and surgery-related risk factors of the complications were also investigated.

First, the body of literature was explored through a systematic review, which assembled a group of 983 segments. Device, bone, and joint complications were the most frequent complication origins, and the overall frequency of complications was one complication for every three segments lengthened. Most complications occurred in the distraction and consolidation stage prior to implant removal.

A retrospective two-center cohort study of 314 segments provided the basis for the second study, showing a complication frequency of one complication for every two segments lengthened. While most complications occurred in the distraction and consolidation stage prior to implant removal, a surprisingly high number of complications was observed after nail removal. Similar to the review study (Study I), device, joint, and bone were the three most frequent origins of

complication. The following risk factors with a significant increased relative risk of complication were discovered: age groups ≥20 years, FITBONE nail, tibia segment, acute deformity correction combined with lengthening, and increasing bone lengthening.

In the last study, the intra- and inter-rater reproducibility of the complication severity and origin classification system was evaluated. A good inter-rater and good to excellent intra-rater agreement for the severity and origin classification was found in the two examined case groups.

In short, the thesis presents evidence on the frequency, origin, and severity of complications in bone lengthening nails. The results of this thesis suggest that complications in the treatment of bone lengthening nails frequently occur and that risk factors of complications exist; both implications provide valuable knowledge in the assessment and the treatment of bone lengthening patients.

DANSK RESUME

Knogleforlængelse med externe fiksationssystemer var for tyve siden en veletableret behandling for knogleforlængelse på under-ekstremiteten. Den store ulempe ved externe fiksationssystemer er de høje komplikationsrater og de fysiske gener fra den externe fiksation. Knoglemarvs forlængelses søm blev introduceret med forventning om at reducere komplikationer og mindske generne. Med mere end 14.000 FITBONE og PRECICE knoglemarvs forlængelses søm indsat på verdensplan er knoglemarvs forlængelsessøm blevet mange ortopædkirurgers første valgs behandling til knogleforlængelse. Imidlertid er viden omkring komplikationer ved knoglemarv-forlængelses søm dog forsat mangelfuld. Litteraturen består af mindre retrospektive kohorte studier som ikke bruger et fælles komplikationsklassifikationssystem. Komplikationer relateret til behandlingen med knoglemarvsforlængelses søm blev derfor det primære mål for Ph.d.-studiet med særligt fokus på hyppigheden af komplikationer samt deres oprindelse og sværhedsgrad. Patient og kirurgi relaterede risikofaktorer blev undersøgt som et sekundært formål.

Først blev litteraturen undersøgt igennem en systematisk oversigt som samlede 983 knogleforlængelses segmenter. Komplikationer relaterede til forlængelsessøm, knogle og led var de hyppigste. En komplikation for hver tredje forlænget knogle var den overordnede komplikationshyppighed og komplikationer blev hyppigst observeret i distraktions- og konsoliderings-fasen inden implantat fjernelse.

Et retrospektive kohortestudie fra to kirurgiske centre med 314 inkluderet knogle forlængelser danner grundlaget for studie to. Hyppigheden af komplikationer blev fundet til en komplikation for hvert andet forlænget knoglesegment. De fleste komplikationer blev observeret i distraktions- og konsoliderings-fasen inden implantat

fjernelse. Dog var der overraskende mange komplikationer efter fjernelse af knoglemarvsforlængelsessømmet. Som i oversigtsstudiet var forlængelses søm, led og knogle komplikationer de hyppigste komplikationstyper. Risikofaktorer med signifikant øget relativ risiko var: alder>20 år, FITBONE søm, tibia-forlængelse, aksekorrektion i forbindelse med forlængelse og øget længde af knogleforlængelsen.

I det sidste studie blev intra- og inter-rater reproducerbarheden evalueret for komplikations klassifikation for sværhedsgrad og oprindelsestype. En god inter-rater overensstemmelse for både komplikations sværhedsgrad og oprindelses type blev fundet i begge de undersøgte grupper.

Kort beskrevet præsenterer Ph.d. afhandlingen hidtil manglende viden omkring hyppighed, oprindelse samt sværhedsgrad af komplikationer ved behandlingen af knoglemarvsforlængelsessøm. Afhandlingens resultater tyder på, at komplikationer ved behandlingen med knoglemarvsforlængelsessøm er hyppige og at der findes forskellige risikofaktorer. Begge dele er vigtig viden i vurdering og behandling af patienter med forlængelsesmarvsøm.

ACKNOWLEDGEMENTS

First, I would like to direct my highest gratitude to all the people and institutions involved in the scientific work performed in my time at the Orthopedic Research Unit at Aalborg University hospital. This research journey would not have been accomplished without your effort.

The field of evidence-based research was introduced to me during my time as a research year student in the Dept. of Cardiothoracic and Vascular Surgery, Aarhus University Hospital under the skillful suspension of Professor Michael Hassenkam and Jonas A. Funder, Ph.D. Their systematic guidance in how to structure research and the long study hours spent in the basement of the Institute of Clinical Medicine have taught me countless and priceless research and surgical skills, for which I am immensely grateful.

To my supervisors, Professor Søren Kold and Professor Ole Rahbek, I owe you the greatest thanks for providing me the opportunity to perform this work and thereby contribute to advancing the field of evidence-based orthopedics. Your doors have always been open, and your guidance has been constructive, with good clinical angles, fast responses, and a well of new project ideas.

Many thanks to Kirsten Duch, Dept. of biostatistics for her patience and competent and certain guidance through the areas of biostatistics.

Furthermore, I am grateful for the financial support from the Orthopaedic Research Unit at Aalborg University hospital, which allowed the opportunity to perform this Ph.D. project.

To our partners at Nationwide Children's Hospital, Ohio, clinical associate professor Christopher Iobst and his team Anirejuoritse Bafor and Molly Duncan, I thank you for the smooth collaboration and prompt responses on our joint projects.

For all the kilometers traveled during the years of the Ph.D., and not least all the constructive and positive input, a special thanks goes to my running mate, Jakob Dal.

Finally, I thank my family, for without you this Ph.D. would never have been realized. To my dear life companion, Mette, thanks for always believing in me and your continuous support and patience. To my children, thank you for continuously reminding me to leave the computer and come play and for bearing with your distracted father.

Markus Winther Frost

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LIST OF ABBREVIATIONS

AAUH: Aalborg University Hospital, Denmark

Albizzia: Albizzia nail (DePuy, Villeurbanne, France)

AP: anterior/posterior

CI: confidence interval

ERC: external remote control

FITBONE: FITBONE® (Wittenstein Intens, Ingersheim, Germany)

LLD: leg length discrepancy

Ilizarov method: transosseous compression distraction osteosynthesis

IQR: interquartile range

I.M.: intra medullary

ISKD: Intramedullary Skeletal Kinetic Distractor, Orthofix Inc.

NCH: Nationwide Children's Hospital, Ohio, USA

PRECICE: PRECICE® (Nuvasive, San Diego, CA, USA)

P: P-value

RR: relative risk

QQ-plot: quantile-quantile plot

REDCap: Research Electronic Data Capture

Std. Err: standard error

SD: standard deviation

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1 INTRODUCTION TO LEG LENGTH DISCREPANCY

What is limb length discrepancy (LLD)? The simple everyday answer is one limb that is longer than the other. However, from the view of the reconstruction orthopedic surgeon, the situation becomes more complex. What limb segment contributes to the limb length discrepancy? How large is the limb length discrepancy? Is it a functional shortening due to joint contracture of the hip or knee or is it an anatomical shortening due to short bones? What is the etiology behind the LLD? Those are just some of the considerations that the reconstruction orthopedic surgeon must examine and take into consideration when treating LLD. In the sections below, a short overview of LLD is given to introduce the main topic of complications in bone lengthening nails.

In this Ph.D. thesis, LLD and bone lengthening refers to the lower extremity unless noted otherwise.

1.1 ASSESSMENT

Regarding LLD, pelvic obliquity can be assessed through clinical and radiological examinations (1–3). The clinical assessment comprises an ‘‘indirect’’ assessment of the LLD in which the pelvis is leveled by placing blocks under the short limb of the erect patient (1). Figure 1.1.1. shows the principle of a pelvic leveling block examination of LLD.

However, this method does not differentiate between functional and anatomical LLD (1). Functional LLD results from an asymmetrical leg length; while this is not necessarily a true bony length difference (anatomical), it may be caused by an alteration in lower limb

mechanics, such as joint contracture, static or dynamic mechanical axis malalignment, or muscle weakness or shortening (4,5). A thorough clinical limb examination is, therefore, needed to analyze the different components contributing to the LLD.

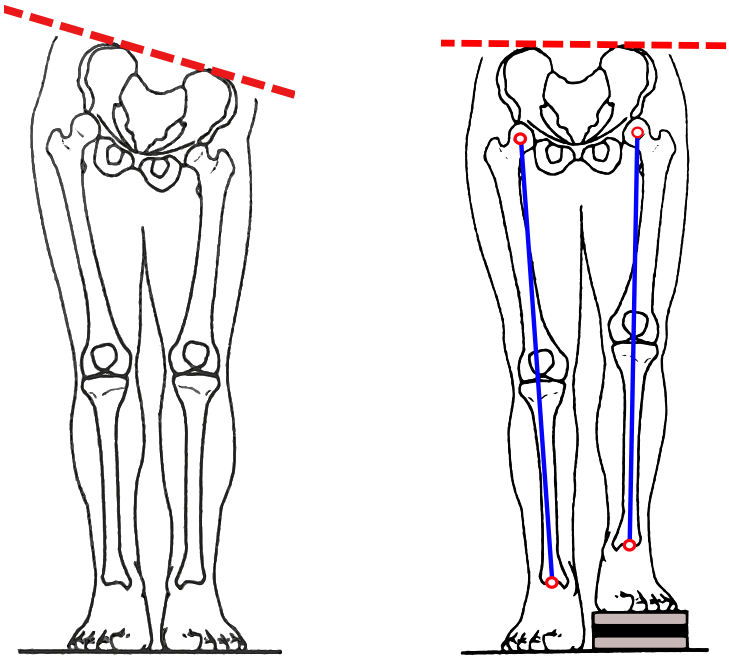

Figure 1.1.1: Pelvis leveling block test.
Left: First the pelvis level is assessed at the iliac crest (red line) without the block. It is seen that the pelvis is not leveled (red line). Right: Blocks are placed under the short leg until the pelvis is level at iliac crest. The depth of the blocks required under the foot to level the pelvis is the limb length discrepancy (LLD) of the short leg. Blue line: The anatomical leg length. The anatomical LLD is the difference between the two anatomical leg lengths. Optimal patient placement is critical for reliable assessment/ measurements of LLD by clinical and x-ray examinations. Particular attention should be paid to the knee joints, which should both be fully extended, and the feet should be placed next to each other.

Radiographs are considered more reliable for the LLD assessment than the clinical examination (1). Two reviews have found that a standing full-length anterior/posterior (AP) computed radiograph, which includes a level pelvis, magnification marker, and both lower limbs,

should be the principal imaging examination for the evaluation of LLD (1,3).

The anatomical leg length is equivalent to the mechanical axis of the leg; verifying the anatomical leg length/mechanical axis is the first step in evaluating bone deformity (See Figure 1.1.1)(6). X-ray analysis can be used to identify bone deformity, and corrective intervention can be planned and corrected with or without lengthening (6,7).

1.2 PREVALENCE AND SYMPTOMS

In a review by Knutson (8), LLD was found in 90% of the study population. However, 41%–64% of the population had LLD less than 0.5 cm, and only 2%–7% had LLD greater than 1.5 cm (8–10). In a French study, one per 1000 persons studied had LLD of at least 2 cm (11). The prevalence of LLD is not well established; furthermore, Brady et al. stated that there was little agreement in what constitutes a clinically significant LLD (12). LLD has been associated with different conditions, such as lower back pain, functional scoliosis, asymmetric gait, hip and knee osteoarthritis, and stress fractures (10,13–18). In regard to bone lengthening, LLD over 2 cm seems to be the accepted starting point for considering lengthening treatment (2,19,20).

1.3 ETIOLOGY

LLD arises from many different etiologies, and it can be categorized as adult or child LLD, depending on the time of evolution. Adult LLD can develop from trauma, infection, arthrosis, or surgeries, such as bone resection (tumor) or arthroplasty. In children, LLD often develops due to disturbances (stop/slower/faster) during this bone growth period (21). Epiphysial damage may slow or even stop bone growth, while

metaphyseal osteomyelitis may increase growth (21). Further, overlapping fracture ends can reduce bone length (21). Table 1.3.1 presents a list of LLD etiologies.

Overall Etiology	Shortening	Lengthening
Congenital	Fibular or Tibial hemimelia Proximal femoral focal deficiency Congenital tibial pseudarthrosis	Hemihypertrophy Arterio-venous malformation
Syndrome	Russell-Silver Conradi-Hunerman	Klippel-Trenaunay syndrome
Physeal growth disturbance	Ischemic physeal arrest Juxta-physeal tumor or bone cyst Radiation therapy	
Tumor	Enchondromatosis Osteochondromatosis	Hemangioma Neurofibromatosis
Trauma	Traumatic physeal growth arrest Fracture malunion (shortening or malalignment) Segmental bone loss Slipped capital femoral epiphysis (SCFE)	Post-traumatic overgrowth
Infection	Growth plate damage from osteomyelitis	Metaphyseal osteomyelitis Septic arthritis
Neuromuscular	Poliomyelitis Spastic hemiplegia Spinal cord anomaly	
Degenerative	Arthrosis	

Table 1.3.1: LLD etiologies divided into groups.
Some of the many etiologies/diseases of LLD are divided into groups with their effect on bone length. Their allocation can be discussed. For example, osteomyelitis, which causes growth plate damage, could also be placed

under physeal growth disturbance. Partially reproduced from work by Stricker et al. and Moseley (21,22)

Even though the etiologies of LLD are numerous, a systematic history of hereditary conditions, birth complications, infection, and trauma, in combination with meticulous clinical examination can quickly reduce the number of possible disease/etiologies for a specific patient (22).

In relation to bone lengthening, the etiology of short stature should be considered even though most patients with short stature do not have LLD. Short stature can be hereditary, idiopathic, or due to various universal growth disturbances, such as hypo-/achondroplasia or growth-hormone deficiency. Some patients with universal bone disease, such as those with hypophosphatemic rickets, might develop both short stature and LLD due to differences in the severity of malalignment between the lower limbs.

1.4 TREATMENT

Vittori Putti, probably the leading reconstruction orthopedic surgeon at his time, stated in 1921 that:

> "A shortening of the femur which does not surpass 2 inches (5.08 cm) and is not complicated by a deviation of the static axis of the limb does not require operative treatment"(23).

So, what comprises the bone lengthening practices and evidence one hundred years after Vittori Putti? The literature lacks studies that assess the natural course of LLD compared with the course of LLD following one or more treatments (2). This creates a deficiency in evidence-based LLD treatment (2). If initiated, treatment must be based on the individual patient, considering the treatment's risks, advantages, and family/social effects (2,24).

Non-surgical treatments are recommended for LLDs between 0 and 2 cm (if treatment is needed). Shoe lifts can be used to reduce or equalize

the LLD (2,24,25). When the LLD increases to 2–5 cm, different treatment options need to be considered. A sole lift can be used as a non-surgical treatment (2,21). However, some patients feel that larger sole lifts impair ankle stability when walking. Furthermore, sole lifts can only relieve symptoms when worn. Another treatment option involves shortening of the long bone, either by epiphysiodesis in patients with residual physeal growth or by shortening osteotomy (2,21,24). Another option, bone lengthening by distractions osteogenesis, is described below. Historically, bone lengthening has been initiated for LLDs above 5 cm, in conjunction with other treatments (2,24). Today, LLDs smaller than 5 cm are treated with bone lengthening, and the accepted indication for bone lengthening seems to be LLD greater than 2 cm (2,19,20). Amputation and prothesis fitting is a treatment option for LLDs over 20 cm (24). An orthosis might also be a treatment option for smaller LLDs in severe congenital cases, where the risk of complications is too high to consider bone lengthening. The strength of the described treatment must be viewed in relation to the lack of evidence, such as prospective studies comparing the treatments or indications for LLD.

2 METHOD OF DISTRACTION OSTEOGENESIS

2.1 AN INTRODUCTION TO THE HISTORY OF LIMB LENGTHENING

The first bone lengthening procedure might have been performed by a Roman, a Viking, or even an Egyptian, but no one knows the circumstances since we only have anecdotal documentation (26). The Italian surgeon, Alessandro Codivilla, from Bologna was the first to use skeletal traction for lengthening purposes and is, therefore, known as the "Father of Modern-Day Leg Lengthening" (26). Details of his 34 femoral lengthenings, ranging from 3 to 8 cm, performed via acute osteotomy and distraction with a sectioned plaster spica cast and calcaneal nail, was published in 1905 (27). Here Codivilla elucidates his concept by stating:

> "I am convinced that in so far as regards the extension of the fleshy parts, and when great force is necessary, the best results are obtained from forced lengthening, practiced under narcotics; by using a sudden and intense force…"(27).

This statement contrasts today's concept of bone lengthening by gradual distraction after osteotomy, which was first described by Codivilla's protégé, Vittori Putti, in 1921 (23,26). In Vittori Putti's philosophy, a continuous and elastic force should overcome elastic resistance of the soft tissue, and excessive force was potentially dangerous (23).

In 1939, a consistent description of the common complications in tibial lengthening was published by Abbott and Saunders (28). They believed that complications were attributed to imperfections in their methodology (28). However, modern reconstructive bone surgeons will

probably acknowledge that the list remains valid (see list in table 2.1.1). So, one can ask, are the complications in bone lengthening still attributable to imperfections in the methodology, or is it a high-risk treatment?

Complication of Tibia/fibula lengthening
Deformities of the foot o Valgus o Equinus o Equinovalgus o Calcaneovalgus
Deformities of the knee o Genu valgum o Flexion contracture o Relaxation of the knee
Anterior and medial bowing of the fragments of the tibia with malunion or nonunion
Limitation of motion at the ankle
Weakening of the muscles of the leg
Nerve complications: o Paralysis or weakening of the muscles o Disturbance of sensation
Disturbance of circulation: Chronic swelling of the leg
Infection: o Infection of the operative wound o Infection of pin wounds
Aseptic necrosis of bone

Table 2.1.1: Abbott and Saunders list of complications.
List of complications of tibia/fibula lengthening. Reproduced after Abbott and Saunders 1939 (28).

Heinz Wagner from Germany, a leading surgeon in limb lengthening in the 1970s until the mid-1980s, created the Wagner external fixator for leg lengthening (26,29). The unique device allowed patients to become ambulatory during the treatment period (26). However, the regenerated bone often needed grafting and plating when the external fixator was removed, likely due to an aggressive surgical osteotomy combined with

the rapid distraction (26), and therefore, the method often required three surgeries (30).

Two important contributions to the bone lengthening technique came from the De Bastiani group; they developed an osteotomy technique with small incisions and limited periosteal stripping for “corticotomy” and they described the distraction rate of 1 mm/day after 10–15 days of delayed “callotasis”(26,31). De Bastiani also designed a modular unilateral bar fixation device that became the “dynamic axial fixation system” from Orthofix (26,31)

In 1951, professor Gavriil A. Ilizarov started his work, which became the foundation of modern bone lengthening (30). Ilizarov’s work was conducted behind the iron curtain in Kurgan, Union of Soviet Socialist Republics (USSR). Due to the politics of the time, Ilizarov’s experimental and clinical work was not disseminated outside of the USSR until 1989 (26,32). Ilizarov developed an external ring fixation in which the bone was transfixed with wires. This technological and biological concept became known as the “Ilizarov method” or “transosseous compression distraction osteosynthesis” (32). Through extensive experimental work in the scientific institute (KNIIEKOT) combined with his clinical work, Ilizarov established the basic biological laws and technological philosophy of the “transosseous compression distraction osteosynthesis” based on the following tenets (32–35):

- “Tension stress effect that stimulates the biosynthetic activity in tissues
- Adequacy of loading and blood supply
- Gradual lengthening and correction
- Possibility of full-time control of callus formation

- Early limb functioning and loading”(36)

2.2 DISTRACTION OSTEOGENESIS

The formation of new bone and soft tissue by gradual and controlled distraction after osteotomy is referred to as distraction osteogenesis (35). This method of bone formation can be divided into the following four stages: (1) osteotomy, (2) latency, (3) distraction, and (4) consolidation (33–35). Figure 2.2.1 shows a schematic description of the four stages of distraction osteogenesis on a bone.

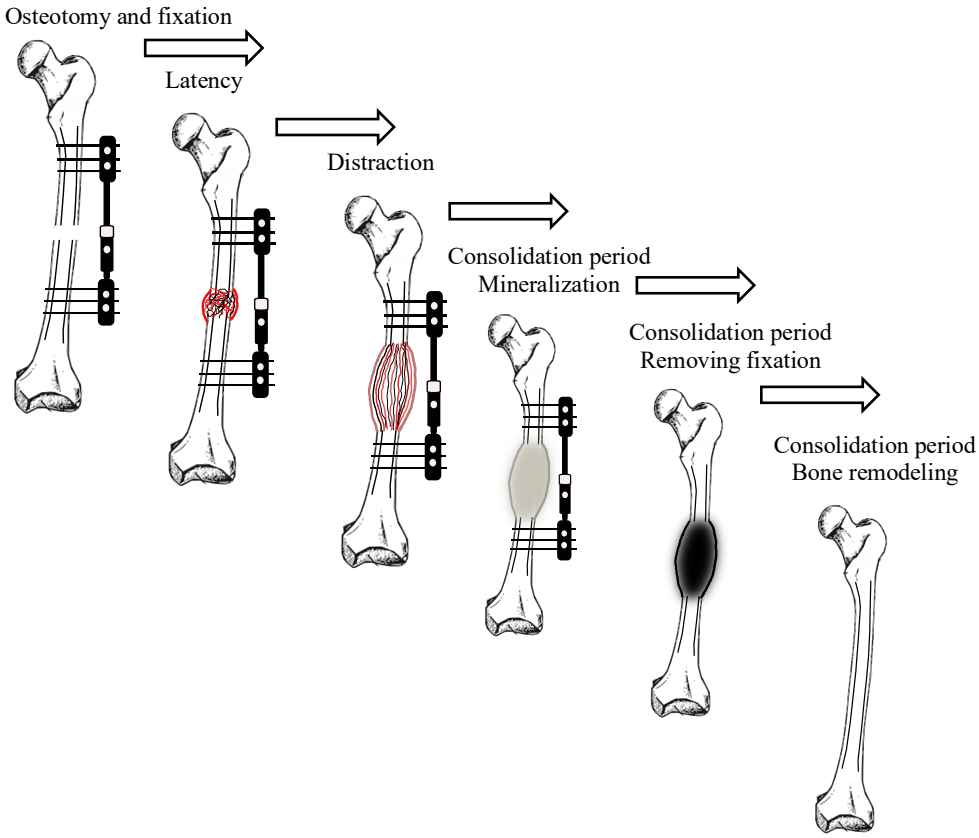

Figure 2.2.1: Stages of distraction osteogenesis.
The four-stage of distraction osteogenesis are osteotomy and fixation,

latency, distraction, and consolidation. Consolidation can be divided into three periods: mineralization, in which the bone strengthens and becomes mineralized; fixation removal, in which adequate bone strength is achieved and the fixation device can be removed; and bone remodulation, in which the bone continues remodeling until normal or near normal bone configuration is obtained.

In combination with adequate fixation, the distraction osteogenesis process is initiated by surgical osteotomy, where after carefully controlled separation of the bone is performed to preserve the biological conditions for bone regeneration (33,34,37).

The latency stage typically lasts from 5 to 10 days depending on factors, such as age, site, diagnosis, medication, previous infection, irradiation, and smoking (38). First, in the latency stage, the blood clot created by the osteotomy starts to transform into granulation tissue with inflammatory cells and fibroblasts, which can be seen around day three (37). New capillaries combined with collagen are seen in the transforming blood clot, and mesenchymal stem cells are recruited from the bone marrow, periosteum, and endosteum, which later differentiate (34,37,38). Between days 5 and 10, the tissue at the osteotomy site matches that of a soft tissue callus found in a fracture and is inhabited by fibroblasts, chondroblasts, and osteoblasts (38). In the distraction stage, the bone ends of the osteotomy are distracted from each other at an appropriate rhythm and amplitude to gain new bone until the required length is reached (33,34,38). The mechanotransduction of distraction changes the healing process into distraction osteogenesis, in which the unorganized meshwork of collagen type I + II is transformed into an ordered network of predominately type I collagen alongside an angiogenic increase (33,34,37,38). Distraction organizes the tissue of collagen, chondroblasts, fibroblasts, and osteoblasts into a recognizable parallel pattern with four zones that are symmetrical around a center zone (33,34,38,39). Figure 2.2.2 shows the four zones of the regenerated bone.

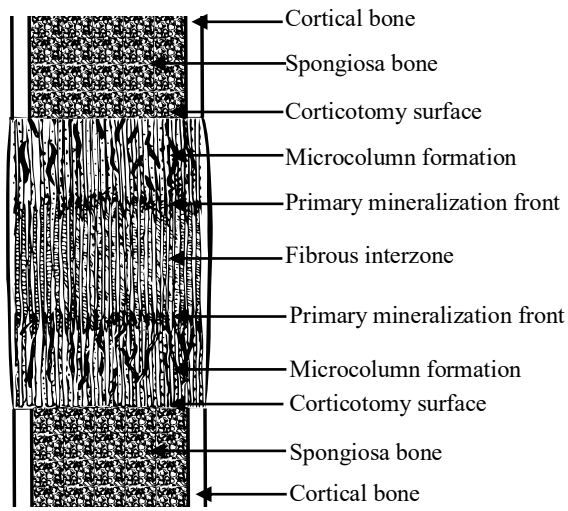

Figure 2.2.2: Four histological zones of the regenerated bone.
The zones of the regenerated bone are symmetrical around a central fibrous zone, which consists of organized, longitudinally oriented strands of collagen with spindle-shaped fibroblasts. The primary mineralization front contains osteoblasts arranged longitudinal together with undifferentiated mesenchymal precursor and fibroblasts. The zone of microcolumn formation has an increased number of osteoclasts in relation to its apposition and resorption. The corticotomy surface consist of early compact cortical bone. Partially made after Aronson et al. and Karp et al. (39,40)

The neoformation of bone tissue starts in the central fibrous zone under the influence of distraction and then mineralizes toward the osteotomy surface in a continuum (33,34,39). The distraction terminates when the required bone length is reached. At the end of the distraction stage, the regenerated bone comprises a continuum of unmineralized fibrotic tissue in the central fibrous zone over mineralizing tissue to woven bone in the peripheral zones (33,34,38).

The consolidation stage starts with the gradual mineralization of the unmineralized fibrous tissue. This is followed by further maturation and corticalization of the regenerated bone (37). When the regenerated bone has gained sufficient strength, the fixation can be removed, after which the bone remodeling continues (37).

2.3 EXTERNAL FIXATION

An external fixation system for bone stabilization is a mechanical device that is placed outside the body and fixated to the bone fragments with wires or half pins, thereby bridging the two bone fragments. External fixation systems can be divided into two groups: Ring fixation systems and uni-lateral bar systems. Figure 2.3.1 shows an example of both types of external fixation systems.

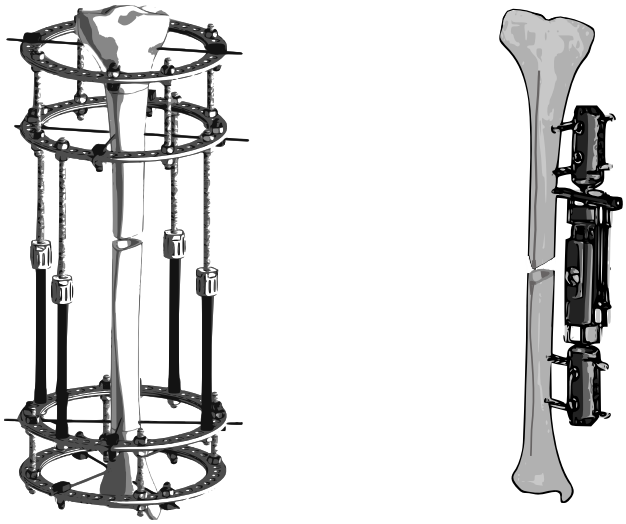

Figure 2.3.1: External bone fixation system.
Left: Tibia with osteotomy and stabilized with ring fixation system. Right: Tibia with osteotomy stabilized with uni-lateral bar system

The pioneers Putti and Wagner both used the uni-lateral bar system, and De Bastiani optimized one model with improved modular function for modern use (26). The “Ilizarov method” ring fixation system became popular and was further developed into a six-strut (hexapod) frame for improved gradual axis correction (30). However, external fixation systems are not without complications, and 1–3.2 complications per patient have been reported (41,42). Most

complications of bone lengthening with external fixation occur in the postoperative period, and patients may carry the frame for over one year of treatment (30). In external fixation, pin site infections are the most frequent complication, observed in up to 100% of the patients (30). However, these can often be treated with oral antibiotics and pin site cleaning (30). The pins can also produce scarring, muscle transfixation, and pain. The transfixation/tethering of the soft tissue is considered one mediator for the decreased range of joint motion observed during the treatment of bone lengthening with external fixation (43,44). Another contributor to the observed loss of joint movement is believed to be muscle tension produced during the lengthening (44).

Patients undergoing external fixation can bear weight during gait; however, the device frame is bulky and inconvenient to live with. This difficulty is likely greater for the ring fixation system than for a uni-lateral bar (due to its positioning between the leg) and greater for femoral fixation than for tibial (due to the increase in soft tissue at the femur). This might be why the patients wearing external frames seem to be socially disruptive for the family (45). Surgeons also report that the treatment affects the patients psychologically (45,46). Often, both the patient and surgeon strive to remove the external fixation as early as possible after the regenerated bone is fully consolidated. However, there are reports of both axial malalignment and fracture in the regenerated bone after the removal of the external fixation device (47,48). Many of these problems are, to a high degree, assumed to be related to external fixation.

2.4 LENGTHENING OVER NAIL

A technique combining an external fixator with an intramedullary nail was introduced to reduce the time in frame, with expectations of a reduction in complications (43,46). Bost and Larsen first described the

use of intramedullary nailing and temporary external fixation in 1956 (49). However, in 1997, Paley et al. presented the contemporary use of the intramedullary nailing and temporary external fixator combination for bone lengthening, showing a reduced external fixation time, reduced infection rate, and a faster return of knee movement compared with external fixation alone (50). Patients who underwent lengthening and then nailing showed a shorter time in the frame and a lowered bone healing index (46). This combination technique was probably a step on the way toward the intramedullary bone lengthening nail.

2.5 INTRAMEDULLARY LENGTHENING NAIL

With expectations of a reduction in complications and patient discomfort compared with conventional external fixations, the fully implantable intramedullary lengthening nail became the dream of many reconstructive orthopedic surgeons (26,51).

The first individual accredited for bringing the dream of a fully intramedullary lengthening device to life was the Ukrainian, Bliskunov, in 1983 (26). Yet, the Bliskunov lengthening device did not gain ground, maybe due to its inclusion of pelvic fixation or because it was not published in English. Instead, two other mechanical bone lengthening nails were introduced in 1999 and 2001, called the Albizzia (DePuy, Villeurbanne, France) and “Intramedullary Skeletal Kinetic Distractor” (ISKD) (Orthofix Inc.), respectively (52,53). These two devices work in a similar mechanical manner, whereby rotation of the leg, by either the patient or the doctor, provoked a distraction (26,53,54). The rotation of the Albizzia was painful, and the patients often needed to be anesthetized for repeated lengthening (54,55). The distraction mechanism of the ISKD was reported with difficulties of runaway and non-distracting nails (56–58). Today, neither of these two devices remain available, likely due to patients’ intolerance to the distraction mechanism and the mechanical failures (26).

The next step in development was the externally controlled motorized intramedullary bone lengthening nails. Report of the FITBONE® (Wittenstein Intens, Ingersheim, Germany) nail was the first published in 1999 by Baumgard et al., followed by the PRECICE® (Nuvasive, San Diego, CA, USA) nail that was released in 2011 (59,60).

The FITBONE nail is a motorized stainless steel lengthening nail in which a motor is hermetically sealed, and the motor torque is transformed through a gear and spindle to an axial lengthening movement of up to 80 mm, with a force of more than 1800 N (61,62). An antenna system delivers the motor energy through the skin via a high-frequency energy coupling (61,62). A subcutaneous antenna connected to the nail by a wire receives the energy from the external remote control unit (ERC) that controls the lengthening (61,62).

The PRECICE nail is a magnetically driven bone lengthening nail composed of medical-grade titanium alloy (Ti-6Al-4V)(63). The nail is driven by a magnet on a spindle, and the power is transferred through a gearbox to a coupling, which is attached to a threaded drive shaft that produces the axial lengthening (64). The gears and the magnet are sealed to isolate mechanical parts from the body fluid (63). The nail is lengthened by the use of the ERC, in which two magnets are rotated by a motor (64). These two rotating magnets magnetically couple and rotate the magnet in the nail spindle, thereby delivering the power for axial lengthening (63,64).

In the ten to twenty years since these two externally controlled motorized intramedullary bone lengthening nails were first introduced, with the expectations of a reduction in complication and improvement in patient comfort, more than 14,000 nails have been implanted worldwide (65).

3 COMPLICATIONS

Even with the high volume of research performed today, there is no consensus on the classification of surgical complications (66). Still, today the public and medical community look pejoratively upon complications (67). However, we should acknowledge the complications of any medical treatment and see it as an unfortunate event for the single patient, but also as important medical knowledge that is needed to improve treatments. Knowledge of complications is crucial for improving existing treatments and assessing new ones. It is, therefore, important to both quantify and qualify complications to interpret their possible etiologies. This gives us the potential to educate ourselves as medical workers and to inform our patients about the risks of their treatment (67).

3.1 CLASSIFICATION OF COMPLICATIONS

As complications of bone lengthening nails are the focus of this Ph.D. thesis, it raises the question: What is a complication? This question was also raised in recent CORR Insights by Sabharwal (68). To date, there is no standard definition of a surgical complication, and studies often assume that the readers know the definition (69). During my research in the field of bone lengthening, no gold standard or consensus for a definition or classification system has been identified. However, eight different classification systems on the severity of complications were encountered in the limited area of bone lengthening, and four of the classifications were used in studies of bone lengthening nails (70–77). The ninth reporting way, descriptive complication reporting, is frequently used, possibly because small cohort series are the most frequent study type (Study I). Table 3.1.1 presents the four

complication classification systems that have been used in bone lengthening nails (FITBONE/PRECICE) (Study I).

***Paley* (75)**

Grading	Problem	Obstacle	Minor true complication	Major true complication
Definition	Potential expected difficulty arising during distraction or fixation period which is fully resolved non-operatively by end of the treatment period.	Potential expected difficulty that arises during distraction or fixation period that is fully resolved by the end of the treatment period by operative means.	Complications include any local or systemic intra-operative or peri-operative complication, difficulty during distraction or fixation that remains unsolved at the end of treatment period, and any early or late post-treatment difficulty. The original treatment goal was achieved	Complications include any local or systemic intra-operative or peri-operative complication, difficulty during distraction or fixation that remains unsolved at the end of the treatment period, and any early or late post-treatment difficulty. The original treatment goal was not achieved

***Black et al.* (74)**

Grading	Grade I	Grade II	Grade IIIA	Grade IIIB
Definition	Minimal intervention required; treatment	Substantial change in the treatment plan; treatment	Failure to achieve treatment goal; no new pathology or	Failure to achieve treatment goal and/or new pathology or

	goal still achieved.	goal still achieved.	permanent sequelae.	permanent sequelae.

***Dahl et al.* (77)**

Grading	Minor	Serious	Severe
Definition: *Any unwanted event was considered a complication*	Complication did not affect outcome or require extensive intervention.	Complication that was either major and temporary or minor and permanent.	Complication that required major unplanned surgery or resulted in major permanent sequelae.

***Dinçyürek et al.* (76)**

Grading	Minor	Major	True complications
Definition	Could be remedied without the need for surgical intervention	Could only be remedied with another surgical intervention	Sequelae

Table 3.1.1: Four complication classification systems.
The four complication systems that have been used in studies of bone lengthening nails (FITBONE/PRECICE) are presented. The classification systems are arranged with the lowest (least severe) grading on the left and increasing to the right (more severe). The classification systems are arranged on top of each other with grading in the column. It does not mean that the grades in the same column of the different classifications are the same.

The classification systems in Table 3.1.1 appear to be quite similar. There are, however, differences between the classification systems that make comparison difficult. For example, in the grade of Problems and Obstacles, the Paley classification included the time element in which the complication occurred (75). This time factor was later removed (43,75). There are several advantages of a standardized and

scientifically tested method of grading surgical complications. First, it ensures a uniform way of reporting data (78). A classification might also offer a more effective perception of the study result and a more consistent and accessible comparison would be possible between studies and surgical centers (78). Furthermore, an accurate and reliable classification system would increase the quality of the reported results and allow for the early identification of areas of treatment practice that need improvement (78). A standardized classification system could also facilitate the development of risk scoring systems (78).

Bone lengthening is a complex and long treatment with multiple steps, of which the primary operation is the only the first part (See figure 2.2.1). All stages of limb lengthening require physical therapy and a clinical surveillance system. Particularly, during the distraction stage, physical therapy is used intensively to prevent joint contracture or joint subluxations, and patients are monitored regularly with radiographs and clinical follow-up. In the consolidation stage, the patients increase weight-bearing as the newly formed bone needs to be stimulated to consolidate for adequate strength. We have earlier shown that bone lengthening nails have a complication in 16% at or after nail removal (79). Therefore, we believe that the complete treatment period should be reported when investigating the overall risk of the treatment. This will be supported by the complication distribution over time presented in studies I and II. Complications in bone lengthening are reported to arise from numerous different origins, including the lengthening device, joints, and the bone (75). We have, therefore, separated the complication classification by severity and origin.

3.2 SEVERITY COMPLICATION CLASSIFICATION

The severity classification system chosen for the studies of this Ph.D. thesis was from Black et al. and is a modification of the one Cherkashin et al. used for external fixation (67,74). The classification was developed for bone lengthening and has, therefore, considered multiple aspects of its complication and treatment. It defines a

> "'complication' as an unpredicted undesirable deviation from the treatment plan, which without appropriate resolution will lead to a failure to achieve treatment goals or to the development of a new pathology" (67).

With this definition, a complication can be acknowledged at any point in the treatment (67). The classification unites the perception of a complication and its threat to the patient's treatment goal and the essential, timely intervention (67). The system is partly built on an empirical understanding that a complication not handled optimally will continue its progress in severity and that early intervention is less extensive than late intervention. Thus, the timing (recognition and start of intervention) of the intervention and its curative achievement on the complication determine the intervention's success (67). Even though a complication can be recognized early in the treatment, the grade can first be assessed at the end of the treatment since the complication is not graded based on the first presentation, but rather on the degree and the response to intervention as the complication develops (67). Because complications expectedly would evolve into severe complications, it is the correctness of the treatment of the complication that determines whether the complication has a minor or major impact on the overall treatment plan (67). Therefore, it is the success of the complication management that is categorized (67). Empirically, a more severe complication is harder to manage and would often be expected to result in a severe grade. Table 3.2.1 presents the complication severity grade

based on the magnitude of the required corrective actions and their outcome results (67).

Complication severity grade		Examples of complications
I	Minimal intervention required; treatment goal still achieved.	Temporary joint contracture was resolved by physiotherapy. Temporary failure of the nail to lengthen due to suboptimal placement of the external transmitter resolved by positioning the external transmitter at another site.
II	Substantial change in treatment plan; treatment goal still achieved.	Unplanned return to surgery, such as delayed consolidation requiring additional intervention and device problem needing revision.
IIIA	Failure to achieve treatment goal; no new pathology or permanent sequelae.	Premature consolidation with aborted lengthening, inability to tolerate lengthening, and fracture at fixation site or regenerate bone with shortening.
IIIB	Failure to achieve treatment goal and/or new pathology or permanent sequelae.	Joint subluxation, joint dislocation, regenerate fracture with deformity, and deep infection. Thromboembolic complications such as deep vein thrombosis.

Table 3.2.1: Complication severity classification system.
The classification system for grading complication was modeled after Black et al. Description and examples of the complication severity grade reproduced after Black et al.'s classification (74)(Study I)

3.3 COMPLICATION ORIGIN

In bone lengthening, the stretching of bone and surrounding tissues is the likely reason for the numerous sites from which complications can arise. In an article on complications, Paley described 11 main

complications of external fixation, which ranged from premature consolidation over joint luxation to neurological injury (75). To contrive a standardized grouping of complication origin, we have categorized origin into eight main groups (Soft tissue, Joint, Vascular, Bone, Neurology, Infection, Device-related, and Others) of areas/tissue from which complication can arise. In device-related complications, we adapted the classification from Lee et al., with a minor modification of attachment failure (80). The eight main groups are a rough division. Therefore, a further subgrouping was chosen, ending op with a total of 33 subgroups. In Table 3.3.1, the eight main groups and 33 subgroups of origin are described.

Main origin	Sub-origin	Definition
Soft tissue	Skin	Skin irritation related to incision, internal/ external devices, braces, or other treatment-related issues
	Muscles	Muscles irritation/ pain/ capturing/ rupture related to incision, internal devices, other treatment-related issues
	Tendon	Tendon irritation/ pain/ captured/ rupture related to incision, internal devices, other treatment related issues
	Pain	Pain-related to the treated extremity that is assessed to originate from the treatment
	Others	Other soft-tissue complications that are not classified in the above categories, including compartment syndrome
Joint	Pain	Pain-related to the joint above or below the treated bone
	Contracture	Reduced joint range of motion compared to start of treatment
	Subluxation	A subluxation of a joint is where a connecting bone is partially out of the joint

	Dislocation	A dislocation of a joint is a complete separation of the joints
	Others	Other joint complications that are not classified in the above categories
Vascular	Vascular damage	Blunt injury or penetrating injury to a major blood vessel causing thrombosis, bleeding, or permanent vessel damage
	Deep vein thrombosis/ Pulmonary embolism	Deep vein thrombosis refers to blood clots in large veins of the lower limb. Pulmonary embolism: Pulmonary embolism is a substance blockage of an artery in the lungs.
	Hemorrhage/hematoma	A hemorrhage is blood escaping from the circulatory system from damaged blood vessels. A hematoma is localized bleeding outside of blood vessels.
	Others	Other vascular complications not classified in the above categories
Bone	Premature consolidation	The regenerated bone forms a bone bridge between the two bone segments. The bridge stops lengthening, and an intervention more than standard lengthening is needed
	Delayed healing	Slow consolidation of the regenerated bone or non-union as the end stage of slow consolidation.
	Secondary malalignment	Occurrence of new bone malalignment
	Fracture	A partial or complete break in the continuity of the bone
	Others	Other bone complications not classified in the above categories
Neurology	Paresthesia	An abnormal dermal sensation with no apparent physical cause and of transient time

	Paralysis	Loss of muscle function in one or more muscles and/or sensory disturbances in the affected area. Can be permanent or transient
	Others	Other neurological complications that are not classified in the above categories
Infection	Superficial soft tissue	Clinical soft tissue infected above the fascia
	Deep soft tissue	Clinical soft tissue infected below the fascia
	Osteomyelitis	Infected bone marrow
	Others	Other infectious complications not classified in the above categories
Device-related (modified) (80)	Distraction mechanism-related	Runaway, difficult to distract, non-distracting, non-functioning, and running back
	Mechanical strength	Nail/ring/bar bending or breakage. Rotational instability
	Attachment failure	Failure screw / wire / pins failure
	Other	Other device-related complications that are not classified in the above categories. It could be corrosion, tissue reaction
Others	Patient	Patient-related complications that cannot be classified elsewhere
	Surgical	Surgically related complications that cannot be classified elsewhere
	Others	All other complications that cannot be classified elsewhere

Table 3.3.1: Types and subtypes of complication origins. Description and definition of the main types and subtype of complication origin. Reproduced after Study I.

4 AIM

The overall aim of this Ph.D. thesis was to investigate complications related to treatment with externally controlled bone lengthening nails, focusing on the frequency, severity, origin, and time point of complications.

4.1 STUDY I – SYSTEMATIC REVIEW

Aim: To perform a systematic review of the literature on bone lengthening nails and extract information on the complications to assess their timing, frequency, severity, and origin.

Hypothesis: It was hypothesized that complications occur in more than 25% of the lengthened segments, among which joint- and device-related complications are the most prevalent.

4.2 STUDY II – COHORT SERIES

Aim: The primary aim of this study was to determine the incidence, severity, and origin of complications in a consecutive cohort series receiving bone lengthening nails (FITBONE and PRECICE) from two surgical centers. The secondary aim of this study was to investigate potential risk factors for complications in the cohort.

Hypothesis: We hypothesized an incidence of one complication for every three segments lengthened. Furthermore, we hypothesized that device-, bone-, and joint-related complications occurred most frequently. Regarding the secondary aim, we hypothesized that complications of bone lengthening nails increased with age and

increased lengthening, and were more prevalent in the tibia compared to in the femur, for the retrograde femur approach compared to antegrade femur approach, for acute deformity correction compared to non-correction, for short status patients than other patient groups, and for FITBONE compared with PRECICE nails.

4.3 STUDY III - AGREEMENT STUDY

The aim of the study was to test the inter- and intra-rater reproducibility of the complication severity grading and origin categorization used in studies I and II. The reproducibility was tested in the following two ways: retrieved cases from the literature were analyzed as in study I; then, patient charts cases were analyzed as in study II.

Hypothesis: It was hypothesized that the inter-and intra-rater reproducibility for the severity grading and origin complication classification would reveal a kappa estimate above 0.51, indicating good strength.

5 METHOD

The purpose of research methodology is to limit the potential data pollution that may obfuscate the association between the independent and dependent variables (81). Therefore, data for research are only valuable if the data correctly represent the true value for the variables under investigation (81). In the three studies of this Ph.D. thesis, we have worked to achieve valuable data in all three methodologies. In study I, the literature of bone lengthening nails was systematically examined for complications. From this literature, data on complications were collected and evaluated to assess the overall complication risk and the origins of complications. A retrospective multicenter study was performed in study II, wherein the cohort's incidence and origins of complications were established and used to identify risk factors. Study III was performed as a reliability study of the classification systems concerning severity and origin of complications used in assessing the complications in Study I and II.

5.1 ETHICAL CONSIDERATIONS

Study II and III implicate access to patient charts, and here, all data was handled according to Danish law. North Denmark Region approved the conduction and storing of data with project registration number: 2020-157. The identifiable patient data was kept in the Redcap database. Extraction of data at Nationwide Children's Hospital (NCH), Ohio, USA was granted a local institutional approval (Institutional approval numbers: 2020-157 and STUDY00000908).

5.2 STUDY I – SYSTEMATIC REVIEW

A structured study approach of the systematic review stages was used to ensure a consistent and reproducible study result. We consulted the reporting guidelines (PRISMA/MOOSE) of systematic reviews during the planning and in the reporting of the review to secure an optimal reporting outcome (Study I) (82,83). To ensure transparency of the review's aim and methods, the protocol was published on the PROSPERO database, with the registration number (CRD42020159272) (PROSPERO registration of paper/Study I under Appendices).

A systematic literature search of the PubMed, Embase, and Cochrane Library electronic databases was performed in November 2019 with the help of an expert health science librarian. The comprehensive search strategy/string and the search restrictions are available in supplementary 2 for Study I (Study I).

The search results and studies identified through other sources (authors database and included article references) were assembled and screened in the online Covidence platform (84).

Studies that reported on lower extremity bone lengthening with the use of FITBONE and/or PRECICE nails were included. Second, the origin, severity, and management of complications or a statement of no complications were obligatory. Studies of bone transport treatment, compression nails, non-lower extremities lengthening, or stump lengthening were excluded.

Screening of the abstract and full text was performed by the Ph.D. student, and in collaboration with the senior author, inclusion criteria were assured before final inclusion in the review. The same approach was performed for data extraction and grading on complications. Table 5.2.1 presents the data extraction points.

Information group	Extraction parameters
Study information	Title, author(s), year of publication, study design, evidence level
Participants	Number of patients, number of lengthening segments, sex, age range, etiology (after Stricker and Hunt (22)), range of leg length discrepancy, bone segments (femur or tibia).
Surgery	Nail type (FITBONE or PRECICE) Perioperative soft tissue release
Complication	Timing of the complication in the treatment course (Supplementary 1 of Study I). Complication description.

Table 5.2.1: Data point extraction of the systematic review

Two grading systems for uniform reporting of complications were used: one for severity and another for origin. The classification of Black et al. was used for severity, while a categorized system of eight main groups and 33 subgroups was composed for complication origin (74)(see Table 3.2.1 & Table 3.3.1). Since a subset of the complications was graded with the Paley classification system, we established a method to merge the Paley classification into the Black et al. classification (see Table 1 of Study I) (74,75). For example, we defined deep vein thrombosis as grade IIIB; an intra-articular protruding nail causing irritation or residual deformity after lengthening was categorized as Others/Surgical; and bone lengthening termination by patient request was categorized into the origin of Others/Patient.

For the quality assessment, two orthopedic surgeons assessed the included studies and graded them using three tools. First, the levels of evidence were graded using the Oxford Centre for Evidence-Based Medicine—Levels of Evidence 2009 grading of Harm. Second, the Methodological Index for Non-Randomized Studies (MINORS) for non-randomized studies and Murad et al. evaluation for case reports was used for a general quality assessment score (85,86) (Supplementary I for study I). The third was a subset of questions that focused on harm

based on the McHarm scale (87,88) (Supplementary I of Study I). Disagreements in quality assessment were solved through discussion.

STATISTICS

Data storage and descriptive analysis were performed using Microsoft Excel 2019 version 16.33 (Microsoft Corp, Redmond, WA, USA). The demographic and complications are described by an absolute number, range, and/or percentage.

5.3 STUDY II – COHORT SERIES

This study employed a retrospective design with combined case series from two hospitals: Aalborg University Hospital (AAUH), Denmark and Nationwide Children's Hospital (NCH), Ohio, USA (Institutional approval numbers: 2020-157 and STUDY00000908). Only completed cases (defined as the nail had been removed) of bone lengthening treatments with PRECICE or FITBONE nails were included. Exclusion criteria were stump lengthening nails, bone transport nails, PRECICE STRYDE, nail insertion or removal at another hospital than NCH or AAUH, compression nails, non-intramedullary lengthening, or lengthening nails in the upper extremities. Treatments were performed in AAUH from 2005 to 2021 and in NCH from 2017 to 2020. The following study information was identified using the patient charts: sex, age at nail insertion, other surgical procedures at nail insertion, and clinical pre-operative limb length discrepancy (short stature patients were reported as zero). Etiology was classified as developmental, short stature or congenital, or posttraumatic after the Stricker and Hunt classification with the added category of Unknown (Stricker and Hunt 2004)(Study II). The number of days from nail insertion to nail removal was considered the duration of implantation, and the number of days

between nail insertion to the last follow-up was considered the length of follow-up.

The osteotomy was assessed for deformity correction at the first x-ray after nail insertion: a lack of cortical alignment in the sagittal or frontal x-ray was defined as an osteotomy with deformity correction (for example see figure 5.3.1.). Nail information was categorized by nail type (FITBONE, PRECICE), nail approach (femur: antegrade/retrograde, tibia: antegrade/suprapatellar), and site (femur/tibia). The total regenerated bone length (in mm) was measured using X-ray: [End length of telescopic part – length of the telescopic part at nail insertion]. If a patient underwent lengthening treatment of more than one bone, such as lengthening of multiple- or sequential-bone segments, the patient was categorized as having multiple segments.

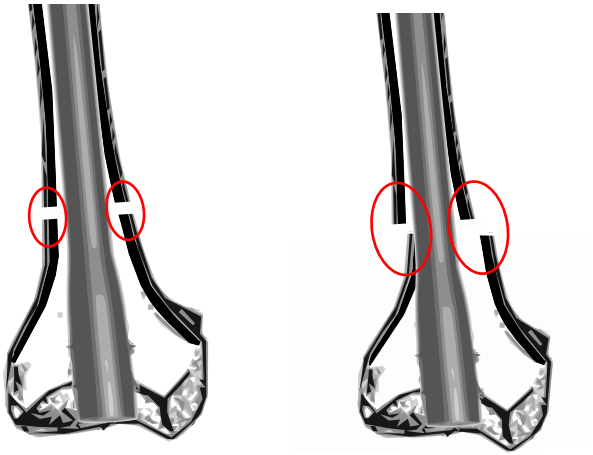

Figure 5.3.1: Cortical alignment at X-ray after osteotomy.
At the first X-ray after nail insertion, deformity correction was assessed by cortical alignment. A schematic example of distal femur in the frontal plane with osteotomy and retrograde femur nail is shown. Left: Cortical alignment was assessed at red circles (no deformity correction). Right: Non-cortical alignment was assessed at the red circles (deformity correction).

The severity of complications was classified according to the system by Black et al. (Table 3.2.1) (74). The following complications were

defined as a grade IIIB complication: deep vein thrombosis, osteomyelitis, and joint subluxation/luxation (Study II). The occurrence of treatment complications was allocated into six periods: (a) intra-operative, (b) post-operative before distraction, (c) distraction period, (d) after the end of distraction and before nail removal, (e) at nail removal, (f) after implant removal (Study II). The manufacturers of both the FITBONE and PRECICE nails recommend mandatory nail removal (89,90). A standard schedule and uneventful nail removal was, therefore, not classified as a complication.

The origin of complications in study I were classified into eight main groups and 33 subgroups (table 3.3.1) (study I). The applying predefined set of interpretations can be seen in Appendix 2 of Study II.

STATISTICS

The data collection of the two units (NCH and AAUH) was performed separately and recorded into two identical Electronic Data Capture tools (REDCap). Data were merged after anonymization and subsequently analyzed using Stata/MP 15.1 (StataCorp, College Station, TX, USA). Significance levels were set at 5%, and 95% confidence intervals (CI) were used.

Complications and demographics were presented after their sample distribution. The mean and standard deviation (sd) or range and median and interquartile range (IQR) are used to denote continuous variables, as appropriate. A quantile-quantile (QQ)-plot was used to assess the normality of continuous variables. Categorical variables are described by count, fraction, or percentage. A modified Poisson regression (RR: relative risk) with robust confidence intervals was used to assess the possible risk factors of complications in the cohort that underwent bone lengthening (91). A yes or no response for complication was fabricated

for each segment as the dependent variable. To avoid correlation bias due to multiple-segment lengthening in some patients, one segment per patient was chosen at random (using a pseudo-randomization algorithm) and included in the risk analysis (Study II). A predefined hierarchical testing approach was used to select and investigate risk factors, adjusting variables. Regarding the analysis of risk factors, the patients were grouped by decades of age (from 10 to 60 years), except for individuals aged 60 years and above, who were grouped together to ease interpretation (Study II). When adjusting for age, age was considered to continuously increase power.

5.4 STUDY III – AGREEMENT STUDY

In the agreement study, four raters assessed two groups of 49 cases, comprising article and cohort complication cases (one cohort case was excluded due to a double-entry error). The cohort and article cases of complications with bone lengthening nails were rated twice by all raters at a minimum interval of six weeks. The cases were selected to address the full range of complication severity in multiple origins. The article complications cases were selected from 41 papers included in the systematic review (Study I). The cohort complication cases were selected from the AAUH subpopulation from Study II. A REDCap database presented the text of the same cases from the article or cohort cases for the raters. REDCap handled the rater's assessment with push-button registration. In the article cases, the paper's text description was copied into REDCap, and in the cohort cases, the patient's charts were copied into REDCap in an anonymous form. All complications were classified by severity and origin via the classification system used in Study I-II (table 3.2.1 and 3.3.1). The grade IIIB diagnosis definition and origin description used in study II were adopted into this study (study II).

Rater A (MM), a senior reconstruction orthopedic surgeon with eight years of experience in bone lengthening, had some experience with the severity classification from a previous small cohort study but no experience with the origin classification (92). Rater B (M.F.), a pediatric orthopedic surgeon with two years of knowledge and expertise handling bone lengthening nail patients, was introduced to the severity and origin classification system at the pre-study workshop. Rater C (MWF) had no clinical experience with bone lengthening nails but had comprehensive research experience with the complications of bone lengthening devices. Rater D (S.K.) was a clinical professor and consultant with more than ten years of experience in bone lengthening. Both raters C and D had extensive experience with the severity and origin classification from a previous review study (Study I).

In a pre-study workshop, the two classifications systems and the assumptions for article/cohort cases were explored through seven review cases and five cohort cases to achieve a uniform rater assessment. A written guideline was created at the end of the workshop and distributed to the raters. To obtain an independent assessment of the cases, each rater was instructed not to communicate about the study/ratings and was blinded from their previous assessments and the other observer ratings.

STATISTICS

The classification system of severity and origin used in study III produced categorical data. The kappa estimate and its modifications have become recognized methods of evaluating observer agreement for categorical data (93). Thus, we presented the intra- and inter-rater agreement of the article and cohort cases as the Cohen/Congers kappa estimate and accompanied it with percent agreement. The kappa estimate is comparable to correlation coefficients in regards to the range

from –1 to 1 (81). A value of one denotes perfect agreement, and a value less than one indicates disagreement between raters. A kappa value close to 0 is interpreted as agreement observed by random chance, and kappa values below 0 can emerge but are unlikely in practice (81). There are no gold standards to assess the strength of the kappa agreement; nevertheless, two different standards (those of Landis and Koch and Svanholm et al.) have become widespread in orthopedics and other parts of medicine (93). For this agreement study, we report the strength of the kappa estimate in relation to the Svanholm et al. standard (94).

6 RESULTS

6.1 STUDY I – SYSTMATIC REVIEW

The literature search recognized 952 articles, among which 41 were included in the review. The article selection flowchart is depicted in figure 6.1.1.

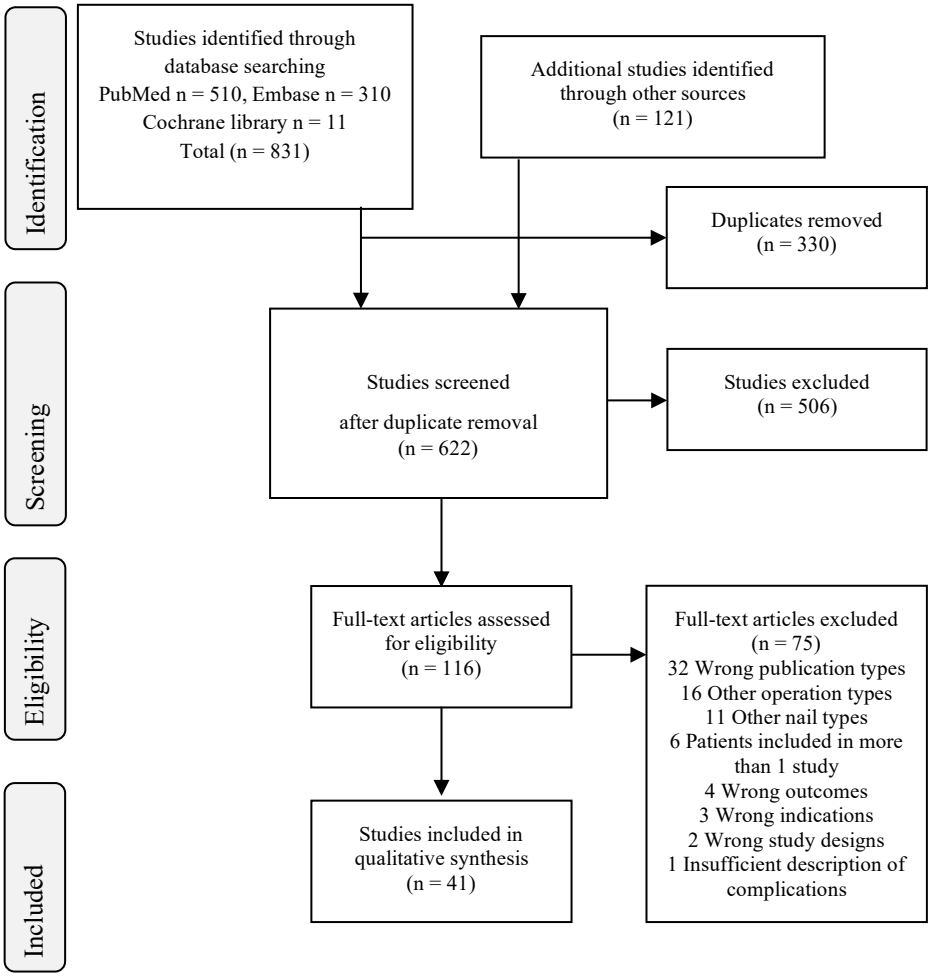

Figure 6.1.1: Articles selection.
Flow diagram of the selection of articles. The figure is reproduced after

Study I.

The study types comprised 26 case series, eight case reports, six cohort studies, and one case-control study. Seventeen percentage (7/41) of the studies had prospective collected data. The MINORS score of the comparative studies was 15.1, and that of the non-comparative studies was 8.3 (for a total score of the studies, see supplementary data 1 for Study I). In relation to McHarm's question, 31 studies numbered every complication and specified the total number of complications (87,88). Fifteen studies used a standard complication scale, and only one study included predefined/standardized descriptions of the complications (see supplementary I of Study I).

The study included 332 complications corresponding to 34% of the 983 bone lengthening segments (14 complications were not classified with an origin but only with severity (study I)). Table 6.1.1 presents the demographic data of the included patients.

	Numbers	**Numbers of studies reporting data**
Number of patients	782	41
Number of bone segments	983	41
Male / female	384/234	29/33
Age. Min / Max	8/74	39
Etiology		
-Congenital disease	208	22
- Short stature	111	14
-Acquired/developmental LLD	305	29
Femur / Tibia	813 /170	40/28
Bone lengthening cm min/max	1 /14	35/35
FITBONE® / PRECICE® nails	214 /747	15/27

Table 6.1.1: Demographic data of the review study.
Demographic data collected from the studies reporting group-level data. Data regarding sex were unidentified for 164 patients, and that of etiology

was unidentified for 158 patients; 22 nails could not be differentiated between FITBONE® or PRECICE®. (Table reproduced after Study I).

A total of 113 type I and 146 type II complications were disclosed in the review, corresponding to 11% and 15%, respectively, of the complications per segment. Failure to achieve the lengthening goal (type IIIA complication) was observed in 5% of the segments (45 cases). Type IIIB complications were reported in 28 cases, meaning that 3% of segments had new pathology or permanent sequelae.

The most frequent complication origin was device-related complications, seen in 12% of segments, followed by bone origin at 8%. Table 6.1.2 presents the number of complications (for detailed distribution on the 33 subtypes, see table 5 Study I).

Complication origin type	**Sum**	**% Of segment**
Soft tissue	13	1%
Joint	61	6%
Vascular	10	1%
Bone	78	8%
Neurology	8	0.8%
Infection	8	0.8%
Device-related	122	12%
Others	18	1.8%

Table 6.1.2: Origin of complications in the review study
Complications presented as the absolute number and percentages per segment in the eight main groups. (4.2% of the complications were not classified with an origin, only severity). Table reproduced after Table 5 in study I.

In 12% (5/41) of the studies, systematic soft-tissue release during primary surgery was reported (95–99). Yet, in 53% (177/332) of the complication cases, the timing of complication could be established

(Table 6.1.3). Furthermore, none of the included studies systematically described the timing of the complication.

Timing of complication in treatment	Sum	% of (N=177)
Intraoperative complication	6	3.4%
Post-operative complication prior to distraction start	5	2.8%
Distraction period	85	48.0%
After end of distraction and prior to implant removal	81	45.8%
After implant removal.	0	0

Table 6.1.3: Presentation time of complications in the review study. The timing of the Complications presented as the absolute number and percentages of complication (N=177, number with available time point of complication).

6.2 STUDY II – COHORT SERIES

Out of a consecutive cohort series of 393 segments treated with bone lengthening nails, 314 completed treatment, including removal of the FITBONE or PRECICE nail in the lower limb. The seventy-nine segments were excluded according to exclusion criteria (Treatment not ended: 30; Bone transport nail: 15; PRECICE STRYDE: 15; Humerus lengthening: 6; Extramedullary lengthening: 5; Stump lengthening: 4; Lost to follow up: 4). The median age of the 257 patients was 19.5 years. Table 6.2.1 summarizes the demographic data.

		Total number of segments		The unique selected group of segments used for risk analysis	
		n	(n/N)	n	(n/N)
Total number of lengthened segments (N)		314		257	
AAUH, Denmark		279	87.2%	223	86.8%
NCH, USA		35	12.8%	34	13.2%
Patients		257		257	
Patients with multiple segments **Number of lengthened segments = number of patients**		35 2=24 3=3 4=7 7=1	13.6% (N=257)	0	
Sex	Male	165	52.6%	143	55.6%
	Female	149	47.5%	114	44.4%
Age at nail insertion median *(IQR)[min/max]*		19.5	(16.4:29.9) [9.5:76.9]	19.5	(16.4:33.6) [9.5:76.9]
LLD Etiology	Congenital	64	20.4%	61	23.7%
	Acquired/develop-mental	143	45.5%	133	51.8%
	Short stature	69	22%	25	9.7%
	Unknown Etiology	38	12.1%	38	14.8%
Pre-op limb length discrepancy (short stature is not included)		3.1	(2.5:4) [1:14]	3	(2.5:4) [1:13]
Other procedure at primary surgery	No	161	51.3%	130	50.6%
	Yes	153	48.7%	127	49.4%
Duration of implantation (days) *median (IQR)[min/max]*		410	(336:632) [45:2372]	393	(329:569) [45:2166]

Length of follow-up (days) *median (IQR)[min/max]*		646	(478:1073) [176:3718]	583	(471:885) [176:3718]
Previous lengthening in the same patient.	None	248	79%	214	83.3%
	Segment	32	10.2%	24	9.3%
	Limb	34	10.8%	19	7.4%
Angle correction in frontal or sagittal plane:	No	234	74.5%	193	75.1%
	Yes	80	25.5%	64	24.9%

Table 6.2.1: Demographic data of the cohort study.
Demographic data presented as absolute numbers, percent (100·n/N), and/or median (IQR)[minimum/maximum]). The total number of segments was 314. The unique selected sub group of segments used for risk analysis: The unique group was selected randomly to ensure that every patient was only represented once. LLD: limb length discrepancy (table reproduced after Study II).

Among the 314 segments included in the consecutive series, 35 and 279 segments were treated at NCH and AAUH, respectively. Most lengthening procedures were performed in the femur (79.9% of the total number of segments), and the FITBONE nail was predominantly used (74.5% of the total number of segments). Table 6.2.2 presents information on the included nails.

		Total number of segments (n=314)		The unique selected group of segments used for risk analysis (n=257)	
Nail site:	Femur	251	79.9%	208	80.9%
	Tibia	63	20.1%	49	19.1%
Laterality	Right	157	50%	130	50.6%
	Left	157	50%	127	49.4%
Nail type	FITBONE	234	74.5%	191	74.3%
	PRECICE	80	25.5%	66	25.7%
Nail appro-ach	Antegrade femur	41	13.1%	37	14.4%
	Retrograde femur	210	66.9%	171	66.5%
	Antegrade tibia	56	17.8%	44	17.1%
	Suprapatellar	7	2.2%	5	2%
Length of inserted nail (mm) (n=303) *median (IQR)[min/max]*		245	(225:245) [115:365]	245	(225:245) [115:365]

Table 6.2.2: Nail demography of the cohort-study.
Nail demography data are presented as absolute numbers and percentages of the total number in the group. Data are presented as median (IQR) [minimum/maximum]. Selected group of segments used for risk analysis. The unique group was chosen by random selection to ensure that every patient was only represented once. Reproduced after study II.

Most complications occurred in the “Distraction period” (45.9%), followed by those occurring “After the end of distraction and prior to nail removal” (31%) and “After implant removal” 14.9%, whereas those in the “Intra-operative” period, “Post-operative before distraction,” and “At nail removal” accounted for 1.9%, 2.6%, and 3.7%, respectively, of the total complications.

We observed that device-related complications were most frequent, followed by joint and bone complications, respectively. Table 6.2.3 presents the distribution of complications distributed after origin.

Complication origin type	Sum	% Of segment
Soft tissue	11	4%
Joint	72	23%
Vascular	3	1%
Bone	37	12%
Neurology	7	2%
Infection	17	5%
Device-related	100	32%
Others	22	7%

Table 6.2.3: Origin of complications in the cohort-study. Complications presented as absolute numbers and percentages per segment in the eight main groups. Table reproduced after Study II.

For detailed results of the distribution of complications into main plus subtype origins, see table 4 in study II.

The risk analysis based on observed complications showed that higher age had an increased risk for complications compared to the baseline group (10–19 years). Table 6.2.3. presents the results of the adjusted risk model. The 20–29-year-old age group also showed a lower RR when compared to the older age groups. When comparing the 20–29-year-old age group to the 30–39- and 40–49-year-old age groups, we found RR values of 0.72 CI (0.50: 1.04; p = 0.086) and 0.77 CI (0.51:1.16; p = 0.211), respectively, while when compared with the 50–59- and ≥60-year-old age group, we found RR values of 0.55 (CI: 0.39;0.78; p = 0.001) and 0.63 (CI: 0.41; 0.95; p = 0.029), respectively. This demonstrates that the 20–29-year-old age group had a reduced risk of complications compared with that of the older age groups.

	Adjusted model				
Age *	RR	Std. Err.	P	CI	
10-19	1 baseline				
20-29	1.39	0.24	.06	0.99	1.94
30-39	1.91	0.36	<0.001	1.33	2.75
40-49	1.80	0.37	.005	1.20	2.71
50-59	2.50	0.45	<0.001	1.77	3.55
Age³60	2.21	0.47	<0.001	1.46	3.36
Nail type #	RR	Std. Err.	P	CI	
FITBONE	1 baseline				
PRECICE	0.72	0.11	.040	0.53	0.99
Etiology #	RR	Std. Err.	P	CI	
Unknown	1 baseline				
Congenital	1.19	0.28	.445	0.76	1.89
Acquired/level	1.12	0.23	.575	0.75	1.66
Short stature	1.99	0.43	.002	1.29	3.04
Bone*	RR	Std. Err.	P	CI	
Femur	1 baseline				
Tibia	1.59	0.17	<0.001	1.30	1.95
Primary osteotomy correction $	RR	Std. Err.	P	CI	
No-correction	1 baseline				
Correction	1.26	0.15	.043	1.01	1.59
Femur nail approach €	RR	Std. Err.	P	CI	
Antegrade	1 baseline				
Retrograde	0.99	0.21	.945	.63	1.50
Previously bone lengthening $	RR	Std. Err.	P	CI	
No lengthening	1 baseline				
At the extremity	1.34	.26	.129	.91	1.96
At the Bone	1.04	.20	.834	.71	1.52

Total bone length gained #	RR	Std. Err.	P	CI	
Length gained	1.01	.004	.002	1.00	1.02

Table 6.2.3: Modified Poisson regression model of relative risk.
The unique group was chosen by random selection to ensure that every patient was only represented with one segment for the data foundation. A depending variable: Complication, yes or no for each included observation. A modified Poisson regression model with robust confidence intervals described the relative risk of a complication developing during bone lengthening (91). * Adjusted for etiology and nail type, # adjusted for age (continuously variable), $ adjusted for etiology and age (continuously variable), € adjusted for hospital, etiology, and age (continuously variable). Age³60=Patients above 60 years. Table reproduced after study II. For crude model, see study II

The adjusted risk model showed that an increased risk for complication was significantly associated with the FITBONE nail, tibial bone, correction osteotomy at primary surgery, short stature, and increasing achieved bone length.

6.3 STUDY III – AGREEMENT STUDY

We found good inter-rater agreement, with a kappa estimate of 0.64 CI (0.53:0.75), for the assessment of the complication severity for the published article cases (Table 3, study III). Figure 6.3.1 presents the kappa estimates of the severity grading.

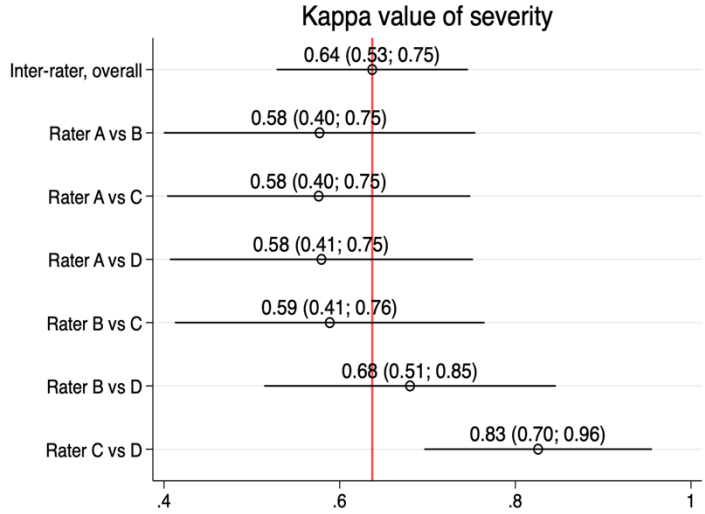

Figure 6.3.1: Review cases inter-rater agreement of severity.
The kappa estimate on complication severity grading with conditional confidence intervals for all raters and between raters of the review cases. The red line is the kappa value of overall inter-rater agreement.

The inter-rater evaluations of the main type and main plus subtype origins showed kappa estimates of 0.80 CI (0.72:0.89) and 0.74 CI (0. 64:0.83), respectively, with a CI ranging from good to excellent agreement. In figure 6.3.2, the kappa results of the main plus subtype origins are presented.

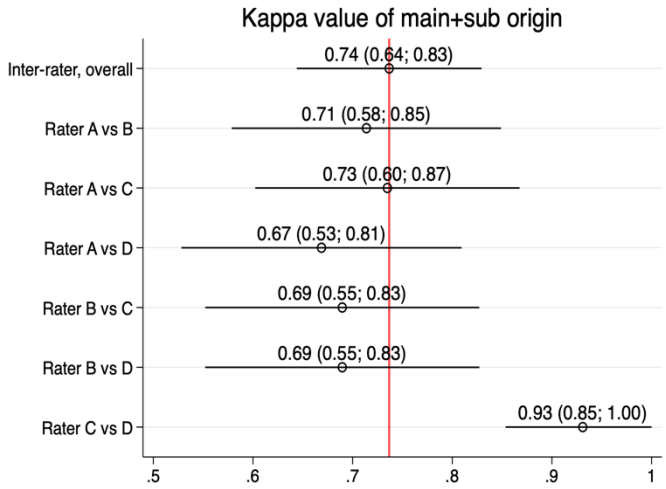

Figure 6.3.2: Review cases inter-rater agreement of origin.
The kappa estimates of the main plus subtype complication origins are presented with conditional confidence intervals for all raters and between raters of the review cases. The red line is the kappa value of overall interrater.

Raters C and D showed the highest agreement in severity and main plus subtype origin grading, and Raters A and D had the lowest. An excellent agreement was observed in the intra-rater assessment of severity and main plus subtype classification with a kappa estimate of 0.78 CI (0.70:0.85) and 0.77 CI (0.71:0.83), respectively. However, the CI indicated good-to-excellent intra-rater agreement. Figures 6.3.3 and 6.3.4 present the intra-rater kappa value on severity and origin of main plus subtype grading in the article cases (Table 5, study III).

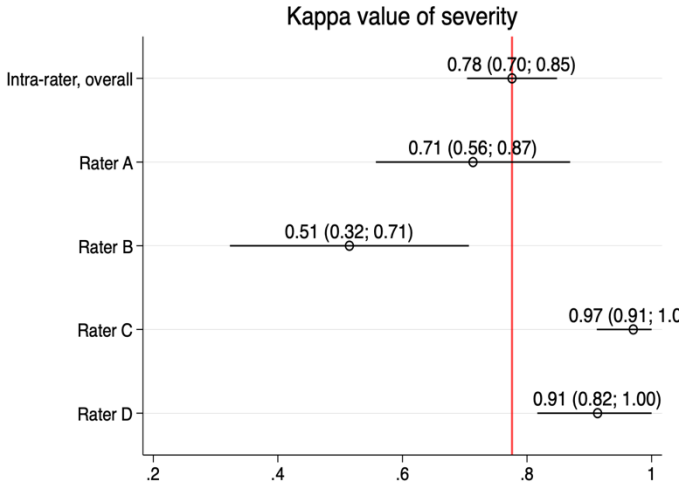

Figure 6.3.3: Review cases intra-rater agreement of severity.
The intra-rater kappa estimate on complication severity grading with conditional confidence intervals for all raters and each rater of the review cases. The red line is the kappa value of the overall intra-rater agreement.

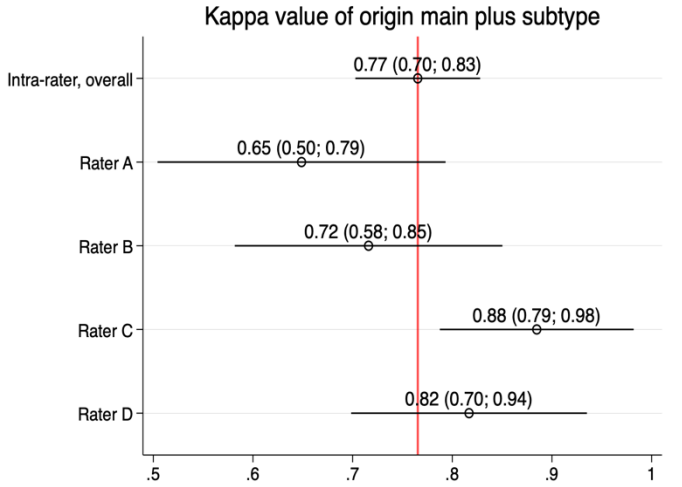

Figure 6.3.4: Review cases intra-rater agreement of origin.
The intra-rater kappa estimate on main plus subtype grading with conditional confidence intervals for all raters and each rater of the review

cases. The red line is kappa value of overall intra-rater agreement.

A kappa estimate of 0.68 (CI 0.56:0.79) for severity and of 0.63 (CI 0.53:0.73) for main plus subtype origin was observed for the inter-rater agreement of the cohort cases, which the CI interpreted as good-to-excellent agreement strength (Table 2 Study III). The inter-rater kappa value on the severity and main plus subtype origin grading in the cohort cases is presented in Figures 6.3.5 and 6.3.6.

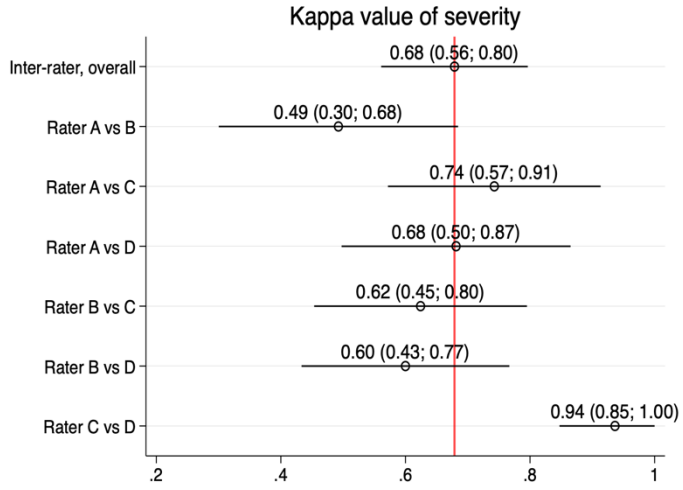

Figure 6.3.5: Cohort cases inter-rater agreement of severity.
The kappa estimate of severity grading of the complications presented with conditional confidence intervals for all raters and for between raters of the cohort cases. The red line is the kappa value of the overall inter-rater agreement.

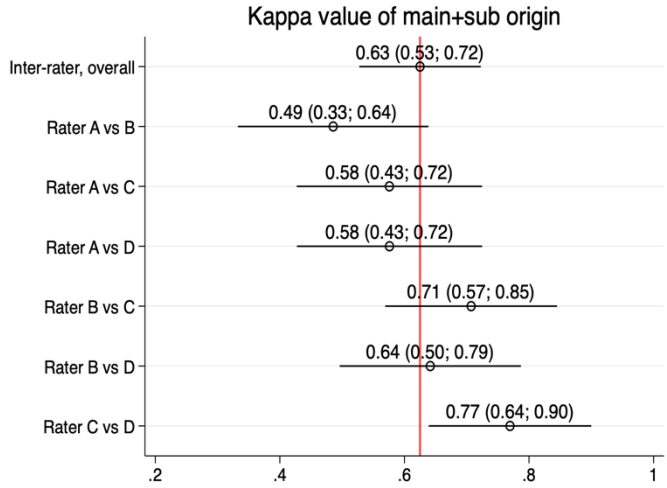

Figure 6.3.6: Cohort cases inter-rater agreement of origin.
The kappa estimate of complication origin graded by main plus subtype is presented with conditional confidence intervals for all raters and between raters of the cohort cases. The red line is the kappa value of the overall inter-rater agreement.

Raters A and B had the lowest kappa agreement between raters, while Raters D and C had the highest agreement. A good-to-excellent agreement was found in the intra-rater agreement of the cohort cases, with a kappa value of 0.74 (CI 0.66:0.82) and 0.70 (CI 0.63:0.76) for severity and origin, respectively. Figures 6.3.7 and 6.3.8 present the results of the intra-rater agreement of severity and main plus subtype origin grading (Table 4 study III). Agreement results on the main origin only, including the observed agreement of all kappa estimates and the unconditional CI for inter-rater agreement, can be seen in Table 2-5 Study III.

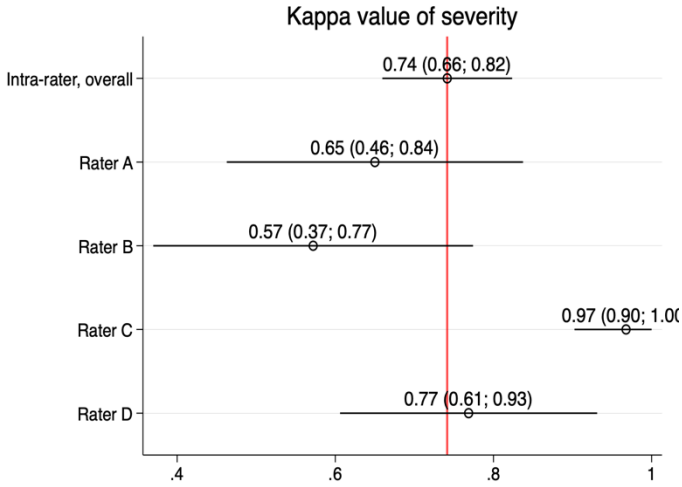

Figure 6.3.7: Cohort cases intra-rater agreement of severity.
The intra-rater kappa estimate on complication severity grading with conditional confidence intervals for all raters and each rater of the cohort cases. The red line is the kappa value of the overall intra-rater agreement.

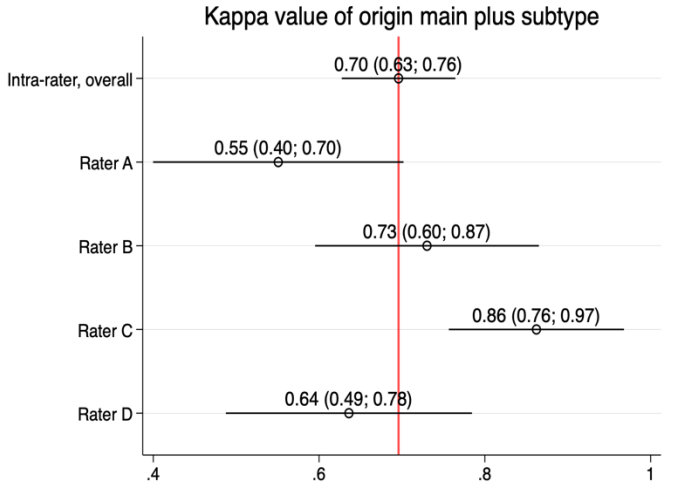

Figure 6.3.8: Cohort cases intra-rater agreement of origin.
The intra-rater kappa estimate on main plus subtype grading with conditional confidence intervals for all raters and each rater of the cohort cases. The red line is the kappa value of the overall intra-rater agreement.

7 DISCUSSION AND LIMITATIONS

7.1 STUDY I – SYSTEMATIC REVIEW

This systematic review shows that complications occurred in 34% of lengthened segments. Our primary outcome for type IIIB complications was observed in 3% of the segments, resulting in a new pathology or permanent sequelae. Furthermore, 15% of the segments required unplanned re-surgery (type II complication), and 5% did not accomplish their lengthening goal due to a complication (type IIIA complication). Complications that needed minimal intervention to achieve the lengthening goal (type I complication) were noted in 11% of the segments.

Most complications occurred during or after the end of distraction (45% and 48%, respectively). Only 3.4% and 2.8% of the complications occurred in the intraoperative period or prior to distraction (Table 6.1.3). This emphasizes that focus on the detection of complications is paramount during the stages of distraction and consolidation. The study shows that the origin of complications is highly diverse, as shown in Table 6.1.2 (Table 5 of Study I). The most prevalent complication origin was device-related, observed in 12% (122/983) of the segments; 1% of those segments did not reach the lengthening goal (type IIIA). These results indicate that there is room for improvement in the technology of bone lengthening nails. Ideally, complications due to mechanical strength and distraction mechanism should be negligible. Therefore, current bone lengthening nails are still being improved upon, and new nail designs will be introduced. We encourage future studies to report their specific nail type and generation to facilitate risk assessment between different nail types and generations.

Bone was the second most frequent (8%) origin of complications, with delayed healing occurring in 5% (46/983) of the segments, followed by

premature consolidation in 2% (19/983) of the segments. Due to the grouped analysis of the review, any underlying factors, such as age or smoking, affecting complications could not be assessed. An individual patient register of patient demographics and complications are needed to assess the individual factors affecting complication. This individual registration of patient demographics and complication was found in 18 studies (8 of these were case reports) and represented 160 patients, which we found too low for subgroup analysis, considering the wide spectrum of origins for complications.

The third most prevalent complication origin was the joint, at 6% (61/983) per segment; however most type IIIB complication with new pathology or permanent sequelae originated at this site. A risk of 7 joint subluxations/dislocations per 1,000 segments lengthened was found, and joint contracture was observed in 5% (53/983) of the segments. Primary soft-tissue release was only reported in 12% (5/41) of the included studies but could be one of the keys to addressing joint contracture complications. Other factors that might reduce joint complications and are, therefore, important to report include the frequency of physiotherapy and the use of external orthoses or splints.

A challenge of the study was that four different classification systems and descriptive approaches were used in the 41 studies to assess the severity of the complications (74–77). This shows that there is no gold standard or consensus of a classification system. To achieve consistent reporting in the review, the extracted complications were re-classified into one system. This procedure is a study weakness since the classification was performed using the reported complications and not the original data. Furthermore, the study has an incorporated risk of systematic under grading of the severity due to the prerequisite of downgrading severity in the case of uncertainty between different grades of a complication.

A limitation of the review is the quality of the included studies, of which only one study had level 3 evidence, whereas 32 had level 4 evidence and eight were case reports. The included studies scored about half of the ideal MINORS quality score. There were 33 more type II (n=146) than type I (n=113) complications in the study, meaning that many patients had a more complex complication. The low number of type I complications could be due to i) lack of acknowledgment of the complication by the surgeon, ii) insufficient handling of the complication or, iii) failure to report the complication in the patient chart due to the minor change in treatment. Furthermore, case reports and studies with severe complications may be easier to publish, leading to potential publication bias. In contrast to the potential underreporting of type I complications, the high prevalence of type II complications found in the systematic review seems to reflect the true pattern of complications with bone lengthening nails. Thus, a similar pattern with a higher prevalence of type II complications than with type I complications was found in the cohort series (study II); it might be that when a complication occurs with bone lengthening nails, this complication has a higher tendency to substantially change the treatment plan. Contrariwise, highly prevalent pin site infections that are reported with external lengthening are most often graded as type I severity.

Conclusion: This systematic review reports a group analysis of complications in 983 segments from 41 studies and found that 34% of the segments lengthened with an intramedullar bone lengthening nail had a complication. Thus, the hypothesis of study I, that a complication would occur in more than 25% of bone lengthening nails, was confirmed. As hypothesized, device-related complications were the most frequent complication. However, the second most prevalent complication was not a joint complication as hypothesized but rather a bone complication. However, joint-related complications did represent the third most frequent complication. Due to the lack of a gold standard

for reporting complications and the low quality of the included studies, it might be that the true frequency and origin of complications might differ from our presented results. We encourage future research to use standardized reporting methods to improve shared knowledge and understanding of complications, hopefully leading to a reduction in complications.

7.2 STUDY II – COHORT SERIES

This sequential series of 257 patients who underwent a bone lengthening nail procedure involving 314 segments is, to our knowledge, the most extensive series of externally controlled intramedullary bone lengthening nails to report on complications. In 56% of the treated segments, one or more complications were disclosed. Grade II or higher complications were observed in 68% of the segments, reflecting a major impact on the treatment, represented by 56% grade II, 4% grade IIIA, and 11% grade IIIB complications. In the regression analysis of complication risk factors, we found that increasing age, FITBONE nail, acute correction through the lengthening osteotomy, tibial lengthening, short stature, and increasing bone lengthening all increased the risk of a complication.

This cohort suggests that the true frequency of complications is greater than the one complication to every three segments and one major impact complication to every four segments reported in a recent systematic review (100). Our results are supported by a study from Frommer and colleagues demonstrating complications in 76% of the 90 patients undergoing antegrade femoral lengthening with the PRECICE nail (101). There may be multiple reasons for the difference in frequency between the systematic review and the cohort case series. In contrast to the systematic review (study I), we only included patients that had completed treatment, including nail removal. We found that

19% of the complications arose at or after nail removal. Furthermore, our study focused on the complications with bone lengthening nails. In contrast, most studies included in the systematic review did not pay special attention to the complications associated with lengthening nails, so underreporting of the complications might be expected.

Approximately 15% of the observed complications occurred after implant removal, which might appear as a very high frequency of complications at this late time of treatment. However, most of these complications were due to reported anterior knee pain after nail treatment through the knee joint, either with a retrograde femoral nail or a tibial nail. The high frequency of joint complications per segment (23%) in this cohort study compared with the 6% of joint complications reported in the review study (study I) can partly be explained by the inclusion of anterior knee pain as a complication in study II. We believe anterior knee pain should be included when reporting on complications as it most likely is a direct result of the treatment. Furthermore, the frequency of anterior knee pain is anticipated to depend on the lengthening technique, such as external fixation versus nail in tibial lengthening or antegrade versus retrograde nail in femoral lengthening.

Distraction complications in the earliest mechanically driven lengthening nails (ISKD and Albizzia) were a leading impetus for the development of externally controlled bone lengthening nails (PRECICE and FITBONE) (51,54,102–104). In our study, complications from distraction-related mechanisms were observed in 7% (22/314) of the segments, among which 5% (17/314) and 1.6% (5/314) were distributed among type I and type II complications, respectively. Nail exchange due to distraction malfunctioning was reported in 3% (3/90) of patients with the PRECICE nails by Frommer et al. (101). Furthermore, distraction-related failures were reported in earlier versions of both the FITBONE and PRECICE lengthening nails (63,104–107). It was reported that 5% of the FITBONE cases had backtrack before a nail update fixed this issue (104). In the PRECICE

nail, an anti-rotation part called the “crown” caused distraction failure in a prior version (63,105–107). In our cohort study, device-related complications were observed in 32% of the segments, making this the leading origin of complications. This high frequency of device-related complications represents complications occurring from the very introduction of externally controlled nails to the present time. We did not differentiate between different time periods or different generations of nail designs. However, the high frequency of device-related complications might call for further technical enhancement of the bone lengthening devices. A higher frequency of complications was found with the FITBONE than the PRECICE nail both in study I and study II, and it might be beneficial to avoid both a subcutaneous receiver as well as a connecting chord from this receiver to the nail.

Temporary joint contractures were reported in 20% of patients by Frommer et al., which is in line with the 23% of joint-related complications that we observed, making it the second most frequent origin of complications (101). Even though the bone lengthening nail has eliminated soft tissue-tethering, soft tissue wire transfixation, and external rings that impose physical constraints on joint movement, we still observed joint contracture in 16% (51/314) of the segments. This is unexpected in the light of the earlier return of knee movement for lengthening over nail compared to external fixation alone (43,55). However, muscle group imbalance was proposed by Paley as a frequent reason for contracture, which could be the underlying reason for the observed joint complications (75).

Patients over the age of 30 years showed a significantly increased risk (RR of 4.7) of poor bone regeneration in an ISKD nail group by Kenawey et al. (108). Likewise, there was an increased risk of complications in patients above the age of 30 years in our cohort. We observed that age groups above 30 years had a higher risk of complication than the age groups of 10–19 and 20–29 years. However, the study by Kenawey et al. reports on the use of the ISKD nail, which

is known for a potentially fast and uncontrollable lengthening rate and which may contribute to the higher risk of poor bone regenerate (64,108).

Acute deformity correction with translation, angulation, or rotation at the osteotomy site might be performed and subsequently followed by lengthening through the same osteotomy when using bone lengthening nails. Furthermore, minor but unintentional translation, angulation, or rotation of the bone ends might occur at the osteotomy site. In our case series, we observed an intentional or unintentional translation of bone ends at the osteotomy site in 25.5% of the segments. Kenawey et al. found a relative risk of 1.8 for insufficient bone regeneration when performing acute deformity correction (108). However, in another paper by Karakoyun et al., it was safe to perform metaphyseal osteotomy because it did not affect bone healing (108,109). We observed an increased risk of complications (RR 1.26) with acute deformity correction and lengthening through the same osteotomy. Iobst et al. and Horn et al. reported that 15%–16% of the patients undergoing acute deformity correction followed by gradual limb lengthening experienced complications, which was much lower than the 45% incidence of complications observed by Hammouda et al. (110–112).

In this cohort, the PRECICE nail showed a lower risk (RR 0.71 CI (0.53;0.95)) of complication compared with the FITBONE nail. These results are in line with the lower overall complication per segment found for the PRECICE nail (31%) compared with 46% reported for the FITBONE nail in a recent systematic review (study I) (100). In assessing severity grading between nail types, the difference in complications seems to reside between types I and II (Table 7 Study II). Complications originate from distraction mechanism (9% / 1.3%), attachment failure (11% / 3.8%), and other (15.8% / 6.3%) for FITBONE/PRECICE nails, respectively (study II). The FITBONE

antenna contributed to the major difference in the origin group device-related/other.

The tibia/femur segment distribution was 20%/80% in our study, and tibia lengthening had a higher risk of complications (RR 1.59) than the femur did. The complication rate for tibial lengthening was 1.4 complications per segment, which was comparable with the observed 1.8 complications per segment for tibial lengthening over nail in the study by Kim et al (113). Complications were observed in 82% (14/17) of lengthening segments by Wright et al, and 35% (6/17) of those complications were due to malalignment (114). There were complications in 0.73 of the segments that underwent femur lengthening, which was similar to Frommer et al.'s report of complications in 76% of the femoral segments (101).

Besides the FITBONE and PRECICE lengthening nails, the two centers in study II also used the STRYDE nail for lower limb lengthening during the study period. The STRYDE nail was introduced to allow for early full weight-bearing. However, recent studies have shown that the STRYDE nail has a very high frequency of early corrosion leading to bony abnormalities and pain (115,116). Therefore, the STRYDE nail has been withdrawn from the market, and we, therefore, decided not to include the STRYDE nails in the study II analysis. The bony abnormalities observed with the STRYDE nail are not a concern when treating with the FITBONE or PRECICE nails (117).

The retrospective design is a limitation of this study since it can lead to underreporting or lack of precision in reporting complications (118). However, the complication severity score from Black et al. can only be assessed retrospectively, necessitating this study design (67,119). The observational nature of the retrospective study is a weakness since patient risk factors (such as age) may affect the selection of the treatment, which could produce bias, so the complication rate appears better or worse than the underlying true incidence. The large cohort size

of segments and patients supports the strength of the study's validity and results. The complications were graded by a non-validated classification system, which is a weakness, but to our knowledge, no golden standard or scientifically tested classification for bone lengthening nails exists. A two-rater inter-rater assessment of the classifications system was performed by Frost et al. in a review study (Study I). This assessment disclosed a kappa inter-rater agreement of 0.87 for severity grading and 0.94 for origin categorization, which is an excellent result according to Svanholm et al. (94,100). However, precision reproducibility of the four raters was assessed in study III. Here a good inter-rater agreement and varying intra-rater agreement were observed. It is a weakness that only one center (AAUH) used the FITBONE nail and performed tibial lengthening, which means that these results are affected by the center's performance. At NCH, a single surgeon treated all patients in contrast to AAUH, where multiple surgeons were involved in the treatment over a prolonged period. Our study can only demonstrate associations between complications and possible risk factors due to its retrospective design. We need prospective studies to prove the causality.

Conclusion: The study found that the occurrence of one or more complications in segments lengthened by externally controlled bone lengthening nails was 56%. Thus, the pre-study hypothesis of a complication occurring in one out of every three lengthened segments can be rejected. As hypothesized, the three most frequent complications were device-, bone-, and joint-related, in that order. However, device-related and joint-complications were the two most frequent origins of complication, at 0.32 and 0.23 complications per segment, respectively.

The following hypotheses of the secondary aim were confirmed: the risk of complications of bone lengthening nails increased with age and longer lengthening and were more prevalent in the tibia compared to the femur, in acute deformity correction compared to in non-correction,

in short status patients than in other patient groups, and in procedures using the FITBONE nail compared with those using PRECICE nails.

This large multicenter cohort examining complications of bone lengthening nails demonstrates that complications are more frequent than earlier reported. Surgeons should consider patients' risk factors before surgery. We encourage meticulous documentation of complications in bone lengthening nails so the exact underlying risk can be revealed and hopefully prevented.

7.3 STUDY III – AGREEMENT STUDY

The main finding of this study was the good strength of inter-and intra-rater agreement for grading the severity and origin of complications in bone lengthening nails using the devised classification system and the agreement benchmarks by Svanholm et al. (Study III) (94).

The raters were trained prior to their participation, and written instructions were provided to the raters. Furthermore, the severity and origin grade of some complications were prespecified, i.e., deep venous thrombosis was considered a grade IIIB complication. Therefore, the observed kappa values of reliability may represent an optimal setting. However, the intra-rater variation still demonstrated substantial variability, and it might be that more detailed rater instructions could improve the reliability. Thereby, the variability in ratings arising from different interpretations of complications would be reduced.

To promote the study's internal validity, we chose an electronic platform for the rater assessment to ensure identical and consistent presentation of cases and classification systems. To reduce the potential of the raters' ability to recall ratings in the intra-rater assessment, we randomly switched the presentation order of cases between the two rating assessments, which were conducted at least six weeks apart. The

raters were technically blinded to other raters' assessments and were instructed to perform the ratings independently.

The article cases are all available online in papers from the systematic review (study I). These cases represent the literature presentation of complications in bone lengthening nails, which substantiates the external validity. The cohort case information, on the other hand, included a relevant clip of the patient charts, which reflects the standard of journal documentation in Denmark by different physicians in the orthopedic department of AAUH and their different experiences. Thus, the reliability was tested for settings that resembled both the extraction of complication data from a systematic literature search (as performed in study I) and from a retrospective cohort study (as performed in study II).

Raters were selected from the cohort of physicians in the department of orthopedics, AAUH to ensure that they were capable of interpreting patient charts written in Danish and had experience with bone lengthening nails. However, this experience is a potential weakness due to the risk of a developed everyday common understanding of complication etiology and handling, which might be seen differently by a physician from other hospitals. If this has been the case, the effect on the agreement in study III would be higher than that of raters from multiple hospitals. The effect would reduce the external validity of the study.

The differences found between different raters in study III both for interrater and intra-rater reliability may reflect that there is a learning curve for both severity grading and origin classification. Being the first author of studies I, II and III, and a Ph.D. student investigating complications with bone lengthening nails, rater C had the highest knowledge of the applied classification systems. This seems to be reflected by the finding that rater C had the highest intra-rater agreement of all raters both for severity grading and origin

classification. The second rater most familiar with the classification systems was rater D, a senior author of studies I, II, and III, as well as the supervisor of the Ph.D. student. Rater D also had the second highest intra-rater agreement. Furthermore, comparing pairwise interrater agreements between the four raters, raters C and D had the highest interrater agreement for both severity and origin.

We chose kappa statistics for the agreement assessment since it considers the possibility of the rater agreement due to chance (guess). This was pointed out by Jacob Cohen in 1960 when traditional agreement was assessed by percent agreement (81,93). Kappa statistics are an improvement to percent agreement but are not without weaknesses. First, understanding the kappa estimate is not straightforward; therefore, the kappa estimate needs a benchmark for its interpretation of clinical research. While there are currently no gold standards, two different standards have become widely used in orthopedics and other parts of medicine. The criteria for both of the standards were selected arbitrarily and published by Landis and Koch, and Svanholm et al. (81,93,94,120). In table 7.3.1, the distributions of the kappa values in relation to the percentage of reliable data are presented in relation to the three different standards of strength of agreement.

Kappa value	% of reliable data	Strength of agreement by authors		
		Cohen's	Landis and Koch	Svanholm et al.
0-0.20	0-4%	None	Slight	Poor. (κ≤0.50)
0.21-0.39	4-15%	Minimal	Fair	
0.40-0.59	15-35%	Weak	Moderate	Good (κ=0.51-0.74)
0.60-0.79	35-63%	Moderate	Substantial	Excellent (κ ≥ 0.75)
0.80-0.90	64-81%	Strong	Almost perfect	
Above 0.90	82-100%	Almost perfect		

Table 7.3.1: Three benchmark divisions of kappa values.
Table presents the % of reliable data in relation to kappa value and the three benchmarks of strength of agreement. Partly reproduced after McHugh (81,94,120)

One of the known weaknesses of the kappa estimate is its dependence on the proportion of subjects in each category (93), known as the two paradoxes of very low kappa values with a high observed agreement (121). To illustrate one of these two paradoxes of very low kappa, fracture for displacement +/- on x-ray was evaluated by two orthopedic surgeons (93). Tables 7.3.2 and 7.3.3 show two evaluating events in which the kappa value drops as a result of a change in the proportion of subjects, but the observed agreement remains constant (93).

		Surgeon No 1		
		Displaced	Nondisplaced	Total
Surgeon No 2	Displaced	50	15	65
	Nondisplaced	15	20	35
	Total	65	35	100

$$Observed\ Agreement = \frac{50 + 20}{100} = 0.70$$

$$Chance\ agreement = \frac{\frac{65 \times 65}{100} + \frac{35 \times 35}{100}}{100} = 0{,}545$$

$$Kappa = \frac{0.70 - 0.545}{1 - 0.545} = 0.34$$

Table 7.3.2: An example of agreement with very low kappa part 1. An example of agreement between two surgeons assessing a fracture for displacement on x-ray part 1. The observed agreement, chance agreement, and kappa value are calculated. Reproduced after Garbuz et al. (93).

		Surgeon No 1		
Surgeon No 2		Displaced	Nondisplaced	Total
	Displaced	65	15	80
	Nondisplaced	15	5	20
	Total	80	20	100

$$Observed\ agreement = \frac{65 + 5}{100} = 0.70$$

$$Chance\ agreement = \frac{\frac{80 \times 80}{100} + \frac{20 \times 20}{100}}{100} = 0.68$$

$$Kappa = \frac{0.70 - 0.68}{1 - 0.68} = 0.06$$

Table 7.3.3: An example of agreement with very low kappa part 2. An example of agreement between two surgeons assessing a fracture for displacement on x-ray part 2. The observed agreement, chance agreement, and kappa value are calculated. Reproduced after Garbuz et al. (93)

A table presentation of the agreement prevalence is normally presented to assess the kappa paradox. It is a limitation of this study that this table presentation was not included. However, this table will be difficult to interpret and an unworkable task considering the comprehensiveness of the possible outcome of four raters, severity classification with four outcomes, and origin classification with 33 categories (study III). In the result table 2-5 of study III, we have presented the observed agreement

for all kappa estimates. No signs of the kappa paradox were observed (study III) (121).

Study III is a reliability (precision) study, which should not be confused with a validity study (accuracy) (122). Validity studies focus on the accuracy of data, and they can be described by an arrow hitting a center target (Fig 7.3.1). Reliability focuses on the reproducibility of a measurement, illustrated by an arrow hitting the same spot on a target but not necessarily the center of the target (Fig. 7.3.1 the two examples on the right).

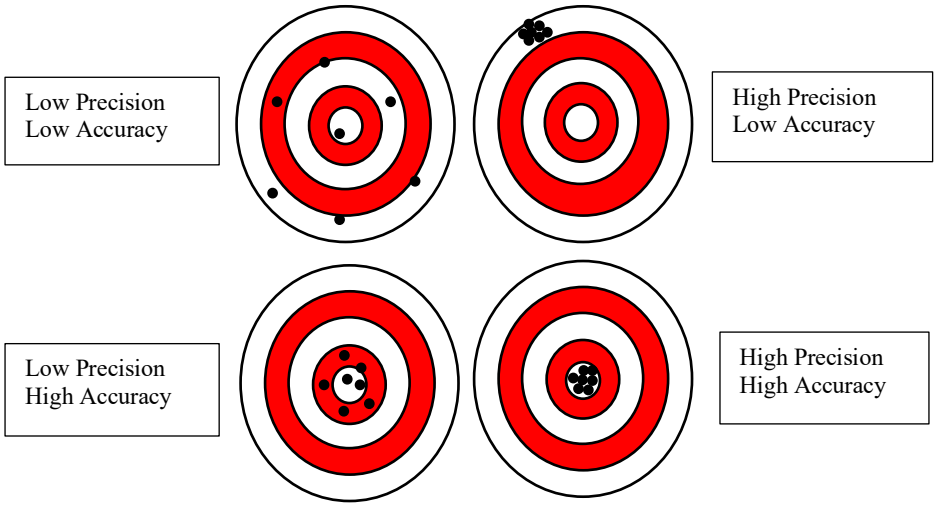

Figure 7.3.1: Precision and accuracy illustration.
Schematic illustration of the difference between precision and accuracy with an image of arow hitting a target. The four different combinations of precision and accuracy.

Conclusion: We tested the reproducibility of a severity and origin classification using four raters in two case circumstances. Kappa values of 0.64 and 0.74 were found for the severity and origin, respectively, of the article cases. In the cohort cases, the kappa estimates of severity and origin were 0.62 and 0.74, respectively. Thus, the pre-study hypothesis

was confirmed: inter-rater and intra-rater reproducibility on severity grading and origin complication classification showed good strength, with a kappa estimate above 0.51. As we observed a good inter-rater agreement, the classification system is recommended for future reporting of complications.

8 CONCLUSION

The overall aim of the thesis was met in studies I and II. The thesis studies used a new approach wherein the assessment of complications was separated by severity and origin, which revealed the impact of different origins on complications with bone lengthening nails. A thorough investigation of complications in the treatment of externally controlled bone lengthening nails was conducted. Two different study designs assessed the severity and origin of complications in the literature and in a large multicenter cohort.

The results of studies I and II show that a complication in externally controlled bone lengthening nails might be expected in every second to third lower limb segment undergoing bone lengthening. The origin of the complication will most frequently arise from the lengthening device, followed by either bone or joint complications. Regarding complication severity, type II complications occurred most frequently (15%–46% of the segments), followed by type I complications which were seen in 11%–27% of the segments. Approximately 3%–5% of the segments did not reach their lengthening goal due to a complication (type IIIA), and a new pathology or permanent sequala (type IIIB complication) occurred in 3%–10% of the segments. The time point of complication is important in relation to the detection of complications; herein, the distraction stage had the highest frequency of complications (26%–46%), followed by the consolidation stage (24%–31%). Surprisingly, 19% of the complications were observed at or after the nail removal.

Finally, study III investigated the reliability of the severity and origin assessment of complications. In this study, the inter- and intra-rater agreement of severity and origin classification showed good-to-excellent agreement under conditions simulating studies I and II, which

substantiates the use of the classification system and increases the strength of those studies.

9 SUGGESTION FOR FUTURE RESEARCH

While this Ph.D. thesis has emphasized the evident problem of inconsistent reporting of complications in the literature, it has also presented results regarding the severity and origin of complications and a uniform way of reporting them.

For the research area of complications, the most significant advancement would be a gold standard for the assessment and reporting of complications. This would allow for a systematic and uniform platform when performing research on complications. In this thesis, a proposed classification system for the severity and origin of complications was presented and tested. We encourage others to use this classification system on their patient population and reproduce the precision in other settings for further validation.

The classification system assesses the recognition of complications and the correctness of the treatment. Yet, when is a symptom or a complication severe enough to change the treatment plan, and what is the correct treatment? Does joint contracture of 20°, 30°, or 40° require intervention? Should the treatment involve further physiotherapy, reduced lengthening pace, or even surgery with soft tissue release or bone shortening. To my knowledge, there is a paucity of evidence regarding these topics, as well as many of the other complications seen with bone lengthening nails.

The studies of the thesis were conducted in a methodology transparent manner and have used a consistent classification to permit scrutiny and reproduction in future studies. In the light of the low quality of studies disclosed in the systematic literature review, reevaluation of the study results should be performed in another population.

Bone lengthening in these patient populations was etiologically heterogeneous, and a rough division of the patients in study II showed an increased risk for complications for only the short stature patients. The large differences in etiological/pathologies influence both soft- and bone-tissue, and it, therefore, seems unlikely that the heterogeneity of etiologies is not better reflected by the risk of complications. The use of four groups may have blurred the risk of complications by some etiologies due to the sizeable difference in etiological/pathologies seen within the groups. A way of grouping patients with respect to their etiologies and pathological characteristics of bone and soft tissue would be interesting to investigate.

Overall, the body of literature on bone lengthening lacks prospective studies, which weakens the evidence on the topic. The low volume of bone lengthening cases seen in many centers could be a challenge to prospective research. Further multicenter studies might address this problem. Another way to strengthen data could be a structured prospective data collection into a database, which would be feasible with a low patient volume.

The complication incidences disclosed in this thesis are higher than the impression given in the literature on bone lengthening nails. The trend of using a 2 cm LLD as an indication for bone lengthening could be motivated by an expectation of a low-risk treatment. Since our data points towards high risk of complication, with an encounter complication in every second to third segment, a key research area should, therefore, be to establish the correct LLD threshold for performing bone lengthening.

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11 LIST OF APPENDICES

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1. Paper I

Systematic review of complications with externally controlled motorized intramedullary bone lengthening nails (FITBONE and PRECICE) in 983 segments

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Background and purpose — In recent years motorized intramedullary lengthening nails have become increasingly popular. Complications are heterogeneously reported in small case series and therefore we made a systematic review of complications occurring in lower limb lengthening with externally controlled motorized intramedullary bone lengthening nails.

Methods — We performed a systematic search in PubMed, EMBASE, and the Cochrane Library with medical subject headings: Bone Nails, Bone Lengthening, and PRECICE and FITBONE nails. Complications were graded on severity and origin.

Results — The search identified 952 articles; 116 were full text screened, and 41 were included in the final analysis. 983 segments were lengthened in 782 patients (age 8–74 years). The distribution of nails was: 214 FITBONE, 747 PRECICE, 22 either FITBONE or PRECICE. Indications for lengthening were: 208 congenital shortening, 305 acquired limb shortening, 111 short stature, 158 with unidentified etiology. We identified 332 complications (34% of segments): Type I (minimal intervention) in 11% of segments; Type II (substantial change in treatment plan) in 15% of segments; Type IIIA (failure to achieve goal) in 5% of segments; and Type IIIB (new pathology or permanent sequelae) in 3% of segments. Device and bone complications were the most frequent.

Interpretation — The overall risk of complications was 1 complication for every 3 segments lengthened. In 1 of every 4 segments, complications had a major impact leading to substantial change in treatment, failure to achieve lengthening goal, introduction of a new pathology, or permanent sequelae. However, as no standardized reporting method for complications exists, the true complication rates might be different.

Distraction osteogenesis through an externally applied fixator is a well-established treatment for lower limb lengthening (De Bastiani et al. 1987, Paley 1988, Ilizarov 1990). However, complication rates of this treatment are high, amounting to 1–3.2 complications per patient (Tjernström et al. 1994, Noonan et al. 1998). The wires or pins penetrating soft tissues result in complications such as pin site infection, pain, scarring, muscle transfixation, reduced joint movement, and immobility (Paley 1990, Mazeau et al. 2012, Landge et al. 2015). When the external fixator is removed, there is a risk of further complications such as fracture or malalignment (Noonan et al. 1998, Simpson and Kenwright 2000). To reduce complications and improve patient comfort, limb lengthening by fully implantable bone lengthening nails has been introduced (Guichet 1999, Cole et al. 2001). Problems with purely mechanically driven lengthening nails were resolved by the introduction of motorized (FITBONE) or magnetically driven (PRECICE) bone lengthening nails (Baumgart et al. 1997, Kirane et al. 2014, Paley et al. 2014, Shabtai et al. 2014). A few case-control studies have compared these nails with external fixation (13–15 patients), and the largest case series on intramedullary bone lengthening reports on 92 patients (Black et al. 2015, Horn et al. 2015, Calder et al. 2019). However, the majority of reports of complications of the FITBONE and PRECICE lengthening nails are small case series (Krieg et al. 2008, Dinçyürek et al. 2012, Birkholtz and De-Lange 2016, Hammouda et al. 2017). In recent years motorized intramedullary lengthening nails have become increasingly popular, and we thus hypothesized that standardized data on complications could now be extracted from the literature. We performed a systematic literature review of complications using PRECICE and FITBONE bone lengthening nails in lower limb bone lengthening. The primary outcome was risk of complications imposing a new pathology or permanent sequelae in the patient.

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Table 1. Classification of severity of complications in accordance with Black et al. and Paley

Complication severity grade				
Modified Black et al. 2015		Paley 1990		Examples of complications
I	Minimal intervention required; treatment goal still achieved	Problems	Potential expected difficulty arising during distraction or fixation period which is fully resolved non-operatively by end of the treatment period	Pin-site infection. Temporary joint contracture
II	Substantial change in treatment plan; treatment goal still achieved	Obstacle	Potential expected difficulty that arose doing distraction or fixation period that is fully resolved by end of the treatment period by operative means	Unplanned return to surgery, such as delayed consolidation requiring additional intervention, and device problem needing revision
IIIA	Failure to achieve treatment goal; no new pathology or permanent sequelae. Peri- or intraoperative complication without sequelae	Complication	Complication include any local or systemic intraoperative or perioperative complication, difficulty during distraction or fixation that remains unsolved at the end of treatment period, and any early or late post-treatment difficulty	Premature consolidation with aborted lengthening, inability to tolerate lengthening, and fracture at fixation site or regenerate bone with shortening
IIIB	Failure to achieve treatment goal and/or new pathology or permanent sequelae		Complications were divided into minor and major depending on whether the original treatment goal was achieved	Joint subluxation, joint dislocation, regenerate fracture with deformity, and deep infection. Thromboembolic complication such as deep vein thrombosis

Method

Search criteria

An electronic search in the databases PubMed, Embase, and Cochrane Library was performed by a health science librarian with expertise in systematic literature searching. For details of the search strategy see Supplementary data 1. There was no limit concerning study design, publishing date, or language. We searched reference lists of included studies, relevant reviews identified through the systematic search and authors' personal files to ensure literature saturation.

Inclusion and exclusion criteria

We included only published full-text original studies designed as randomized controlled trials, prospective and retrospective cohort studies, case-control studies, case series, and case reports. Cross-sectional studies were excluded. Studies in both English and German were included.

Studies were included if: the bone lengthening nails applied were FITBONE (Wittenstein Intens GmbH, Igersheim, Germany) and/or PRECICE (Nuvasive, San Diego, CA, USA), conducted in humans, and bone lengthening was performed on lower extremities. Descriptions of complications included origin, severity, and management of complications or a statement of no complications. Studies were excluded if: reporting only bone transport treatment, nails were used only for compression, there was no involvement of lower extremities, or reporting stump lengthening. If patients were represented in more than one study, only one of the studies was included. A single patient or a group of patients from one study could be included if patient-/group-specific data was available.

Data collection and management

The primary search was performed at the end of November 2019 and updated at the end of March 2020. The literature search was assembled in www.covidence.org as well as the management of article selection flow. Titles and abstracts were screened by the first author (MWF) to select articles for full text reading. Among the full text articles, MWF selected papers for possible inclusion. SK and MWF assessed articles in accordance with inclusion criteria and agreed on studies relevant for final inclusion.

During the initial data collection, MWF collected the following information from each study: title, author(s), year of publication, study design, evidence level, number of patients, number of lengthening segments, sex, nail type (FITBONE or PRECICE), participant age range, and bone segments (femur or tibia). Etiology was divided into 3 groups: (1) congenital, (2) short stature, (3) acquired/developed limb length discrepancy diagnoses in accordance with the modified Stricker and Hunt classification (Stricker and Hunt 2004) (see Supplementary data 2), min./max. leg length, and perioperative soft tissue release. Complications were assessed according to the particular point in time when they occurred: intraoperative complication (Early 1:E1), postoperative complication prior to distraction start (Early 2:E2), during distraction period (Late 1:L1), after end of distraction and prior to implant removal (Late 2:L2), and after implant removal (Late 3:L3) (see Supplementary data 3). The severity of complications was classified

according to Black et al. (2015) (Table 1). If a complication was graded according to Paley, we used Table 1 to compile the complication into the Black classification. If the treatment of a complication was not thoroughly described, we generally downgraded it, assuming that the treatment goal was achieved and no new pathology or permanent sequalae had emerged. As an example, a joint contracture with no described changes in treatment was classified as grade I. If a complication was graded by article authors as grade I, but the described treatment included additional surgery, we graded it as grade II. A deep vein thrombosis was graded as grade IIIB. The type of complication was categorized into origin representing 8 main groups (soft tissue, joint, vascular, bone, neurological, infection, device-related, others) and 33 subgroups according to Table 5 (for specific examples see Supplementary data 4). Intra-articular nail placement causing irritation and residual deformity was categorized into origin as Others/Surgical. Patient requesting to stop the lengthening procedure was categorized into origin as Others/Patient.

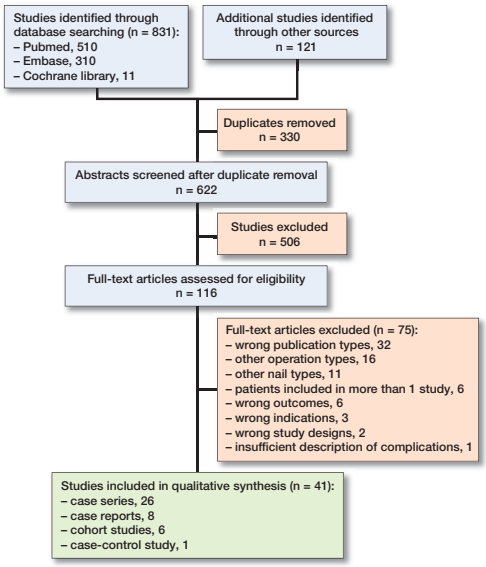
MWF identified all complications and graded them according to severity, time of treatment, and origin. A second reviewer (SK) subsequently evaluated and graded the complication concerning severity and origin. Disagreement between reviewers was solved by consensus discussion.

The Oxford Centre for Evidence-Based Medicine—Levels of Evidence 2009 grading of Harm was used to assess the level of evidence in the included studies (case reports were not included). A study was classified as a case report if reporting less than 5 bone lengthening segments. Case series with a subgroup analysis were classified as a cohort study. A study was considered prospective if data were collected prospectively; all other studies were considered retrospective.

We used a methodology quality assessment score for all studies: Methodological Index for Non-Randomized Studies (MINORS) for non-randomized studies; Murad et al. for case reports (Slim et al. 2003, Murad et al. 2018). MWF and AG independently assessed the studies and solved difference through discussion. 3 specific questions concerning harms (from the McHarm scale) were used (Santaguida et al. 2011, Kronick et al. 2014) (see methodology quality assessment score, Supplementary data 5).

Statistics

Microsoft Excel 2019 version 16.33 (Microsoft Corp, Redmond, WA, USA) was used for data storage and descriptive analysis. Inter-rater agreement between the 2 assessors of complications was calculated as Kappa values for both severity grading of complications (4 types) and categorization of origin (8 main groups and 33 sub-groups) with Stata/MP 15.1 (StataCorp, College Station, TX, USA). For the strength of agreement, values less than 0 were rated as Poor; 0–0.20 Slight; 0.21–0.40 Fair; 0.41–0.60 Moderate; 0.61–0.8 Substantial; and 0.80–1 Almost perfect (Landis and Koch 1977).



Flow diagram of selection of studies.

Registration, funding, and potential conflicts of interest

Prior to conducting the study, we searched the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO) for ongoing reviews and recently completed systematic reviews; we did not identify any results. This study was then submitted to PROSPERO on November 22, 2019. Due to waiting time at PROSPERO, this pre-study registration has unfortunately not been published before submission (April 23, 2020). During the review period, the pre-study registration was published by PROSPERO (ID number: CRD42020159272). The majority of studies included were case series and case reports and we changed the risk of bias/quality assessment tool to MINORS and added Murad et al. for case reports (Slim et al. 2003, Murad et al. 2018). Thus, reporting guidelines were also changed to Meta-analysis of Observational Studies in Epidemiology (MOOSE), and this systematic review was organized in agreement with this (Stroup et al. 2000). The change was submitted to PROSPERO. The authors' institutions funded the study. No conflicts of interest are declared.

Results

Our search identified 952 articles of which 41 were included (Table 2); for flowchart of article selection see Figure. There was 1 case-control study, 6 cohort studies, 26 case series, and 8 case reports. Of the 33 studies that were not case reports,

Table 2. Included studies with the corresponding number of patients, segments, and complications used in this review

Reference	Prospective	Patients n	Segments n	Nail type [a]	Complications
Accadbled et al. 2019	Yes	5	7	F	1
Accadbled et al. 2016	Yes	23	26	F	9
Al-Sayyad 2012	Yes	10	14	F	1
Baumgart et al. 1997	No	11	11	F	6
Baumgart et al. 2005	No	1	3	F	0
Birkholtz and De-Lange 2016	No	9	11	P	2
Black et al. 2015	No	13	15	F	20
Calder et al. 2019	No	92	107	P	31
Cosic and Edwards 2020	No	21	21	P	9
Couto et al. 2018	No	1	2	P	0
Dinçyürek et al. 2012	No	14	15	F	12
Frommer et al. 2018	No	54	60	P	7
Haider and Wozasek 2019	No	20	20	P	8
Hammouda et al. 2017	No	17	17	P	4
Harkin et al. 2018	No	3	3	P	0
Havitcioglu et al. 2020	No	8	16	P/ F	4
Horn et al. 2019	No	47	50	P/ F	16
Iobst et al. 2018	No	27	27	P	4
Karakoyun et al. 2016	No	23	27	P	10
Karakoyun et al. 2015	No	22	22	F/P	2
Kariksiz and Karakoyun 2019	No	1	1	P	0
Kirane et al. 2014	No	24	25	P	6
Krieg et al. 2008	Yes	8	8	F	4
Krieg et al. 2011	No	32	32	F	10
Küçükkaya et al. 2015	No	22	25	F	5
Laubscher et al. 2016	No	15	20	P	5
Lee et al. 2017	No	41	80	P	36
Lenze et al. 2011	No	11	11	F	6
Morrison and Sontich 2016	No	1	1	P	1
Muratori et al. 2018	No	4	4	P	1
Nasto et al. 2020	Yes	26	26	P	10
Paley et al. 2015	No	51	116	P	20
Paley et al. 2014	No	46	62	P	31
Rozbruch 2017	No	2	2	P	1
Schiedel et al. 2014	Yes	24	26	P	9
Shabtai et al. 2014	Yes	18	21	P	9
Singh et al. 2006	No	10	24	F	14
Steiger et al. 2018	No	5	5	F	2
Tiefenboeck et al. 2016	No	10	10	P	13
Wiebking et al. 2016	No	9	9	P	2
Wu and Kuhn 2018	No	1	1	P	1

[a] F = FITBONE; P = PRECICE.

Table 3. Descriptive study data collected from the studies reporting group-level data

Factor	Numbers	Studies reporting data
Number of patients	782	41
Number of bone segments	983	41
Male / female, n	384 / 234	29 / 33
Age, min / max	8 / 74	39
Etiology, n		
Congenital disease	208	22
Short stature	111	14
Acquired/developmental LLD	305	29
Femur / tibia, n	813 / 170	40 / 28
Bone lengthening cm, min / max	1 / 14	35 / 35
FITBONE/ PRECICE nails	214 / 747	15 / 27

164 patients were unidentified regarding gender, and 158 patients regarding etiology.
22 nails could not be differentiated between FITBONE or PRECICE.
LLD: limb length discrepancy

Table 4. Severity grading of complications divided into specific numbers and percentages of lengthened segments and patients

Factor	Severity grade of complications I	II	IIIA	IIIB	Sum
Number of complications	113	146	45	28	332
Complications per segment, %	11	15	5	3	34
Complications per patient, %	14	19	6	4	42

Grading according to severity by Black et al. (2015).

there was 1 level 3 study and 32 level 4 studies. The mean MINORS score was 8.3 (n = 26, range 5–12, ideal score 16) for non-comparative studies and 15.1 (n = 7, range 12–18, ideal score 24) for comparative studies (for full score of studies, see Supplementary data 6). The mean score for case reports was 4.3 (n = 8, 3–6 range, ideal score 8). Concerning the McHarm questions: (1) 1 study included predefined/standardized descriptions of complications, (2) standard scale of complications was used in 15 studies, and (3) number of each type of event and total number were specified on study groups in 31 studies (see Supplementary data 6).

The 41 studies included 782 patients and 983 bone lengthening segments (Table 3). We found 332 complications corresponding to 34% of segments; 14 complications were not classified with origin, only severity. We observed 28 type IIIB complications, which was our primary outcome, corresponding to 3% of segments. Type IIIA complications not achieving the lengthening goal were seen in 45 cases (5% of segments). There were 113 type I complications and 146 type II complications, corresponding to 11% and 15% complications per segment, respectively (Table 4). Device-related complications (12% of segments) were the most frequent type of complication followed by bone (8% of segments) and then joint complications (6% of segments) (Table 5).

5 studies reported a systematic approach to soft-tissue release during primary surgery (Shabtai et al. 2014, Paley et al. 2015, Laubscher et al. 2016, Rozbruch 2017, Calder et al. 2019). None of the 41 studies systematically reported the timing of the complication; in 332 complications, timing was established in 177 (53%) cases with 6 and 5 complications of E1 and E2, respectively. L1 and L2 were seen in 85 and 81 cases, respectively and no L3 complications were found. In 18 (8 of these were case reports) of the 41 studies, it was possible to connect the complication and the individual patient data. These 18 studies represent only 160 patients and we considered this number too low for subgroup analysis of complica-

Table 5. Complications categorized into 8 main groups (soft tissue, joint, vascular, bone, neurological, infection, device-related, others) and 33 subgroups

Group	Severity grade and origin of complications I	II	IIIA	IIIB	Sum
Soft tissue					
Skin	2	1			3
Muscles					0
Tendons					0
Pain	5				5
Others	2	1		2 (CS)	5
Sum of soft tissue					13
Soft tissue complications in % of segments					1
Joint					
Pain	1				1
Contracture	19	24	5	5	53
Subluxation				6	6
Dislocation				1	1
Others					0
Sum of joint					61
Joint complications % of segment:				6	
Vascular					
Vascular damage				1	1
Deep vein thrombosis				4	4
Hemorrhage/hematoma	2				2
Others	2			1 (AV)	3
Sum of vascular					10
Vascular complications in % of segments:					1
Bone					
Premature consolidation		15	4		19
Delayed healing	16	27	2	1	46
Secondary malalignment		1		2	3
Fracture		6	1	1	8
Others	1	1			2
Sum of bone					78
Bone complications in % of segments:					8
Neurology					
Paresthesia	2	1	2		5
Paralysis					0
Others	3				3
Sum of neurology					8
Neurology complication in % of segments:					0.8
Infection					
Superficial soft tissue	2	1			3
Deep soft tissue		1			1
Osteomyelitis			3	1	4
Others					0
Sum of infection					8
Infection complications in % of segments:					0.8
Device-related					
Distraction mechanism	16	20	9		45
Mechanical strength	25	14	3	2	44
Attachment failure	8	24	1		33
Others					0
Sum of device-related					122
Device-related complications in % of segments:					12
Others					
Patient			6		6
Surgical		3	7	1	11
Others			1		1
Sum of others					18
Others, complications in % of segments					1.8

CS: compartment syndrome;
AV: arteriovenous fistula of the posterior tibial artery decompensated during tibial lengthening and an embolization procedure had to be performed. 14 complications could not be categorized due to missing descriptions.

tion risks. A few possible risk factors for complications could be estimated at a study group level. We found 31% complications per segment for the PRECICE nail and 46% complications per segment for the FITBONE nail. Surgical unit experience was assessed by dividing studies into studies with less than 20 patients (49% complications per segment) and studies with more than 40 patients (30% complications per segment) (see Supplementary data 6 for studies included in sub-analysis and Supplementary data 7 for full data presentation).

The inter-rater agreement between the 2 assessors of complications was 0.87 for severity grading and 0.94 for categorization of origin.

Discussion

To our knowledge, this is the first systematic review on complications related to bone lengthening nails. The primary outcome was the risk of type IIIB complications resulting in a new pathology or permanent sequelae. This review found such IIIB complications in 3% of lengthened segments. Furthermore, a complication of any type was found in 34% of lengthened segments, and 5% of segments did not achieve the planned lengthening due to a complication (IIIA). In 15% of segments treated with intramedullary PRECICE and FITBONE lengthening nails, a complication (II) resulted in substantial change in treatment, such as unplanned re-surgery. 6% (11/177) of time-determined complications occurred intra- or perioperatively prior to start of distraction, and 94% of complications (166/177) occurred during or after the end of distraction. The high diversity of complications demonstrates that several means must be applied to reduce the high number of complications in intramedullary bone lengthening. Concerning the primary outcome, where the (type IIIB) complication resulted in a new pathology or permanent sequelae, the majority of complications were a result of joint-related complications such as contracture, subluxation, or dislocation. It is likely that a reduction in joint-related complications is accomplished by improved patient selection and attention to soft-tissue release as well as individualized protocols for lengthening, temporary extraarticular screw arthrodesis, splints/orthoses, or physiotherapy. The risk of joint subluxation and dislocation was 6 and 1 per 1,000 segments, respectively. Joint contracture was seen in 5% (53/983) of the segments, and primary soft-tissue release might be a key to address this complication; this was, however, only reported in 5 of the 41 studies (Shabtai et al. 2014, Paley et al. 2015, Laubscher et al. 2016, Rozbruch 2017, Calder et al. 2019). Calder et al. made a systematic division of the iliotibial band (ITB) if the planned lengthening was above 3 cm. They found that, in femoral lengthening, females lost joint movement in the hip and knee earlier than males. Moreover, it took substantially more time to regain range of motion in patients treated with retrograde compared with antegrade nails. However, we believe that higher rates of severe joint

complications must be anticipated in high-risk patients such as congenital femoral deficiency and fibular hemimelia. We believe there is a need for systematic reporting of primary soft-tissue release as there is a lack of knowledge of benefits and challenges concerning this issue.

A device-related complication was seen in 12% (122/983) of segments with 5% (45/983) assigned to distraction mechanism-related complications, and 1% (13/983) of segments did not reach the lengthening goal due to device-related type IIIA complications. The overall complication rate per segment was 46% for studies only reporting the use of a FITBONE nail and 31% for studies only reporting the use of a PRECICE nail. However, the quality of data is not sufficient to compare complication rates between the 2 nail types; for example, did the studies that used only FITBONE nails include tibial lengthening in 27% compared with 16% in the PRECICE studies. In addition, in the FITBONE group the average number of patients per study was only 13 compared with an average number of 28 patients per study in the PRECICE group. However, the relatively high rate of device-related complications shown in this review warrants a constant focus on the technology of bone lengthening nails. Future studies should specifically report the type and generation of the applied nail to assess complication risk related to different nails and generations.

Complications related to bone regeneration were mainly due to delayed healing in 5% (46/983) of segments or premature consolidation in 2% (19/983) of segments. These complications might be reduced by increasing knowledge and handling of nail stability, patient compliance, mobilization, and biological factors such as type of osteotomy, latency period, and distraction rate/force. Another solution might be providing real-time feedback on surrogate markers of bone healing to allow for individualized distraction treatment. It seems logical that a surgeon's ability to avoid or recognize, manage, and solve complications strongly correlates with the surgeon's experience of this highly specialized treatment. This was to some extent supported by this review as studies with fewer than 20 patients had more complications per segment compared with studies with more than 40 patients.

The validity of a review depends on the quality of the included studies and on the validity of the data extraction. The level of evidence in the studies included in this review was low. Of the 41 included studies, there were 1 level 3 study, 32 level 4 studies, and 8 case reports and mean MINORS scores of about half of the ideal scores. Our study found 146 type II complications compared with 113 type I complications, and most patients thus had a more complex type of complication. This might reflect both underreporting and the lack of accurate reporting of complications in elective surgery (Martin et al. 2002).

We assessed complications in relation to segment lengthening and not to each patient because, in some patients, bone lengthening occurred in more than 1 bone in the same leg, lengthening involved both legs (short stature patients), and some patients underwent multiple lengthening procedures of the same bone. Complications per segment were lower than complications per patient, but since most of the patients had lengthening of only one segment, segment was chosen for main reporting.

41 studies with 983 bone lengthening segments reported either complications or stated absence of complications. With the increased popularity of lengthening by PRECICE and FITBONE nails, there is a knowledge gap concerning the distribution of severity grade and origin of complications in all treated patients. We believe that the demographics and number of included patients in this review are sufficiently diverse to illuminate even rare complications.

4 different classifications for reporting severity in bone lengthening complications were used (Paley 1990, Dahl et al. 1994, Dinçyürek et al. 2012, Black et al. 2015), and 29 studies did not use a classification. We are familiar with at least 4 more classifications of complications in limb lengthening, which challenges comparison between reported complications (Caton et al. 1985, Popkov 1991, Donnan et al. 2003, Lascombes et al. 2012). In this review we have classified the reported complications to achieve consistent reporting. However, it is a limitation that data on complications could be classified only from reported complications and not from original data. In the case of uncertainty between different grades of a complication, the complication was graded with the lower severity grade. Thereby, a systematic risk of reporting too low a complication severity grade was introduced. Another limitation of our review is that the reported complication rates could not be specified on subgroup level. We would expect that the complication rates differ substantially between a patient with idiopathic lower limb lengthening undergoing 3 cm of simple antegrade femoral lengthening without deformity correction and a patient with congenital fibular hemimelia and multiple previous operations undergoing 5 cm of tibial lengthening. However, it was not possible to extract data on a single patient level from the current literature. Therefore, we could not make correlations between complication rates and individual risk factors. We encourage future studies to report complications on a single patient level where complications can be related to possible risk factors such as age, diagnosis/etiology, segment, approach, nail type nail, nail generation, and timing of complications.

Conclusion

This review of the literature shows an overall high rate of complications, with complications occurring in 1 of every 3 segments undergoing lower limb lengthening. In 1 of every 4 segments, complications have a major impact leading to substantial change in treatment (15%), failure to achieve lengthening goal (5%), or introduction of a new pathology or permanent sequelae (3%). As no standardized method of reporting complications exists, the true complication rate might be different.

A standardized reporting method would substantially improve the knowledge needed to reduce the rate of complications.

Supplementary data

Supplementary data items 1–7 are available in the online version of this article, http://dx.doi.org/10.1080/17453674.2020.1835321

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2. PROSPERO registration of Paper I

Citation

Markus Winther Frost, Søren Kold. Complication in intramedullary bone lengthening nails (Fitbone & Precice): a Systematic Review.. PROSPERO 2020 CRD42020159272 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020159272

Review question

The Aim of the review is to identify and categorize and establish frequency of complications in Fitbone and Precice bone lengthening nails.

Searches

-Search for paper in: MEDLINE, Embase, Cochrane Library and PROSPERO data base.

-Setting: There will be no restrictions by type of setting.

-Only publicized full text articles will be reviewed.

-Studies in language: English, German, Danish, will be including. If other languages are found, we will do our best to get them included.

-To ensure literature saturation, we will scan the reference lists of included studies or relevant reviews identified through the search. We will also search the authors' personal files to make sure that all relevant material has been captured.

-Studies time period: from the database was started till Search date.

- Searches will not be re-run prior to the final analysis

Types of study to be included

-We will include randomized controlled trials, prospective and retrospective cohort studies, and case-control and case series, and case reports. Studies of level IV evidence or better. We will exclude cross-sectional studies.
Inclusion criteria of studies:

o Nail producent: Fitbone and Precice

o Human population

o Bone lengthening on lower extremities

o Minimums follow up till end treatment

o Complication detail reported in the study: Type of category and severity graded or description of complication and handling or a statement of non-complication

Exclusion criteria of studies.

o If patients are represented in more than one studies only one of the studies can be include.

o Bone transport

o Nail used for compression

o Not lower Extremities

o Stump lengthening

Condition or domain being studied
Treatment with intramedullary bone lengthening nail (Fitbone or Precice) on the lower limb.

Participants/population
Patients that have been treated with intramedullary bone lengthening nail (Fitbone or Precice) on the lower limb.

Intervention(s), exposure(s)
Lower limb bone lengthening with Fitbone Or Precice intramedullary nail

Comparator(s)/control
We are not comparing complication between two treatments.

Main outcome(s)
The primary outcome will be the number of complication pr. segment lengthen for severity grade IIIB

Measures of effect

When in the treatment periode the complication arise. Measured with severity grade after Black et al. 2015,

Additional outcome(s)
Secondary outcome

• Number of complication per segment lengthen for the other severity grades

• Numbers of patients include, number of complications, number of patients with a complication

• Number: Fitbone or Precice, Femurs or Tibias segment, Per-operative soft tissue release, Number of complication per time periode

• Distribution of complication in percentage of the type complication

Measures of effect

Demografi data will be collected at treatment start: Age, sex, Fitbone nail, Precice nail, Bone segment, per-operative soft tissue release.
Complication: When in the treatment periode the complication arise. Measured with severity grade after Black et al. 2015. The type of complication will be categorize and Subcategorize

Data extraction (selection and coding)

• Selection process

o The corresponding author conducted the primary review of the search results and the identification of full-text articles for assessment.

o Covidence.org stofware was used to handle the article.

o Minimum of 2 authors would agree on inclusion of studies in the analysis; disagreement was solved by consensus.

o Neither of the review authors will be blind to the journal titles or to the study authors or institutions

Data extraction

oThe corresponding author independently completed data extraction according to the study protocol and data were verified by a second reviewer; disagreement was solved by consensus.

• The following things were extract on study level: Study type and evidence level, Numbers of patients in the study, Numbers of segments in the study

• On individual outcomes basis the following outcomes will be collected and as reported. If not reported on an individual basis it will be included on group level. The final report will be done as the majority of reported outcome.

o Lengthen segment: Femurs segment, Tibias segment

o Age

o Sex

o Disease etiology will be group in to three groups: Congenital Disease, Short status, Acquired/developmental limb-length discrepancy

o Length Lengthening in the leg

o Per-operative soft tissue release

o Nail producent: Fitbone or Precice.

o Time in treatment the complication arise

o Complication: Time in treatment the complication arises, Complication severity graded after Black et al. 2015, Complication category and Subcategory

Risk of bias (quality) assessment

-Study type will be assessed on the description of the study and not on titel. The study will then classified by Level of Evidence (Oxford Centre for Evidence-Based Medicine).

-Randomised control trials will be evaluate with: A revised tool to assess risk of bias in randomized trials (RoB 2)

-Non-randomised studies will be evaluate with Methodological Index For Non-Randomized Studies (MINORS).

Case report will be evaluate with Murad et al. 2018 for case reports.

-3 selected questions on harms from McMaster tool for assessing quality of harms assessment and reporting in study reports (McHarm)

-The assessment will be used to show the general study quality

-The corresponding author will assess study quality assessment and confirmed the assessment with the other researcher. Disagreements between them will be resolved with consensus.

Strategy for data synthesis

The data synthesis will be conducted with minimum of 400 patient included and studies of level IV evidence or better.
Data analysis will be performed in Stata statistics program
• Complication ratio for I: Grading I/total number of segments

• Complication ratio for II: Grading II/total number of segments

• Complication ratio for IIIA: Grading, IIIA/total number of segments

• Complication ratio for IIIB: Grading IIIB /total number of segments

• Age Range

• Sex ratio

• Disease etiology number per group

• Leg lengthening in range

• Numbers of Femurs segment

• Numbers Tibias segment

• Number of Per-operative soft tissue release

• Number of Nail producent: Fitbone or Precice

• Time in treatment the complication arises: Number of complication per time periode

Analysis of subgroups or subsets

Subgroup analysis: To try to reduce reporting bias on problems. All studies with a reported complication grading I will be selected and form a subgroup for analysis. Number complication grading I in the subgroup /total Number patient in the subgroup.

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Type and method of review

Intervention, Systematic review, Other

Anticipated or actual start date
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Anticipated completion date
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Language
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Country
Denmark

Stage of review
Review Completed published being updated

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Bone Lengthening; Fracture Fixation, Intramedullary; Humans; Internal Fixators; Nails

Date of registration in PROSPERO
28 April 2020

Date of first submission
22 November 2019

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note
Due to the majority of observational Studies (case series) and case reports the quality assessment score was chance to Methodological Index For Non-Randomized Studies (MINORS) and Murad et al. 2018 for case reports. The main outcome was Grade IIIB per segment Data analysis was complication gradring/ total number of segments.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

28 April 2020
11 November 2020
11 November 2020

3. Supplementary of Paper I

Supplementary data

Supplementary data 1: Search strategy for the 3 electronic databases

PubMed

Search	Query
#11	Search ((((“Bone Lengthening”[Mesh]) OR bone lengthening*[Text Word]) OR leg lengthening*[Text Word])) AND (((((“Bone Nails”[Mesh]) OR (((magnetic*[Text Word] OR motorised[Text Word] OR motorized[Text Word])))) OR ((fitbone[Text Word] OR precice[Text Word]))) OR bone lengthening nail*[Text Word]) OR bone nail*[Text Word])
#10	Search ((((“Bone Nails”[Mesh]) OR (((magnetic*[Text Word] OR motorised[Text Word] OR motorized[Text Word])))) OR ((fitbone[Text Word] OR precice[Text Word]))) OR bone lengthening nail*[Text Word]) OR bone nail*[Text Word]
#9	Search bone nail*[Text Word]
#8	Search bone lengthening nail*[Text Word]
#7	Search (fitbone[Text Word] OR precice[Text Word])
#6	Search ((magnetic*[Text Word] OR motorised[Text Word] OR motorized[Text Word]))
#5	Search “Bone Nails”[Mesh]
#4	Search ((“Bone Lengthening”[Mesh]) OR bone lengthening*[Text Word]) OR leg lengthening*[Text Word]
#3	Search leg lengthening*[Text Word]
#2	Search bone lengthening*[Text Word]
#1	Search “Bone Lengthening”[Mesh]

Embase

No.	Query
#11	#4 AND #10
#10	#5 OR #6 OR #7 OR #8 OR #9
#9	‘bone nail*’
#8	‘lengthening nail*’
#7	fitbone OR precice
#6	magnetic* OR motorised OR motorized
#5	‘intramedullary nail’/exp
#4	#1 OR #2 OR #3
#3	‘bone lengthening*’
#2	‘leg lengthening*’
#1	‘leg lengthening’/de

Cochrane

ID	Search
#1	MeSH descriptor: [Bone Lengthening] explode all trees
#2	(bone NEXT lengthening):ti,ab,kw
#3	(leg NEXT lengthening):ti,ab,kw
#4	{OR #1-#3}
#5	MeSH descriptor: [Bone Nails] explode all trees
#6	(magnetic* OR motorised OR motorized):ti,ab,kw
#7	(fitbone OR precice):ti,ab,kw
#8	(lengthening NEXT nail*):ti,ab,kw
#9	(bone NEXT nail*):ti,ab,kw
#10	{OR #5-#9}
#11	#4 AND #10

Supplementary data 2

Disease etiology was grouped into 3 items: Congenital, Short stature, and Acquired/developmental limb-length discrepancy. Items were constructed by modification in accordance with Stricker and Hunt classification (Stricker and Hunt 2004)

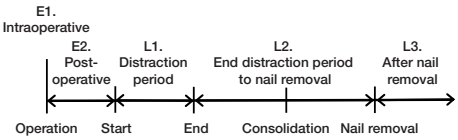
- **Congenital**
  - Congenital disease
    - Tibial hemimelia
    - Fibular hemimelia
    - Developmental coxa vara
    - Developmental dysplasia of the hip
    - Proximal femoral focal deficiency
    - Hemihypertrophy idiopathic
    - Nonsyndromic hemihypertrophy
    - Congenital tibial pseudarthrosis
    - Congenital posteromedial bowing tibia
  - Syndrome
    - Klippel–Trenaunay syndrome
    - Neurofibromatosis
    - Beckwith–Wiedemann syndrome
    - Ollier disease (multiple enchondromas)
    - Russell–Silver
    - Proteus
    - Conradi–Hunerman
    - Vivid cutis marmorata
    - Hemiatrophy
- **Short stature**
  - Short stature cosmetic
  - Achondroplasia
  - Growth-hormone deficiency
- **Acquired/developmental limb-length discrepancy**
  - Physeal growth disturbance
    - Ischemic physeal arrest (Perthes, post-infectious, limb ischemia, septic shock)
    - Blount’s disease (tibia vara)
    - Radiation therapy
    - Juxta-physeal tumor or bone cyst
    - Multiple exostosis/osteochondromatosis
  - Trauma
    - Traumatic physeal growth arrest
    - Fracture malunion (overriding)
    - Slipped capital femoral epiphysis (SCFE)
  - Hyperemia
    - Post-traumatic overgrowth (common after femur shaft fracture)
    - Chronic knee synovitis with overgrowth
    - Chronic osteomyelitis
    - Hemophilia
    - Rheumatoid arthritis
    - Osteoid osteoma
    - Arterio-venous malformation (AVM) or hemangiomatosis
    - Post-surgical hyperemia
  - Neuromuscular
    - Poliomyelitis
    - Spastic hemiplegia (cerebral palsy, stroke)
    - Spinal cord anomaly (tethered cord, syrinx)
  - Adult
    - Malunion
    - Post-traumatic and bone infection
    - Secondary to acute shortening
    - Non-union
    - Bone infection

Supplementary data 3

Complication was scored by time point using the following items.

Early complication
- E1. Intraoperative complication
- E2. Postoperative complication prior to distraction start

Late complication
- L1. Distraction period
- L2. After end of distraction and prior to implant removal
- L3. After implant removal



Supplementary data 4

Main origin	Sub-origin	Definition
Soft tissue	Skin	Skin irritation related to incision, internal/external devices, braces, or other treatment-related issues
	Muscles	Muscles irritation/pain/capturing/rupture related to incision, internal devices, other treatment-related issues
	Tendon	Tendon irritation/pain/captured/rupture related to incision, internal devices, other treatment-related issues
	Pain	Pain related to the treated extremity that is assessed to originate from the treatment
	Others	Other soft tissue complications that are not classified in above categories, including compartment syndrome
Joint	Pain	Pain related to the joint above or below the treated bone
	Contracture	Reduced joint range of motion compared with start of treatment
	Subluxation	A subluxation of a joint is where a connecting bone is partially out of the joint
	Dislocation	A dislocation of a joint is a complete separation of the joints
	Others	Other joint complications that are not classified in above categories
Vascular	Vascular damage	Blunt injury or penetrating injury to a blood vessel causing thrombosis, bleeding, or permanent vessel damage
	Deep vein thrombosis /Pulmonary embolism	Deep vein thrombosis refers to blood clots in large veins of lower limb Pulmonary embolism is a blockage of an artery in the lungs by a substance
	Hemorrhage/hematoma	A hemorrhage is blood escaping from the circulatory system from damaged blood vessels A hematoma is a localized bleeding outside of blood vessels
	Others	Other vascular complications not classified in above categories
Bone	Premature consolidation	The bone regenerated forms bone bridge between the two bone segments. The bridge stops lengthening and an intervention more than standard lengthening is needed
	Delayed healing	Non-union or slow consolidation of the bone regeneration
	Secondary malalignment	Occurrence of new bone malalignment
	Fracture	A partial or complete break in the continuity of the bone
	Others	Other bone complications not classified in above categories
Neurology	Paresthesia	An abnormal dermal sensation with no apparent physical cause and of transient time
	Paralysis	Loss of muscle function in one or more muscles and/or sensory disturbances in the affected area. Can be permanent or transient
	Others	Other neurological complications that are not classified in above categories
Infection	Superficial soft tissue	Clinical soft tissue infected above the facies
	Deep soft tissue	Clinical soft tissue infected below the facies
	Osteomyelitis	Infected bone marrow
	Others	Other infectious complications not classified in above categories
Device-related [a]	Distraction mechanism	Runaway, difficult to distract, non-distracting, non-functioning, and running back
	Mechanical strength	Nail/ring/bar bending or breakage. Rotational instability
	Attachment failure	Failure screw/wire/pins failure
	Other	Others device-related complications not classified in above categories. Could be corrosion, tissue reaction
Others	Patient	Patient-related complication that cannot be classified elsewhere
	Surgical	Surgical-related complication that cannot be classified elsewhere
	Others	All other complications that cannot be classified elsewhere

[a] (modified) (Lee et al. 2017)

Supplementary data 5

The following 3 quality assessment tools were used:

Quality assessment tool: METHODOLOGICAL INDEX FOR NON-RANDOMIZED STUDIES (MINORS) (Slim et al. 2003)
The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score is 16 for non-comparative studies and 24 for comparative studies.

MINORS—General part
1. ***A clearly stated aim:*** the question addressed should be precise and relevant in the light of available literature.
2. ***Inclusion of consecutive patients:*** all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion).
3. ***Prospective collection of data:*** data were collected according to a protocol established before the beginning of the study.
4. ***Endpoints appropriate to the aim of the study:*** unambiguous explanation of the criteria used to evaluate the main outcome, which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.
5. ***Unbiased assessment of the study endpoint:*** blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated.
6. ***Follow-up period appropriate to the aim of the study:*** the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events.
7. ***Loss to follow-up less than 5%:*** all patients should be included in the follow-up. Otherwise, the proportion lost to follow-up should not exceed the proportion experiencing the major endpoint.
8. ***Prospective calculation of the study size:*** information on the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes.

Additional criteria in the case of comparative study
9. ***An adequate control group:*** having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data.
10. ***Contemporary groups:*** control and studied group should be managed during the same time period (no historical comparison).
11. ***Baseline equivalence of groups:*** the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results.
12. ***Adequate statistical analyses:*** whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk.

Quality assessment tool specifically concerning harm: McHarm scale from McMaster University (Santaguida et al. 2011, Kronick et al. 2014).
3 items from the McHarm scale were selected; items were scored as Yes or No.
1. Were the harms **predefined** using standardized or precise definitions?
2. Did the author(s) use **standard** scale(s) or checklist(s) for harms collection?
3. Did the author(s) specify the **number** for each **type** of harmful event for each study group?

Quality assessment tool for case report: Methodological quality and synthesis of case series and case reports (Murad et al. 2018)
Items were scored as Yes (1) or No (0). The global ideal score was 8.
1. Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?
2. Was the exposure adequately ascertained?
3. Was the outcome adequately ascertained?
4. Were other alternative causes that may explain the observation ruled out?
5. Was there a challenge/rechallenge phenomenon?
6. Was there a dose–response effect?
7. Was follow-up long enough for outcomes to occur?
8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

Supplementary data 6

Data from NON-RANDOMIZED STUDIES without comparative part 1

Study reference [a]	A	B	C	D	E	F	G	H	I
Level of evidence	IV	IV	IV	IV	IV	IV	IV	IV	IV
Included in sub-analysis [b]	F / 20	F	F / 20	F / 20	P	P / 20	P	F / 20	F
MINORS Quality assessment tool									
1. A clearly stated aim	2	2	2	2	2	2	1	2	1
2. Inclusion of consecutive patients	2	1	1	0	2	0	0	0	2
3. Prospective collection of data	2	2	2	0	0	0	0	2	0
4. Endpoints appropriate to the aim of the study	2	2	2	2	1	2	1	2	2
5. Unbiased assessment of the study endpoints	0	0	0	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	2	2	2	0	2	1	2	2
7. Loss to follow-up less than 5%	2	2	2	2	2	2	2	2	2
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0	0
Sum	12	11	11	8	7	8	5	10	9
Assessing quality of harms assessment (McMaster selected questions):	Yes/no								
1. Were the harms PREDEFINED using standardized or precise definitions?	No	No	No	No	No	No	No	No	No
2. Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	Yes	Yes	No	Yes	No	No	No	No	Yes
3. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes

[a] Study references: A. (Accadbled et al. 2019); B. (Accadbled et al. 2016); C. (Al-Sayyad 2012); D. (Dinçyürek et al. 2012); E. (Haider and Wozasek 2019); F. (Hammouda et al. 2017); G. (Karakoyun et al. 2016); H. (Krieg et al. 2008); I. (Krieg et al. 2011)
[b] F = FITBONE; P = PRECICE

Data from NON-RANDOMIZED STUDIES without comparative part 2

Study reference [a]	A	B	C	D	E	F	G	H	I
Level of evidence	IV	IV	IV	IV	IV	IV	IV	IV	IV
Included in sub-analysis [b]	P	P	F	F / 20	P / 20	P / 20	F / 20	P / 40	P
MINORS Quality assessment tool									
1. A clearly stated aim	2	2	1	1	2	2	2	2	2
2. Inclusion of consecutive patients	2	0	0	2	0	2	2	2	0
3. Prospective collection of data	2	2	0	0	0	0	0	0	0
4. Endpoints appropriate to the aim of the study	2	2	2	2	1	2	2	2	2
5. Unbiased assessment of the study endpoints	0	0	0	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	1	1	2	2	2	1	2	2	2
7. Loss to follow-up less than 5%	0	0	2	2	2	0	2	0	2
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0	0
Sum	9	7	7	9	7	7	10	8	8
Assessing quality of harms assessment (McMaster selected questions):	Yes/no								
1. Were the harms PREDEFINED using standardized or precise definitions?	No	No	No	No	No	No	No	No	No
2. Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	Yes	No	No	No	Yes	Yes	Yes	Yes	No
3. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[a] Study references: A. (Schiedel et al. 2014); B. (Shabtai et al. 2014); C. (Singh et al. 2006); D. (Steiger et al. 2018); E. (Tiefenboeck et al. 2016); F. (Wiebking et al. 2016); G. (Lenze et al. 2011); H. (Frommer et al. 2018); I. (Kirane et al. 2014)
[b] F = FITBONE; P = PRECICE

Data from NON-RANDOMIZED STUDIES without comparative part 3

Study reference [a]	A	B	C	D	E	F	G	H
Level of evidence	IV	IV	IV	IV	IV	IV	IV	IV
Included in sub-analysis [b]	P	P / 20	F / 20	P	20	P	F	P / 40
MINORS Quality assessment tool								
1. A clearly stated aim	2	2	1	2	1	2	1	1
2. Inclusion of consecutive patients	1	2	0	2	0	2	0	1
3. Prospective collection of data	0	0	0	0	0	2	0	0
4. Endpoints appropriate to the aim of the study	2	2	1	2	2	2	2	2
5. Unbiased assessment of the study endpoints	0	0	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	1	1	2	1	2	2	2	2
7. Loss to follow-up less than 5%	0	2	2	2	2	2	0	2
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0
Sum	6	9	6	9	7	12	5	8
Assessing quality of harms assessment (McMaster selected questions): Yes/no								
1. Were the harms PREDEFINED using standardized or precise definitions?	No	No	No	No	No	No	No	No
2. Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	No	Yes	No	No	No	Yes	No	No
3. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

[a] Study references: A. (Iobst et al. 2018); B. (Birkholtz and De-Lange 2016); C. (Baumgart et al. 1997); D. (Cosic and Edwards 2020); E. (Havitcioglu et al. 2020); F. (Nasto et al. 2020); G. (Küçükkaya et al. 2015); H. (Paley et al. 2014)
[b] F = FITBONE; P = PRECICE

Data from NON-RANDOMIZED STUDIES with a comparative part

Study reference [a]	A	B	C	D	E	F	G
Level of evidence	III	IV	IV	IV	IV	IV	IV
Included in sub-analysis [b]	F / 20	P / 40		P	P / 40	P / 40	40
MINORS Quality assessment tool							
1. A clearly stated aim	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	0	2	2	2	2
3. Prospective collection of data	0	0	0	0	0	0	0
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2
5. Unbiased assessment of the study endpoints	0	0	0	0	2	0	0
6. Follow-up period appropriate to the aim of the study	2	1	2	1	2	0	2
7. Loss to follow-up less than 5%	2	2	2	2	0	0	2
8. Prospective calculation of the study size	0	0	0	0	0	0	0
Additional criteria in the case of comparative study							
9. An adequate control group	2	2	2	2	2	2	2
10. Contemporary groups	2	2	2	0	0	0	2
11. Baseline equivalence of groups	1	1	2	0	0	2	2
12. Adequate statistical analyses	2	2	2	2	2	2	2
Sum	17	16	16	13	14	12	18
Assessing quality of harms assessment (McMaster selected questions): Yes/no							
1. Were the harms PREDEFINED using standardized or precise definitions?	No	No	No	No	No	No	No
2. Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	Yes	No	No	No	Yes	Yes	Yes
3. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[a] Study references: A. (Black et al. 2015); B. (Calder et al. 2019); C. (Karakoyun et al. 2015); D. (Laubscher et al. 2016); E. (Lee et al. 2017); F. (Paley et al. 2015); G. (Horn et al. 2019)
[b] F = FITBONE; P = PRECICE

Data from case reports

First authors Publication year	Couto 2018	Morrison 2016	Harkin 2018	Wu 2018	Muratori 2018	Baumgart 2005	Rozbruch 2017	Kariksiz 2019
Included in sub-analysis [b]	P / 20	P / 20	P / 20	P / 20	P / 20	F / 20	P / 20	P / 20
Quality assessment [c]								
1	1	1	0	1	0	1	0	1
2	1	1	1	1	1	1	1	1
3	1	1	1	1	1	1	1	1
4	0	1	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0
7	1	1	1	0	1	0	1	1
8	1	1	1	0	0	1	1	1
Sum	5	6	4	3	3	4	4	5

[a] Study reference: (Couto et al. 2018), (Morrison and Sontich 2016), (Harkin et al. 2018), (Wu and Kuhn 2018), (Muratori et al. 2018), (Baumgart et al. 2005), (Rozbruch 2017), (Kariksiz and Karakoyun 2019)
[b] F = FITBONE; P = PRECICE
[c] Case reports Quality assessment tool by Murad et al. (Yes = 1, No = 0)

Supplementary data 7

Data from analysis of subgroups

FITBONE complications. Studies that only report use of a FITBONE nail were included. The included studies can be identified in Electronic Supplementary data 6 under included in sub-analysis, marked with FITBONE

Numbers of studies				13	
Numbers of segments				196	
Number of patients				165	
Age range				11–53	
Sex: M / F				63 / 47	
Unidentified regarding sex				55	
Congenital disease				48	
Short stature				13	
Acquired/developmental LLD				81	
Unidentified disease etiology				23	
Femur				144	
Tibia				52	
Severity grade of complications:	I	II	IIIA	IIIB	Sum
Number of complications	38	33	9	10	90
Complications per segment, %	19	17	5	5	46
Complications per patient, %	23	20	5	6	55

PRECICE complications. Studies that only report use of a PRECICE nail were included. The included studies can be identified in Electronic Supplementary data 6 under sub-analysis, marked with PRECICE

Numbers of studies				25	
Numbers of segments				699	
Number of patients				540	
Age range				8–74	
Sex: M / F				283 / 148	
Unidentified regarding sex				109	
Congenital disease				130	
Short stature				84	
Acquired/developmental LLD				191	
Unidentified disease etiology				135	
Femur				589	
Tibia				110	
Severity grade of complications:	I	II	IIIA	IIIB	Sum
Number of complications	73	102	29	16	220
Complications per segment, %	10	15	4	2	31
Complications per patient, %	14	19	5	3	41

Small case-series versus large case-series

As an indirect measure of experience, we have divided the studies into studies with less than 20 patients and studies with more than 40 patients. We have made the assumption that a higher number of patients reflect a higher volume and not just a longer inclusion period. We collected the studies into two groups. Group 1: Studies reporting less than 20 cases. Group 2: Studies reporting more than 40 cases. The studies including between 20 and 40 cases were not included.

Less than 20 patients per study. Studies that only report on fewer than 20 patients were included. The included studies can be identified in Electronic Supplementary data 6 under sub-analysis, marked with 20

Numbers of studies				21	
Numbers of segments				166	
Number of patients				144	
Age range				9–74	
Sex: M / F				86 /58	
Unidentified regarding sex				0	
Congenital disease				36	
Short stature				14	
Acquired/developmental LLD				94	
Unidentified disease etiology				0	
Femur				133	
Tibia				33	
Severity grade of complications:	I	II	IIIA	IIIB	Sum
Number of complications	27	35	11	8	81
Complications per segment, %	16	21	7	5	49
Complications per patient, %	19	24	8	6	56

More than 40 patients per study. Studies that only report on more than 40 patients were included. The included studies can be identified in Electronic Supplementary data 6 under sub-analysis, marked with 40

Numbers of studies				6	
Numbers of segments				475	
Number of patients				331	
Age range				9–68	
Sex: M / F				188 / 96	
Unidentified regarding sex				47	
Congenital disease				104	
Short stature				80	
Acquired/developmental LLD				106	
Unidentified disease etiology				41	
Femur				413	
Tibia				62	
Severity grade of complications:	I	II	IIIA	IIIB	Sum
Number of complications	39	67	26	9	141
Complications per segment, %	8	14	5	2	30
Complications per patient, %	12	20	8	3	43

4. Manuscript II

5. Appendix of Manuscript II

6. Manuscript III

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