The Effectiveness of Different Minimally Invasive Epiphysiodesis Techniques in the Management of Paediatric Leg Length Discrepancies:
A Systematic Review

Dr Megan Cain

Master of Clinical Science
The Joanna Briggs Institute
Faculty of Health Sciences
The University of Adelaide, South Australia

18th November 2018

Table of Contents

Acknowledgements

I would like to acknowledge and wholeheartedly thank my primary supervisors, Dr Matthew Stephenson and A/Prof Nicole Williams, for their ongoing advice and support throughout this Masters programme. A thank you must also go to Dr Kandiah Umapathysivam my secondary supervisor for his valued opinions throughout. A special thank you is required for Dagmara Riitano who aided the editing process and Dr Jamie Ianunzio for his assistance with critical appraisal and data extraction.

I would also like to thank all the remaining staff at the Joanna Briggs Institute for their valuable lectures, advice and genuine interest. I have gained much more than the answer to my research question by undertaking this degree.

Finally, I would like to thank all my family and friends for their support throughout this journey.

Declarations

I, Megan Cain, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Signed

Megan Cain
18th November 2018

Abstract

Paediatric leg length discrepancies (LLDs) are more common than might be expected with the literature reporting that between 0.1 and 7% of the paediatric population has a LLD of >2 cm. Causes can be subdivided into congenital and acquired aetiologies. LLDs greater than 2 cm can lead to functional complications such as altered gait kinetics and abnormal loading of joints. For children predicted to have a LLD of 2-5 cm, minimally invasive epiphysiodesis (MIE) is the current management of choice. Presently, there are four MIE techniques commonly used throughout the world, however, no systematic reviews have compared these techniques.

The objective of this thesis was to conduct a systematic review to synthesise the best available evidence on the use of MIE for the management of paediatric LLD. The effectiveness of four different techniques was compared: percutaneous epiphysiodesis using transphyseal screws (PETS); physeal drilling and curettage (PDC); physeal stapling; and guided growth with eight-Plates.

Studies that evaluated two or more of the interventions or those that investigated a single intervention were considered for inclusion. Primary outcomes for the review included absolute LLD at skeletal maturity; rate of correction; percentage of correction; and incidence of long term complications.

This review found that all techniques were sufficient at reducing the burden of a LLD with the mean final LLD of each being calculated to be <2 cm. Despite this, the rate of complications was higher in the eight-Plates and staples groups than the PDC and PETS groups. The PETS cohort had a reported failure of growth plate arrest (GPA) of 2.5% compared with 6% in the PDC and staples groups and 14% in the eight-Plate groups. The rate of inadequate correction (i.e. over or under correction), were also higher in the eight-Plate and staples groups (15% and 23%, respectively) than the PETS and PDC groups (8% and 13%, respectively). The incidence of angular deformities was much higher in the staples cohort (33%) than in the other groups (PDC 2%; PETS 9%; and eight-Plates 5%). The incidence of acute complications, such as haematoma, infection and acute knee pain, was similar across all techniques.

Unfortunately, the overall level of evidence was low, due to the suboptimal and heterogeneous nature of the study designs included in this systematic review, and thus, treatment guidelines could not be developed. Notwithstanding this, the available evidence showed that all the evaluated techniques can adequately reduce a LLD, although PDC and PETS appear to be more effective at this. Further research is required to substantiate these claims; for now, all techniques remain an acceptable technique for addressing LLDs of 2-5 cm.

Dissertation structure

This dissertation is presented in five chapters.

Chapter 1:

- Overview: This chapter gives context to the topic in question, including a review of the objective, research questions, classification of pathology, methods for diagnosing and monitoring LLDs, complications of LLDs and a summary of current treatment modalities. In this chapter the need for a systematic review is considered and its purpose defined.

Chapter 2:

- Methods: This chapter describes the methods used to conduct the systematic review for this thesis. It outlines the inclusion criteria including the types of participants, interventions, comparators and outcomes. It also details the search strategy, and the method used for critical appraisal, data collection and data synthesis.

Chapter 3:

- Results: This chapter details all research results, analyses the methodological quality of each included study and synthesises the individual study characteristics.

Chapter 4:

- Discussion: This chapter discusses the main findings of the extracted data and attempts to place them within the context of the existing literature. It includes a discussion on individual study limitations and limitations of this systematic review.

Chapter 5:

- Conclusion: The thesis concludes with a chapter that examines the implications for practice and makes recommendations for future research directions.

List of abbreviations

Abbreviation	Meaning
AD	Angular deformity
AFO	Ankle foot orthosis
AP	Anteroposterior – radiographic dimension
ASIS	Anterior superior iliac spine
CR	Computed radiography
CT	Computed tomography
DDH	Developmental dysplasia of the hip
EBM	Evidence-based medicine
EOS	EOS imaging (Paris, France)
GPA	Growth plate arrest
GT	Greater trochanter
IPD	Individual patient data
JBI	Joanna Briggs Institute
LLD	Leg length discrepancy
MIE	Minimally invasive epiphysiodesis
MRI	Magnetic resonance imaging
PDC	Percutaneous drilling and curettage
PETS	Percutaneous epiphysiodesis transphyseal screws
RCT	Randomised control trial
US	Ultrasound

List of definitions

Skeletal maturity	All bony growth has been completed.
Epiphysiodesis	The process of prematurely halting growth through a physis.
Anisomelia	Limb length discrepancy.
Malunited	United in a position of abnormality or deformity.
Functional LLD	A unilateral asymmetry of the lower extremity without any concomitant shortening of the osseous components of the lower limb.
Apparent LLD	Assessed by measuring the distance from the umbiliscus to the medial malleolus.
True LLD	Assessed by measuring the distance from the ASIS to the medial malleolus.
Salter Harris fracture classification system	The standard classification for physeal fractures was set forth by Salter and Harris. This classification divides fractures into five types based on whether the metaphysis, physis or epiphysis is involved as demonstrated radiographically.
Ipsilateral	Same side of body.
Contralateral	Opposite side of body.
Valgus	A deformity involving oblique displacement of the distal segment of a limb away from the midline.
Varus	A deformity involving oblique displacement of the distal segment of a limb towards the midline.
Galeazzi test	Enables assessment of femoral and tibial shortening. The patient is supine with the hips flexed to 45º and the knees flexed up to 90º. Place the malleoli together (the test is inaccurate if you are unable to do so). Assess the position of the knees: • When one knee projects farther forwards – the problem lies with the femur. • When one knee is higher than the other – tibia is the culprit.
Bryant's triangle	Line perpendicular to greater tuberosity (GT) of femur and ASIS.
Nelaton's line	Line from ischial tuberosity to ASIS. The GT should be on or below the line.
Klisic's line	Line from GT to ASIS – should aim to the umbilicus.
Minimally invasive surgical procedure	Minimally invasive surgeries encompass surgical techniques that limit the size of incisions needed and so lessen wound healing time, associated pain and risk of infection.

Orthoroentogenogram	An imaging technique to assess leg length discrepancies utilising three exposure centres at the hip, knee and ankle so as to minimise the magnification error. A single large cassette remains under the patient who lays still throughout the exposures.
Scanogram	A radiographic method for assessing leg length discrepancy utilising three exposure centres: hip, knee and ankle to minimise the magnification error. The patient lies supine adjacent to a radio-opaque ruler. Three separate standard sized radiographic cassettes are used for this technique and are moved following each exposure.
Teleoroentgenogram	Teleoroentgenogram: radiographic method for assessing leg length discrepancy. It involves a single long cassette being placed behind the patient with a single exposure centre over the knee joint. During the radiographic assessment the patient is ideally standing with a block placed under their shorter limb in attempt to equalise the LLD, though it has been reported to have similar accuracy with the patient supine.
Computed radiography (CR)	Three separate radiographic exposure centres where images are taken and stored on a photosimulator allowing for images to be stitched together with customised software.
Microdose radiography	Computer assisited imaging process whereby a continuous series of photon beams is collimated to act as a point source, which is then projected through the patient to strike a computerised detector. The detector and photon source move together scanning the field in a line by line motion so that the beam is always horizontal to the patient.
Computed tomography (CT) scanogram	CT technique untilised to measure discrepancies in leg length. CT scout images are taken of the joints of the lower limb, followed by the cursor being placed over the joints to obtain true measurements.
EOS	A biplanar medical imaging system whose aim is to provide frontal and lateral radiography images, while limiting the x-ray dose absorbed by the patient in a sitting or standing position.
Ultrasound (US)	Imaging modality whereby high frequency soundwaves are utilised to map out tissue. This is possible as penetrance of the sound waves varies for each different tissue substrate. These echoes are then converted into a picture referred to as a sonogram.

Magnetic resonance imaging (MRI)	Is a diagnostic technique that uses magnetic fields and radio waves to produce a detailed image of the body's soft tissue and bones. During the acquisition of an MRI image the magnet that rotates around the body excites hydrogen atoms, which results in delineation of different tissues.
PDC	PDC refers to the surgical technique of epiphysiodesis whereby the physis is destroyed with aid of a drill and curette passed through a small medial and lateral incision.
PETS	PETS refers to the surgical technique of epiphysiodeiss whereby the physis is compressed with the aid of a cannulated screw being passed across both the medial and lateral side of the physis resulting in growth cessation through this physis.
Staple epiphysiodesis	Staple epiphysiodesis refers to the surgical technique of epiphysiodesis whereby the physis is compressed with the aid of three staples on both the medial and lateral side of the physis, resulting in growth retardation through this physis.
eight-Plate epiphysiodesis	eight-Plate epiphysiodesis refers to the surgical technique of epiphysiodesis whereby the physis is spanned by a plate that provides a tension band force across the physis resulting in growth modulation through the physis.
Phemister	Phemister is the previous 'gold standard' of epiphysiodesis that represents an open form, whereby a bone bridge is created across the physis which haults growth. This is achieved by a one centimetre rectangular block of cortical bone from both the medial and lateral aspect of the joint being excised. The block of bone contains the peripheral physis with adjacent metaphyseal and epiphyseal bone. The physis is then destroyed and the bone block rotated 180 degrees prior to being reinserted.
Gold standard	An object, technique or procedure of superior quality, which serves as a point of reference against which other things of its type may be compared.

Chapter 1: Introduction

This review aimed to synthesise the best available evidence evaluating the use of minimally invasive epiphysiodesis (MIE) techniques in the management of paediatric leg length discrepancies (LLDs). Epiphysiodesis is a surgical procedure undertaken to slow or stop growth through an open physis (growth plate) to correct LLD. The surgical procedure was initially proposed by Phemister[1] in 1933, who first described an open approach for halting the growth of the physis. Over the years, a number of new methods have been developed that achieve the same surgical outcome, most of which can be placed under the umbrella term of 'minimally invasive'.

LLDs are a common phenomenon affecting approximately 23% of the population to some extent.[2, 3] However, a LLD of less than 2 cm rarely has any impact on function and consequently, has been considered by some as within the 'normal' range of variation.[4-6] A study by Dmach et al[7] found that up to 7% of children between the ages of 8 and 12 years had a LLD of >2 cm. This was markedly more than the 0.1% identified in the epidemiological study conducted by Guichet et al[8] in 1991. As LLD increases, so does the negative impact on gait biomechanics and patients' quality of life.[9-13] Accordingly, a number of surgical interventions have been developed to correct LLDs. For children predicted to have a LLD of 2-5 cm at skeletal maturity, epiphysiodesis is a good management option, although a limb lengthening procedure may be more appropriate if the discrepancy is over 5 cm. This introductory chapter aims to provide context for the review and outlines the review objectives, research questions, the classification of pathology, methods for diagnosing and monitoring LLDs, complications of LLDs and a summary of current treatment modalities. The need for a systematic review will also be considered and its purpose defined.

What is a leg length discrepancy?

A LLD or anisomelia[14] is an inequality between the overall length of the right versus the left limb. This may be secondary to the overgrowth of a limb or failure of a limb to grow, and can affect one or all bones in the lower limb.

Causes of leg length discrepancies

There are many different causes of LLDs although they can be broadly subdivided into three categories: congenital disorders or syndromes, paralytic disorders and acquired physeal injuries. These have been summarised in Table 1. It is important to distinguish between a true LLD caused by the shortening or lengthening of a single or several bones, as opposed to a apparent LLD caused by joint contractures, scoliosis and other soft tissue deformities.[15]

Table 1: Causes of leg length discrepancies

Category	By growth retardation	By growth simulation
Congenital disorders	Hemiatrophy Proximal femoral deficiency Developmental dysplasia of the hip Unilateral club foot Neurofibromatosis Ollier's disease (dyschondroplasia) Familial multiple exostosis Russel-Silver syndrome	Hemihypertrophy Klippel-Trenaunay syndrome Parkes-Weber syndrome Haemarthrosis secondary to haemophilia Proteus syndrome Beckwith-Wiederman syndrome
Paralytic disorders	Cerebral palsy Polio Spinal dysraphism	
Acquired physeal injuries	**Bone or joint infection** Epiphyseal plate osteomyelitis Septic arthritis (Tom Smith arthritis) Tuberculosis **Trauma** Damage to epiphyseal plate Diaphyseal fracture with large overriding fragment Burns **Tumours** Osteochondroma (solitary exostosis) Juxta-physeal tumours Neurofibromatosis	**Bone or joint infection** Diaphyseal osteomyelitis Brodie's abscess Septic arthritis **Trauma** Diaphyseal and metaphyseal fractures Diaphyseal operations – stripping of periosteum, bone graft, osteotomy **Tumours** Haemangioma Juxta-physeal tumours Neurofibromatosis Fibrous dysplasia
Other	Prolonged immobilisation Peripheral nerve injury Legg-Calvé-Perthes disease	Traumatic arteriovenous aneurysms

Polio was historically the most common cause of LLDs, however, in modern times LLD is more likely to be associated with a congenital abnormality or trauma.

Leg length discrepancy classification

LLDs can be classified as either static or progressive depending on the pathology.[16, 17] A static LLD is where the deformity does not become larger as the patient grows, as is the case with a malunited tibial or femoral diaphyseal fracture. Comparatively, a progressive LLD is where the deformity enlarges as the patient grows, for example, due to physeal growth arrest. Congenital LLDs typically maintain proportional growth over time. For example, if the tibia is 10% shorter than the normal side at birth, it will be approximately 10% shorter than the normal side at maturity.[16]

Clinical assessment

When performing a LLD examination, there are four main physical outcomes that can be obtained: a symmetrical stance with a level pelvis; a symmetrical stance with an oblique pelvis; an asymmetrical stance with a level pelvis; and an asymmetrical stance with an oblique pelvis.[18]

A patient with a symmetrical stance, a level pelvis and leg length equality, is not always 'normal' as they may have a bilateral symmetrical deformity, such as bilateral varus knees (i.e. bowed knees). Patients with a symmetrical stance and an oblique pelvis commonly have an uncompensated LLD. Those with an asymmetrical stance and level pelvis can either have a fully compensated LLD, obtained, for example, through flexing (bending) the contralateral knee or an equinus compensation (standing on toes) of the ipsilateral ankle. Compensatory mechanisms are seen with both sagittal and coronal plane deformities. Finally, an asymmetrical stance with an oblique pelvis is referred to as a partly compensated LLD. This may be secondary to a coronal hip deformity with a sagittal compensation, or vice versa, a sagittal deformity with a coronal compensation. Thus, it is always important to assess for confounding angular and torsional deformities as well as soft tissue contractures of the ipsilateral or contralateral extremity, which may influence patients' functional leg lengths. On the whole, flexion contractures around the knee and hip will result in an apparent shortening of the that limb, while adduction contractures of the hip and equinus deformities of the ankle are likely to result in apparent lengthening of the affected extremity.

When clinically assessing a LLD, it is also important to use a systematic approach that starts with an assessment of posture, which should include identifying any signs of contractures (hip, knee or ankle), congenital anomalies, hemihypertrophy and the presence of scarring. It is then important to assess gait. Children usually compensate for their discrepancies well, by walking on the toes of their short leg resuling in an equinus deformity, or flexing their knee of the longer limb. Next, it is important to measure the LLD. In the assessment of a functional LLD, a block test is utilised, which involves levelling the pelvis of an erect patient by placing blocks of a known height under the short limb. This is referred to as the ‘indirect’ clinical method for measuring LLD.[16] This method considers the disparity in foot height between the two limbs, can correct pelvic tilt and should correct scoliosis. However, Hanada et al[19] found this method to consistently underestimate the LLD by between 3.8 and 5.1 mm.

Apparent LLDs (artificial differences in limb length – pelvic obliquity or contractures) can be simply assessed with the aid of a tape measure: a measurement from the umbilicus to the medial malleolus on both sides is made and compared. This is the ‘direct’ clinical method for assessing LLDs. The disadvantage of this technique is that it can be difficult to identify bony prominences if the girth of the two limbs is different. It can also lead to an error in measurement if the patient has angular deformities. Beattie et al[20] cautioned against relying solely on the clinical assessment of LLD though, if necessary encouraged using the average of at least two separate measurements when using a tape measure, to assess the magnitude of a LLD. A study by Lampe et al[21] compared the similarity of LLD measurements obtained with blocks and radiology versus tape measure and radiology. They found that 95% of the measurements obtained by using the blocks were within 1.6 cm of those obtained with radiology, however, the results were not as accurate when the use of a tape measure was compared with radiological measurements.

Once a LLD has been identified it is important to determine the site of the shortening. This is sometimes clinically obvious, but in cases where the deformity is less easily localised, assessment can be aided by multiple tests, including the Galeazzi test (enables you to assess femoral and tibial shortening); Bryant’s triangle (formed by lines perpendicular to the greater trochanter [GT] of the femur and anterior superior iliac spine [ASIS]); Nelaton’s line (the line from ischial tuberosity to ASIS, whereby the GT should be on or below the line); and Klisic’s line (the line from GT to ASIS, which should aim to the umbilicus).[18]

Radiological assessment of leg length discrepancies

Clinical assessment of a LLD may be accompanied by a radiological assessment if it will be useful in the ongoing management of the patient. There are several different radiographic methods available to quantitate a LLD. The technique used is very much dependent on the location of the discrepancy, the age of the child and what the treating institution has available to them. Traditionally, plain radiographs have been used to document the objective measurement of LLD. There are three different plain radiographic techniques described in the literature for assessing LLDs: orthoentogenograms, scanograms and teleroentgeograms.

Despite plain radiographs being most widely used, computed scanograms or computed tomography and EOS are now considered more accurate alternatives. With all techniques, it is important to obtain a series of images over a period of time, to monitor the rate of change in the discrepancy and thus, time the surgical correction adequately.[16] Further to obtaining sufficiently reliable or accurate limb length and alignment assessments, it is highly important to minimse a child's exposure to radiation. It is estimated that children (especially younger children) are two to five times more sensitive to radiation than adults.[22] Table 2 compares a number of different imaging modalities with respect to their accuracy, magnification error, radiation exposure and other imaging characteristics.

Orthoroentogenogram

The orthoroentogenogram is a technique initially described by Green[23] in 1946. It was developed to minimise measurement error that resulted from variable 'magnification'. An orthoroentogenogram utilises a long ruler, which is placed on one large film cassette and three distinct exposure centres: the hip, knee and ankle (depicted in Figure 1). This technique has been validated as providing reliable and accurate measurements of LLDs, and for this reason is still frequently utilised today.[24]

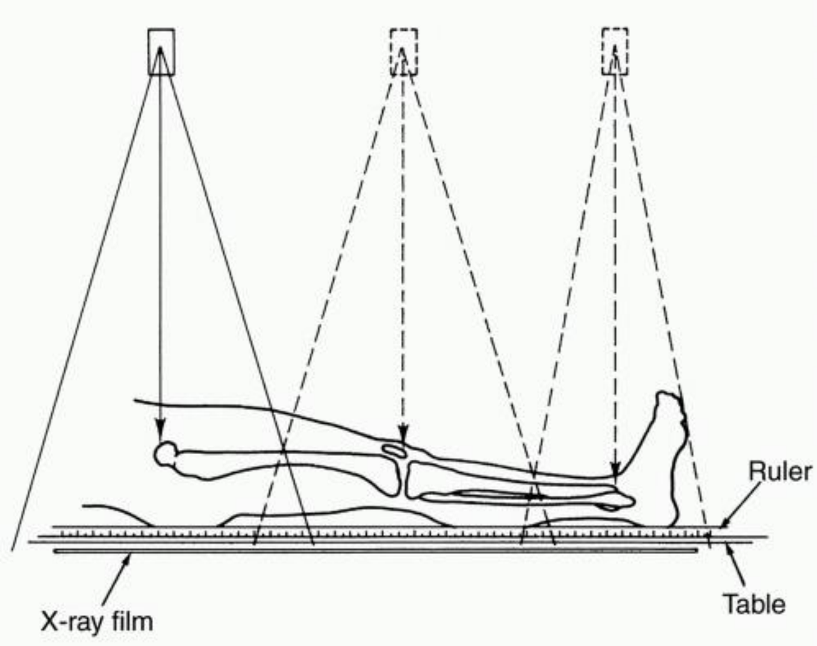

Figure 1: The orthoroentogenogram imaging technique assesses leg length discrepancies utilising three exposure centres (at the hip, knee and ankle) to minimise magnification error. A single large cassette remains under the patient who lays still throughout the exposures. (From Morrissy RT, W. S., eds. (2017). Lovell and Winter's Pediatric Orthopedics. Philadelphia, Lippincott Williams & Wilkins.[25] - no formal copyright obtainable)

Scanogram

The scanogram was first described in 1942 by Merill et al.[26] Their article detailed the use of a uniquely constructed 18 x 48 inch plywood grid with copper wires that were placed one inch apart, lead numbers were then placed on all the 'even' wires. The patient lay supine on the grid with sandbags at their feet, and straps across their thighs, to minimise movement error or artifact. Once again, three radiographic exposures centred over the hip, knee and ankle were used. This technique has since been modified, with patients now being positioned supine with patellae to the ceiling and a radio-opaque ruler taped to the table between their limbs. A standardised patient-to-tube distance of 101 cm is used and three exposures are once again obtained[27] (depicted in Figure 2).

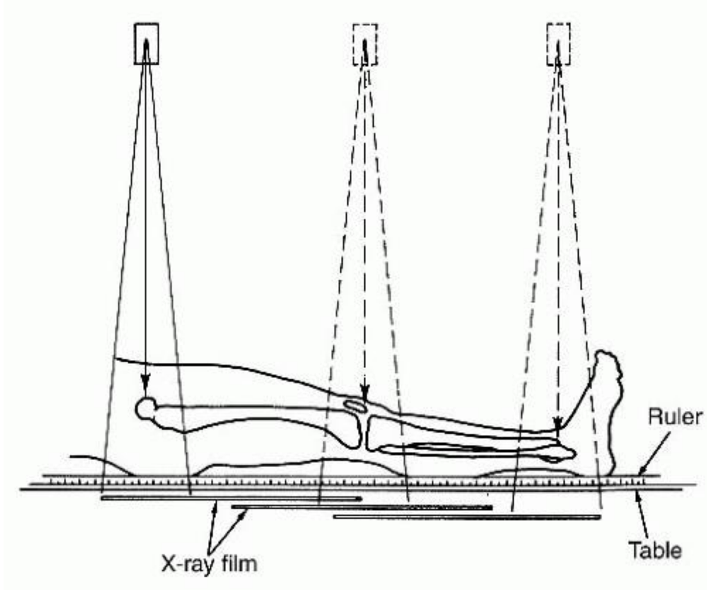

Figure 2: The scanogram is a radiographic method that asseses leg length discrepancy using three exposure centres (at the hip, knee and ankle) to minimise magnification error. The patient lies supine adjacent to a radio-opaque ruler. Three separate standard sized radiographic cassettes are used for this technique and are moved following each exposure. (From Morrissy RT, W. S., eds. (2017). Lovell and Winter's Pediatric Orthopedics. Philadelphia, Lippincott Williams & Wilkins.[25] - no formal copyright obtainable)

Teleoroentgenogram

The teleoroentgenogram utilises a full length standing (traditionally) or supine anteroposterior (AP) radiograph of the lower extremity. With the x-ray beam centred at the knee, a single radiographic exposure of both lower limbs is obtained. The tube is placed approximately 180-200 cm from the patient, who stands or lies with their patellae pointing directly forward[16] (Figure 3a). An attempt is made to level the pelvis with an appropriately sized block that is placed under the 'short' limb (Figure 3b). If the radiograph shows that iliac crests are at the same level (pelvic obliquity corrected) indicating equalisation of LLD, the LLD can be simply taken as the height of the blocks. This technique is the best radiographic assessment for young children as it requires only a single image eliminating motion artifact. Additionally, visualisation of the entire skeleton can assist in determining the aetiology of the LLD. A known disadvantage of this technique is magnification error due to parallax as reported by Green,[23] Hornsfield et al,[28] Moseley,[25] and Sabharwal et al[29]. Despite this disadvantage, it is a quick and easy investigation with lower radiation exposure than scanograms and orthoreotograms.[16]

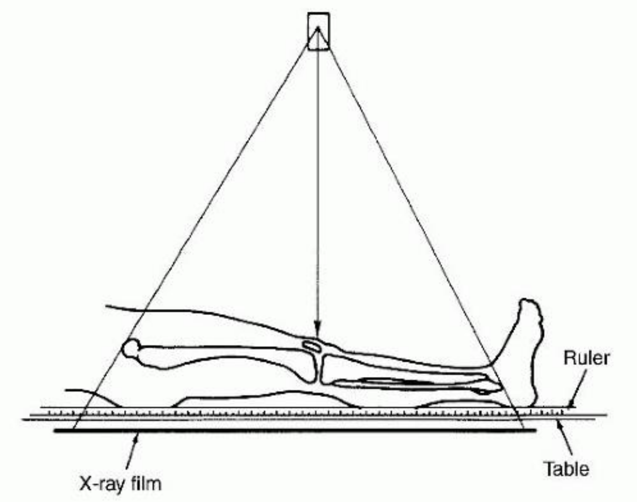

Figure 3a: The teleoroentgenogram radiographic method for assessing leg length discrepancy involves a single long cassette being placed behind the patient with a single exposure centre over the knee joint. (From Morrissy RT, W. S., eds. (2017). Lovell and Winter's Pediatric Orthopedics. Philadelphia, Lippincott Williams & Wilkins.[25] - no formal copyright obtainable)

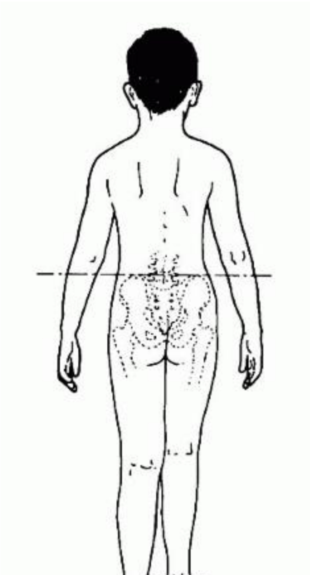

Figure 3b: During the teleoroentgenogram radiographic assessment the patient is ideally standing with a block placed under their shorter limb in attempt to equalise the LLD, however, it has been reported to have similar accuracy with the patient in supine. (From Morrissy RT, W. S., eds. (2017). Lovell and Winter's Pediatric Orthopedics. Philadelphia, Lippincott Williams & Wilkins.[25] - no formal copyright obtainable)

Computed radiography

Computed radiography (CR) is a newer technique for quantifying LLDs. To obtain an adequate radiograph, the minimum patient-to-tube distance is 203 cm, which needs to increase for taller individuals. As described by Sabharwal et al,[16] the radiographs (three different exposure centres: hip, knee and ankle) are taken and stored on a photostimulatable phosphor receptor within a standard radiographic cassette. The images can then be transferred to and recorded on a computed radiography long length imaging system. The three images are then 'stitched' together with the aid of customised software. The operator can use the computer to adjust the image parameters and enhance the final image.

Sabharwal et al[29] compared CR with teleoroentgenogram and found a strong correlation (R=0.96) between the two in the measurement of LLD, however, the mean radiation dose was 1.6 to 3.8 times greater for the CR-based scanograms. There are still teething issues with this technique, as is the case with many 'new techniques'. For example, if the 'digital stiching' of the images is done incorrectly, it can hide the pathology or lead to a false impression on the degree of the deformity.[30]

Microdose radiography

Microdose radiography is another computer assisted imaging process that has been reported to substantially reduce the radiation exposure to patients.[31] With this technique, the patient stands stationary in front of the x-ray machine for 20 seconds during which time a continuous series of photon beams collimate to act as a point source and are then projected through the patient to strike a computerised detector. The detector and photon source move together scanning the field in a line-by-line motion so that the beam is always horizontal to the patient. Altongy et al[31] found this method to be more accurate than standard orthoroentgenograms.

Computed tomography scanogram

During a computer tomography (CT) radiographic assessment, the patient is placed on a table and AP scout views of their bilateral tibias and femurs are obtained.[32] It is also possible to obtain lateral scout views, which can aid in correcting for contractures/saggital deformities.[33, 34] The actual length of the limb determines how many shots are required, with each shot covering a maximal distance of 48 cm.[32] Cursors are then placed over the superior aspect of the imaged femoral head and the distal portion of the medial femoral condyle, with the distance between these two cursors representing the overall length of the individual femur. The tibial length is similarly determined and involves measuring the distance between cursors placed on the medial tibial plateau and the central portion of the tibial plafond. It has been reported that the radiation dose of a CT scanogram is 80% less than that of an orthoroentgenogram.[33] Several research groups have compared CT scanograms to standard orthoroentgenography and found that the accuracy is similar or better for CT scanograms.[32, 33, 35]

EOS (EOS imaging, Paris, France)

EOS is a more novel way to assess limb length and alignment. It is a low-dose biplanar digital radiographic imaging system that utilises highly sensitive gaseous photon detectors.[36] It involves the child standing in a Plexiglas cabin (which allows for an assessment of their overall limb alignment), wherein two linear x-ray sources and two gaseous detector arrays, move in a synchronised manner to scan the patient in two orthogonal planes. Once the scanning region has been determined, a default set of image acquisition parameters is applied based on both the examination type and one of three body sizes (large adult; average adult; child). Each of these separate acquisition modes has a set kilovolts and milliamps for the x-ray tube and the vertical translation speed of the scan. As each scan takes approximately 20 seconds there is potential for motion artefact.[37]

Other less commonly used imaging modalities

Ultrasound

In Europe, ultrasound (US) has been used for many years to facilitate the identification of LLD magnitudes. This technique utilises a US transducer probe to identify bony landmarks at the hip, knee and ankle to determine the distance between them.[38-40] Due to the abscense of radiation exposure, good reproducibility and intra/inter-observer reliability, it is recommended as a first line investigation of LLDs in many European countries.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is not traditionally used to assess bony abnormalities and is not widely accepted for determining the extent of a LLD. However, a study by Leitzes et al[41] found it to be a reproducible method for assessing LLD with high inter- and intra-observer reliability. However, MRI was on average 2.9 mm outside the true measurement of LLD compared with 0.56 mm on a scanogram and 0.62 mm on a CT scanogram.

Table 2: Comparison of the different methods of assessing leg length discrepancies (modified from 'Methods for Assessing Leg Length Discrepancy' by Sabharwal et al [16]).

Method	Reliability	Accuracy	Magnification	Approximate radiation exposure (mrads)	Incorporated height of foot and pelvis	Weight bearing
Clinical						
Standing block test measure functional	++	+	None	NA	Yes	Yes
Supine tape measure 'apparent' (umbilicus to malleolus)	+	+	None	NA	Partial	No
Supine tape measure 'real' (ASIS to malleolus)	+	+	None	NA	No	No
Imaging						
Teleoreontgenogram	++++	+++	-5%	42	Yes	Yes
Orthoroentgenogram	+++	+++	Minimal	200	No	No
Scanogram	++++	+++	Minimal	200	No	No
Computed radiography	++++	+++	Variable	Variable – less than standard radiography	Variable	Variable
Microdose digital radiography	+++	++++	None	2	Yes	Yes
Ultrasound	+++	++	None	None	No	Yes
CT scanogram	++++	++++	Minimal	3.8	No	No
MRI	++++	+++	Minimal	None	No	No
EOS	++++	++++	Minimal	0.7	Yes	Yes

NA = not applicable.

Consequences of leg length discrepancies

Most studies that have investigated the effects of LLDs on arthritis of the hip and knee, lower back pain, stress fractures, standing balance, gait economy and more, have reported conflicting results. No study to date has been able to adequately addressed this issue or question because to do so, a large cohort study would need to be conducted that involved study groups of sufficient size to control for individuals' genetic predisposition for arthritis as well as traumatic and lifestyle (obesity, smoking and exercise) factors, and other comorbid conditions that can impact on the rates of arthritis and back pain.

It is generally accepted that for an individual to experience complications or altered gait kinetics secondary to a LLD, it must surpass 2 cm in magnitude,[2, 42] although once again, this is not supported by all (Table 3). A recent study published in the Journal of Pediatric Orthopaedics[43] identified that the location of the shortening, for example, at the tibia or femur, impacted the gait compensation strategy and thus, patient symptomatology. The study authors reported that if the discrepancy was in the femur, patients tended to compensate more distally, such as with ankle movements, which resulted in more work at the ankle joint in the shorter limb as compared to the normal limb. Conversely, patients with tibial shortening demonstrated compensation more proximally with increased pelvic obliquity. This results in more work or energy expenditure being required at the hip joint on the shorter limb compared to the normal limb. It is postulated that this increase in work by a joint over time can lead to joint pain and arthritis.

Table 3: Leg length discrepancy necessary to impact patients – objective criteria (adapted from Gurney, 2002[44])

Author	Magnitude of leg length discrepancy (mm)	Problem/outcome measure
Giles[a45]	9 mm	Lumbosacral facet joint changes.
Giles[a 46]	9 mm	Lumbar back pain and lumbosacral arthritic changes.
Young[b 47]	15 mm	Pelvic torsion/obliquity.
Cummings[b 48]	6.3 mm	Pelvic tilt – pelvic obliquity with posterior rotation of the innominate over the longer leg and simultaneous anterior rotation over the shorter leg.
Specht[a49]	6 mm	Scoliosis and altered lordosis (hypo and hyper) occurs in just over half of subjects with an LLD of >6 mm.
Papaioannou[a 50]	>22 mm	Scoliosis - significant asymmetry of lateral flexion and the lumbar scoliosis was compensatory and non-progressive.
Mahar[b51]	10 mm	A 1 cm lift resulted in a significant increase in postural sway (medial to lateral), and significant increase in the mean centre of gravity/pressure towards the longer leg.
Brand[b52]	35 mm	Altered forces at hip – although variable. Increased predominately in the shorter side.
Schuit[a53]	10.4 mm	Altered ground force reactions – this persisted but changed with a heal lift being placed. Without a lift, increased lateral force on the shorter leg.
Bhave[a54]	49 mm	Altered ground force reactions, asymmetrical stance phase – the difference mean stance phase between the short and long limb was 12%. This normalised to 2.4% following a lengthening procedure.

Author	Magnitude of leg length discrepancy (mm)	Problem/outcome measure
Blake[a55]	3.2mm	Increased rear foot eversion during midstance – by 3 degrees or more on the longer side.
Kaufman[a10]	>20mm	Gait asymmetry increased as LLD increased, although the degree of asymmetry was not predictable between patients.
Vink[b56]	40 mm	Increased lower back electromyographic activity during heel strike of the longer limb – likely secondary to increased trunk flexion due to increased deceleration of the pelvis during heel strike.
Delacerda[a57]	26.7 mm	Increased kinetic energy during walking, increased oxygen consumption submaximal during running. This was corrected by applying a shoe lift to the individual.
Song[a12]	5.5%	Increased mechanical work of the short limb, greater vertical centre of mass displacement with gait. Demonstrated that children have great compensation mechanisms.
Liu[a11]	>23 mm	Gait asymmetry – their results differed from Kaufmann[10] stating that ground force reaction and LLD did not correlate well.
Gurney[b58]	20 mm	Increased oxygen consumption during gait and rating of perceived exertion.
Gurney[b58]	30 mm	Increased heart rate, minute ventilation and electromyography activity in quadriceps of the long leg, leading to earlier quadriceps fatigue.
Gurney[b58]	40 mm	Significant increase in EMG activity of lower extremity and especially plantar flexors on shorter limb.
[a] assessments of actual LLD [b] assessments on artificially induced LLD		

Song et al[12] reported that a discrepancy greater than 5.5% of the long extremity increased the mechanical work load of the longer limb and increased the vertical displacement of the child's centre of body mass. This was associated with a significant increase in the child's energy requirements for mobility. The idea of altered gait kinetics and increased energy expenditure is now well supported in the literature and is known as the 'short leg gait' phenomenon.[10, 44, 54, 58]

Impact on patients' quality of life

A number of studies have assessed, or attempted to assess, the impact of LLD on patients' quality of life, although, in general, have essentially just examined how gait abnormalities can impact patients by identifying the difficulties they face when participating in day-to-day activities. Ramaker et al[59] showed that children with a congenital or acquired LLD of >3 cm often experience significant pain and discomfort either at rest or during physical activities. Ghoneem et al[60] took it a step further and showed that an impairment in gait will restrict how a child functions and thus, participates in day-to-day life activities, which has been shown to lead to social and psychological difficulties.

Montpetit et al[61] conducted a study assessing the pre- and post-operative quality of life in children undergoing a lengthening procedure. They found that despite patients subjectively reporting minimal preoperative pain and generally good functional mobility, they consistently scored poorly on the quality of life and physical health questions due to difficulties with running, sport participation, the lifting of heavy objects and having persistently low energy levels (likely due to altered gait mechanics and economics.). This population of patients has also been shown to struggle psychologically due to the visible physical difference secondary to their LLD.[62]

In a separate cohort of patients, those with a LLD due to developmental dysplasia of the hip (DDH) reported significantly higher rates of depression and anxiety than those with DDH with no perceived LLD.[63] The reason for this is not clearly known, however, it is thought that the physchological perception of a LLD makes the patient more fixated on the pathology, which results in them focusing more on their pain and functional limitations. Unfortunately, a systematic review conducted in 2017[64] found that, at present, no validated patient reported outome instruments exist that have been specifically designed to measure the quality of life of children with lower limb deformities.

Predicting the magnitude of a leg length discrepancy

There are a number of different methods used to predict the extent of a final LLD, as outlined in Table 4. All methods for predicting the extent of an LLD are based on a range of assumptions including:

1. A girl's physis will fuse at the chronological age of 14 years;
2. A boy's physis will fuse at the chronological age of 16 years;

3. Each physis (e.g. distal femur and proximal tibia) has a constant rate of growth until maturity.[3, 65]

In addition to these assumptions, it is important to consider the patient's ongoing growth potential and whether future growth will be retarded or accelerated. For example, if a young child developed a LLD following a femoral shaft fracture mal-union, one would expect the LLD to stay constant throughout the remaining growth period, given that the growth plate will remain healthy (static). Conversely, if a child has sustained a Salter-Harris type 1 fracture where one would expect growth plate arrest (GPA), it would be anticipated that the discrepancy will continue to grow as the child does (progressive). With regards to congenital deformities, the ratio of short limb to long limb remains essentially constant throughout. This understanding has enabled generalisations to be made, including that the final discrepancy at skeletal maturity will be five times larger than it was at birth; it will be three times the discrepancy that was present at one year of age; and it will be one and a half times the difference at seven years of age.[25]

As mentioned, multiple methods have been developed to help predict a final LLD and thus, guide treatment options and timing. To ensure these results are as reliable as possible it is important to obtain serial data points – ideally, four measurements over a minimum 12 month period.

Table 4: Summary of the different methods for predicting the magnitude of a leg length discrepancy

Method of predicting leg length discrepancy	Description of technique	Pros	Cons
Green-Anderson – growth-remaining model	Leg lengths are plotted against age and over time, enabling the determination of an individuals' percentile growth on the 'normal side' and inhibition of growth on the 'abnormal side'.	Gender specific	Estimates growth potential in the distal femur and proximal tibia only. Only uses the most recent determination of bone age to advise epiphysiodesis.
Moseley method	Uses the Green-Anderson data but through a logarithmic equation allows data to be plotted on a straight line.	Simple graph to interpret.	Graph requires > 3 sequential measurements of bone age at 4 month intervals. Assumes inhibition of growth is linear.
Paley method - multiplier	Synthesised by using available databases. The femoral and tibial	Uses chronological age, which is useful when	Lack of inter-observer reliability.

Method of predicting leg length discrepancy	Description of technique	Pros	Cons
	lengths at skeletal maturity were divided by the femoral and tibial lengths at each age for each percentile group. The resultant number was called the multiplier. Using the multiplier, formulae were derived to predict the limb-length discrepancy and the amount of growth remaining.	clinicians don't have serial x-rays to base decisions on. Quick calculation independent of generation, height, socioeconomic class, ethnicity and race.	
Menelaus method arithmetic	Requires calculation of initial discrepancy and then calculates the change in discrepancy per year. Then using the knowledge that girls stop growing at 14 and boys a 16, the following calculation can be made: Discrepancy at maturity = (current discrepancy + (years remaining x discrepancy per year))	Only two measurements separated by a 12 month period are technically required to synthesise results.	Significant error in children with advanced or delayed maturation.
Eastwood method	Very similar to the arithmetic method, although modified to take into account different growth patterns (e.g. Shapiro patterns of growth).	Takes into account the different growth patterns Gender specific	reference lines are based on the average annual growth of 0.6 cm from the proximal tibial physis and 1 cm from the distal femoral physis

The prediction of LLD magnitude and assessment of skeletal age and growth trajectory aids in the timing of epiphysiodesis. Growth is complex and thus timing can be difficult and is not the same for all children. It is important to ensure that there is enough time to obtain the correction required – thus the larger the predicted discrepancy, the earlier the intervention is required.

Different techniques for predicting the magnitude of a leg length discrepancy

Green-Anderson growth-remaining model

This model uses pre-existing longitudinal data on the growth profiles of the lower extremities to predict the amount of growth remaining about the knee (distal femur and proximal tibia) (Figures 4a and 4b). Data were initially obtained from 800 children, however, the study was only semi-longitudinal. In 1963, a smaller cohort of 50 males and females was followed that allowed for a more precise growth-remaining chart and a nomogram of both the femur and tibial to be produced. This also enabled for skeletal age to be plotted on the chart and the amount of growth remaining in each bone to be determined/predicted. Theoretically, this in turn enabled the achievable outcome of epiphysiodesis to be predicted. Unfortunately, these charts did not take into account differences in the size of the child or inhibition/aetiology, which can lead to differences in final LLD.[66]

Green and Anderson improved on their initial growth nomograms with a new cohort of 67 males and females aged 1-18 years. They followed these children yearly, documenting their chronologic age, average tibial and femoral lengths. This chart allowed for leg lengths to be plotted against age, which over time enabled them to determine an individual's percentile growth on the 'normal side' and inhibition of growth on the 'abnormal side'. When using this method it is important to obtain serial measurements so the 'pattern' of growth can be observed.[67] This method has been used for many years and has been identified as being accurate at predicting the timing of epiphysiodesis.

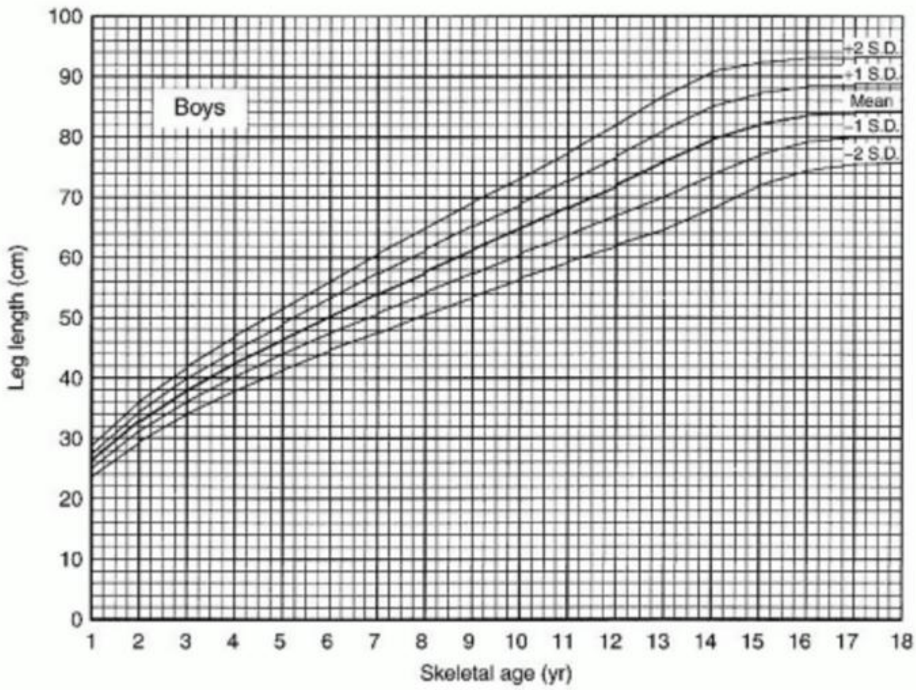

Figure 4a: Graph showing total leg length versus skeletal age for boys. This allows a specific boy to be related to the population by plotting his leg length as a function of his skeletal age. It is useful in the analysis of leg length data because it allows a projection into the future based on the present situation. (From Anderson M, Green WT. Lengths of the femur and tibia; norms derived from orthoroentgenograms of children from five years of age until epiphyseal closure. *Am J Dis Child* 1948;75:279-290 – no formal copyright obtainable).

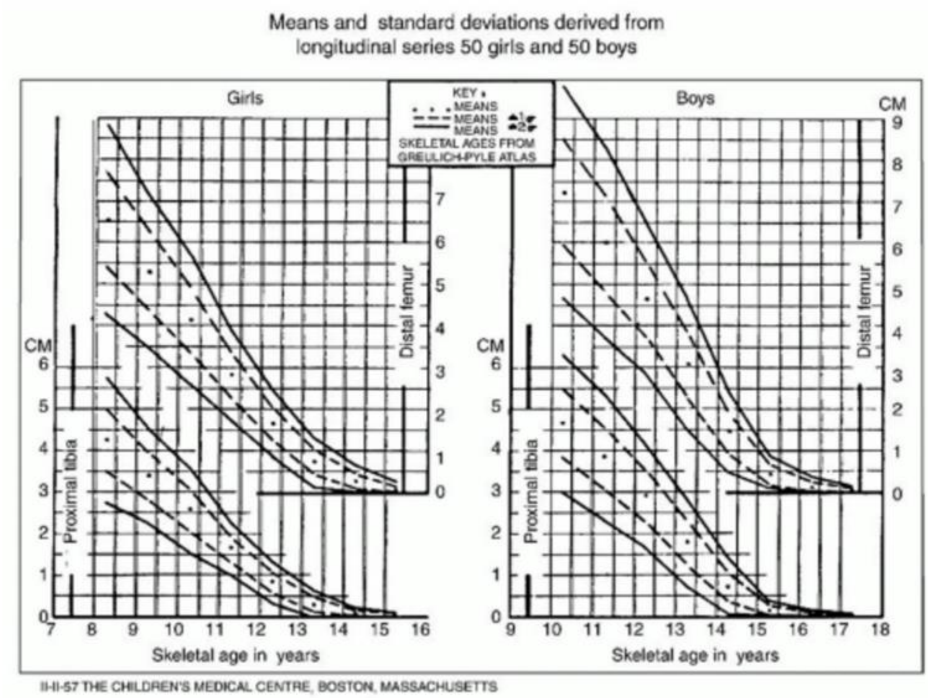

Figure 4b: Green-Anderson growth-remaining graph. This graph shows the amount of growth potential remaining in the growth plates of the distal femur and the proximal tibia of boys and girls as functions of skeletal age. The graph is useful in determining the amount of shortening that will result from epiphysiodesis. (From Anderson M, Messner M, Green W. Distribution of lengths of the normal femur and tibia in children from one to eighteen years of age. *J Bone Joint Surg Am* 1964; 46A(6):1197-1202 - no formal copyright obtainable).

Moseley straight-line graph method

The Moseley straight-line graph method[68] was synthesised using Green and Anderson's data to simplify the process and improve accuracy. On a nomogram the growth of each limb is recorded as a straight line, which allows the effects of the epiphysiodesis to be determined using any one of the three reference lines (the proximal tibia, distal femur or both) so that equalisation of the LLD can be achieved (Figure 5). Over three different time points the length of the normal and abnormal limbs are plotted against skeletal age (as determined by Greulick and Pyle[69]). A best fit line is then drawn, followed by a vertical line that is drawn from the intersection of the skeletal age nomogram at maturity. It is the difference between these two lines at maturity that is the predicted discrepancy.[25, 68]

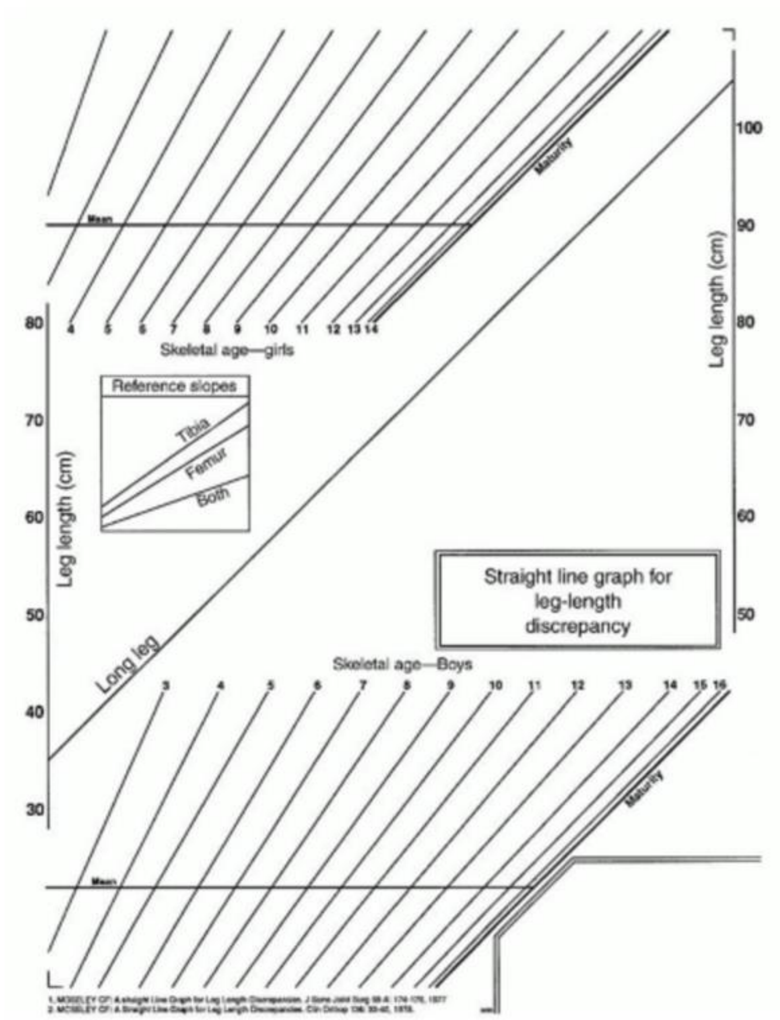

Figure 5: The straight-line graph comprises three parts: the leg-length area with the predefined line for the growth of the long leg, the area of sloping line to plot the skeletal age, and reference slopes to predict growth following epiphysiodesis. (From: Moseley, C. F. (1977). "A straight-line graph for leg-length discrepancies." J Bone Joint Surg Am **59**(2): 174-179. - no formal copyright obtainable)

Menelaus and White arithmetic model

The Menelaus and White arithmetic model was first proposed by White and Stubbins in 1944[70] and affirmation of the technique with slight modification was made by Menelaus[71] a few years later in 1966. It is a useful method when only one data point exists for the prediction of ultimate discrepancy. It was developed to help predict the timing of epiphysiodesis and not to describe growth. White[70] suggested that the distal femur grows 3/8 inch (10 mm) per year, the proximal tibia grows 1/4 inch (6 mm) per year, and the discrepancy increases by 1/8 inch (3 mm) per year. This equates to 37% of total limb growth at the distal femur and 28% of total limb growth at the proximal tibia. White assumed boys stopped growing at 17 years and girls at 16 years. Menelaus[71] adjusted the age of growth cessation to 16 years for boys and 14 years for girls (in keeping with standard modern predictions). While chronological age was used to develop this method, Menelaus[71] suggested it only be used when bone age and chronologic age were within one year of each other. He used LLD, as determined by blocks/clinical examination, and not radiographic measurements. Thus, this method is best suited for patients in the last few years of growth when their skeletal age correlates well with their chronologic age.

Paley multiplier method

To calculate the ultimate discrepancy, Paley et al[72] defined multipliers determined from previously published growth data. Tables of multipliers were produced (for each age and gender), as expected the multiplier decreases as age increases and when multiplied by the existing deformity, an ultimate discrepancy can be predicted. By using the multiplier, current leg lengths, and knowledge of whether the discrepancy is congenital or developmental, the clinician can estimate LLDs at maturity. For congenital discrepancies, the discrepancy at skeletal maturity is easier to calculate.

Discrepancy at maturity = **(L — S)** × **M,** where L and S are the long- and short-limb measurements and M is the age appropriate multiplier (as taken from Lovell and Winter's Pediatric Orthopaedics).[25] As developmental discrepancies have a constant rate of inhibition, the clinician must be able to calculate the rate of inhibition and the amount of growth remaining in the long limb. Thus, **Discrepancy at maturity** = **(L — S) + [1 — (S — S')/(L — L')]** × **L (M — 1),** where S, L are the current lengths and S′, L′ are the lengths 6 to 12 months ago. From these two calculations, the effects and timing of epiphysiodesis can be estimated using similar appropriate formulae. This method has been reported to be accurate, and the inventors state that chronologic age is as accurate as bone age using this method.

Eastwood method

The Eastwood method is a clinical graphic method that utilises the main concepts of the arithmetic method of LLD determination but has been modified to account for the different patterns of growth retardation (does not assume constant growth rates).[73] The chronological age is plotted in years against the LLD, and the graphs are gender specific and utilise the skeletal maturity ages of 14 years for females and 16 for males, as proposed by Menelaus.[71] A epiphysiodesis reference slope is also superimposed on the graphs, which converges to the skeletal maturity lines at zero LLD. These reference lines are based on the average annual growth of 0.6 cm from the proximal tibial physis and 1 cm from the distal femoral physis after the age of 8 years in girls and 10 years in boys.[70, 74, 75]

In summary, all of the abovementioned methods assume a constant growth rate and constant inhibition. Despite the knowledge that several inhibition patterns exist, these do not appear to be of real clinical importance in estimating ultimate leg lengths. Studies have consistently shown that one method is not superior over others and that skeletal age does not necessarily improve estimation in final discrepancies. For example, Kasser et al[76] found a mean error of 2.4 cm using Anderson and Green's[66, 67, 74] data with chronologic age, versus 2.6 cm using the straight-line graph[68] with skeletal ages in children <10 years of age. The accuracy of the skeletal age determination has been brought into question. Although no one technique is fail safe, the authors recommend always utilising at least two techniques when determining treatment. If there is a sizable discordance between techniques, a third should be employed. Of course, this is not always possible; both the Moseley and Green, and Anderson methods require using multiple data points. When a clinician encounters a patient for the first time near the epiphysiodesis date (10 to 14 years of age), a treatment decision based on elbow and hand radiographs may better help to determine their true skeletal age.

Treatment of leg length discrepancies

The treatment modality of choice for a LLD depends entirely on the predicted LLD at maturity. For example, if the predicted LLD at maturity is less than 2 cm, non-operative management should be the treatment of choice; if there is a predicted LLD of 2-5 cm then shortening of the 'healthy' or 'longer' side is recommended; and LLDs greater than 5 cm are best managed with a lengthening procedure that is undertaken on the 'diseased' or 'shorter' limb. In the most severe cases of LLDs, prosthetics and/or partial amputation to allow for prosthetic fit is another option that can be explored.

Non-operative

Non-operative management should be reserved for those who are asymptomatic or who have a symptomatic discrepancy of less than 2 cm. In those who are symptomatic, treatment usually consists of a shoe raise. Shoe raises of less than 2 cm can be placed inside the shoe and moved from shoe to shoe, although as a lift becomes larger, it must be attached to the sole of the shoe. Notably, a shoe raise of more than 5 cm can potentiate ankle instability and thus, an ankle-foot orthosis (AFO) is often required.

Shortening of the long limb

Shortening when the physis is open refers to the process of epiphysiodesis - a surgical procedure undertaken to slow or cease growth through an open physis to correct a LLD. As mentioned, this procedure is usually performed in a symptomatic deformity of 2-5 cm. It can either be permanent or temporary depending on the technique utilised, but is most commonly performed at the distal femoral physis and/or the proximal tibial physis with or without the fibular physis. To achieve epiphysiodesis, the physis may be destroyed medially and laterally allowing for a bony bridge to form between the epiphysis and metaphysis, which facilitates growth inhibition in that physis. This can be achieved with percutaneous drilling and curettage (PDC). Epiphysiodesis can also be achieved using transphyseal screws, eight-Plates or staples with no formal destruction of the physis, instead compression or a tether is applied over the physis to inhibit further bone growth, meaning these three methods are theoretically reversible.

As these procedures retain an intact cortex at the level of the physis (with the exception of the two small drill holes created during PDC), bone stability is preserved allowing the patient to weight bear as tolerated post-operatively. Despite this, some surgeons choose to protect the child with a brace and/or crutches for the first few weeks. There is no good evidence on when a child should return to sports following epiphysiodesis, however, given the potential destabilising effect of disrupting the physis, and theoretical risk of a Salter-Harris fracture occurring, return to sport is generally delayed 6 weeks post-operatively. The different epiphysiodesis techniques will be described later.

In older populations (where the physis has already closed), or in those where the final magnitude of the deformity cannot be determined, osteotomies (skeletal shortening) is a potential method of managing the limb length discrepancy. An osteotomy refers to the removal of a specific portion of bone (either tibia or femur) from the ‘health’ or ‘longer’ limb. The benefits of this technique include the ability to perform a precise correction of the deformity and it can be performed in patients who have already reached skeletal maturity. However, some disadvantages include the inability to weight-bear following the procedure; more invasive procedure; and with larger shortenings there is the potential to cause relative overlengthening of the muscles thus resulting in weakness.[77] An accepted rule of thumb when considering a shortening procedure is removal of 10% of the bone length, is usually tolerated. Osteotomies are usually performed in the femur rather than the tibia due to reduced neurovascular risk and they provide larger shortening potential.[78] Techniques include proximal shortening with plate fixation (proximal femoral osteotomy) and physeal excision.

Lengthening of the short limb (distraction osteogenesis or callotasis)

Lengthening procedures are often reserved for larger deformities, for example, those who are predicted to have a magnitude of more than 5 cm at maturity. It is a bone-regenerative process in which gradual distraction yields two vascularised bone surfaces, from which new bone is formed.[79] Over the years there have been many advancements in limb lengthening techniques. Techniques described include step cuts, periosteal sleeves, onlay cortical grafts, slotted plates, intramedullary rods and several internal and external devices that allow for gradual controlled lengthening. However, all the techniques work on the same concept – tissues are subjected to a steady and constant tension enabling them to become metabolically activated, which allows for new bone to form along the distraction stress line.[80]

The current methods utilising 'gradual controlled lengthening' came into vogue in the 1970s thanks to Wagner. Wagner proposed the method of performing a diaphyseal osteotomy and placing an external fixator that allowed distraction osteogenesis at a rate of 1.5 mm per day. When desired lengthening had been obtained, a plate would be placed and external fixator removed to add stability during the final consolidation phases. There are now three well described phases of limb lengthening:[79]

1. Latency phase:

    After the osteotomy has been performed there is a latency period to allow the bone to go through the initial inflammatory changes and phases of healing. It takes approximately 5-10 days, depending on both the osteotomy site and the patient's age. This allows the child and parents to prepare for the upcoming lengthening process.

2. Distraction phase:

This is the phase where the bone is gradually lengthened. Currently, the accepted rate of lengthening is 1 mm per day as proposed by Ilizarov.[81, 82] It is generally recommended that this growth is achieved with four quarter millimeter increments a day. It is important to obtain an x-ray at the completion of the first week of lengthening to ensure:

- Lengthening is being achieved at the expected rate; and
- The rate is adequate for the patient, i.e. not too fast or slow, which can be determined by assessing the level of callus formation.

Notably, the total lengthening that can be achieved is limited to the surrounding soft tissue tightness and thus, the development of skin and joint contractures. The morphological and histological changes occurring within the distracted gap have been well described by Aronson et al.[80]

3. Consolidation phase:

Once adequate distraction/length has been achieved, distraction ceases and the bone is given a rest period to consolidate. In this period the bone and extensive amounts of osteoid undergo mineralisation and remodelling. Commonly the device is left in situ or exchanged to an internal fixation throughout this phase to reduce the incidence of regenerate failure or fracture.

Methods of lengthening

External fixator

This may be achieved with a circular frame (Ilizarov[82]), a monolateral frame (De Bastiani) or a hybrid of both. When planning for a lengthening procedure using an external fixator it is important to consider that:

- When an osteotomy is performed in metaphyseal bone, greater amounts of bone formation can be expected;
- Greater blood supply and thus healing potential is observed in periosteal rather than endosteal blood supply areas;
- Using low energy methods to cut the bone (osteotome versus power saw) decreases thermal energy and thus, improves bone healing potential.

The Ilizarov fixators have the benefit of allowing dynamic loading of the limb throughout the lengthening process. This is because the construct provides rigidity against bending in the sagittal plane and coronal plane, however, is not so rigid in the axial direction, which allows for some movement over the segment.

Internal rod lengthening

This concept was first introduced by Bost and Larsen in 1956[83] to try and overcome some of the issues with pure external fixator use for lengthening, such as multiple scars and pin site infections. In this technique, the rod serves to maintain the alignment, while an external fixator is placed to control the lengthening. Once the distraction phase is complete, the external fixator can be removed and the intramedullary rod acts as support during the consolidation phase, thus theoretically reducing the rate of regenerate fractures. This technique, like many others, has drawbacks including:

- The femur has to be lengthened in the anatomical axis, which can result in medialisation of the knee when significant lengthenings are performed
- The proximal femoral physis is the primary barrier to blood flow to the femoral head, thus, on placement of a piriformis fossa entry nail, there is a theoretically high risk that proximal femoral avascular necrosis will develop.

This technique is less widely used than external fixator distraction osteogenesis because of the risk that a deep rod infection secondary to a tracking pin site infection may develop. For this reason, much research is currently being undertaken to refine devices that can lengthen without the requirement of an external fixator, e.g. magnetic devices, computed constant lengthening.

Complications of limb lengthening

These limb lengthening techniques are definitely not complication free; some of the more frequently observed complications are listed in Table 5.

Table 5: Complications associated with limb lengthening

Short term	Long term
Neurovascular injury	Osteomyelitis
Infection	Early physeal or osteotomy closure
Compartment syndrome	Poor bone formation
Hypertension during lengthing process	Fracture of regenerate following removal of fixator
Construct failure	Malalignment
	Contractures
	Chronic pain
	Stiffness/reduced range of motion

History of epiphysiodesis

As described previously, epiphysiodesis is the process of surgically halting the growth of a long bone prematurely through manipulation of its physis. It is a concept first described in 1933 by Phemister.[1] Epiphysiodesis can be used to restrict the growth of part of a physis, which is of benefit in the management of angular deformities, or can be used to inhibit the growth of an entire physis for management of pure LLDs (shortening the longer limb). Some epiphysiodesis techniques permanently cease the growth of the physis while other more recently developed techniques are able to transiently modulate the growth of that bone, which hypothetically results in greater control and flexibility in correcting LLDs.

The Phemister technique (previous 'gold standard') involves the excision of a 1 cm rectangular block of cortical bone containing the peripheral physis and adjacent metaphyseal and epiphyseal bone from the medial and lateral aspects of the physis. The physis is then curetted and the bone blocks reinserted after being rotated 180 degrees, thus, creating a bone bridge that bypasses the growth plate[1] (Figure 6). This technique is performed using an open approach and results in permanent cessation of physeal growth. Since 1933, multiple new techniques of epiphysiodesis have been proposed, most of which are percutaneous or minimally invasive.[84] Compared to the Phemister technique, these MIE approaches have been shown to have similar effectiveness and complication rates, as well as shorter hospital stays, and for these reasons the Phemister technique has become obsolete.[85-87] Accordingly, this systematic review will focus on the effectiveness of MIE techniques, which are described below.

Canale and Christian (1990),[88] Ogilvie and King (1990),[89] and Timperlake et al (1991),[90] have focused on permanent methods of MIE using image intensification, which involves the physis being ablated or destroyed with drills and curettes through small medial and lateral incisions.

Blount and Clarke (1949)[91] proposed the first reversible method of epiphysiodesis using three staples on each side of the physis. One staple spike is placed in the metaphysis and the other in the epiphysis. There have been a number of reported complications with this form of reversible epiphysiodesis, including unpredictable patterns of growth following the removal of staples, and the development of angular deformities.[92, 93]

In 1998, Metaizeau et al[94] described a further permanent method of epiphysiodesis using two transphyseal screws obliquely placed across the physis forming a cross in both the coronal and sagittal planes.[95] This concept is thought to work by applying compressive forces through the physis.

In 2007, Stevens[96] introduced an alternative reversible technique that relied on a tension band construct using eight-Plates, so-called because the design of the implant is seen to resemble that of a figure eight. This concept was initially used for the correction of angular deformities but has since been modified to treat moderate LLDs. The use of eight-Plates for the correction of LLDs to date is quite controversial with Stewart et al[97] claiming they are not effective for epiphysiodesis about the knee. Their study found that the eight-Plates achieved suboptimal correction when compared to physeal ablation. However, following the publication of their study, commentaries including that by Kaymaz and Komurcu[98] have questioned the study's methodology. In the last few years, studies evaluating more experimental forms of epiphysiodesis such as radiofrequency ablation have been published;[99, 100] however, due to the fact that these interventions remain in 'experimental phases' they will not be included in this review.

Types of epiphysiodesis

Phemister

Phemister was the first to document a method of epiphysiodesis back in 1933,[1] known as 'epiphyseodiaphyseal fusion'. The technique required the excision of a 1 cm rectangular block of cortical bone from both the medial and lateral aspect of the joint. The block of bone contained the peripheral physis with adjacent metaphyseal and epiphyseal bone. The physis was then destroyed and the bone block rotated 180 degrees prior to being reinserted.

This technique creates a bone bridge that bypasses the growth plate, which facilitates fusion and cessation of further growth of the limb. The Phemister technique has since become obsolete since the emergence of multiple minimally invasive techniques, despite this, it is still seen to have similar effectiveness and complication profiles.[86]

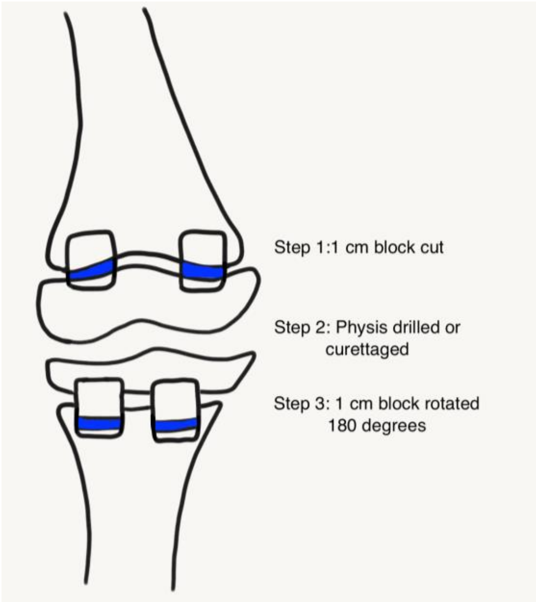

Figure 6: Graphical representation of the phemister technique of epiphysiodesis whereby a 1-3 cm (approximate) cube or rectangle is taken from across the physis and rotated 180 degrees, which results in a bone bridge being placed across the physis that prevents further longitudinal growth.

Percutaneous drilling and curettage

Bowen[101] and later Timperlake and Bowen[90] went on to describe the first method of 'percutaneous epiphysiodesis'. This technique saw the medial and lateral thirds of the physis curetted, resulting in sufficient damage to the growth plate to inhibit further growth (Figure 7). Since then, a number of subsequent authors, including Canale and Christian,[88] and Ogilvie and King,[89] have described variations of the technique that facilitate percutaneous physeal damage. More recently, unilateral approaches have been described by the likes of Surdam,[87] Macnicol,[102] and Gabriel et al,[103] however, subsequently Edmonds and Stasikelis[104] showed that the use of a unilateral approach was associated with a four-fold increase in major complications such as failure of growth plate arrest, angular deformities, fractures and joint penetration compared to the double portal approaches.

Percutaneous epiphysiodesis when compared to the original open technique enables more cosmetic scars, smaller surgical dissection, reduced hospital stays, earlier post-operative weight-bearing and improved postoperative pain.[87-90, 105] However, complication rates remain comparable to the original open Phemister technique.[85, 87] In general, the complications seen are relatively minor and include effusions, hematomas and wound infection.[88-90, 103, 106]

PDC like the open Phemister technique, is irreversible, and thus relies on accurate timing for success. Inaccurate timing can result in the premature closure of the physis and overcorrection, which can lead to the patient requiring epiphysiodesis on the contralateral limb.[105] Conversely, if PDC is performed too late it can result in undercorrection, and in severe cases of undercorrection a salvage osteotomy may be required to equalise the LLD.[107]

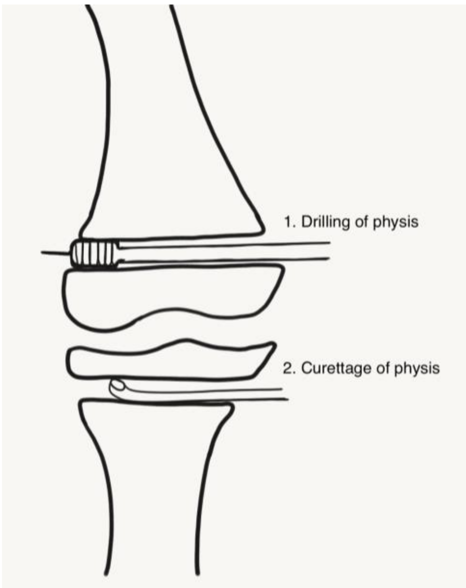

Figure 7: Example of percutaneous drilling (1) and curettage (2) of an open physis to facilitate epiphysiodesis.

Percutaneous epiphysiodesis using transphyseal screws

'Percutaneous epiphysiodesis using transphyseal screws' (PETS) was proposed by Metaizeau et al[94] in 1998. It is a technique exploiting the concept that compressive forces across a physis have the ability to inhibit its activity. PETS utilises cannulated 'lag screws' introduced percutaneously under fluoroscopy to compress the physis and inhibit growth through the physis permenately. These 'lag screws' are placed on both the medial and lateral side of the physis and can be directed either in parallel or crossed (more common) (Figure 8A and B). To ensure maximal compressive forces a true lag screw concept requires the screw threads to be wholely within the epiphysis – this is not always performed with some placing screw threads across the physis (Figure 8C), thus theoretically, converting the technique to a reversible epiphysiodesis technique as it reduces the compressive force placed through the physis.[108]

Since its proposal, PETS have produced promising results in both LLD and angular deformities.[85, 94, 108, 109] The complication profile of PETS is similar to that of the PDC and Phemister techniques, although there is a higher reported incidence of haemathrosis. There can also be issues with hardware failure and irritation.[94, 108, 109] Coronal deformities have been reported, however, sagittal deformities do not seem to be an issue.[85, 94, 109, 110]

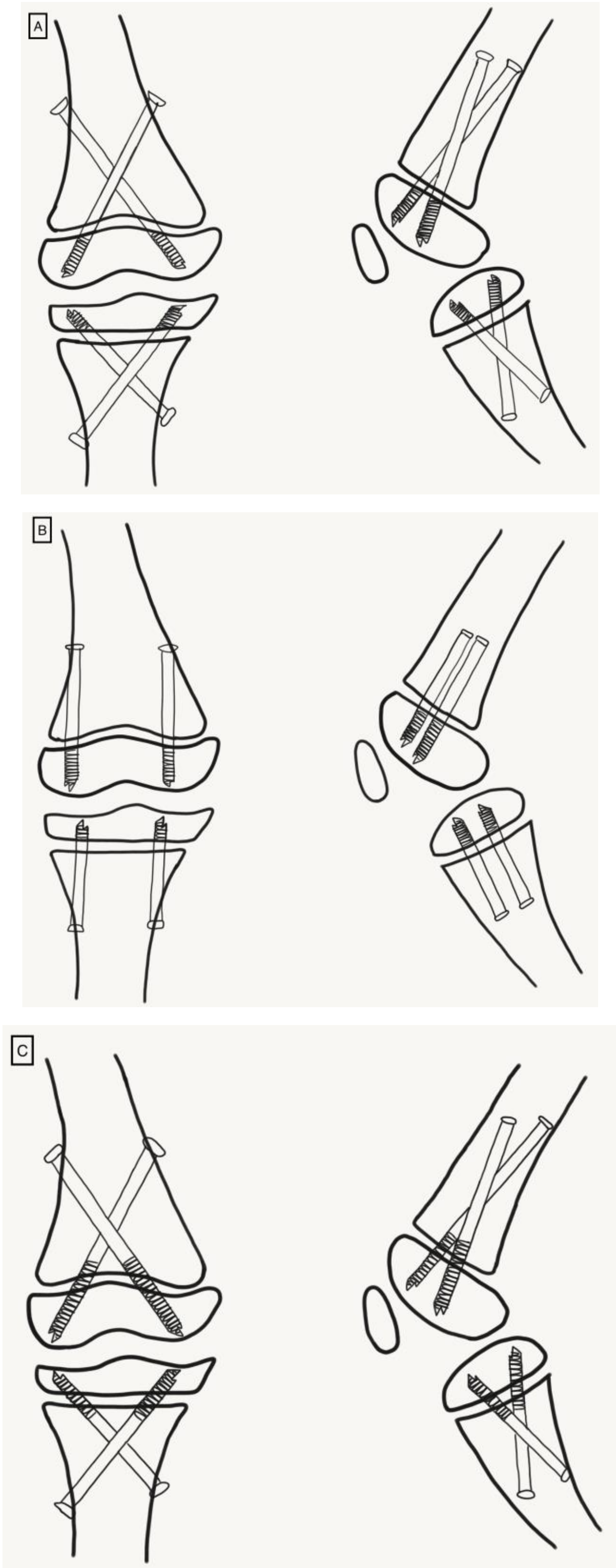

Figure 8: A) anteroposterior and lateral image of cannulated screws being introduced in cross fashion; B) anteroposterior and lateral image of cannulated screws being introduced in cross fashion; C) anteroposterior and lateral image of cannulated screws with threads crossing the physis allowing for potential reversibility of the procedure.

Physeal staples

In 1949, Blount and Clarke [91] were together the first to perform and publish on a reversible epiphysiodesis technique that attempted to negate the need for precise procedure timing. Their technique required three staples about the physis on both the medial and lateral side; each staple had one leg in the metaphysis and the other in the epiphysis (Figure 9). Over the years there has been substantial data supporting the full reversibility of the staples.[111, 112] For reversibility to be possible with this technique, care must be taken to protect the epiphyseal vessels, periosteum and perichondral ring when undertaking the index and subsequent procedure.[111-113] If damage occurs, it can result in premature growth plate arrest that affects the final results. Despite this technique being theoretically reversible, the pattern of growth can be very unpredictable following the removal of staples and issues with rebound overgrowth are not infrequent.[92, 114]

Since 1949, when the technique was initially proposed, many studies have reported complications, most of which have centred around hardware failure. When using staples, hardware failure can include staples bending, which can result in angular deformities (ADs); staples backing out, which can resulting in loss of compression across the physis and thus, the inadequent correction of the LLD; the potential development of an AD if the force is uneven over the physis; and finally, staple breakage.[92, 93, 107, 112] Some of these complications can be significant enough to require subsequent intervention, such as repeat epiphysiodesis, corrective osteotomies and surgical intervention on the contralateral side.[92, 93] Due to these complications a number of surgeons have ceased using the technique, some of whom have published their concerns.[93]

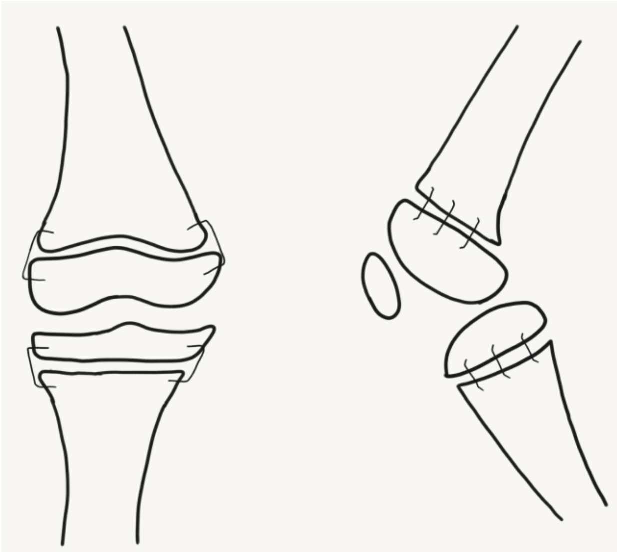

Figure 9: Anteroposterior and lateral image of transphyseal staples being placed for the purpose of epiphysiodesis. Three staples are placed on both the medial and lateral side of the physis.

Eight-Plates

More recently (2007), Stevens[96, 107] presented an alternative technique of reversible epiphysiodesis using an eight-Plate with two non-locked screws. His focus was mainly on the correction of ADs, although this has since been extrapolated and used for the correction of LLD (Figure 10). The eight-Plate has the ability to act as a 'flexible tension band construct', for example, instead of it exerting an immediate and direct compressive force it enables 'guided growth'. The eight-Plates, like staples, are placed on both the medial and lateral side of the physis with one half secured in the metaphyseal bone and the other in the epiphyseal bone. This technique has been reported to have a lower incidence of hardware failure when compared to staples,[115-119] although the issue of unpredictable rebound growth following implant removal remains.[96, 120] Accordingly, as with staples, if hardware removal is planned it should happen a little after overcorrection has been achieved.[115] Initial studies reported eight-Plates enabled faster rates of correction,[96] however, subsequent studies have not always supported this.[119] A benefit of this implant compared to PETS, is that eight-Plates do not disrupt the physis, although they do require a larger surgical incision and more dissection, resulting in a potential disruption to the periosteal and physeal blood supply.[107, 115]

Although it has not been officially studied or reported that eight-Plates are better indicated for AD than LLD, many feel that their flexibility does not induce sufficient forces across the physis to produce efficient and permanent growth arrest for the management of LLD.[121]

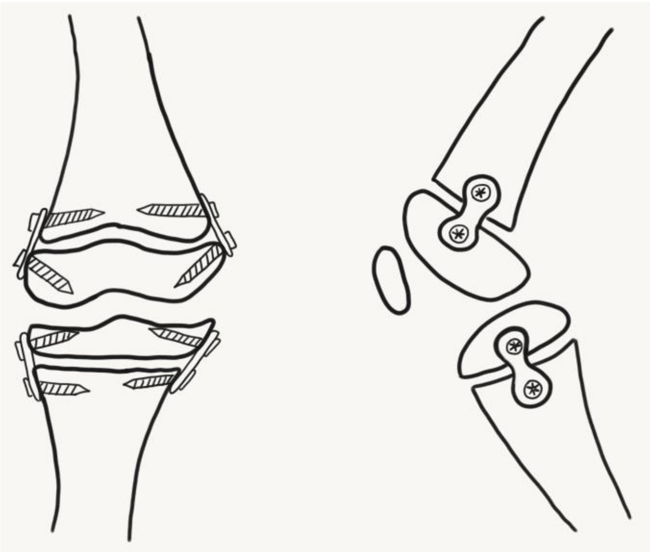

Figure 10: Anteroposterior and lateral image of eight-Plate's being placed for the purpose of epiphysiodesis. A plate is to be placed on both the medial and lateral aspect of the physis with a non-locking screw placed in both the metaphysis and the epiphysis.

Experimental and other epiphysiodesis techniques

Many study groups are evaluating a range of new epiphysiodesis techniques in animal models. Waris et al[118] is examining the use of bio-absorbable screws in rabbits to avoid subsequent hardware removal in children undergoing PETS. Rosen et al[122] and Morein et al[116] have assessed electrocautery and CO_2 laser beam therapy to induce epiphysiodesis, although neither technique has progressed to a clinical trial despite their promising results in rabbits. Since 2007, there has been a surge in experimental studies looking at the use of photodynamic therapy,[123] radio-frequency therapy[99, 100] and the application of stromal cell-derived factor 1,[124] as potential methods of epiphysiodesis. All have had promising early results but require validation with larger animal studies (all in rabbits or mice to date) to determine adequate delivery regimens, and subsequently, with clinical studies to ensure their effectiveness in human subjects.

Anatomy of epiphysiodesis

Every long bone in the body has five main areas, namely, the articular cartilage covered epiphyses at the proximal and distal end of the bone, each of which is attached to a funnel shaped metaphysis and a central diaphysis. Each component plays a pivotal role in bone growth, turnover and overall bone integrity.[125]

All children during growth have a cartilaginous physis separating the epiphyseal and metaphyseal bony regions. It is this cartilaginous physis that facilitates longitudinal growth. The physis in combination with the secondary ossification centre makes the epiphysis.

The physis itself is composed of five zones: the resting, proliferative, maturation, degeneration and calcification zones. The resting zone is a thin layer located at the epiphyseal pole of the growth plate that has little metabolic activity and is thought to be the main source of stem cells for the proliferative zone. The proliferative zone is where chondrocytes are seen to be rapidly dividing, growing and arranging themselves into a functional matrix. The remaining three zones can be clumped together and referred to as the hypertrophic zone. It is in this zone that cell size can be seen to dramatically increase and cellular organisation lost – the chondrocytes become swollen and vacuolated as a result of maturation and subsequently die. Specifically, the maturation zone is where the matrix is further structured and prepared for calcification; the degeneration zone is where cartilaginous cell death occurs; and finally, the calcification zone is where the chondroid matrix is impregnated with calcium salts from the mitochondria of the destroyed cartilage cells. Compressive forces or destruction of this physis results in eventual cessation of growth through that physis. It is this knowledge that has led to the development of multiple epiphysiodesis techniques.

In conclusion, it can be appreciated that not only are there a number of different methods for quantifying a LLD, there are a number of different methods that can be utilised to correct a LLD. Other important considerations to be taken into account when planning this sort of operative procedure include: which physis; what technique; and when the procedure should be performed. All of these questions should be answered with the aid of evidence, and it is for this reason, that a systematic review was undertaken.

Methodological basis for the review

Evidence-based medicine and the emergence of systematic reviews

The term evidence-based medicine (EBM) was first coined by Guyatt et al[126] in 1991, however, the move to incorporate EBM into daily practice was initiated back in the 1960s.[127-129] The concept came about from a growing awareness of the weaknesses of standard clinical practice and its impact on both the quality and cost of patient care within the United States of America,[130, 131] which was one of the first to link the world of epidemoiology and medical research.

Due to the varying levels of evidence within the literature, one must not only know how to assess the quality of the literature but then also how to apply the sometimes only existing, yet suboptimal evidence, to practice. It is for this reason that the Journal of American Medical Association (JAMA) User's Guide concept was born and 25 papers between 1993 and 2000 were published to help assist the everyday clinician to understand and apply the literature.[132]

EBM incorporates "the best available external clinical evidence from a systematic search"[133(pg 71)] and requires an understanding of what constitutes 'best evidence'. It has since been accepted that the RCT and systematic review/meta-analysis are the 'gold standard' in EBM over non-experimental approaches for questions about treatment.[131] While the importance of randomised trials has been highlighted in the hierarchy of evidence that guides therapy, much of medical research is observational.[134-137] Unfortunately, the reporting of observational research is often low in quality and not sufficiently detailed or clear, which hampers the assessment of the strengths and weaknesses of a study and the generalisability of mixed results. Consequently, systematic reviews and meta-analyses have become the preferred choice. A systematic review is defined as "the application of scientific strategies that limit bias by the systematic assembly, critical appraisal and synthesis of all relevant studies on a specific topic"[133, 138-140 (133 pg 71)]

The Joanna Briggs Institute (JBI) model[141] incorporates the four major components of the evidence-based healthcare process, which contributes to the feasible, acceptable, meaningful and effective delivery of healthcare:

- Healthcare evidence generation
- Evidence synthesis
- Evidence/knowledge transfer
- Evidence utilisation.

Where the term ‘evidence’ is used in the model it means that substantiation or confirmation is needed in order to believe that something is true. Health professionals seek evidence to substantiate the value and effectiveness of a very wide range of interventions, conditions and issues, therefore the type of evidence needed depends on the nature of the activity and its purpose.

Difference between a literature review and a systematic review

In evidence-based practice, systematic reviews are considered one of the highest levels of information available. Systematic reviews encompass a high level overview of primary research on a focused question that identifies, selects, synthesises and appraises all high quality research evidence relevant to that question. In comparison, non-systematic literature reviews subjectively summarise evidence on a topic using informal or subjective methods to collect and interpret studies. Systematic reviews eliminate bias to answer a focused clinical question whereas literature reviews provide a summary or overview of a topic. In a systematic review, there is a clearly defined and answerable clinical question whereas literature reviews can be on a general topic or a specific question. The components of systematic reviews include pre-specified eligibility criteria, a systematic search strategy, assessment of the validity of the findings, interpretation and presentation of the results and a reference list. It takes months to years for a systematic review to be completed whereas a literature review can be completed within weeks. Thorough knowledge of a topic, conducting a search in all relevant databases and a statistical resource analysis (for meta-analyses) are required to perform a systematic review. Other strengths of a systematic review include peer review of an a priori, published protocol; exhaustive, library scientist-aide search of the global literature; dual independent reviewers who make retrieval, appraisal and extraction decisions; maximum transparency through publication of search strategies, appraisal and extraction tools; and finally rigorous peer review of the review report. Literature reviews only require an understanding of a topic and do not normally encompass a systematic search. Systematic reviews connect practising clinicians to high quality evidence and support evidence-based practice whereas literature reviews provide a potentially biased summary of the literature on a topic.[142-144] It is for this reason it was decided to conduct a systematic review in on this topic.

Why is a systematic review needed in this area?

The use of many surgical interventions is dependent on the teacher, student and location. Consequently, different techniques are utilised throughout the world and even across different states within the same country. Surgical techniques, although based on published data, are very rarely validated with the aid of a systematic review, or even randomised control trial due to the ethical and logistical hurdles required to set up a study of this type and magnitude. For this reason, most surgical techniques are only ever investigated using cohort studies. This allows surgeons to stick with the procedure they are familiar with, as there is often no real ‘gold standard’ technique.

Epiphysiodesis is one of these surgical interventions. Although a variety of different techniques have been published throughout the world using case series and cohort studies, there is no substantial evidence that one technique is better (safer, more efficient or cost effective) than the others. A LLD has the potential to greatly impact on a child’s quality of life, and if things go wrong with this sort of ‘simple’ surgery, the child can be left requiring much more invasive operations to correct the deformity.

The goal of this review was to determine whether one method of MIE was more effective than another at restoring leg length equality. To assess this, complication profiles and patient satisfaction were also reviewed. The results will assist in developing a set of guidelines to aid clinicians in treating children with significant leg length discrepancies.

Chapter 2: Systematic Review Methods

This chapter describes the methods used to undertake this systematic review, which was conducted in accordance with a published *a priori* systematic review protocol entitled, "The Effectiveness of Different Minimally Invasive Epiphysiodesis Techniques in the Management of Paediatric Leg Length Discrepancies: A Systematic Review Protocol."[145]

Question synthesis

A researchable question is one that explores and challenges an uncertainty so as to provide useful information. [146] Hulley et al[147] proposed that a research question should be formulated using the FINER (feasible, interesting, novel, ethichal and relevant) criteria, and its goal should be to answer or fill a gap in the existing knowledge-base. The crafting of a good research question also aids in the identification of evidence to answer the question.[148] With the aforementioned in mind, the follwing research question was formulated: "Is one minimally invasive epiphysiodesis (MIE) technique more effective than another in the treatment of paediatric leg length discrepancies."

Review objectives

The objective of this review was to synthesise the best available evidence on the use of MIE for the management of paediatric LLD. The effectiveness of four common MIE techniques were compared, namely, percutaneous epiphysiodesis using transphyseal screws (PETS), percutaneous drilling and curettage (PDC), physeal stapling and guided growth with eight-Plates.

More specifically the review questions were:

- What method of MIE is most effective at achieving growth arrest and correcting a LLD in children?
- Are there different post-operative complication profiles between MIE techniques?
- How do children respond to each MIE technique? Is there evidence of improved quality of life post-operatively?

Inclusion criteria

The search strategy utilised, followed the PICO (population, intervention, comparator, outcome) inclusion criteria format.[139, 149]

Population

This review considered all studies that included patients, either male or female, with documented open physes and predicted LLD at skeletal maturity of 2-5 cm. We predicted that only patients under the age of 16 would be eligible for inclusion in the review as physeal closure typically occurs at the age of 14 in females and 16 in males, however, no participants were excluded based on age. Any patient with a predicted LLD of more than 5 cm was excluded from the review, as in such cases epiphysiodesis should not be the first line management (i.e. a leg lengthening procedure should be offered instead).

Interventions

Four different techniques of MIE were reviewed: PETS, PDC, physeal stapling and guided growth with eight-Plates. Studies that investigated one or more of these techniques, or slight variations of the techniques, were considered for inclusion.

Outcomes

Papers that reported one or more of our primary and/or secondary outcomes were considered for inclusion in this systematic review. It was considered that a good primary outcome should be easily quantifiable, specific, valid, reproducible and appropriate to the specific research question.[150]

- Absolute LLD (measured in centimetres) at skeletal maturity:
    - Methods of assessment included clinical assessment with measurements taken from the ASIS to medial malleolus or block testing, or with the aid of imaging modalities such as plain films, ultrasound or CT.
- Rate of correction:
    - This assessed how quickly growth through the physis ceased following the operation and thus, how quickly the correction could be obtained. Data from some studies enabled us to directly calculate this if it was not specifically reported.
- Percentage of correction relative to desired correction:
    - This outcome aimed to determine how much correction was obtained compared to what was expected from the treatment. For example, if the predicted LLD at skeletal maturity was 4 cm and the resulting LLD

following treatment was 2 cm, the percentage of correction relative to the desired correction would be 50%.

- Incidence of long term complication, including:
  - Failure of GPA
  - Failure to achieve adequate reduction in LLD (< 2 cm)
  - Development of AD about the knee secondary to the epiphysiodesis procedure
  - Hardware failure, for example, backing out of screws or breakage of staples
- Incidence of acute complications, including:
  - Post-operative infection
  - Unplanned return to theatre
  - Haematomas or effusions large enough to impact on post-operative recovery
- Patients' ability to return to pre-operative function measured by the time taken for the patient to return to school, sport etc., or knee range of motion and the like.
- Length of overall hospital stay
- Impact on child's overall quality of life, measured using any validated scale

Types of studies

This review gave priority to higher evidence-level study designs such as randomised control trials,[151] although in the absence of randomised control trials on this topic, all prospective or retrospective cohort studies or case series were considered appropriate for inclusion.

Date of publication time frame

Studies published from 1st, January 1998 to 3rd January 2017 were considered for inclusion in this review. This start date was selected as it was in 1998 that the PETS method of epiphysiodesis was first reported.[94] Moreover, this date was chosen so that the different treatment modalities could be fairly compared and would adequately reflect current practice.

Language of publications

Only studies published in English were considered for inclusion in this review as the researchers involved were only fluent in English, and no adequate resources were available to translate studies published in languages other than English.

Search strategy

The search strategy implemented aimed to identify both published and unpublished studies exploring the primary and secondary outcomes of the review topic. It was conducted in accordance with the JBI method guidelines for undertaking a systematic review that assesses the effectiveness of an intervention or therapy.[141, 152] Initially the suitability of the proposed review topic was determined through a preliminary search of electronic databases, including the Cochrane Library, CINAHL, PubMed, PROSPERO and EMBASE. This preliminary search identified that no systematic reviews had been recently published on the proposed review topic: "The Effectiveness of Different Minimally Invasive Epiphysiodesis Techniques in the Management of Paediatric Leg Length Discrepancies." The search strategy was subsequently designed to be broadly inclusive of all domains of interest to capture as much relevant data as possible.

Three-step search strategy

To identify both published and unpublished (grey literature) studies, a three-step search strategy was utilised, whereby, an initial limited search of PubMed, EMBASE and Scopus was undertaken. The aim of this initial search was to identify all relevant search terms that reflected the review's PICO inclusion criteria, which was achieved through an analysis of text words contained in the title and abstracts and index terms of identified papers. The keywords used during this initial database search included terms relating to age-range (child, children, adolescent), condition (leg length discrepancy/inequality) and the intervention (epiphysiodesis, transphyseal screws, percutaneous drilling and curettage, eight-Plates, physeal staples).

A comprehensive search strategy was then developed for each of the databases in tabulated form (see Appendix I for an example). This search strategy was then customised and applied across all included databases in a second comprehensive search. Finally, the reference lists of all relevant identified reports and articles were searched for additional studies. When undertaking this step, it became apparent that many relevant studies had not been captured by the initial searches, with a number of studies being identified on reference list review. To address this, the sensitivity of the search strategy was improved through removal of search terms designed to limit the number hits on the population of interest, however, once again, many studies were not captured. In consultation with a number of librarians, the decision was made to search the intervention in isolation with the term ‘epiphysiodesis’, which was found to be a broad and all encompassing term that returned a manageable number of hits. The databases searched included:

- PubMed
- EMBASE
- Scopus
- Web of Knowledge

Grey literature was also searched (Mednar, Proquest), although no papers were identified from these sources that met the inclusion criteria. Trial registries were also searched (The Cochrane Central Register of Controlled Trials, WHO ICTRP and ClinicaTrials.gov) however, once again, no relevant trials were identified.

Example of initial database search strategy in PubMed

(Child [MH] OR Child* [tw] OR Pediatric* [tw] OR Paediatric* [tw] Adolescent [tw]) AND (“leg length inequality” [MH] OR “leg length discrepancy” [tw] OR Leg length inequal* OR Unequal leg length OR Limb length discrepancy OR anisomelia) AND ((Epiphyses[mh] AND (surgery[tw] OR surgical[tw])) OR (Epiphysis[tw] AND (surgery[tw] OR surgical[tw])) OR Epiphysiodesis [tw] OR “transphyseal percutaneous screws”[tw] OR “Transphyseal screws”[tw] OR “minimally invasive surgical procedures”[MH:noexp] OR Minimally invasive [tw] OR Metaizeau [tw] OR Canale [tw] OR Blount [tw] OR physeal stapl*[tw] OR “eight-Plate” [tw] OR “8-Plate” [tw] OR “Physeal manipulation” [tw] OR Physeal drillings OR Physeal curettage OR Physeal ablation)

Study selection

All studies identified from the database searches were screened by title and abstract to assess their relevance to the review topic. Assessment of eligibility was then undertaken using full-text review, to determine whether the studies met the inclusion criteria; if a study was excluded following full text review reasons for its exclusion were recorded. Notably, study selection was performed by a single assessor (MC), this process could have been strengthed with use of a second independent reviewer.

Assessment of methodological quality

All papers that met the inclusion criteria were assessed by two independent reviewers (MC and JI) to ensure transparency and reduce the risk of bias. Assessment of methodological validity was undertaken using the standardised critical appraisal instruments from the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI)[141] (Appendix II).

Threshold for inclusion

It was decided that every critically appraised study would be included in the review. Although this would lower the quality of the data presented in the review it was determined as appropriate given the field of research was small and one that was often overlaid with various ethical and resource issues, which creates barriers to study quality.

Agreement between co-reviewers

It was pre-determined that if any disagreements between the reviewers (MC and JI) could not be settled with discussion, a third reviewer (MS) would be consulted to resolve the matter. However, all disagreements were resolved through discussion and thus, consultation with a third reviewer was not required at any stage. Notably, the most frequent reason critical appraisal scores initially differed between reviwers was due to differential interpretations of the critical appraisal questions, and what was required to fulfil the criteria.

Data extraction

Data was extracted from papers included in the review using the standardised data extraction tool from JBI SUMARI.[141] The data extracted included specific details about the interventions, population, study methods and outcomes of significance to the review question and its objectives. The authors of all the included studies were contacted to obtain de-identified individual patient data (IPD), however, authors either did not respond to multiple email requests for this information or were not able to provide the data due to no longer working in the institution, no longer having access to the data or privacy/confidentiality laws. If IPD could have been obtained, it would have allowed for a meta-analysis to be performed and outlier data to be excluded. Individual patient data would have also enabled us to determine if there were specific causes of LLDs that were best suited to a specific surgical technique.

Data synthesis

The initial aim of this review was to undertake a meta-analysis, however, due to the types of studies included, the lack of IPD and the heterogeneity between studies on population and intervention characteristics, a meta-analysis could not be performed. Given statistical pooling of data was not possible, a narrative synthesis was prepared instead.

Summary

This chapter described the methods used to undertake the present systematic review. Specifically, it focused on question formation and definition, study selection, the process of extracting data and the process of synthesizing the data in a meaningful way.

Chapter 3: Results

Primary and secondary objectives of this review

The overarching goal of this review was to identify the best quality evidence to assess the effectiveness of different MIE techniques in correcting paediatric LLDs. The review also sought to determine the complication profiles of each technique as well as their impact on the quality of life of children undergoing the procedures. This review successfully met its primary objective by identifying the best evidence on the effectiveness of different MIE techniques. It was also able, to a lesser extent, to address the secondary objectives that sought to determine the acute complications and length of hospital stay associated with these interventions. Unfortunately, no studies reported on the patients' ability to return to pre-operative function, thus we were unable to comment on any patient specific surgical outcomes.

Study inclusion process

The process of study identification and inclusion is represented in Figure 11. This figure was derived by following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[153]

Papers identified

The search strategy outlined in Chapter 2 was conducted on the 3rd January 2017 and identified a total of 3073 articles. A further 12 articles were identified upon review of reference lists and systematic reviews. Following removal of duplicates, a total of 1104 papers remained for further assessment of eligibility.

Title and abstract screening

The screening process involved viewing each article's title and/or abstract against the review inclusion criteria and excluding those records that clearly did not meet the inclusion criteria. A total of 1071 papers were excluded at this stage leaving 33 for full text review.

Full text review

Thirty-three articles underwent a full text review and 12 were excluded as they did not meet the inclusion criteria. The most common reason papers were excluded was because epiphysiodesis was used to treat angular deformities or extreme height rather than a

LLD.[154-157] A handful of papers were excluded that described a variation on the procedure with no accompanying results.[158-161] This left a total of 21 papers that underwent critical appraisal.

Included studies

All 21 papers that made it to critical appraisal were included in the final review. In total, 8 cohort studies[85, 87, 97, 104, 162-165] and 13 case series[93-95, 105, 106, 108, 109, 166-171] were included.

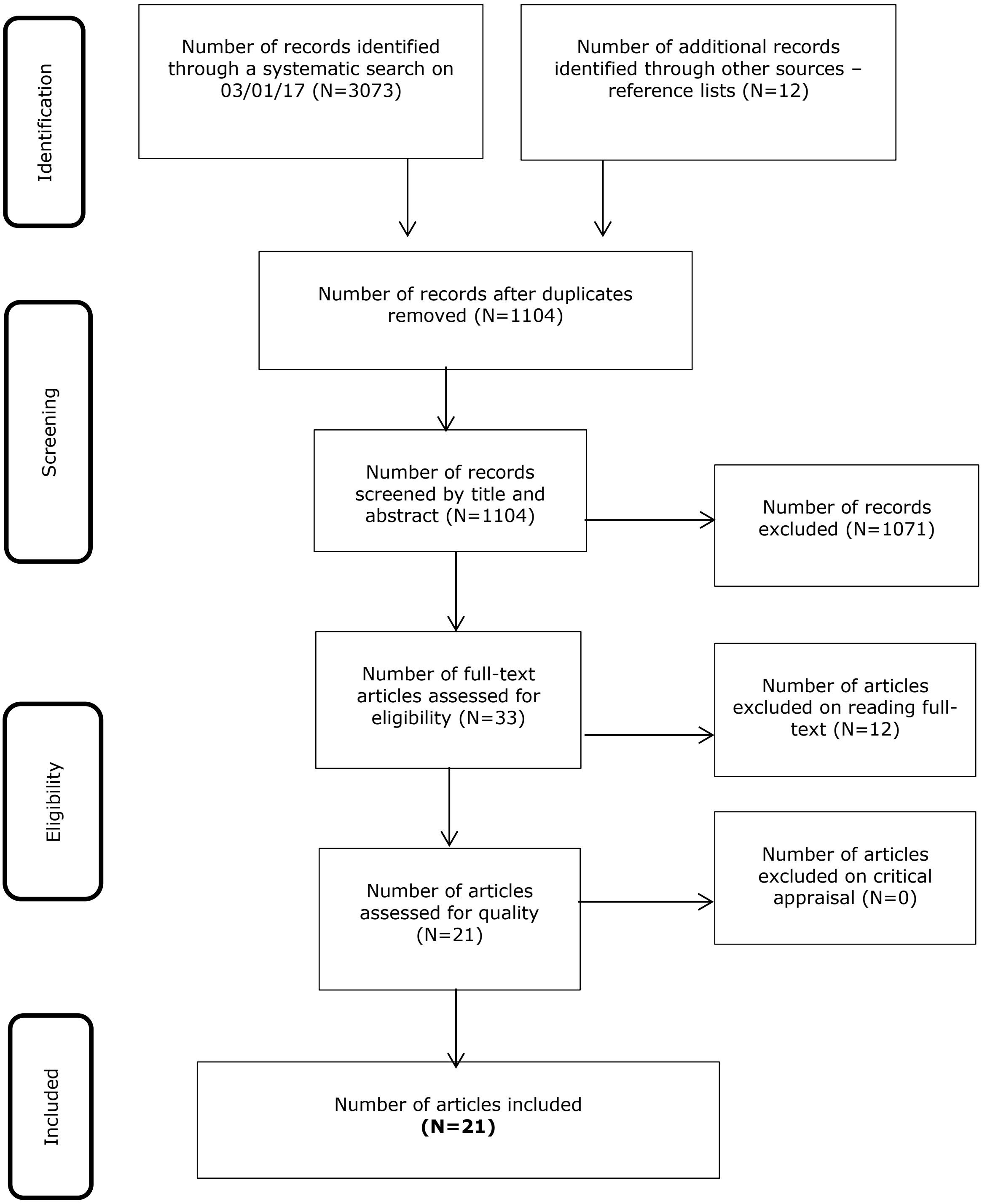

Figure 11: Flow chart of study selection

Assessment of methodological quality

The overall quality of the studies included in this review was moderate to high. Disagreements between reviewers (MC and JI) on critical appraisal scores were generally due to different interpretations of the question or requirements to fulfill the criteria. Following brief discussion all disagreements were settled. For example, clear reporting of demographic information was commonly disagreed upon in case series studies, however, following discussion it was agreed that if age and gender were specified the criteria was fulfilled.

For cohort studies, the critical appraisal question, "Were strategies to address incomplete follow-up utilized?" was felt to be irrelevant for this review as all were retrospective studies and thus, follow-up was expected as part of the inclusion criteria. Shortfalls for this group of studies was a lack of documentation on whether or not strategies to deal with confounding factors were implemented so generally it was marked as unclear. The included cohort studies had an average critical appraisal score of 8/10 (ranging from 7-9) (Table 6).

A common methodological shortfall of published case series was a lack of reporting on whether the case series had consecutive and complete inclusion of participants. Often it was also unclear whether the statistical analysis undertaken was appropriate. On average, the included case series had a critical appraisal score of 7/9 (ranging from 4-8; Table 7).

Table 6: Critical appraisal results for cohort studies (for questions covered see appendix II)

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
[162]Babu LVE. 2014.	U	Y	Y	Y	Y	Y	Y	Y	N/A	U
[85]Campens CM. 2010.	Y	Y	Y	N	Y	Y	Y	Y	N/A	Y
[97]Stewart DC. 2013.	Y	Y	Y	N	Y	Y	Y	Y	N/A	Y
[165]Siedhoff MR. 2014.	Y	Y	Y	N	Y	Y	Y	Y	N/A	Y
[163]Bayhan IAK. 2015.	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y
[164]Lykissas MGJ. 2013.	Y	Y	Y	N	Y	Y	Y	Y	N/A	U
[87]Surdam JWM. 2003.	Y	Y	Y	N	Y	Y	Y	Y	N/A	Y
[104]Edmonds EW. 2007.	Y	Y	Y	N	Y	Y	Y	Y	N/A	Y
%	87.5	100.0	100.0	25.0	100.0	100.0	100.0	100.0	0.0	75.0

Table 7: Critical appraisal results for case series (for questions covered see appendix II)

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
[95]Ilharreborde BG. 2012.	Y	Y	Y	Y	Y	Y	Y	Y	Y
[108]Khoury JGT. 2007.	Y	Y	Y	N	Y	Y	U	Y	U
[94]Métaizeau JPW-C. 1998.	Y	Y	N	Y	Y	Y	Y	Y	Y
[109]Nouth FK. 2004.	Y	Y	Y	Y	Y	Y	Y	Y	U
[105]Ramseier LES. 2009.	U	Y	Y	Y	Y	Y	Y	Y	Y
[171]Song MHC. 2015.	N	Y	U	Y	Y	Y	N	Y	Y
[170]Pendleton AMS. 2013.	Y	Y	U	Y	Y	Y	Y	Y	U
[169]Monier BCA. 2015.	Y	Y	U	Y	Y	Y	Y	Y	Y
[168]Lauge-Pedersen HH. 2013.	N	Y	U	N	Y	Y	N	Y	U
[166]Horn JG. 2013.	N	Y	U	Y	Y	Y	N	Y	Y
[106]Inan MC. 2008.	Y	Y	Y	Y	Y	Y	Y	Y	U
[93]Gorman TMV. 2009.	Y	Y	N	Y	Y	Y	Y	Y	Y
[167]Kemnitz SM. 2003.	Y	N	Y	N	Y	Y	N	Y	U
%	69.23	92.3	46.15	76.92	100.0	100.0	61.53	100.0	53.84

JBI levels of evidence

The approach developed by JBI in 2014 for classifying the levels of published research evidence[172] provided a good framework for evaluating the levels of evidence included in this review. Using this approach, the levels of evidence of the included papers were classified as: 3.e (eight studies) and 4.c (13 studies) (Table 8). This indicates that the overall level of evidence in this review was low.

JBI defines a cohort study as a longitudinal study that is typically used to analyse the relationship between exposures and disease by comparing the outcomes between two groups over time[173] where the sampling is based on exposure rather than outcome. It is for this reason that we classified some studies as cohort studies despite them not having a specific 'control group'. Conversely, for case series the JBI has adopted the definition by Dekkers et al,[174(pg 38)] who defined a case series as a study in which "only patients with the outcome are sampled…….either those who have an exposure or those who are selected without regard to exposure, which does not permit calculation of an absolute risk". This is different to cohort studies where sampling is based on exposure or characteristics.

Table 8: Level of evidence table of included studies

JBI Levels of Evidence	Sub-categorisation of levels; descriptions	No. of studies	Citations
Level 1 Experimental design	1.a - SR of RCTs		
	1.b - SR of RCTs and other study designs		
	1.c - RCT		
	1.d - Pseudo-RCT		
Level 2 Quasi-experimental designs	2.a - SR of quasi-experimental studies		
	2.b - SR of quasi-experimental and other study designs		
	2.c - Quasi-experimental prospectively controlled study		
	2.d - Pre-test – post-test or historic/retrospective control group study		
Level 3 Observational – analytic designs	3.a - SR of comparable cohort studies		
	3.b - SR of comparable cohort and other study designs		
	3.c - Cohort study with control group		
	3.d - Case-controlled study		
	3.e - Observational study without a control group	8	[162] Babu et al – Epiphysiodesis for limb length discrepancy: a comparison of two methods. [85] Campens et al – Comparison of three surgical epiphysiodesis techniques for the treatment of lower limb length discrepancy. [97] Stewart et al – Dual eight-Plate techniques is not as effective as ablation for epiphysiodesis about the knee. [165] Siedhoff et al – Temporary epiphysiodesis for limb length discrepancy. [163] Bayhan et al – comparing percutaneous physeal epiphysiodesis and eight-Plate epiphysiodesis for the treatment of limb length discrepancy. [164] Lykissas et al – Guided growth for the treatment of limb length discrepancy: a comparative study of the three most commonly used surgical techniques. [87] Surdam et al – leg length inequality and epiphysiodesis: review of 96 cases. [104] Edmonds et al – Percutaneous epiphysiodesis of the lower extremity, a comparison of single- versus double portal techniques.
Level 4	4.a - SR of descriptive studies		

JBI Levels of Evidence	Sub-categorisation of levels; descriptions	No. of studies	Citations
Observational – descriptive studies	4.b - Cross-sectional study		
	4.c - Case series	13	[95] Ilharreborde et al – Efficacy and late complications of percutaneous epiphysiodesis with transphyseal screws. [108] Khoury et al – Results of screw epiphysiodesis for the treatment of limb length discrepancy and angular deformity. [94] Metaizeau et al – Percutaneous epiphysiodesis using transphyseal screws (PETS). [109] Nouth et al – Percutaneous epiphysiodesis using transphyseal screws (PETS). [105] Ramseier et al – Minimal invasive epiphysiodesis using modified "canale" – technique for correction of angular deformities and limb length discrepancies. [171] Song et al- Percutaneous epiphysiodesis using transphyseal screws in the management of leg length discrepancy: Optimal operation timing and techniques to avoid complications. [170] Pendleton et al – Guided growth for the treatment of moderate leg-length discrepancy. [169] Monier et al – Percutaneous epiphysiodesis using transphyseal screws for limb-length discrepancies: high variability among growth predictor models. [168] Lauge-Pedersen et al – eight-Plate should not be used for treating leg length discrepancy. [166] Horn et al – Percutaneous epiphysiodesis in the proximal tibia by a single-portal approach: evaluation by radiostereometric analysis. [106] Inan et al – Efficacy and safety of percutaneous epiphysiodesis. [93] Gorman et al – Mechanical axis following staple epiphysiodesis for limb-length inequality. [167] Kemnitz et al – Percutaneous epiphysiodesis for leg length discrepancy.
	4.d - Case study		
Level 5 Expert opinion and bench research	5.a - SR of expert opinion		
	5.b - Expert consensus		
	5.c - Bench research/single expert opinion		

RCT = randomised control trial; SR = systematic review

Description of included studies

Of the 21 studies included in this systematic review, nine papers assessed PETS, 10 assessed PDC, six reviewed eight-Plates, and three assessed staples. Nine studies were undertaken in the United States of America, six throughout the European Union, four in surrounding European countries, and one each in Asia and Australia. Notably, none were conducted in the developing world. See Appendix III for a table of included studies.

The included studies were published between 1998 and 2016 with participants entering the studies or undergoing the epiphysiodesis procedures as far back as 1975. Six studies within the PDC group reported on the primary outcome of interest (the effectiveness of reducing LLD) while the remaining four papers that evaluated PDC addressed secondary outcomes only. All 10 studies evaluating PETS addressed the primary outcome of interest (effectiveness in reducing a LLD) as did the three within the staples group. Finally, of the four papers assessing eight-Plates, two addressed the primary outcome while two focused exclusively on the secondary outcomes of the procedure.

Demographics

Table 9 presents the demographic characteristics across the evaluated interventions.

Percutaneous drilling and curettage

As mentioned, PDC techniques were analysed in 10 papers included in the systematic review. Together, there was a total of 424 patients who underwent PDC for the management of a LLD. The mean age at the time of operation was 12.99 years, 52.6% were males and 47.4% females. These children had a mean pre-operative LLD of 2.98 cm and were followed for a mean of 2.8 years post surgical intervention.

Aetiology of the LLD was documented in eight papers and the range of causes are listed below. The most common causes were trauma, idiopathic, developmental dysplasia of the hip and a congenitally short femur

- Amniotic band syndrome
- Blount’s disease
- Clubfoot
- Congenitally short femur
- DDH
- Femoral head avascular necrosis
- Fibrous dysplasia
- Fibular hemimelia
- Hemihypertrophy
- Hereditary multiple exostosis
- Idiopathic
- Infection
- Juvenile idiopathic arthritis
- Kippel-Trenaunay syndrome
- Neoplastic
- Neurofibromatosis
- Ollier’s disease
- Perthes
- Post traumatic
- Proximal focal femoral deficiency
- Slipped capital femoral epiphysis

Percutaneous epiphysiodesis using transphyseal screws

The PETS technique was reviewed in nine papers and together was utilised to manage a LLD of greater than 2 cm in 240 children with a mean age of 13.15 years. In this cohort, 59.2% were male and the remaining 40.8% female. The initial pre-operative LLD had a mean of 2.8 cm and mean follow-up was 3.2 years post surgical intervention. Aetiology of the LLD was documented in eight papers and had a similar spread to that seen in the PDC cohort. The causes are listed below; once again the most common causes were trauma and idiopathic.

- Cerebral palsy
- Clubfoot
- Congenital fibular deficiency
- Congenital pseudoarthrosis of tibia
- Congenitally short femur
- DDH
- Fibular hemimelia
- Hemihypertrophy
- Hemiplegia
- Hereditary multiple exostoses
- Idiopathic
- Infection
- Klippel-Trenaunay syndrome
- McCune-Albright syndrome
- Neoplastic
- Ollier's disease
- Perthes
- Post-traumatic
- Proximal focal femoral deficiency
- Slipped capital femoral epiphysis
- Tibial bowing/varus

eight-Plates

Eight-Plates was utilised for the management of LLDs of more than 2 cm in 83 children across six papers. The children involved had a mean age of 12.13 years; 53.5% were male and the remaining 46.5% female. They had an initial pre-operative LLD mean of 2.5 cm and average follow-up was 3.7 years post surgical intervention. Aetiology of the LLD was documented in five of the six papers that reviewed eight-Plates. The aetiologies seen in this cohort are listed below:

- Clubfoot
- Congenital femoral hypoplasia
- DDH
- Ectrodactyly
- Fibular hemimelia
- Hemihypertrophy
- Idiopathic
- Kippel-Trenaunay syndrome
- Neoplastic
- Ollier's disease
- Perthes
- Post-axial hypoplasia
- Post-traumatic
- Slipped capital femoral epiphysis

Staples

Staple epiphysiodesis was assessed in three papers and together was utilised to manage LLDs of greater than 2 cm in 82 children with a mean age of 12.4 years. In this cohort, 57.1% were male and the remaining 42.9% were female. The initial pre-operative LLD had a mean of 2.75 cm and average follow-up was 5.2 years post surgical intervention. Aetiology of the LLD was documented in all three papers, and represented in the list below.

- Amniotic band syndrome
- Congenital femoral deficiency
- DDH
- Fibular hemimelia
- Hemihypertrophy
- Hypoplastic fibular
- Kippel-Trenaunay syndrome
- Ollier's disease
- Perthes
- Postaxial hypoplasia
- Post traumatic

Notably, in no paper was the outcome of the procedure linked to the aetiology of the LLD given the included numbers were too small to draw such conclusions. When extracting and synthesising the data this remained impossible as most studies did not provide linked IPD/outcomes to allow for the data to be pooled. This information may have lead to the identification that some techniques are better for certain pathologies. For example, Ollier's disease, which refers to the development of intraosseous benign cartilaginous tumours, may be better treated with PETS or PDC due to the altered bone quality around the physis. This is contrary to trauma cases where the deformity is often static and a reversible method of epiphysiodesis may be preferred.

Overall

A total of 829 patients with a mean age range of 12 – 14 years underwent a MIE technique for the management of their LLD. The range of initial LLD pre-surgical intervention was 1.88 – 4.1cm, and patients were followed up for between 1.6 – 8.7 years post surgical intervention on average (Table 9).

Table 9: Study demographics

Technique	Number of patients	Mean age (years)	Percentage male	Mean initial leg length discrepancy (cm)	Mean follow-up (years)
PDC	424	12.2 – 13.6	52.6	2.6 – 3.7	2.1 – 3.8
PETS	240	12.8 – 14	59.2	1.88 – 3.3	2.0 – 5.4
eight-Plates	83	12.0 – 13	53.5	1.9 – 4.1	1.6 – 8.7
Staples	82	12.0 – 12.8	57.1	2.3 – 3.65	2.8 – 7.5
TOTAL/RANGE	**829**	**12 – 14**	**52.6 – 59.2**	**1.88 – 4.1**	**1.6 – 8.7**

Findings of the review

The effectiveness of different MIE techniques is presented in Table 10.

Absolute leg length discrepancy at skeletal maturity

As previously discussed, the main goal of epiphysiodesis is to stop/slow growth through the physis on the long leg to reduce the burden of the LLD to less than 2 cm in magnitude. Given this, the primary outcome assessed was the overall ability of the procedure to achieve/correct a LLD to less than 2 cm.

Percutaneous drilling and curettage

The absolute LLD at skeletal maturity was reported in seven of the 10 papers assessing the use of PDC in the management of LLDs. It can be seen in Table 10 that from the seven papers there was a mean pre-operative LLD range of 2.6 – 3.7cm, which was reduced to a mean absolute LLD at skeletal maturity of 1 – 1.3cm with the aid of PDC. Thus, all papers saw a mean final LLD of less than 2 cm, which is the benchmark of success for the procedure.

Unfortunately, a big issue was that many of studies did not report on what the predicted LLD at skeletal maturity was.[85, 105, 163, 167] It was often documented in the introduction that the procedure was indicated in those that had a predicted LLD between 2 (or 2.5) and 5cm, or the inclusion/exclusion criteria stated that patients had a LLD of less than 5 cm. Thus, it was assumed that all patients in the studies fell into this category. On further analysis, it became apparent that some papers had included patients that had a predicted LLD of more than 5 cm or less than 2 cm. For example, although Campens et al[85] stated in their introduction that the indication for the procedure was a LLD of 2-4 cm and maybe up to 6 cm, they still ncluded patients with LLDs of up to 8.1 cm (recorded at time of operation, not the final predicted LLD so likely even larger). Similarly, Inan et al[106] despite reporting a mean predicted LLD of 4.7 cm they included patients with a LLD of up to 16 cm in their study. Conversely, Kemnitz et al[167] may have included patients with a LLD of less than 2 cm. They did not provide a predicted LLD, but reported a range of LLDs at operation of 1.6 to 4.1 cm. In each of these cases, no IPD was provided and as such, the patients sitting outside the ideal range could not be excluded. Horn et al[166] and Ramsier et al[105] both included patients with predicted LLDs outside the range of 2-5 cm, however, these patients could be excluded from the review due to the availability of the IPD. Ramsier et al[105] also detailed the reason why two patients had been included (patient preference to prevent deformity progressing) despite them not falling within the ideal range.

Another weakness of the included studies was the variety of different ways the surgical procedures were undertaken, for example, single portal or double portal, which may have impacted on the overall results. Finally, the methods for reporting success also varied widely. For example, some reported means,[105, 162, 163, 167] while others such as Kemnitz[167] and Campens et al[85] reported categories. Only one paper by Ramsier et al[105] reported a standard deviation for the results.

Interestingly, both papers that included patients with a LLD greater than 5 cm[85, 106] still reported very good results when it came to final LLD. Campens et al[85] reported 89% of their cohort obtained good results with a residual LLD of <1.5 cm; a poor result was seen in only 4% (1 patient). We were not able to determine whether this was the child that had a discrepancy of 8.1cm at the beginning of the study, or not. Inan et al[106] saw a mean reduction in LLD of 3.4 cm (mean predicted = 4.7cm; mean final = 1.3 cm).

Percutaneous epiphysiodesis using transphyseal screws

The absolute LLD at skeletal maturity was reported in all nine papers assessing the use of PETS in the management of LLDs. As presented in Table 10, it can be seen that the mean pre-operative LLD reported in the nine papers ranged from 1.88 – 3.33 cm, this was reduced to an absolute LLD at skeletal maturity of 0.3 – 1.79 cm. Once again all papers had a final mean LLD of less than 2 cm indicating a successful procedure.

As with PDC, the majority of papers assessing the effectiveness of PETS did not report on the predicted LLD at skeletal maturity.[85, 94, 109, 164, 169, 171] Of these studies Campens,[85] Nouth[109] and Metaizeau[94] were the only studies to state in the introduction that the indication for the surgical procedure was a LLD of 2-5 cm or 2-6 cm. Despite this, Campens[85] clearly included patients with a LLD of more than 5 cm in the cohort as they reported an initial LLD range of 1.5-8.1 cm. Other studies within this group that included patients with a LLD outside the defined 2-5 cm range were Illharreborde,[95] who included patients with a LLD of up to 15 cm, (mean predicted LLD remained within the 2-5 cm range), and Khoury et al,[108] who included patients with both predicted LLDs of less than 2 cm and more than 5 cm at skeletal maturity. Despite Monier[169] not reporting the predicted LLD, patients had a initial LLD ranging from 1.3-6 cm at the time of surgery, indicating that patients with a LLD greater than 5 cm were included, however, it was unclear whether patients with a predicted LLD of <2 cm were included. Unfortunately, in all these studies IPD was not provided, and thus, patients with predicted LLDs outside the 2-5 cm range could not be excluded from the analysis. In the remaining studies it was not possible to determine whether patients with predicted LLDs falling outside the required range were included in the cohorts as nothing other than means were reported.

Song et al[171] explicitly reported that PETS was indicated in those with a LLD of less than 5 cm, however, they included a number of patients with a LLD of less than 2 cm. They reported an average predicted LLD of only 2.07 cm with a range from 1.07 to 3.73 cm; unfortunately, once again, IPD was not available. Given the mean predicted LLD was >2 cm the paper was considered appropriate for inclusion in the systematic review. The inclusion of patients with a low predicted LLD may explain why they had such success with the technique and the average final LLD was only 0.3 cm.

Despite all the studies obtaining a final mean (or median) LLD of less than 2 cm (0.3 – 1.79 cm), all those that included patients with a LLD of greater than 5 cm, other than Khoury et al,[108] had a slightly higher mean final LLDs as would be expected. Thus, the inclusion of these patients in the studies may have impacted on the overall results presented and PETS could have reduced the final LLD further if only those with a LLD of 2-5 cm had been operated on.

Once again, both the technique and reporting varied between studies. For example, it was often not defined whether either or both the tibial and femoral physis were treated. There were also different methods of screw placement (cross vs vertical), which were often not documented in the methods. Thus, it cannot be determined whether these variables impacted on the implants effectiveness. With regards to the reporting of results, Campens et al[85] reported in categories, while Lykissas et al[164] reported a median (with no standard deviation) rather than a mean final LLD, which could not be converted given the lack of IPD. All remaining studies reported results in terms of a mean.

eight-Plates

Four studies assessed the effectiveness of eight-Plates in correcting a LLD. The data from these papers being represented in Table 10, showing a mean of pre-operative LLD ranging from 1.9 – 5.5 cm. This LLD was reduced to a mean final LLD ranging from 1.1 – 1.8 cm at skeletal maturity secondary to the use of eight-Plates. All papers reported a mean final LLD of less than 2 cm, once again, implying a successful procedure.

Unfortunately, only one paper[165] reported on the predicted LLD at skeletal maturity. This paper by Siedhoff et al[165] did not include any patients with a LLD of more than 5 cm, although it did include patients with a LLD of less than 2 cm. We were able to exclude these patients from the analysis as IPD was supplied. The remaining papers did not report a predicted LLD at skeletal maturity.[163, 164, 168, 170] Ostensibly, Bayhan et al[163] did not include any patients with a LLD over 5 cm as they stated in their introduction that the indication for the procedure was a LLD of less than 5 cm, however, it could not be determined if they included patients with a LLD of less than 2 cm. On the other hand, Lykissas et al[164] included one patient with a LLD of greater than 5 cm at the time of surgical intervention and Pendleton et al[170] included patients with an initial LLD as low as 0.7 cm making it highly likely they they included patients with predicted LLD at skeletal maturity outside the 2-5 cm range. In both cases no IPD was supplied.

Finally, the study by Lauge-Pedersen et al[168] only involved two patients who both discontinued the trial due to poor early results. The study had initially been approved to perform the procedure on 10 patients, however, as the first two enrolled patients (initial LLDs of 3.9 and 5.5 cm, respectively) showed persistent longitudinal growth through the physis post-operatively, which resulted in only a slight growth retardation over a 1.5 year period, the study was terminated. The authors concluded that they could not recommend eight-Plates for the treatment of paediatric LLDs.

Staples

Only three papers assessed the effectiveness of staples in correcting a paediatric LLD. Once again represented in Table 10, the range of mean pre-operative LLDs across the papers was 2.74 – 3.2 cm which was reduced to an average LLD at skeletal maturity of 0.85 – 1.6 cm. Thus, all three papers obtained a final mean LLD of less than 2 cm indicating overall success of the procedure.

As in the studies evaluating the other three techniques, the reporting of predicted LLD at skeletal maturity was very poor and only performed in one paper,[93] which stated that at their institution the indication for staples to correct a LLD was a predicted LLD of between 2-5 cm. Despite this, two patients outside this range were included – one with a LLD of 7.9 cm and the other with a LLD of 0.4 cm. The authors did, however, clearly document the reasons why these patients had been included, namely in one case, that the patient did not want a leg lengthening procedure and that in the other, they were trying to prevent an increasing LLD following a fracture. Unfortunately, as IPD was not presented, these two patients could not be excluded from the analysis. Lykissas et al[164] was the only remaining paper to assess the effectiveness of staples. It is not clear if patients with a LLD of more than 5 cm or less than 2 cm were included given no predicted values were reported, however the median LLD at the time of operation was 3.65 cm with an interquartile range of 3.4-3.95 cm.

In all the studies, staple epiphysiodesis was performed by placing three staples across the physis on either side (six staples total per physis), although once again, it was not clearly reported in each case how many physis were involved (either or both the femoral and tibial). The results were also differentially reported, for example, Gorman et al[93] and Siedhoff et al[165] reported means with standard deviations while Lykissas et al[164] reported medians with an interquartile range, making it difficult to compare the studies.

Table 10: Effectiveness of different minimally invasive epiphysiodesis techniques

Technique/Study	Number of patients	Mean initial leg length discrepancy (cm)	Mean predicted leg length discrepancy (cm)	Mean final leg length discrepancy (cm)
PDC				
Babu et al[162]	26	3.7	4.8	1.2
Bayhan et al[163]	48	2.9 (+/-1.6)	Not reported	1.3
Campens et al[85]	34	2.8	Not reported	Reported in categories
Horn et al (dual)[166]	10	2.9	3	Not reported
Horn et al (single)[166]	10	2.9	3.2	Not reported
Inan et al[106]	88	3.3	4.7	1.3
Kemnitz et al[167]	57	2.7	Not reported	1.2
Ramseier et al[105]	16	2.6 (+/-1.1)	Not reported	1.0 (+/- 1.4)
TOTAL/RANGE	**289**	**2.6 – 3.7**	**3 – 4.8**	**1 – 1.3**
PETS				
Babu et al[162]	14	3.2	4.5	1.4
Campens et al[85]	15	3	Not reported	Reported in categories
Ilharreborde et al (femoral)[95]	30	3.17 (+/-1.46)	4.66	1.79 (+/-1.5)
Ilharreborde et al (tibial)[95]	34	2.75 (+/-1.05)	3.99	1.5 (+/-1.21)
Khoury et al[108]	20	2.59 (+/- 0.5)	2.85 (+/-0.5cm)	1.2 (+/- 0.6)
Lykissas et al[164]	22	Reported as median (3.15)	Not reported	Reported as median (1.45)
Metaizeau et al[94]	32	2.47	Not reported	0.51
Monier et al[169]	16	3.1	Not reported	1.7
Nouth et al[109]	9	3.33	Not reported	1.38
Song et al[171]	48	1.88	2.07	0.3
TOTAL/ RANGE	**240**	**1.88 – 3.33**	**2.07 – 4.66**	**0.3 – 1.79**
eight-Plates				
Bayhan et al[163]	24	3 (+/-1.3)	Not reported	1.8
Lauge-Pedersen et al[168]	2	5.5 and 3.9	Not reported	Not reported
Lykissas et al[164]	9	Reported as median (4.1)	Not reported	Reported as median (1.3)
Pendleton et al[170]	34	1.9 (+/-0.7)	Not reported	1.1 (+/-0.9)
Siedhoff et al[165]	3	2.9 (+/-0/7)	3	1.3 (+/-0.53)
TOTAL/RANGE	**72**	**1.9 – 5.5**	**Insufficient data**	**1.1 – 1.8**
Staples				
Gorman et al[93]	54	3.2 (+/-1.4)	Not reported	1.6 (+/- 1.3)
Lykissas et al[164]	8	Reported as median (3.65)	Not reported	Reported as median (1.95)
Siedhoff et al[165]	20	2.74 (+/-0.88)	3.01 (+/-0.91)	0.85 (+/-0.89)
TOTAL/RANGE	**82**	**2.74 – 3.2**	**Insufficient data**	**0.85 – 1.6**

Rate of correction

Rate of correction was addressed in only three papers and not in a standardised way. Unfortunately, given the lack of data and the quality of the IPD presented (e.g. no reporting on specific time points and no standardised follow-up) we were unable to extrapolate this from the data provided.

Lykissas et al[164] found that the mean overall rate of correction for patients treated with eight-Plates was 1.11 cm/year; those treated with staples had a correction of 1.22 cm/year; and those treated with PETS had a rate of correction of 0.59 cm/year. They reported that there was a statistically significant difference in the rate of correction between stapling and PETS (p=0.045), however there was no significant difference between stapling and eight-Plates, and eight-Plates and PETS.

Bayhan et al[163] reviewed the rate of correction corresponding to the location of epiphysiodeis. They found that when using eight-Plates the average rate of growth retardation at the distal femur was 0.37 mm/month (0.44 cm/year) while at the proximal tibia it was 0.4 mm/month (0.48 cm/year) equating to 0.92 cm/year. This was quite similar (no significant difference) to the rates achieved with PDC, which were 0.41 mm/month (0.49 cm/year) at the distal femur and 0.43 mm/month (0.52 cm/year) at the proximal tibia, equating to a total correction of 1.01 cm/year.

Finally, Horn et al[166] assessed the difference between single and double portal PDC. They reported on the sequential rates of growth cessation over the first 24 weeks of treatment. When using a single incision, the mean longitudinal growth from 0-6 weeks on the operated physis was 0.26 mm (0.01-0.6); during the time-period of 6-12 weeks there was a growth of 0.06 mm (0.00-0.18); and finally, from 12-24 weeks there was no appreciable growth through the physis. Using the dual incision from 0-6 weeks there was a longitudinal growth of 0.17 mm (0.01-0.5); from 6-12 weeks, the average longitudinal growth was 0.03 mm (0.00-0.2); and like the single incision, there was no appreciable growth through the physis from 12-24 weeks. No significant difference was found between the two techniques. They reported the average growth of all patients in the first 6 weeks was 0.22 mm, which represented approximately 30% of normal growth. This reduced to a mean growth of 0.046 mm over the coming 6 weeks that corresponded to 6% of usual growth, and as previously mentioned, there was no appreciable longitudinal growth through the physis following 12 weeks, indicating a progressive dynamic process.

Percentage of correction relative to desired correction

To determine the percentage of correction relative to desired correction, a study was required to compare the predicted LLD at skeletal maturity to the final results. Unfortunately, no paper directly reported on this, however, three papers assessed and reported the effectiveness of the technique using differing methods.[95, 163, 171] Bayhan et al[163] reported the percentage of improvement, however, it is not known if this utilised the predicted LLD at maturity or purely a calculation of pre-operative LLD compared to LLD at final skeletal maturity. The authors reported that the PDC group had a significantly higher percentage of improvement compared to eight-Plates (58% vs 41%, respectively). Illhareborde et al[95] compared the effectiveness of the femoral group to the tibial group undergoing PETS, and found each site to be equally efficacious, however, once again it is not known how they calculated these results. They reported that the mean effectiveness at 6 months post-operative in the femoral group was 35% and this improved to 66% at skeletal maturity compared to the tibial group who at six months post-operatively had an effectiveness of 46%, which improved to 66% at skeletal maturity.

Finally, Song et al[171] evaluated the success of PETS by calculating the correction effectiveness. They defined this as the amount of LLD correction achieved as a percentage of the amount of LLD correction theoretically expected ([Predicted operated bone segment length without PETS – final length]/{[Predicted operated bone segment length without PETS-Initial length]}xg]). In this situation g referred to the proportional growth at the operated physis in the whole longitudinal growth of the bone segment (71% at the distal femur and 57% at the proximal tibia). They reported the mean LLD correction at the distal femur using PETS was 75.5% while at the proximal tibia it was 78.9%.

The percentage of correction relative to the desired correction was calculated from the papers where IPD was available using the following calculation:

$$\frac{\text{Predicted LLD at skeletal maturity} - \text{Final LLD at skeletal maturity}}{\text{Predicted LLD at skeletal maturity}} \times 100$$

Accordingly, the paper had to report both the predicted LLD at skeletal maturity and the actual final LLD at skeletal maturity for the calculation to be made. We were unable to complete this calculation in papers without IPD as there was no consistency in the reporting of data collection time points, and unfortunately, only a handful reported a predicted LLD, consequently extrapolation was thought to be too inaccurate. Unfortunately, only two papers provided the appropriate information, namely, studies by Khoury et al,[108] who assessed the effectiveness of PETS, and Siedhoff et al,[165] who examined staples and eight-Plates. The results are presented in Table 11, which shows that staples achieved an average of 69.1% (+/-26.27) correction compared to eight-Plates, which obtained a correction of 61.3% (+/-12.2) in the study by Siedhoff et al.[165] These results were both superior to those seen in the study by Khoury et al[108] who found PETS obtained a correction of 56.9% (+/-20.96).

Table 11: Percentage of desired correction achieved with different MIE techniques

Patient number	Expected leg length discrepancy (cm)	Final leg length discrepancy (cm)	% of desired correction
eight-Plates[165]			
1	2.5	0.7	72
2	3.3	1.7	48
3	4.2	1.5	64
		Average	61.3% (+/- 12.2)
Staples[165]			
1	2	0.1	95
2	2.1	0.2	90
3	2.2	1.6	27
4	2.5	0.7	72
5	2.4	0.3	87.5
6	2.6	0	100
7	2.3	0.8	65
8	2.4	0.3	87.5
9	2.7	-0.3	111
10	2.8	1.8	35.7
11	2.8	1.6	42.9
12	3.4	0.5	85.3
13	3.3	1.9	42.4
14	3.2	0.7	78.1
15	3.4	1.8	47
16	3.3	2.6	21.2
17	3.9	1.6	59
18	5	1	80
19	4.8	0.7	85.4
		Average	69.1% (+/- 26.27)
PETS[108]			
1	3.5	0.5	85.7
2	2.9	0.3	89.7
3	2.8	0.9	67.9
4	2.4	1.1	54.2
5	2.9	0.7	75.9
6	2.6	0.8	69.2
7	2.2	1.8	18.2
8	2.5	1.3	48
9	3.2	1.6	50
10	2.1	1.9	9.5
11	3.8	1.2	68.4

Patient number	Expected leg length discrepancy (cm)	Final leg length discrepancy (cm)	% of desired correction
12	3.3	1.9	42.4
13	2.4	1.1	54.2
14	3.0	1.8	40
15	2.3	0.5	78.2
16	2.5	1.2	52
17	2.3	0.5	78.2
18	3.5	1.8	48.6
19	2.9	1.0	65.5
20	3.8	2.2	42.1
		Average	56.9% (+/- 20.96)

Incidence of long term complications

Each pre-defined long term complication was individually reviewed. A long term complication was defined as one that was present at skeletal maturity or resulted in failure of the hardware, for example, breakage or loss of fixation.

Failure of growth plate arrest (GPA)

In the papers that reported on failure of GPA, it can be seen in Table 12 that 6% (18 of 299) of patients within the PDC cohort had failure of growth plate arrest compared to 2.5% (3 of 119) within the PETS group, 6% (5 of 84) within the staples group, and 14% (4 of 28) within the eight-Plates group. Assuming that those who did not report failure of GPA did not experience them, rates dropped to 4% in the PDC group, 1% in the PETS group and 5% in both the eight-Plate and staples groups. Either way, these results suggest that PETS is superior to the other modes of MIE when it comes to ensuring growth plate arrest.

Failure to achieve adequate reduction in leg length discrepancy (< 2 cm)

Adequate reduction in LLD was defined as obtaining a LLD of less than 2 cm at skeletal maturity. As presented in Table 12, approximately 13% (14 of 107 patients) did not achieve adequate reduction of LLD and were left with a discrepancy of >2 cm in the PDC group. In the PETS group, 8% (14 of 172) of patients had a LLD at skeletal maturity of > 2 cm. Within the eight-Plates group, 15% (7 of 47) had inadequate correction, while in the staples group 23% (21 of 92) of patients did not have their discrepancy corrected to <2 cm. This once again suggests that PETS is the most effective method of MIE. Note this is excluding patients that had failure of GPA and went on to have secondary operations.

Angular deformities

AD were reported in a subgroup of patients, and generally were defined as an axis deviation of greater than 1 cm or more (3-5°), as this is thought to be a clinically relevant deviation.[93] Once again, only papers that reported on AD as a post-operative complication were included in these calculations. AD were noted in 2% (5 of 314) of PDC patients. This is compared to 9% (19 of 202) in the PETS group, 5% (3 of 62) in the eight-Plate group, and 33% (30 of 92) in the staples group. These results suggest that staples have a noteably higher rate of AD than the other three MIE techniques.

Hardware failure

Hardware failure refers to the loosening or breakage of the implant that results in a loss of function of the implant, which is not relevant to the PDC cohort. No patients in the PETS cohort reported experiencing failure of hardware, however, approximately, 14% (5 of 37) in the eight-Plate group, and approximately 7% in the staples cohort, experienced hardware failure. The most common reason for hardware failure in the eight-Plate group was screw failure while in the staples group the staples often deformed (i.e. became concaved or snapped).

Table 12: Incidence of long term complications for different MIE technique

Study	Number of patients	Failure of growth plate arrest	Failure to achieve adequate reduction in leg length discrepancy (<2cm)	Over correction	Development of angular deformity	Hardware failure	Other
PDC							
Babu et al[162]	26	2	-	-	-	N/A	-
Campens et al[85]	34	2	1	-	1	N/A	-
Inan et al[106]	88	3	-	-	0	N/A	3 exostosis
Kemnitz et al[167]	57	-	10	5	2	N/A	3 epiphysiodesis on contralateral side for overcorrection
Ramseier et al[105]	16	0	3	3	0	N/A	3 contralateral epiphysiodeis for overcorrection
Stewart et al[97]	16	2	-	-	-	N/A	2 re-epiphysiodesis for lack of correction
Surdam et al[87]	56	2	-	-	1	N/A	2 re-epiphysiodesis; 1 distal femoral epiphysiodesis with osteotomy
Edmonds et al – dual incision[104]	19	1	-	-	0	N/A	
Edmonds et al – single incision[104]	44	6	-	-	1	N/A	
TOTAL	**356**	**18**	**14**	**8**	**5**	**N/A**	

Study	Number of patients	Failure of growth plate arrest	Failure to achieve adequate reduction in leg length discrepancy (<2cm)	Over correction	Development of angular deformity	Hardware failure	Other
PETS							
Babu et al[162]	14	1	-	-	-	-	1 persistent knee pain requiring screw removal
Campens et al[85]	15	-	1	-	-	-	-
Ilharreborde et al[95]	45	-	-	-	9	-	6 AD corrections; 2 revision surgerys as screws no longer transphyseal
Khoury et al[108]	30	-	3	0	1	0	7 screws removed for persistent pain
Lykissas et al[164]	22	-	8	0	1	0	1 correction of AD
Metaizeau et al[94]	32	0	0	1	3	-	-
Monier et al[169]	16	1	0	0	0	0	6 screws removed for persistent pain
Nouth et al[109]	9	1	2	0	0	-	-
Song et al[171]	48	0	0	1	5	-	*authors reported 3 undercorrections from predicted, although range of final LLD = -1cm to 1.67cm
TOTAL	**231**	**3**	**14**	**2**	**19**	**0**	

Study	Number of patients	Failure of growth plate arrest	Failure to achieve adequate reduction in leg length discrepancy (<2cm)	Over correction	Development of angular deformity	Hardware failure	Other
eight-Plates							
Bayhan et al[163]	24	4* (all had PDC)	-	-	1	2	14 removal of implants
Lykissas et al[164]	9	-	3	1	-	1	1 contralateral epiphysiodesis for overcorrection; 1 replacement of screw.
Pendleton et al[170]	34	-	4	2	2	-	1 correction of AD
Siedhoff et al[165]	4	0	0	0	0	2	2 exchange of loose implants
TOTAL	**71**	**4**	**7**	**3**	**3**	**5**	**-**
Staples							
Gorman et al[93]	54	5	14	1	27	4	6 corrections of AD
Lykissas et al[164]	8	-	4	0	0	-	-
Siedhoff et al[165]	30	0	3	4 (all less than 1cm)	3	2	4 exchange of staple for AD or loose; 1 osteotomy; 1 femoral re-epiphysiodesis; 1 tibial exostosis removed
TOTAL	**92**	**5**	**21**	**5**	**30**	**6**	

Incidence of acute complications

Acute complications were defined as those that occurred in the immediate post-operative period and prolonged recovery but not the overall effectiveness of the implant (Table 13).

Post-operative infection

It was initially hoped that this section would be split into superficial and deep wound infections, as the outcomes of these can be substantially different, with deep infections often requiring surgical intervention. Unfortunately, as this was rarely differentiated, infections are instead presented as a group. Within the PDC group, 2.5% of patients developed a post-operative wound infection compared to 0.5% of those in the PETS group, and 3% in both the eight-Plates and the staples groups (Table 13). This indicates there was no substantial difference in infection rates between the different techniques.

Unplanned return to theatre

Only three instances of an unplanned return to theatre were described across the included papers. Each was due to an acute or intra-operative complication: one for the management of a synovial fistular that formed secondary to PDC, and two for patients in the PETS group that required exchange of one of the cross screws. One screw required changing as it was too long and the other was redirected across the physis. There were no return to theatre events in the eight-Plate or staples group.

Haematomas or effusions large enough to impact on post-operative recovery

When assessing the data presented in the papers, it was not always clear if the haematoma or effusions reported did impact on patient recovery, but this was assumed. There were no haematomas or effusions reported in either the eight-Plate or staple groups. In the PDC cohort, 3% (7 of 225) of patients developed an effusion and 3% (3 of 89) developed a haematoma/haemathrosis post-operatively. In comparison, 6% (8 of 138) had a documented effusion and 2% (2 of 119) developed a hamatoma/haemathrosis in the PETS group. These numbers are consistent with those seen in most intra-articular knee surgeries.

Table13: Acute complications following MIE

Study	Number of patients	Infection	Effusion	Haematoma / haemarthrosis	Knee pain - acute	Reduced knee range of Motion	Fracture	Further surgical intervention
PDC								
Babu et al[162]	26	2	0	2	-	-		-
Bayhan et al[163]	48	0	0	-	-	-		0
Horn et al [166]	20	-	-	-	-	0		-
Inan et al[106]	88	1	2	-	-	-		-
Kemnitz et al[167]	57	0	-	-	-	-		-
Ramseier et al[105]	16	0	-	-	-	0		-
Stewart et al[97]	16	-	-	-	-	-		1 synovial fistula ablated
Surdam et al[87]	56	2	-	-	-	-		-
Edmonds et al – dual incision[104]	19	1	3	0	-	-	-	-
Edmonds et al – single incision[104]	44	3	2	1	-	-	2	
TOTAL	**390**	**9**	**7**	**3**			**2**	**1**
PETS								
Babu et al[162]	14	0	2	0	-	-		
Campens et al[85]	15	-	-	-	-	-		1 exchange of long screw
Ilharreborde et al[95]	45	0	0	-	-	-		-
Khoury et al[108]	30	0	-	-	-	-		-
Lykissas et al[164]	22	1	1	-	4	-		-
Metaizeau et al[94]	32	-	5	2	-	-		-
Monier et al[169]	16	0	0	0	0	0		-

Study	Number of patients	Infection	Effusion	Haematoma / haemarthrosis	Knee pain - acute	Reduced knee range of Motion	Fracture	Further surgical intervention
Nouth et al[109]	9	0	0	0	1	1		1 screw repositioned
Song et al[171]	48	0	-	0	0	-		-
TOTAL	**231**	**1**	**8**	**2**	**5**	**1**		**2**
eight-Plates								
Bayhan et al[163]	24	1	-	-	7	-		-
Lykissas et al[164]	9	0	0	-	2	-		-
Pendleton et al[170]	34	1	-	-	-	-		-
Siedhoff et al[165]	4	0	-	-	0	0		-
TOTAL	**71**	**2**			**9**			
Staples								
Gorman et al[93]	54	2	-	-	1	0		-
Lykissas et al[164]	8	1	0	-	3	-		-
Siedhoff et al[165]	30	0	-	-	0	0		-
TOTAL	**92**	**3**			**4**			

Patients' ability to return to pre-operative function

None of the papers included in this review reported on this outcome so the question could not be answered.

Length of hospital stay

Overall, length of hospital stay was only reported in three papers and varied quite significantly. Babu et al[162] reported that the average length of hospital stay for patients in both the PDC and PETS groups was one day. On the other hand, Campens et al[85] reported that those in the PDC cohort stayed an average of four days while those in the PETS group stayed an average of two days in hospital. Finally, Ilharreborde et al[95] reported that PETS resulted in an average of a two day hospital stay. Length of stay is likely to be institution dependent as some hospitals are now performing these procedures as day cases while others have the patient admitted the day prior to the operation.

Impact on a child's overall quality of life

This was not reported or described in any of the papers included in this review so no comment can be made on this outcome.

Findings from comparative studies

Of the studies included in this review eight provided comparative data. Unfortunately, few compared the same techniques. When the same techiques were compared often different outcome measures were used or different methods of assessing effectiveness were utilised. As such, a summary of the comparative study results is provided, although it is felt that the data above, which assesses specific outcome measures better reflects the overall effectiveness of the individual techniques.

PDC vs eight-Plates

PDC and eight-Plates were compared head-to-head in two studies included in this review, namely, in a study by Bayhan et al[163] and in a study by Stewart et al[97]. Both studies found that eight-Plates were inferior to PDC in their ability to reduce a LLD. Bayhan et al[163] reported that the percentage of improvement in LLD was significantly higher in the PDC group when compared to the eight-Plate group (58% to 41%, respectively; $p=0.031$). Stewart et al[97] reported that the median improvement in the LLD was 15.5 mm in the PDC group and only 4.0 mm in the eight-Plate group, resulting in a p-value of <0.001. The authors performed a general linear regression to ensure this was not due to the difference in follow-up times, however, the PDC group remained significantly more effective.

Interestingly, with regards to complications, the Stewart et al[97] study reported three complications all of which were within the PDC cohort (two failed corrections and one synovial fistula). Although the Bayhan et al[163] paper had the opposite experience with no complications reported in the PDC group, whilst a number of complications occurred in the eight-Plate group including hardware failure, slow or inadequate correction, a stitch abscess and tibial recurvatum. Given the limited number of studies comparing PDC and eight-Plates, no hard conclusions can be made, although it appears that PDC is more effective than eight-Plates at reducing a LLD. The complication profiles appear to be similar in both groups.

PDC vs PETS

Two studies included in this review assessed the effectiveness of PDC and PETS head-to-head, namely, in studies undertaken by Babu et al[162] and Campens et al.[85] In the cohot study by Babu et al, the authros found that the PDC method was more effective than the PETS with a reduction in LLD of 2.5 cm compared to 1.8 cm, respectively, however, given the size of the study they were unable to determine if this was a statistically significant difference. Another consideration to take into account when assessing this study is that the mean initial and predicted LLD in the PDC group (3.7 cm and 4.8 cm, respectively) was higher compared to that in the PETS group (3.2 cm and 4.5 cm, respectively) meaning a larger correction was required from the start. There were two complications in each cohort, although given the difference in group size, it was reported that the complication rate was twice as high in the PETS group than the PDC group. In the PETS group, the complications included one failure of GPA and one instance of pain due to screw prominence, while in the PDC group, both complications were due to failure of GPA. This study also looked at the surgical time and length of hospital stay but found no significant difference between the groups.

Campens et al[85] performed the other comparative study, unfortunately however, the results were presented in a very different manner so could not be easily pooled with data from the Babu et al[162] study, so further conclusion could be drawn. There was no statistically significant difference between the two treatment modalities in this study. In the paper by

Campens et al,[85] the initial LLD (predicted not reported) was on average lower compared to the Babu et al[162] study, with the PDC group having an initial mean of 2.8 cm compared to the PETS group of 3 cm. The final LLD results were reported in categories rather than a mean and indicated that 89% of those in the PDC group (n = 34 patients) had good results (<1.5 cm LLD at skeletal maturity) compared to the PETS group (n = 15 patients) where only 70% achieved a good outcome. Further, 95% of the PDC group had a final LLD of less than 2 cm (1.5-2 cm categorised as a fair result) compared to the PETS group, where 90% of patients had a LLD of less than 2 cm at skeletal maturity. Notably however, only 79% of patients in the PDC group and 67% of patietns in the PETS group were followed to skeletal maturity.

Complication rates between PDC and PETS as reported by Campens et al[85] did not differ significantly with 9% and 7% of patients, respectively, experiencing a complication due to their surgical procedure. One patient within the PETS group, and one within the PDC group, had failure of adequate GPA and a resultant LLD of more than 2 cm at skeletal maturity. Interestingly, in this study the authors found that the average length of hospital stay for the PDC children was four days, which was significantly higher than that in the PETS group where the average length of hospital stay was two days. This study also demonstrated that individual surgeons were much happier to full or partial weight bear patients that had undergone PETS compared to PDC, which is likely what contributed to the length of hospital stay. This study found that the two techniques had very similar effectiveness and complication profiles.

In conclusion, from these comparative studies it appears that PDC is more effective at achieving a LLD of less than 2 cm at skeletal maturity than PETS but the interventions have similar complication profiles.

PETS vs staples

There was a single study conducted by Lykissas et al[164] that compared the use of PETS and staples. The study found that the complication rates and profiles for the two techniques were similar, however, they reported a significant difference in the rate of correction between staples and PETS with the former having a faster rate of correction (1.22 cm/year compared to 0.59 cm/year; p=0.045). Despite this improved rate of correction there was no statistical difference between the initial pre-operative LLD and the LLD at skeletal maturity. Thus, despite staples resulting in a more rapid initial correction, both procedures achieved the same desired result. This finding may impact timing for undertaking the procedure in the future, suggesting PETS need to be placed earlier to allow for aqeuate correction.

PETS vs eight-Plates

Lykissas et al[164] were the only group to assess the effectiveness of PETS and eight-Plates head-to-head, and this time, found no significant difference between the interventions on complications, the rate of deformity correction (1.11cm/yr compared to 0.59cm/year p=0.1), or pre-operative and final LLD.

Staples vs eight-Plates

The effectiveness of staples vs eight-Plates was examined in two included studies, which were conducted by Lykissas et al[164] and Siedhoff et al.[165] Lykissas et al[164] once again found no significant difference in the rate of correction (1.22 cm/year compared to 1.11 cm/year p=0.54) or pre-operative and final LLD between the interventions. However, they did report on a trend with those in the eight-Plate group requiring more additional surgical input for the management of complications (numbers did not allow for sufficient power). In the study by Siedhoff et al[165] only three patients underwent eight-Plate while the remaining 20 underwent stapling; these numbers were too small to accurately compare the difference in effectiveness of the two techniques. However, there were a total of eight complications noted, two were in the eight-Plate group and six were in the staples group, which are much higher rates that previously reported. Patients developed either an angular deformity, implant loosening or failure of GPA.

Summary

This chapter detailed all the research results in a narrative manner, and analysed the methodological quality of included studies. It details the effectiveness of the four different MIE techniques in reducing the burden of a paediatric LLD, and also summarised the short and long-term complications encountered by each technique.

Chapter 4: Discussion

The purpose of this systematic review was to assess the effectiveness of four different epiphysiodesis techniques in correcting a paediatric LLD of 2-5 cm. It also aimed to compare their complication profiles to aid the developement of treatment recommendations. The results of this systematic review as presented in this dissertation suggest that PETS and PDC are more effective at reducing LLDs in children and are accompanied by lower rates of complications. This review included a total of 21 papers assessing the effectiveness of four different MIE techniques, which included eight cohort studies and 13 case series. The quality assessment of the included studies found that all the studies had critical appraisal scores that placed them in the 'good quality' study category. Sample sizes varied from 2 to 88, and the studies were undertaken in a variety of locations including Australia, the United States of America, Europe and Asia.

General discussion

To our knowledge this is the first systematic review that has assessed the effectiveness of different MIE techniques, which included PDC, PETS, eight-Plates and staples. The ability of each technique to reduce a predicted LLD of 2-5 cm to below 2 cm was assessed. The associated short and long-term complications of each procedure were also examined. Although the review results suggest that PETS and PDC are more effective and accompanied with lower complication rates, we were unable to determine if these differences were statistically significant due to the heterogeneity of the included studies.

This review purposefully utilised a broad inclusion criteria so as to facilitate the identification of all relevant studies in what remains a sparse field of clinical research. Despite this, no strong clinical recommendations can be made from this review, primarily due to the heterogeneous nature of the included studies, the way in which the intervention outcomes were assessed, the way in which the patient clinical information was reported, and the way in which the analyses were performed. Secondary to this, we were unable to perform a meta-analysis due to the clinical and methodolgical heterogeneity across the included studies. Notwithstanding this, early research suggests PETS and PDC may be consistently more efficient in correcting a paediatric LLD as was seen in this narrative synthesis.

As mentioned, due to the highly heterogeneous data available for this systematic review, the results were narratively synthesized. A narrative synthesis is "an approach to the systematic review and synthesis of multiple studies that relies primarily on the use of words and text to summarise and explain the findings of the synthesis"[175(pg 1)] allowing you to display your results in a story. In general, a narrative synthesis allows you to make sense of a large body of evidence where the research often utilises a variety of different methods, thus facilitating an iterative rather than a linear approach. Such reviews have the ability to provoke thought and controversy and facilitate the presentation of a philosophical perspective in a balanced manner. This type of review is used frequently in public health reviews and reviews of surgical techniques where data is sparse, as it allows a broader overview or appraisal of factors. [176]

A narrative synthesis plays an important role in clarifying research evidence in emerging fields of study and is able to provide the initial evidence scaffold from which further research can be developed.

Overview of current research in the field of MIE

Interventions to correct leg length discrepancy

The majority of studies in this review assessed the effectiveness of PDC and PETS, with significantly fewer focusing on staples and eight-Plates. As previously mentioned, this may be due to the years studied with staples being an older technique with limited current research and eight-Plates being a much new concept. During the review period there was evidence that this is a growing field of research that has seen the emergence of 'novel techniques' such as radioablation and the use of growth modulators, which may need to be the focus of a new systematic review. These techniques were not included in the current review as most have only been evaluated in animal studies at present.

On the whole, all interventions included in this review were seen to consistently reduce the mean post-operative or final LLD to less than 2 cm. This is a very positive finding, as it indicates that each technique is achieving its purpose, although as will be assessed later, some are consistently better or more predictable performers than others.

Lack of reporting on patient-based outcomes

A lack of reporting on patient-based outcomes such as pain levels, an ability to return to pre-operative function and a patient's general experience with a treatment or surgical procedure is a broader problem not limited to MIE. Unfortunately, we did not find a single study that reported on these patient-based factors in relation to MIE whilst undertaking this review.

Study designs characteristics

There was a general lack of experimental research identified on this topic, and most of the more 'recent' research focused on novel epiphysiodesis techniques. This is likely due to the many recognized difficulties of performing research on surgical techniques, including ethical constraints,[177] costs,[134, 178] patient recruitment, lack of funding and the learning curve of different surgical techniques.[179, 180] When looking specifically at RCTs there are further hurdles including blinding, quality control and monitoring, data collection and commercial competition.[181] These issues are all compounded with procedures or interventions for children. When working with children different ethical requirements and issues are noted including: difficulty of consent, follow-up complications (how long to follow), design challenges and drastic physiological variation with age. Accordingly, most studies evaluating surgical techniques in children are undertaken as case series or cohort studies, which leads to an overall reduction in the statistical power and quality of the research results.

These many challenges are likely to explain, at least in part, why the studies included in this review frequently used small sample sizes, lower confidence research designs, such as case series or observational studies, had lower power and used convenience sampled cohorts. A basic method to improve the quality of the included studies would be to improve the quality of reporting, particularly reporting of patient demographics, results, statistical methods and rigorous inclusion criteria.

Summary of findings

When comparing the four different MIE techniques, it can be seen that all techniques consistently corrected the LLD to below 2 cm. It appears that the PDC and PETS techniques were more consistent with these results. This may be because they represented the large majority of patients included in the review or the fact that the less reversible techniques are better at halting growth through the physis.

The evaluation of PETS versus PDC, found that there was a much higher incidence of failure of GPA in the PDC group, conversely however, the PETS group had a much higher incidence of angular deformity. Both these complications saw a number of patients requiring a second surgical procedure to correct the complication. Another interesting finding was that a number of patients in the PETS group required hardware removal due to persistent knee pain around the screws despite the procedure being performed successfully. As PDC does not involve leaving any implants in situ, it negates this potential complication. However, overall PETs had the lowest rates of failure of GPA and failure to achieve an adequate reduction in LLD.

The number of patients in the eight-Plate and staples groups were much lower, and thus the results may be influenced by a single study, but it appears that they had a much higher incidence of complications in the form of failure of GPA and angular deformities. This is potentially because the implant is placed slightly asymmetrically and the compression or tension applied over the physis differs.

The development and popularisation of MIE techniques has had a number of benefits, with doctors being more confident to allow for early or even immediate mobilisation, and smaller surgical incisions resulting in a reduction in post-op wound complications, including infection.

MIE is a relatively minor procedure (compared to phemister epiphisiodesis or limb lengthening) that has the potential to greatly impact on a child's quality of life. Not only can it correct physical discrepancies but it can also improve gait kinetics, pain and mindset. Epiphysiodesis techniques are a growing area of research that will continue to improve the management of paediatric LLDs.

Limitations of this review

One of the major limitations of this systematic review is that only papers published in the English language were included, which may have lead to reporting bias, and may also explain why no papers were included from developing countries. However, despite this, a review published by Morrison et al[182] found no evidence of systematic bias from the use of a language restriction in a systematic review in conventional medicine. Further limitations included the broad inclusion criteria, low threshold for paper inclusion following critical appraisal, small sample sizes, lack of solid statistical analysis and differences in methodological processes.

Broad study inclusion criteria

Given this review is the first of its kind on the topic, the use of broad inclusion criteria helped to ensure all clinical research on the narrow topic was captured. The consequence of taking this approach is it resulted in a high level of heterogeneity across the included studies, which subsequently precluded the use of statistical pooling in the form of a meta-analysis. Consequently, the strength of the results was impeded and it did not seem appropriate to develop a best practice guideline outlining which MIE technique is the 'gold standard'. Notwithstanding this, as previously mentioned, the papers ultimately included in this review demonstrated that all techniques have the ability to obtain the desired results (i.e. correcting a LLD to below 2 cm at skeletal maturity).

Low threshold for inclusion of studies following critical appraisal

Unfortunately, previous papers on the subject reflected lower levels of evidence according to the evidence tree (observational studies 3.e and case series 4.c.; Table 8). Most studies were either retrospective in nature or small prospective series, representing the experiences of a single institution. The studies were also, on the whole, poor at reporting standard deviations, performed only basic statistical analysis and presented limited data on how confounding factors were controlled for (or if they were controlled for).

Due to the poor reporting of standard deviations and IPD across the studies, only limited analysis could be performed (precluded the conduct of a meta-analysis), however, it also meant that patients were included in the review that had a predicted LLD outside the range of 2-5 cm (indication for operative intervention with epiphysiodesis). Despite this, every paper included in the study had a mean LLD of between 2-5 cm, unfortunately though, this was at the time of surgery, not necessarily the predicted LLD at skeletal maturity.

Despite the poor reporting of statistics in each paper, the process was appropriate for the types of studies conducted. However, future studies should ensure both extact data is reported and full statistical reporting documented. This would enable more simplistic data pooling and the potential for future systematic reviews to perform a meta-analysis.

When looking at the individual techniques it was noted that the staples and eight-Plate groups were under represented in the review when compared to PETS and PDC. This may be because staples is an older technique that is not currently being researched rigorously and consequently, papers evaluating this technique may not have been captured. On the contrary, eight-Plate's is a relatively new technique for the management of an LLD and thus, there may be limited publications looking at this method of epiphysiodesis at present. The results of eight-Plate's may also be skewed by the 'learning curve', meaning that early publications on a technique may be over-represented with complications.[183]

Differences in methodological processes

A few of the key methodological differences included differences in study design, intervention timing, intervention follow-up, study size and the reporting of results.

Further limitations

Another limitation in the evidence is the scarcity of true head-to-head comparisons of the included interventions. Only a handful of studies compared one intervention directly to another.[85, 97, 162-165] Of the studies that did perform a head-to-head comparison no more than two studies looked at the same combination. Babu et al[162] and Campens et al[85] assessed PDC compared to PETS, Bayhan et al[163] and Stewart et al[97] compared PDC to eight-Plates, and Lykissas et al[164] and Siedhoff et al[165] comparted staples to eight-Plates. In each case, no group included more than 50 patients, undertook the same statistical process or reported on the same outcome.

Limitations of the review process

Review limited to papers published in English

As mentioned above, only papers published in English were considered for inclusion in this review, which may have introduced bias, due to the omission of key studies, and consequently, resulted in distorted or invalid results.[184] However, this issue has been recently reviewed in the context of meta-analysis and was found not to be the case. [182]

Full text and citation review process

All study selection, scanning of citations, full text paper review and preparation of a final list of papers for evaulation in critical appraisal was performed by a single person (the primary reviewer and author of this thesis), which increases the risk of relevant papers being omitted from the review and can, once again, lead to review bias. Previous studies have suggested that two or more reviewers are usually required to ensure inclusion criteria are clearly, objectively and consistently applied to each and every paper included in the review.[184, 185]

Critical appraisal and data extraction

Critical appraisal is the only aspect of the review that was performed independently by two reviewers (MC and JI). All data extraction and synthesis was subsequently performed by a single reviewer (the primary review and author of this thesis). Similar to abovementioned safety nets, including a second person in the data extraction and synthesis of the data would potentially reduce the risk of error or bias within the process.[184] This was not implemented in this review process due to the limitations of finding suitable reviewers and associated time constraints, although it is something that should be implemented in future research.

Strengths of the review

Despite this reviews' limitations and weaknesses, it remains the largest review on the topic both in the number of MIE techniques assessed and the number of patients assessed. It is also, to our knowledge, the first systematic review on this topic. The results should make surgeons review their own current practice and give them guidance on the most common complication profiles and the expected effectiveness of each technique.

This review had a well defined question with specific pre-defined outcome measures that aimed to fill a void in current knowledge and clinical practice. To answer the question we then utilised well studied and supported critical appraisal tools and guidelines,[141, 173] enabling us to feel confident with the results presented.

Many of the included studies had long term follow-up results, rather than projections or interim results, allowing absolute LLD at skeletal maturity to be reported. Another important thing to note, is none of the included studes were supported or sponsored by a pharmaceutical or medical implant company. A previous systematic review by Lexchin et al[186] found that company involvement can greatly bias the results and the reporting of results. Finally, there was a good diversity of techniques performed for the correction of a number of different pathologies across a range of different hospitals and clinical settings.

Implications for clinical practice

Paediatric LLDs have the potential to greatly impact a child's quality of life and can also leave them with long-term issues, such as arthritis due to altered gait kinetics and subsequent abnormal loading of joints. For a long time now, the concept of epiphysiodesis has been used and studied to reverse or correct a deformity of magnitude between 2 to 5 cm. Initially an open technique known as the phemister technique was the 'gold standard' although over the years a number of new techniques have emerged, which have the potential to correct the discrepancy with much less invasive surgery, allowing the child to get back to day-to-day life much faster.

This review aimed to look at the most common forms of MIE and determine whether one technique was better than another in correcting a discrepancy. Although a meta-analysis could not be performed, this narrative synthesis was able to identify some interesting clinical findings. As previously mentioned, it demonstrates that all four techniques are effective in reducing the mean LLD at skeletal maturity to less than 2 cm. However, despite this, it appears that 23% of patients within the staples group, and 15% of patients in the eight-Plate group, did not achieve a final LLD of less than 2 cm at skeletal maturity. This is compared to 13% in the PDC group and only 8% in the PETS group, indicating that PETs and PDC are more predictable in achieving an adequate correction.

This review also found that when looking specifically at the rates of GPA, PETS was once again superior to the other three techniques with a failure of GPA rate of 2.5% compared to 6% in the staples and PDC group, and 15% in the eight-Plate group. This is an important findng as all these patients saw no benefit from the initial surgical intervention and thus, would have required a secondary surgical procedure to correct the discrepancy.

Outside their ability to correct for a LLD through cessation of growth through the physis, there appeared to be a similar complication profile across all the techniques. This indicates that like with any surgical procedure, no MIE technique is perfect, however, it appears that

PETS is the most predictable in correcting a 2-5 cm paediatric LLD, have the lowest rate of failure of GPA and have a comparable complication profile.

Implications for research

Recommendations for further research

Future research on this topic needs to be more structured and scientific. Unfortunately, at present most studies assessing epiphysiodesis techniques are single institution case series or cohort studies. This can result in considerable bias in reporting and the success of a technique can also be biased if it is a technique that a single surgeon has been doing for a number of years. Thus, future research should include larger sample sizes, involve cross centre studies and if possible, conduct randomised control studies, or at least a prospective cohort study.

Another area that could be improved is the reporting of results and statistical analyses. It was noted that many studies did not report anything more than a mean, which made it difficult to perform analysis across studies. If even a standard deviation was provided further analysis could have been undertaken.

Clinical topic areas for future quantitative primary research studies

Further quantitative research on this area could include assessment on the ideal timing of an intervention, when to perform two physis (femur and tibia) versus just one, the cost effectiveness of the interventions, and the incidence of rebound growth following attempted reversal of epiphysiodesis. Each of these studies would add to our current understanding and help with both the planning and timing of the surgical intervention.

Future qualitative research topics

Qualitative research is not done well in surgical fields, however, it is extremely important especially in the paediatric population. Assessing a patient's quality of life before and after an epiphysiodesis procedure would help provide evidence on the clinical and psychological benefits of such an operation. It would also be interesting to assess the child's and parents' experience throughout the operation and recovery period, which could be used to educate future patients planning on undertaking such an operation.

Future systematic review

In a constantly evolving field of research, future systematic reviews on this topic will hopefully be able to:

- Perform a meta-analyis to compare each intervention and their outcomes more rigorously;
- Assess qualitative aspects of care, for example, the impact on quality of life measures;
- Assess PDC vs PETS for the management of LLD. It is promising to see that recently Dodwell et al [187] registered a protocol for an RCT comparing PDC to PETS.

This will all be possible if future studies improve the reporting of their results and inclusion criteria.

Considerations for epiphysiodesis in clinical practise

When considering undertaking epiphysiodesis on a child with a LLD of 2-5 cm good clinical results can be seen with all four MIE techniques, however, when attempting a ‘reversible’ technique, such as staples or eight-Plates, a high rate of AD and failure of GPA is to be expected. Whatever technique is chosen, close follow-up is required to monitor growth retardation and the development of ADs so prompt action can be taken when necessary.

Chapter 5: Conclusions

This is the first systematic review assessing the results of four routinely used MIE techniques. A total of 21 papers were included in the narrative synthesis. It was our desire to use these results to develop a treatment guideline, unfortunately, given the lower evidence level of papers included in this review this was not possible.

We were, however, able to answer the research question which was: "Is one technique of minimally invasive epiphysiodesis more effective than any other in the treatment of paediatric leg length discrepancies." The findings indicate that PETS is the most effective way to reduce a paediatric LLD of 2-5 cm, with all the studies assessing PETS showing a mean reduction in LLD to less than 2 cm, the lowest rate of failure of GPA, the lowest rate of patients being identified to have a LLD of greater than 2cm at skeletal maturity and finally they were seen to have comparable complication profiles.

For epiphysiodesis performed within Australia, we would routinely see the use PDC for the management of LLDs. This research has shown that the European technique of PETS is just as, if not more, effective. These results have the ability to change everyday clinical practice in Australia, or at least, support individuals who want to bring the PETS technique to their institution.

Despite this review not having included any high level studies, we were able to assess the individual clinical experiences of a number of different surgeons, and through following a strict critical appraisal and data extraction process, it was possible to answer our initial research question. With the aid of further research, there will be sufficient evidence to create a new 'gold standard' for the management of a 2-5 cm paediatric LLD.

Appendix I: Search strategy

Example of tabulated search strategy in PubMed

Demographic	Pathology	Intervention
Child [MH] OR Child* [tw] OR Pediatric* [tw] OR Paediatric* [tw] OR Adolescent [tw]	“leg length inequality” [MH] OR “leg length discrepancy” [tw] OR Leg length inequal* OR Unequal leg length OR Limb length discrepancy	(Epiphyses[mh] AND (surgery[tw] OR surgical[tw])) OR (Epiphysis[tw] AND (surgery[tw] OR surgical[tw])) OR Epiphysiodesis [tw] OR “transphyseal percutaneous screws”[tw] OR “Transphyseal screws”[tw] OR “minimally invasive surgical procedures”[MH:noexp] OR Minimally invasive [tw] OR Metaizeau [tw] OR Canale [tw] OR Blount [tw] OR physeal stapl*[tw] OR “eight-Plate” [tw] OR “8-Plate” [tw] OR “Physeal manipulation” [tw] OR Physeal drillings OR Physeal curettage OR Physeal ablation

Appendix II: Critical appraisal tools

JBI Critical Appraisal Checklist for Cohort Studies
Reviewer_________________________________Date_________________________

Author _____________________________Year________Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	□	□	□	□
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	□	□	□	□
3. Was the exposure measured in a valid and reliable way?	□	□	□	□
4. Were confounding factors identified?	□	□	□	□
5. Were strategies to deal with confounding factors stated?	□	□	□	□
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	□	□	□	□
7. Were the outcomes measured in a valid and reliable way?	□	□	□	□
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	□	□	□	□
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	□	□	□	□
10. Were strategies to address incomplete follow up utilized?	□	□	□	□
11. Was appropriate statistical analysis used?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □
Comments (Including reason for exclusion)

____

JBI Critical Appraisal Checklist for Case Series

Reviewer____________________________________Date____________________________

Author________________________________Year_________Record Number_____

	Yes	No	Unclear	Not applicable
1. Were there clear criteria for inclusion in the case series?	□	□	□	□
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	□	□	□	□
3. Were valid methods used for identification of the condition for all participants included in the case series?	□	□	□	□
4. Did the case series have consecutive inclusion of participants?	□	□	□	□
5. Did the case series have complete inclusion of participants?	□	□	□	□
6. Was there clear reporting of the demographics of the participants in the study?	□	□	□	□
7. Was there clear reporting of clinical information of the participants?	□	□	□	□
8. Were the outcomes or follow up results of cases clearly reported?	□	□	□	□
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	□	□	□	□
10. Was statistical analysis appropriate?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments (Including reason for exclusion)

Appendix III: Table of included studies

Study Characteristics	Inclusion/exclusion criteria	Participant and intervention characteristics	Outcome measures	Results
Citation *Babu, L., Evans, O., Sankar, A., Davies, A., Jones S., and Fernandes, J. Epiphysiodesis for limb length discrepancy: a comparison of two methods. Strat Traum Limb Recon (2014) 9:1-3* **Study design** Retrospective cohort study **Setting** Sheffield Children's Hospital, Western Bank, Sheffield, Yorkshire **Study period** 1999-2008 **Duration of follow-up** 2.1 years	**Inclusion Criteria** **Exclusion criteria:** LLD >5cm, simultaneous lengthening procedures performed on the contralateral side, follow up under 1 year, and if medical notes and radiographs were incomplete. **Aim:** To determine the difference in the effectiveness of these procedures in treating those patients with moderate limb length discrepancy	**Number of participants:** 40 **Intervention A: PDC** 26 patients **Intervention B: PETS** 14 patients	**Primary**: Discrepancy remaining at final follow up **Secondary**: The site and time taken to perform each surgery, duration of hospital stay, minor and major surgical complications.	PDC Group: average operation time = 42mins, reduction in LLD by 2.5cm (3.7 → 1.2cm mean), 4 minor and 2 major complications. 92% success rate PETS group: average operation time = 45mins, reduction in LLD by 1.8 cm (3.2 → 1.4cm mean), 2 minor and 2 major complications. 85% success rate
Notes: Clinical evaluation with block test, radiological assessment using computed tomography scanograms, and long leg radiographs to confirm accurate assessment of the discrepancy along with left wrist to accurately determine bone age. Both Moseley straight-line charge and Paley's multiplier method were used to estimate the resultant leg-length discrepancy at maturity.				
Funding Source: There was no conflict of interest, nor any funding received by any of the authors.				
Legend				
Citation	**Inclusion criteria**	**Number of participants:** 72	**Primary**:	Both methods were shown to be effective for LLD

<u>*Bayhan, I., Karatas, A., Rogers, K., Bowen, R., Thacker, M. J Comparing Percutaneous Physeal Epiphysiodesis and Eight-Plate Epiphysiodesis for the Treatment of Limb Length Discrepancy. Pediatr Orthop (2015)*</u> **Study design** Retrospective cohort study **Setting** Department of orthopaedics, DuPont, Hospital for Children, Wilminton, DE **Study period** 2004-2012 **Duration of follow-up** 2.5 years	All patients with an LLD between 2.5-5 cm who underwent either eight-Plate epiphysiodesis or PE of the distal femur and/or proximal tibia for correction **Exclusion criteria:** Patients who had additional surgery or angular deformities on the ipsilateral limb at the time of the epiphysiodesis, or diagnosis of skeletal dysplasia, malignancy, or Blount disease **Aim:** To determine whether Eight-plate epiphysiodesis is as effective as PE for LLD correction.	**Intervention A: eight-Plates** 24 patients **Intervention B: PDC** 48 patients	Rate of correction (mm/month) **Secondary**: The percentage of correction (defined as initial discrepancy – final discrepancy/initial discrepancy), and rate of complications	correction, though PE led to greater improvement during the same follow-up time with fewer complications and less need for additional surgical procedures. Mean age at surgery: 12 years The rate of individual femoral and tibial correction did not differ significantly between groups. Average correction eight-Plates = 12mm, average correction PE = 16mm. Percentage of improvement higher in PE group (58% vs 41%)
Notes: If the patient is closer to skeletal maturity a PE may be a better option. Eight-plates should be used approximately a year earlier than PE.				
Funding Source: Nil reported				
Legend				
Citation <u>*Campens, C., Mousny, M., Docquier, P. Comparison of three surgical epiphysiodesis techniques for the treatment of lower limb length discrepancy.*</u>	**Inclusion criteria:** Any patient undergoing surgical epiphysiodesis **Exclusion criteria:** Contralateral leg lengthening or lack of follow-up data.	**Number of participants:** 80 (82 operations) **Intervention A: PETS** 15 patients **Intervention B: PDC** 34 patients	**Primary**: Perioperative morbidity and complications **Secondary**: Effectiveness in correction of LLD	Mean surgical time and LOS was lowest in PETS group. Post-operatively weight bearing status regimes varied greatly between the 3 groups

<u>*Acta Orthop Belg (2010) 76: 226-233*</u> **Study design** Retrospective cohort study **Setting** Department of Orthopaedic Surgery, Cliniques Universitaires, St-Luc, Bruxelles, Belgium **Study period** 1987-2008 **Duration of follow-up** Mean 3.1-3.8 years	Blount stapling procedure – procedure was discontinued at the institution due to poor results. **Aim:** To compare the techniques in terms of perioperative morbidity and complications, and to evaluate their efficiency in correction of the LLD	**Intervention C: Phemister** 33 patients		Complications were noted in 6% of Phemister patients, 9% of PDC patients and 7% of PETS patients. At final follow up to 80% of patients had reached skeletal maturity. Good Results: 74% Phemister, 89% PDC, 70% PETS. Fair Results: 7% Phemister, 7% PDC, 20% PETS. Poor Results: 11% Phemister, 4% PDC, 10% PETS. Poor results: 3 patients Phemister, 1 patient PDC, 1 patient PETS.
Notes: The poor results in the patients in the PDC and PETS group were expected as the procedure was undergone too late to obtain adequate correction. Good results <1.5cm LLD, fair results 1.5-2cm LLD, poor results >2cm LLD				
Funding Source: None reported				
Legend: LOS = length of stay				
Citation Edmonds, E. W. and P. J. Stasikelis (2007). "Percutaneous epiphysiodesis of the lower extremity: a comparison of single- versus double-portal techniques." <u>J Pediatr Orthop</u> **27**(6): 618-622.	**Inclusion criteria:** None reported **Exclusion criteria:** Those who still had open physis, partial epiphysiodesis, temporary growth arrest through physeal stapling or pinning, any other concomitatnt procedure performed at	**Number of participants:** 63 Patients **Intervention A: single portal** 44 patients **Intervention B: dual portal** 19 patients	**Primary**: To assess the effectiveness of single vs dual portal epiphysiodesis **Secondary**: Complication profiles, patient satisfaction	The single-portal group had an overall complication rate of 33.3%, with a major complication rate of 20% per patient The double portal group had a similar overall complication rate but the major

Study Design Retrospective Case Series **Setting** Carolinas Medical Centre, Charlotte, NC and Shriners Hospital for children, Greenville, SC **Study Period** 1983-2002 **Duration of follow up** 5.1 years	the time of epiphysiodesis, and those who underwent epiphysiodesis in a staged process for amputation or augmentation of prosthesis fitting **Aim:** To review our experience with both techniques (single and dual portal PDC) and report a comparison of our outcomes, including complications.			complication rate was significantly lower at 5.3% There was no significant different in patient demographics operative times, or subjective compliants
Notes: Choice to perform single vs dual portal technique was surgeon preference. Minor complications included superficial infections, haematomas and effusions Major complications included failure to arrest growth, partial arrest with angular deformity, fracture and joint penetration LLD assessed with scanogram				
Funding Source: None reported				
Legend:				
Citation _Gorman, T., Vanderwerff, R., Pond, M., MacWilliams, B., Santora, S. Mechanical Axis Following Staple Epiphysiodesis for Limb-Length Inequality. JBJS (2009) 91; 2430-2439_ **Study Design** Retrospective Case Series **Setting**	**Inclusion criteria:** LLD treated with physeal stapling of the lower extremity, using the Blount technique. Stapling had to be performed on a normal lower limb or one with overgrowth secondary to hemihypertrophy. **Exclusion criteria:** In adequate radiography follow-up. < 2years follow-up.	**Number of participants:** 54 Patients **Intervention A: Staples** 54 patients	**Primary**: Evaluate the frequency and severity of changes in the mechanical axis following staple epiphysiodesis. **Secondary**: Efficiency of stapling in correcting LLD.	Mechanical axis: 50% had a shift in mechanical axis >1cm of which 89% having a varus deviation. 33% of these patients had a clinically relevant zone change. Proximal tibia and combined procedures were most likely to show mechanical deviation.

Shriners Hospitals for Children-Intermountain, Salt Lake City, Utah **Study Period** 1990-2005 **Duration of follow up** 2.8 years	**Aim:** Evaluate the mechanical axis in a group of patients who had undergone distal femoral, proximal tibial or combined distal femoral and proximally tibial stapling for the treatment of LLD.			6 patients needed a high tibial osteotomy to correct varus deformity. 91% had reduction in discrepancy with a final mean of 1.6cm (pre-op = 3.2). 37% <1cm, 37% 1-2cm, 26% >2cm
Notes: A patient with a 0.4cm discrepancy underwent stapling following trauma to the contralateral distal femoral physis to prevent an increasing LLD, there was also a patient with a LLD of 7.9 cm included as they did not want a lengthening procedure. Standard practice within this institution is to remove staples once the patient has reached skeletal maturity – though some patients had them removed prior to that due to obtaining clinical LLD equalisation prior to physeal closure.				
Funding Source: There was no external source of funding for this study				
Legend				
Citation _Horn, J., Gunderson, RB., Wensaas, A., Steen, H. Percutaneous epiphysiodesis in the proximal tibia by a single portal approach: evaluation by radiostereometric analysis. J Child Orthop (2013) 7:295-300_ **Study design** Prospective case series review **Setting** Department of Children's Orthopaedics and	**Inclusion criteria:** Not stated **Exclusion criteria:** Not stated **Aim:** To see if percutaneous epiphysiodesis of the tibia with only the lateral approach is as effective as a bilateral approach in order to achieve growth arrest.	**Number of participants:** 20 **Intervention A: single portal PDC** 10 patients **Intervention B: dual portal PDC** 10 patients	**Primary**: Is single portal PDC as effective as dual incision. **Secondary**: How does the incision effect rate of growth through the physis. Does performing a single portal PDC reduce operative time.	From 0-6 weeks: mean longitudinal growth across the operated physis in the tibia in single portal group was 26 mm and in dual portal group was 17 mm. No statistical difference between groups. From 6-12 weeks: mean growth of 0.06 mm in single portal group and 0.03 mm in dual portal group. No statistical difference between groups. Overall mean growth in 0-6 weeks was 0.22 (30% of

Reconstructive Surgery, Oslo University Hospital, Norway **Study Period** Not stated **Duration of follow up** Not stated				usual growth rate) from 6-12 weeks mean growth was 0.046 mm (6% normal growth rate). Mean surgical time for single portal approach was significantly shorter than dual portal approach (26 mins compared to 43 mins). No peri or postoperative complications in either group. All regained full ROM, all were full weight bearing by 14 days.
Notes: Individual patient data is presented in tabulated form				
Funding Source: None reported				
Legend: ROM = range of motion.				
Citation *Ilharreborde, B., Gaumetou, E., Souchet, P., Fitoussi, F., Pressedo, A., Pennecot, GF., Mazda, K. JBJS (2011) 94B:20-275* **Study design** Retrospective case series **Setting** Robert Debre Hosptial, Paris, France	**Inclusion criteria** None reported **Exclusion criteria** Patients with associated deformity in the frontal plane (genu varum or valgum >5°) or insufficient radiological follow-up were excluded.	**Number of participants:** 45 patients **Intervention A: femoral group** 30 patients **Intervention B: tibial group** 34 patients	**Primary**: Effectiveness of PETS in achieving predicted reduction in LLD. **Secondary**: Complications of PETS.	The mean operative time was 28 minutes for tibia and femur. Mean hospital stay was 2 days both groups. Effectiveness of femoral PETS: mean was 35% at 6 months and 66% at skeletal maturity, with overall LLD being reduced from mean of 31.7 mm to 17.9 mm.

Study period 1998-2006 **Duration of follow-up** 65months (all patients had reached skeletal maturity)				<u>Effectiveness of tibial PETS</u>: mean was 46% at 6 months and 66% at skeletal maturity, with overall LLD being reduced from 27.5 mm to 15.0 mm. Overall mean LLD was <10 mm in 54.5% of femoral, 53.3% of tibial epiphysiodesis and in 36.8% of those undergoing combined epiphysiodesis. Complications: Much higher in the tibial epiphysiodesis. 20% developed tibial valgus, 6 patients required corrective surgery. 2 patients required replacement of screws as were no longer transphyseal.
Notes: It was assumed that the distal femoral physis was responsible for 70% of total femoral growth and that the proximal tibial growth plate was responsible for 55% of tibial growth.				
Funding Source: None reported				
Legend:				
Citation <u>*Inan, M., Chan, G., Littleton, AG., Kubiak, P., Bowen, JR. Efficacy and Safety of*</u>	**Inclusion criteria:** Serial preoperative orthoroentgenograms, anticipated	**Number of participants:** 97 patients **Intervention A: PDC** 88 patients	**Primary**: Complications of PDC as a form of epiphysiodesis. **Secondary**:	Average LLD at time of operation was 3.3 cm, with an average estimated predicted discrepancy of 4.7 cm.

Percutaneous Epiphysiodesis. J Pedoatr Orthop (2008) 28:6(648-651) **Study design** Retrospective case series **Setting** Alfred I. DuPont Hospital for Children, Nemours Children's clinic, Wilmington, DE, Malatya, Turkey **Study period** 1983-1999 **Duration of follow-up** 3.8 years	LLD>2.5cm, radiographic evidence of skeletal maturity. **Exclusion criteria** Inadequate follow-up, insufficient data, unknown aetiology of LLD. **Aim:** To determine the safety and effectiveness of PDC in reducing LLD.	**Intervention B: PDC combined with another operation** 8 patients (separate analysis)	Effectiveness of PDC on reducing LLD.	Following PDC the mean LLD was 1.3 cm. Minor complications: seen in six patients: 2 effusions, 1 superficial wound infection, 3 exostosis. Major complications: 3 patients had failure of epiphysiodesis requiring further operative intervention.
Notes:				
Funding Source: None disclosed				
Legend				
Citation *Kemnitz, S., Moensm P., Fabry, G. Percutaneous epiphysiodesis for leg length discrepancy J Ped Orthop B (2003) 12:1(69-71)* **Study design** Retrospective case series **Setting**	**Inclusion criteria:** None stated **Exclusion criteria :** None stated **Aim:** To determine whether or not percutaneous epiphysiodesis is as good as an open Phemister procedure. As well as to see if the authors had improved their results by	**Number of participants:** 57 Patients **Intervention A: PDC** 57 patients	**Primary**: Effectiveness of percutaneous epiphysiodesis in reducing LLD. **Secondary**: Complications of percutaneous epiphysiodesis.	Mean final LLD was 1.2 cm 68.5% good results (<1.5 cm LLD) 14% fair results (1.5-2cm LLD), 17.5% poor results (>2cm LLD). 51 of the 57 had the procedure at both the femoral and tibial physis. 2 patients had just femoral and 4

Department of Orthopaedic Surgery, Katholic University Leuven, Pellenberg, Belgium **Study period** 1992-1998 **Duration of follow-up** Until closure of physis	working on previously identified factors predisposing to failure.			patients just tibial epiphysiodesis. There were 7 complications: asymmetrical closure of physis leading to malalignment in 2 patients, and over correction >1.5 cm in 5 patients, 2 of which needed epiphysiodesis on contralateral side to correct.
Notes: 8 patients were referred late and had less than 3 pre-operative measurements				
Funding Source: none disclosed				
Legend				
Citation *Khoury, JG., Tavares, JO., McConnell, S., Zeiders, G., Sanders, JO. Results of Screw Epiphysiodesis for the Treatment of Limb Length Discrepancy and Angular Deformity. J Pediatr Orthop (2007) 27:6(623-628)* **Study design** Retrospective case series **Setting**	**Inclusion criteria** None reported **Exclusion criteria:** Inadequate follow up, or concomitate procedures on the same bone that would effect the calculation of results **Aim:** To review single institutional outcomes of PETS for the management of LLD and AD	**Number of participants:** 60 Patients **Intervention A: PETS for LLD** 30 patients **Intervention B: PETS for AD** 30 patients (not included in this systematic review)	**Primary**: Predictability of PETS for correction of LLD **Secondary**: Complications of PETS	The average actual final lengths of the femur and tibia were 0.15 cm and 0.05 cm, respectively from predicted lengths – paired t-tests showed no significant difference between the actual and the predicted LLD. Complications: 17 patients underwent removal of hardware, 7 because of irritation and the

Shriners Hospital for Childrem, Erie, PA and Childrens Hosptial of Alabama, Birmingham, AL **Study period** 1998-2002 **Duration of follow-up** All patients were followed to maturity				remaining 10 at the discretion of the operative surgeon. 1 case of recurvatum secondary to the screws being placed too anteriorly across tht tibial physis. No infections/fractures or instrument related complications
Notes: Individual patient data is presented in tabulated form. Predictions of LLD at maturity were made using the multipler method. The final LLD at maturity was compared with the predicted length at maturity for each case.				
Funding Source: None reported				
Legend: AD = angular deformity				
Citation *Lauge-Pedersen, H., Hugglund, G. Eight plate should not be used for treating leg length discrepancy. J Child Orthp (2013) 7:285-288* **Study design** Prospective case series **Setting** Department of Orthopaedics, University hospital, Lund, Sweden **Study period** Not stated **Duration of follow-up** Not stated	**Inclusion criteria** **Exclusion criteria** **Aim:** To determine if placing Eight-plates both medially and laterally over the physis would reduce longitudinal physeal growth without damaging the physis.	**Number of participants:** Plan was for 10 patients only 2 underwent procedure **Intervention A: eight-plates** 2 patients – study stopped secondary to poor results	**Primary**: Effectiveness of Eight-plates in reducing longitudinal growth through a physis **Secondary**: Reversibility of Eight-plates	Patient 1: had 0.08 mm longitudinal growth per week (6.7 mm in 1.5 years) post-op thus LLD continued to progress – initially LLD 5.5 cm, LLD at 1 year was 6 cm. Patient 2: had 0.07 mm longitudinal growth per week (5.6 mm in 1.5 years) thus LLD continued to progress – initially 3.9 cm at 1 year was 4 cm. There was slight retardation in growth towards the end of

				follow up, despite this the study was terminated.
Notes: Medial and lateral plates were inserted for symmetrical growth reduction and the patients were followed by radiostereometric analysis 0, 3, 6, 9, 12, 24, 52 and 80 weeks post-operatively. The reported error in measurement with this technique was less than 0.05 mm. They stated it was theoretically a good idea though not predictable or reproducible.				
Funding Source: None and no conflicts of interest				
Legend				
Citation *Lykissas, MG., Jain, VV., Manickam, V., Nathan, S., Eismann, EA., McCarthy, JJ.Guided growth for the treatment of limb length discrepancy: a comparative study of three most commonly used surgical techniques. (2013) J Pediatr Orthop 22:4(311-317)* **Study design** Retrospective cohort series **Setting** Cincinnati Childrens Hosptial Medical Centre, Ohio, USA **Study period** 2003-2010 **Duration of follow-up** 46 months	**Inclusion criteria:** Limb length discrepancy treated with knee epiphyseal stapling, plating or PETS. Concurrent epiphysiodesis of the distal femur and proximal tibia. Adequate clinical and radiographic follow-up until skeletal maturity or for a minimum of 2 years after implant removal. Epiphyseal stapling, plating or PETS as the primary procedure. Absence of any other bony procedures in the lower extremities. **Exclusion criteria:** **Aim:** The purpose of this study was to compare the safety and effectiveness of 3 mechanical devices (percutaneous transphyseal screws, tension band plates and staples) for	**Number of participants:** 39 Patients **Intervention A: Staples** 8 Patients **Intervention B: Eight-plates** 9 Patients **Intervention C: PETS** 22 Patients	**Primary**: Are all techniques as efficacious in reducing LLD. **Secondary**: Is there a different complication profile for the three techniques.	Staples: Mean initial LLD=3.65cm, mean correction=1.22 cm/yr. Complications - 50% of patients – 3 knee pain and 1 wound infection. Eight-Plates: Mean initial LLD = 4.1 cm, mean correction=1.11 cm/yr. Complications - 44% of patients 2 knee pain, 2 additional surgery – 1 for failure to reduce discrepancy, 1 to replace screws following reaching max divergence. PETS: Mean initial LLD = 3.15 cm, mean correction -0.59cm/yr. Complications - 36% of patients 4 knee pains, 1 effusion, 1 wound infection, 1 AD, and 1 requiring

	the correction of limb length discrepancies in growing children and adolescents.			additional surgery (removal of screw causing AD). They identified a significant difference between the rate of correction stapling and PETS (p=0.045) only. There was no significant difference in final LLD.
Notes: Remaining growth was determined by Anderson-Green growth-remaining chart and the timing for the procedure was set on the basis of the Moseley straight-line graph. Growth of lower limb was considered complete in girls at 14 and 16 for boys. 6 different surgeons – surgical procedure was dependent on surgeon preference; they were able to calculate rate of correction. Good result <1.5cm, fair result 1.5-2cm and poor >2cm. They used an 80% power to detect a difference of 3 cm ? too large ** PETS avoids the perichondrial ring and epiphyseal vessels during insertion or removal, and is theoretically associated with minimal risk for peripheral physeal arrest development and rebound growth.				
Funding Source: No external funding and no conflicts of interest				
Legend: AD = angular deformity				
Citation *Metaizeau, JP., Eong-Chung, J., Bertrand, H., Pasquier, P. Percutaneous Epiphysiodesis Using Transphyseal Screws (PETS) J Pediatr Orthop (1998) 18:3(363-369)* **Study design** Prospective case series **Setting**	**Inclusion criteria:** Not described **Exclusion criteria:** Not described **Aim:** To described the operative technique of a new method of epihysiodesis using percutaneous transphyseal screws, and to assess the effectiveness of the surgical	**Number of participants:** 41 patients **Intervention A: PETS for LLD** 32 Patients **Intervention B: PETS for AD** 9 Patients Only LLD data presented here	**Primary**: Effectiveness of reduction LLD and rate of correction **Secondary**: Complications both early and late	Initial LLD mean =2.47 cm, reduced to 0.51 c. LLD <1 cm achieved in 82% LLD < 0.5 cm achieved in 56%. At 6 months average growth at epiphysiodesed femur was 53% of the contralateral side, between 6-18months was 38% of the contralateral side and overall growth was

Service d'Orthopédie Pédiatrique, Hôpital Belle-Isle, Metz, France; *Department of Orthopedic Surgery, Salmaniya Medical Center, Bahrain; and †Interne des Hôpitaux de Nancy, France **Study period:** Not reported **Duration of follow-up:**	technique in slowing down physeal growth.	They also did a subgroup analysis on those with post fracture limb overgrowth.		retarded by 79% and reduced total femoral growth by 45% of normal. At 6 months average growth at epiphysiodesed <u>tibia</u> was 69% of contralateral side. Between 6-18 months was 48% of the contralateral side and overall growth was retarded by 86% and tibial growth was seen to be 52% of normal. <u>Complications</u>: Early: 2 haemathrosis Late: 1 overcorrection as pateint failed to attend follow-up for 2 years. 3 patients suffered an AD All were back to normal activities within 15 days.
Notes: Between the age of 10-15years, 70% of total femoral growth occurs at the distal femoral physis and 55% of the total tibial growth at the proximal physis. Good description of operative technique .				
Funding Source: Not reported				
Legend:				
Citation *<u>Monier, BC., Aronsson, DD., Sun, M. Percutaneous epiphysiodesis using</u>*	**Inclusion criteria:** Not reported **Exclusion criteria:** Not reported	**Number of participants:** 16 Patients **Intervention A: PETS crossed screws**	**Primary**: Effectiveness of PETS in reducing LLD. **Secondary**:	PETS were successful in reducing LLD in 15 of 16 patients (a 16 year old boy – bone age of 14 and

transphyseal screws for limb-length discrepancies: high variability among growth predictor models. J Child Orthop (2015)9:403-410. **Study design** Retrospective case series **Setting** Department of Orthopaedics and Rehabilitation, University of Vermont College of Medicine, Burlington, VT **Study period** Not reported **Duration of follow-up** Mean = 2 years	**Aim:** To evaluate our results using PETS to treat patients with LLD, and to evaluate the accuracy of the Green-Anderson method, the Moseley method and the Paley method in predicting the final radiographic LLD at skeletal maturity	13 **Intervention B: PETS parallel screws** 3 Patients	Accuracy of the different LLD predicting methods (Green-Anderson method, Moseley method and Paley method).	chronological age 16 showed no improvement). Mean LLD was 3.1 cm and corrected to a mean of 1.7 cm. Complications: 6 patients had screws removed at maturity due to complaints of pain (37%) No other complications were reported – no patient developed asymmetric growth that created an axial, coronal or sagittal deformity. The mean difference between actual and predicted measurements of LLD at maturity was 0.2 cm using GA method, 1.4 cm using MG method, -0.1 cm using PM method - no significant difference between the three. They concluded that the PETS should have been placed at an earlier age than models were predicting.
Notes: Surgical technique well described.				
Funding Source: There was no external funding obtained for this study.				

Legend: GA = Green-Anderson method, MG = Moseley graph method, PM = Paley multiplier method				
Citation *Nouh, F., Kuo, LA. Percutaneous Epiphysiodesis Using Transphyseal Screws (PETS): Prospective case series and review J Pediatr Orthop (2004) 24(6):721-725* **Study design** Prospective case seriew **Setting** Sydney Childrens Hospital, Sydney, Australia **Study period** 1998-2002 **Duration of follow-up** Mean = 2.4 years	**Inclusion criteria:** 2 years remaining growth, follow-up greater than 1 year, undergoing PETS as primary corrective procedure, LLD of 2-5 cm, or progressive AD. **Exclusion criteria:** Not reported **Aim:** To review single institution experience and results using PETS for LLD	**Number of participants:** 18 Patients **Intervention A: PETS for LLD** 9 Patients **Intervention B: PETS for AD** 9 Patients Results for AD not presented in this review.	**Primary**: Effectiveness of PETS in reducing LLD **Secondary**: Complications of PETS	Mean pre-op LLD = 3.33 cm, postoperative = 1.38 cm, with a mean change of 1.97 cm. 56% reached LLD of < 1 cm. Average operation time: 29 mins Average length of stay: 2.3 days Complications: One patient no LLD correction, one patient had persistent knee pain requiring removal of screw. No wound infections, NV injuries, fractures, knee flexion deformities, or over-corrections
Notes: Foreseen benefits – shorter hospital stay and convalescence with minimal postoperative pain, immediate weight bearing, rapid achievement of knee ROM and excellent cosmesis.				
Funding Source: none disclosed				
Legend				
Citation *Pendleton, AM., Stevens, PM., Hung, M. Guided Growth for the Treatment of Moderate*	**Inclusion criteria:** Guided growth of the femur, tibia or both for LLD <5 cm, adequate radiographs, no knee or ankle	**Number of participants:** 34 Patients **Intervention A: Eight-plates** 34 patients	**Primary**: Effectiveness of Eight-plates in reducing LLD. **Secondary**:	Average starting LLD as measured on standing long leg radiographs for the iliac crest height, femoral head

Leg-length Discrepancy. Orthopaedics (2013) 36(5): e575-e580 **Study design** Retrospective case seriew **Setting** Primary Children's Medical Centre, Salt Lake City, Utah **Study period** 2004-2010 **Duration of follow-up** Mean = 28 months	contractures, followed-up to maturity or removal of implant. **Exclusion criteria:** Concomitant lengthening or shortening procedures, angular deformity. **Aim:** To evaluate the effectiveness and complication rate of guided growth for the treatment of patients with a moderate leg length discrepancy.		Complications of Eight-plates when used to correct LLD.	height and leg length height were 22 mm, 19 mm and 17 mm, respectively. Average discrepancies at implant removal or maturity were 13 mm, 11 mm, 10 mm, respectively. Complications: One patient had change in mechanical axis, and one developed genu varum requiring treatment with hemiepiphysiodesis. There was also one case of cellulitis. Authors recommended adding 1 year to the timing of standard physeal closing ephiphysiodesis. Intervention at the tibia was not as effective. Similar delay likely occurs until the plate begins to retard growth as is seen with the percutaneous epiphysiodesis technique using PETS.

Notes: They state that in many patients, the goal was not to equalise the leg-lengths but rather to decrease the discrepancy to a more manageable one that could be treated with a shoe lift. Some patients had neurological disorders in which the limb was purposefully left short to facilitate foot clearance. Individual patient data presented.				
Funding Source: Nil reported				
Legend:				
Citation *Ramseier, LE., Sukthankar, A. Minimally invasive epiphysiodesis using a modified "Canale"-technique for correction of angular deformities and limb leg length discrepancies. J Child Orthop (2009)3:33-37* **Study design** Retrospective case series **Setting** Department of Orthopaedics, University of Zurich, Balgrist, Switzerland **Study period:** 2000-2007 **Duration of follow-up** Mean = 32.2months	**Inclusion criteria:** No reported **Exclusion criteria** Not reported **Aim:** To evaluate the results of a modified Canale technique for definitive epiphysiodesis treatment in the management of LLD's and angular deformities	**Number of participants:** 22 Patients **Intervention A: PDC for LLD** 16 Patients **Intervention B: PDC for AD** 6 Patients (not included in this review)	**Primary**: Ability to correct LLD/AD. **Secondary**: Complications.	All patients achieved goal correction according to the calculated remaining growth potentials. In 3 patients the LLD was equalised prior the closure of contralateral growth plates in these cases they underwent epiphysiodesis of the contralateral side. 2 other patients required re-epiphysiodesis due to failure to closue the physis. There were no wound healing complications, or knee joint contractures. Crucial point is determining remaining growth left.

Notes: Technique – under general or epidural anaesthesia a skin incision is performed directly over the epiphysis medially and/or laterally. Under image intensifier the physis is visualised and directly approached with a 3.5 mm drill. The drill is exchanged to a 4.5 mm. This 4.5 mm drill is directed 'starwise' to reach the full physis. Then the physis is destroyed using an 'olive drill' working as a reamer and an addition angulated curette. Skeletal age according to Greulich and Pyle. Standardised x-rays. Predicted height according to tables by Bailey and Pinneau, and remaining growth of distal femur and proximal tibia based on tables by Anderson and Green. Individual patient data presented.
Funding Source: None reported
Legend

Citation *Siedhoff, M., Ridderbusch, K., Breyer, S., Stucker, R., Rupprecht, M. Temporary epiphyseodesis for limb-length discrepancy – 8 to 15 year follow-up of 34 children. Acta Orthopaedica (2014) 85(6): 262-632* **Study design** Retrospective case series **Setting** Department of Pediatric Orthopaedics, Altonaer Children's Hospital, Hambury **Study Period** Not mentioned **Duration of follow-up** Mean = 7.7 years	**Inclusion criteria:** Temporary epiphysiodesis performed for LLD of up to 5cm (predicted at maturity). Consistent preoperative, post-operative and follow up radiographs, skeletal maturity at time of final follow up. *6 patients were included with an LLD less than 2cm – in these cases the treatment decision was carefully discussed with the child and his/her patients **Exclusion criteria:** None **Aim:** Assessment of longer-term outcomes following temporary epiphyseodesis	**Number of participants:** 34 Patients **Intervention A: Staples** 30 Patients **Intervention B: Eight-plates** 4 Patients	**Primary**: To evaluate the final difference in limb length. **Secondary**: To evaluate the final mechanical axis at the time of skeletal maturity.	The mean LLD changed from 2.3 to 0.8 cm at follow-up (Mean predicted LLD = 2.6 cm) 10 had LLD <0.5 cm 21 had LLD <1 cm 1 child had LLD >2 cm 2 children had a staple placed too far anteriorly – this surgery was rated as inadequate – however no complications occurred as a result. Implants were removed at average of 31 months In 7 patients LLD was balanced before physeal closure. Complications:

	– focusing on LLD and angular deformity development.			4 children had implant failure or loosening – managed with repeated epiphyseodesis in 3 cases. 1 case of medial tibial exostosis, 3 cases of secondary angular deformity necessitated implant removal from the concave side – in all of these cases return to normal mechanical axis was achieved .
Notes: Limitations of study (self reported) – retrospective design and absence of pre-operative standing AP radiographs of the lower extremity, precluding an accurate comparison of the mechanical axis before and after treatment. They are also unable to comment on sagittal plane deformities as they did not have standardised lateral radiographs at follow up. Individual patient data presented.				
Funding Source: None reported				
Legend				
Citation *Song, MH., Choi, ES., Park, MS., Yoo, WJ., Chung, CY., Choi, IH., Cho, TJ. Percutaneous Epiphysiodesis Using Transphyseal Screws in the Management of Leg Length Discrepancy: Optimal Operation Timing and Techniques to Avoid*	**Inclusion criteria** **Exclusion criteria:** Underwent PETS later than estimated optimal epiphysiodesis timing, those with dislodge screws **Aim:** To analyze effects of PETS on LLD, its associated complications, to determine optimal operation timing	**Number of participants:** 69 Patients **Intervention A: PETS for LLD performed at appropriate time** 48 Patients	**Primary**: To evaluate the effectiveness of PETS in reducing LLD	Pre-operative LLD averaged 1.9 cm and was predicted to reach 2.1 cm. 3 patients were under corrected and 1 over corrected – in the remaining 91.7% the final LLD was within +/- 10 mm Mean final LLD was 3 mm – presumably as operations were performed on average

Complications. J Pediatr Orthop (2015) 35(1)89-93. **Study Design** Retrospective case review **Setting** Department of Orthopaedic Surgery, Jeju National University Hospital, Jeju. Division of Pediatric Orthopaedics, Seoul National University Childrens Hospital, Seoul. Department of Orthopaedic Surgery, Seoul National University Bundang Hospital, Seongnam, Republic of Korea **Study period:** Not reported **Duration of follow-up** Mean = 3.9 years	and find ways of preventing complications			1.3 years earlier than estimated by growth calculations. The mean LLD correction was 75.5% at the distal femur and 78.9% and the proximal tibia. Complications: 8 patients had screws removed prior to closure of physis secondary to achieving limb equalisation early. Two broken screws at the threaded portion. Axial deviation in five patients – thought to be due to inadequate purchase in the physis on that side in 3 patients and due to screw dislodgement in 2 patients.
Notes: They decided on additional exclusion criteria at time of analysis this creates a bias.				
Funding Source: Not disclosed				
Legend				
Citation *Stewart, D., Cheema, A., Szalay, EA. Dual eight-Plate Technique is Not as Effective as Ablation For*	**Inclusion criteria** **Exclusion criteria** Inadequate medical records or radiographic follow up to determine	**Number of participants:** 27 Patients **Intervention A - PDC** 16 Patients **Intervention B – eight-Plates**	**Primary**: The effectiveness of eight-Plates and physeal ablation at correcting a LLD **Secondary**:	Median improvement in LLD was 1.55cm in PDC group and 0.4cm in eight-Plate group.

Epiphysiodesis About the Knee. J Pediatr Orthop (2013) 33(8)843-846 **Study design** Retrospective cohort study **Setting** University of New Mexico School of Medicine, University of New Mexico Carrie Tingley Hospital, Department of Orthopaedics and Rehabilitation, University of New Mexico Carrie Tingley Hospital, Albuquerque, NM **Study period** 2003-2009 **Duration of follow-up** 2.2 years PDC, 1.6 years eight-Plate	success or failure of treatment. Those treated with more than one modality (PDC + eight-Plates) **Aim:** To compare the effectiveness of Eight-Plates with physeal ablation techniques	11 Patients	The complication profile of eight-Plates and PDC	** the follow-up was longer in the ablation group though a linear regression model was applied and this still demonstrated that the ablation group had superior outcomes. There were 3 complications all in the PDC group. Two inadequate correction requiring re-operation, and one synovial fistula. They were unable to conclude if there was a true difference in complication rates due to the small numbers in the study.
Notes:				
Funding Source: Nil reported				
Legend				
Citation *Surdam, JW., Morris, CD., DeWeese, JD., Drvaric, DM. Leg Length Inequality and Epiphysiodesis: Review of 96 cases. J Pediatric*	**Inclusion criteria:** Followed to skeletal maturity **Exclusion criteria:** Hemiepiphysiodesis for correction of AD, previous amputation.	**Number of participants:** 96 Patients **Intervention A - Phemister** 40 Patients **Intervention B - PDC** 56 Patients	**Primary**: Ability of the epiphysiodesis technique to achieve physeal closure. **Secondary**:	All 40 Phemister – open technique had successful closure of physis throughout the follow up period. There were no angular deformity complications with in this

Orthopaedics (2003) 23: 381-384 **Study design** Retrospective case series **Setting** Department of Orthopaedic Surgery Boston Medical Centre, Boston University School of Medicine, Boston Massachusetts **Study period:** 1975-1998 **Duration of follow-up** Not reported	**Aim:** To assess single institution experience with open and percutaneous epiphysiodesis procedures as related to failure to achieve physeal closure, and specifically to identify and compare the complications associated with the two procedures.		Complication profile of the epiphysiodesis techniques.	group. One patient developed a deep infection requiring surgical debridement and IVABX. In the PDC group 3 patients had delayed closure or failure of closure of the physis and 2 experienced superficial wound infections.
Notes				
Funding Source: Not reported				
Legend				

References

1. Phemister DB. Operative arrest of longitudinal growth of bone. . J Bone Joint Surg Am 1933;15:1-15.
2. Gross RH. Leg length discrepancy: how much is too much? Orthopedics. 1978;1(4):307-10.
3. J M. Leg Length Discrepancy (LLD): Orthobullets 2016 [updated 4/1/16. Available from: http://www.orthobullets.com/pediatrics/4045/leg-length-discrepancy-lld.
4. Blustein SM, D'Amico JC. Limb length discrepancy. Identification, clinical significance, and management. Journal of the American Podiatric Medical Association. 1985;75(4):200-6.
5. Goel A, Loudon J, Nazare A, Rondinelli R, Hassanein K. Joint moments in minor limb length discrepancy: a pilot study. Am J Orthop (Belle Mead NJ). 1997;26(12):852-6.
6. Gross RH. Leg length discrepancy in marathon runners. The American journal of sports medicine. 1983;11(3):121-4.
7. Drnach M, Kreger A, Corliss C, Kocher D. Limb length discrepancies among 8- to 12-year-old children who are developing typically. Pediatr Phys Ther. 2012;24(4):334-7.
8. Guichet JM, Spivak JM, Trouilloud P, Grammont PM. Lower limb-length discrepancy. An epidemiologic study. Clin Orthop Relat Res. 1991(272):235-41.
9. Friend L, Widmann RF. Advances in management of limb length discrepancy and lower limb deformity. Curr Opin Pediatr. 2008;20(1):46-51.
10. Kaufman KR, Miller LS, Sutherland DH. Gait asymmetry in patients with limb-length inequality. J Pediatr Orthop. 1996;16(2):144-50.
11. Liu XC, Fabry G, Molenaers G, Lammens J, Moens P. Kinematic and kinetic asymmetry in patients with leg-length discrepancy. J Pediatr Orthop. 1998;18(2):187-9.
12. Song KM, Halliday SE, Little DG. The effect of limb-length discrepancy on gait. J Bone Joint Surg Am. 1997;79(11):1690-8.
13. Vitale MA, Choe JC, Sesko AM, Hyman JE, Lee FY, Roye DP, Jr., et al. The effect of limb length discrepancy on health-related quality of life: is the '2 cm rule' appropriate? Journal of pediatric orthopedics Part B. 2006;15(1):1-5.
14. "anisomelia." A Dictionary of Nursing. Encyclopedia.com. [Available from: <http://www.encyclopedia.com>.
15. E. M. Etiology and pathophysiology of leg length discrepancies In: Hungerford D.S. (eds) Leg Length Discrepancy The Injured Knee. Progress in Orthopaedic Surgery, . Berlin, Heidelbery: Springer,; 1977.
16. Sabharwal S, Kumar A. Methods for assessing leg length discrepancy. Clin Orthop Relat Res. 2008;466(12):2910-22.
17. Siffert RS. Lower limb-length discrepancy. J Bone Joint Surg Am. 1987;69(7):1100-6.
18. Dwyer T. Leg Length Discrepancy examination http://www.boneschool.com/paediatrics/lld/lld-examination2011 [updated 29/4/2011. Available from: http://www.boneschool.com/paediatrics/lld/lld-examination.
19. Hanada E, Kirby RL, Mitchell M, Swuste JM. Measuring leg-length discrepancy by the "iliac crest palpation and book correction" method: reliability and validity. Archives of physical medicine and rehabilitation. 2001;82(7):938-42.
20. Beattie P, Isaacson K, Riddle DL, Rothstein JM. Validity of derived measurements of leg-length differences obtained by use of a tape measure. Phys Ther. 1990;70(3):150-7.

21. Lampe HI, Swierstra BA, Diepstraten AF. Measurement of limb length inequality. Comparison of clinical methods with orthoradiography in 190 children. Acta Orthop Scand. 1996;67(3):242-4.
22. Strauss KJ, Kaste SC. ALARA in pediatric interventional and fluoroscopic imaging: striving to keep radiation doses as low as possible during fluoroscopy of pediatric patients--a white paper executive summary. J Am Coll Radiol. 2006;3(9):686-8.
23. Green WT, Wyatt GM, Anderson M. Orthoroentgenography as a method of measuring the bones of the lower extremities. J Bone Joint Surg Am. 1946;28:60-5.
24. Nordentoft EL. The Accuracy of Orthoroentgenographic Measurements. Acta Orthop Scand. 1964;34:283-8.
25. Morrissy RT WS, eds. Lovell and Winter's Pediatric Orthopedics. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2017.
26. OE M. A method for the roentgen measurement of the long bones. Am J Roentgenol Radium Ther Nucl Med. 1942;48:405–6.
27. Pugh DG, Winkler NT. Scanography for leg-length measurement: an easy satisfactory method. Radiology. 1966;87(1):130-3.
28. Horsfield D, Jones SN. Assessment of inequality in length of the lower limb. Radiography. 1986;52(605):223-7.
29. Sabharwal S, Zhao C, McKeon JJ, McClemens E, Edgar M, Behrens F. Computed radiographic measurement of limb-length discrepancy. Full-length standing anteroposterior radiograph compared with scanogram. J Bone Joint Surg Am. 2006;88(10):2243-51.
30. Faurie C, Williams N, Cundy PJ. A stitch in time: stitching errors in digital radiology. Med J Aust. 2017;207(5):224.
31. Altongy JF, Harcke HT, Bowen JR. Measurement of leg length inequalities by Micro-Dose digital radiographs. J Pediatr Orthop. 1987;7(3):311-6.
32. Aitken AG, Flodmark O, Newman DE, Kilcoyne RF, Shuman WP, Mack LA. Leg length determination by CT digital radiography. AJR Am J Roentgenol. 1985;144(3):613-5.
33. Aaron A, Weinstein D, Thickman D, Eilert R. Comparison of orthoroentgenography and computed tomography in the measurement of limb-length discrepancy. J Bone Joint Surg Am. 1992;74(6):897-902.
34. Glass RB, Poznanski AK. Leg-length determination with biplanar CT scanograms. Radiology. 1985;156(3):833-4.
35. Temme JB, Chu WK, Anderson JC. CT scanograms compared with conventional orthoroentgenograms in long bone measurement. Radiol Technol. 1987;59(1):65-8.
36. Dubousset J, Charpak G, Dorion I, Skalli W, Lavaste F, Deguise J, et al. [A new 2D and 3D imaging approach to musculoskeletal physiology and pathology with low-dose radiation and the standing position: the EOS system]. Bull Acad Natl Med. 2005;189(2):287-97; discussion 97-300.
37. Escott BG, Ravi B, Weathermon AC, Acharya J, Gordon CL, Babyn PS, et al. EOS low-dose radiography: a reliable and accurate upright assessment of lower-limb lengths. J Bone Joint Surg Am. 2013;95(23):e1831-7.
38. Konermann W, Gruber G. [Ultrasound determination of leg length]. Orthopade. 2002;31(3):300-5.
39. Krettek C, Koch T, Henzler D, Blauth M, Hoffmann R. [A new procedure for determining leg length and leg length inequality using ultrasound. II: Comparison of ultrasound, teleradiography and 2 clinical procedures in 50 patients]. Der Unfallchirurg. 1996;99(1):43-51.

40. Terjesen T, Benum P, Rossvoll I, Svenningsen S, Floystad Isern AE, Nordbo T. Leg-length discrepancy measured by ultrasonography. Acta Orthop Scand. 1991;62(2):121-4.
41. Leitzes AH, Potter HG, Amaral T, Marx RG, Lyman S, Widmann RF. Reliability and accuracy of MRI scanogram in the evaluation of limb length discrepancy. J Pediatr Orthop. 2005;25(6):747-9.
42. Reid D.C. SB. Leg length inequality: a review of etiology and management. Physiother Can. 1984;36:177-82.
43. Aiona M, Do KP, Emara K, Dorociak R, Pierce R. Gait patterns in children with limb length discrepancy. J Pediatr Orthop. 2015;35(3):280-4.
44. Gurney B. Leg length discrepancy. Gait Posture. 2002;15(2):195-206.
45. Giles LG, Taylor JR. Low-back pain associated with leg length inequality. Spine (Phila Pa 1976). 1981;6(5):510-21.
46. Giles LG, Taylor JR. Lumbar spine structural changes associated with leg length inequality. Spine (Phila Pa 1976). 1982;7(2):159-62.
47. Young RS, Andrew PD, Cummings GS. Effect of simulating leg length inequality on pelvic torsion and trunk mobility. Gait Posture. 2000;11(3):217-23.
48. Cummings G, Scholz JP, Barnes K. The effect of imposed leg length difference on pelvic bone symmetry. Spine (Phila Pa 1976). 1993;18(3):368-73.
49. Specht DL, De Boer KF. Anatomical leg length inequality, scoliosis and lordotic curve in unselected clinic patients. J Manipulative Physiol Ther. 1991;14(6):368-75.
50. Papaioannou T, Stokes I, Kenwright J. Scoliosis associated with limb-length inequality. J Bone Joint Surg Am. 1982;64(1):59-62.
51. Mahar RK, Kirby RL, MacLeod DA. Simulated leg-length discrepancy: its effect on mean center-of-pressure position and postural sway. Archives of physical medicine and rehabilitation. 1985;66(12):822-4.
52. Brand RA, Yack HJ. Effects of leg length discrepancies on the forces at the hip joint. Clin Orthop Relat Res. 1996(333):172-80.
53. Schuit D, Adrian M, Pidcoe P. Effect of heel lifts on ground reaction force patterns in subjects with structural leg-length discrepancies. Phys Ther. 1989;69(8):663-70.
54. Bhave A, Paley D, Herzenberg JE. Improvement in gait parameters after lengthening for the treatment of limb-length discrepancy. J Bone Joint Surg Am. 1999;81(4):529-34.
55. Blake RL, Ferguson HJ. Correlation between limb length discrepancy and asymmetrical rearfoot position. Journal of the American Podiatric Medical Association. 1993;83(11):625-33.
56. Vink P, Huson A. Lumbar back muscle activity during walking with a leg inequality. Acta Morphol Neerl Scand. 1987;25(4):261-71.
57. Delacerda FG, McCrory ML. A case report: effect of a leg length differential on oxygen consumption. J Orthop Sports Phys Ther. 1981;3(1):17-20.
58. Gurney B, Mermier C, Robergs R, Gibson A, Rivero D. Effects of limb-length discrepancy on gait economy and lower-extremity muscle activity in older adults. J Bone Joint Surg Am. 2001;83-A(6):907-15.
59. Ramaker RR, Lagro SW, van Roermund PM, Sinnema G. The psychological and social functioning of 14 children and 12 adolescents after Ilizarov leg lengthening. Acta Orthop Scand. 2000;71(1):55-9.
60. Ghoneem HF, Wright JG, Cole WG, Rang M. The Ilizarov method for correction of complex deformities. Psychological and functional outcomes. J Bone Joint Surg Am. 1996;78(10):1480-5.

61. Montpetit K, Hamdy RC, Dahan-Oliel N, Zhang X, Narayanan UG. Measurement of health-related quality of life in children undergoing external fixator treatment for lower limb deformities. J Pediatr Orthop. 2009;29(8):920-6.
62. Varni JW, Setoguchi Y. Screening for behavioral and emotional problems in children and adolescents with congenital or acquired limb deficiencies. Am J Dis Child. 1992;146(1):103-7.
63. Liu R, Li Y, Fan L, Mu M, Wang K, Song W. Depression and anxiety before and after limb length discrepancy correction in patients with unilateral developmental dysplasia of the hip. J Psychosom Res. 2015;79(6):574-9.
64. Chhina H, Klassen A, Kopec J, Park S, Fortes C, Cooper A. Quality of life of children with lower limb deformities: A systematic review of patient-reported outcomes and development of a preliminary conceptual framework. Journal of Limb Lengthening & Reconstruction. 2017;3(1):19-29.
65. Little DG, Nigo L, Aiona MD. Deficiencies of current methods for the timing of epiphysiodesis. J Pediatr Orthop. 1996;16(2):173-9.
66. Anderson M, Green WT. Lengths of the femur and the tibia; norms derived from orthoroentgenograms of children from 5 years of age until epiphysial closure. Am J Dis Child. 1948;75(3):279-90.
67. Anderson M, Messner MB, Green WT. Distribution of Lengths of the Normal Femur and Tibia in Children from One to Eighteen Years of Age. J Bone Joint Surg Am. 1964;46:1197-202.
68. Moseley CF. A straight-line graph for leg-length discrepancies. J Bone Joint Surg Am. 1977;59(2):174-9.
69. Greulich WW PS. Greulich and Pyle's Radiographic Atlas of Skeletal Development of the Hand and Wrist. 2nd ed. Stanford: Stanford University Press; 1959.
70. White JW SS. Growth arrest for equalizing leg lengths. JAMA. 1944;126:1146.
71. Menelaus MB. Correction of leg length discrepancy by epiphysial arrest. J Bone Joint Surg Br. 1966;48(2):336-9.
72. Paley D, Bhave A, Herzenberg JE, Bowen JR. Multiplier method for predicting limb-length discrepancy. J Bone Joint Surg Am. 2000;82-A(10):1432-46.
73. Eastwood DM, Cole WG. A graphic method for timing the correction of leg-length discrepancy. J Bone Joint Surg Br. 1995;77(5):743-7.
74. Anderson M, Green WT, Messner MB. Growth and predictions of growth in the lower extremities. J Bone Joint Surg Am. 1963;45-A:1-14.
75. Westh RN, Menelaus MB. A simple calculation for the timing of epiphysial arrest: a further report. J Bone Joint Surg Br. 1981;63-B(1):117-9.
76. Kasser JR, Jenkins R. Accuracy of leg length prediction in children younger than 10 years of age. Clin Orthop Relat Res. 1997(338):9-13.
77. Barker KL, Simpson AH. Recovery of function after closed femoral shortening. J Bone Joint Surg Br. 2004;86(8):1182-6.
78. Coppola C, Maffulli N. Limb shortening for the management of leg length discrepancy. J R Coll Surg Edinb. 1999;44(1):46-54.
79. Sailhan F. Bone lengthening (distraction osteogenesis): a literature review. Osteoporos Int. 2011;22(6):2011-5.
80. Aronson J, Good B, Stewart C, Harrison B, Harp J. Preliminary studies of mineralization during distraction osteogenesis. Clin Orthop Relat Res. 1990(250):43-9.
81. Ilizarov GA. The tension-stress effect on the genesis and growth of tissues: Part II. The influence of the rate and frequency of distraction. Clin Orthop Relat Res. 1989(239):263-85.

82. Ilizarov GA. The tension-stress effect on the genesis and growth of tissues. Part I. The influence of stability of fixation and soft-tissue preservation. Clin Orthop Relat Res. 1989(238):249-81.
83. Bost FC, Larsen LJ. Experiences with lengthening of the femur over n intramedullary rod. J Bone Joint Surg Am. 1956;38-A(3):567-84.
84. Tolo V, Skaggs, DL. . Master techniques in orthopaedic surgery: Pediatrics. Master techniques in orthopaedic surgery: Pediatrics: Lippincott Williams & Wilkins; 2008.
85. Campens C, Mousny M, Docquier PL. Comparison of three surgical epiphysiodesis techniques for the treatment of lower limb length discrepancy. Acta Orthop Belg. 2010;76(2):226-32.
86. Koczewski P, Fryzowicz A. Phemister epiphysiodesis in leg length inequality treatment--evaluative outcome analysis. Ortop Traumatol Rehabil. 2013;15(4):315-23.
87. Surdam JW, Morris CD, DeWeese JD, Drvaric DM. Leg length inequality and epiphysiodesis: review of 96 cases. J Pediatr Orthop. 2003;23(3):381-4.
88. Canale ST, Christian CA. Techniques for epiphysiodesis about the knee. Clin Orthop Relat Res. 1990(255):81-5.
89. Ogilvie JW, King K. Epiphysiodesis: two-year clinical results using a new technique. J Pediatr Orthop. 1990;10(6):809-11.
90. Timperlake RW, Bowen JR, Guille JT, Choi IH. Prospective evaluation of fifty-three consecutive percutaneous epiphysiodeses of the distal femur and proximal tibia and fibula. J Pediatr Orthop. 1991;11(3):350-7.
91. Blount WP, Clarke GR. Control of bone growth by epiphyseal stapling; a preliminary report. J Bone Joint Surg Am. 1949;31A(3):464-78.
92. Raab P, Wild A, Seller K, Krauspe R. Correction of length discrepancies and angular deformities of the leg by Blount's epiphyseal stapling. Eur J Pediatr. 2001;160(11):668-74.
93. Gorman TM, Vanderwerff R, Pond M, MacWilliams B, Santora SD. Mechanical axis following staple epiphysiodesis for limb-length inequality. J Bone Joint Surg Am. 2009;91(10):2430-9.
94. Metaizeau JP, Wong-Chung J, Bertrand H, Pasquier P. Percutaneous epiphysiodesis using transphyseal screws (PETS). J Pediatr Orthop. 1998;18(3):363-9.
95. Ilharreborde B, Gaumetou E, Souchet P, Fitoussi F, Presedo A, Pennecot GF, et al. Efficacy and late complications of percutaneous epiphysiodesis with transphyseal screws. J Bone Joint Surg Br. 2012;94(2):270-5.
96. Stevens PM. Guided growth for angular correction: a preliminary series using a tension band plate. J Pediatr Orthop. 2007;27(3):253-9.
97. Stewart D, Cheema A, Szalay EA. Dual 8-plate technique is not as effective as ablation for epiphysiodesis about the knee. J Pediatr Orthop. 2013;33(8):843-6.
98. Kaymaz B, Komurcu E. Comment on the article "Dual 8-plate technique is not as effective as ablation for epiphysiodesis about the knee" by Stewart et al. J Pediatr Orthop. 2014;34(8):e67.
99. Ghanem I, El Hage S, Diab M, Saliba E, Khazzaka A, Aftimos G, et al. Radiofrequency application to the growth plate in the rabbit: a new potential approach to epiphysiodesis. J Pediatr Orthop. 2009;29(6):629-35.
100. Widmann RF, Amaral TD, Yildiz C, Yang X, Bostrom M. Percutaneous radiofrequency epiphysiodesis in a rabbit model: a pilot study. Clin Orthop Relat Res. 2010;468(7):1943-8.

101. Bowen JR, Johnson WJ. Percutaneous epiphysiodesis. Clin Orthop Relat Res. 1984(190):170-3.
102. Macnicol MF, Gupta MS. Epiphysiodesis using a cannulated tubesaw. J Bone Joint Surg Br. 1997;79(2):307-9.
103. Gabriel KR, Crawford AH, Roy DR, True MS, Sauntry S. Percutaneous epiphyseodesis. J Pediatr Orthop. 1994;14(3):358-62.
104. Edmonds EW, Stasikelis PJ. Percutaneous epiphysiodesis of the lower extremity: a comparison of single- versus double-portal techniques. J Pediatr Orthop. 2007;27(6):618-22.
105. Ramseier LE, Sukthankar A, Exner GU. Minimal invasive epiphysiodesis using a modified "Canale"-technique for correction of angular deformities and limb leg length discrepancies. J Child Orthop. 2009;3(1):33-7.
106. Inan M, Chan G, Littleton AG, Kubiak P, Bowen JR. Efficacy and safety of percutaneous epiphysiodesis. J Pediatr Orthop. 2008;28(6):648-51.
107. Stevens P. Guided growth: 1933 to the present Strateg Trauma Limb Reconstr. 2006;1:29-35.
108. Khoury JG, Tavares JO, McConnell S, Zeiders G, Sanders JO. Results of screw epiphysiodesis for the treatment of limb length discrepancy and angular deformity. J Pediatr Orthop. 2007;27(6):623-8.
109. Nouth F, Kuo LA. Percutaneous epiphysiodesis using transphyseal screws (PETS): prospective case study and review. J Pediatr Orthop. 2004;24(6):721-5.
110. De Brauwer V, Moens P. Temporary hemiepiphysiodesis for idiopathic genua valga in adolescents: percutaneous transphyseal screws (PETS) versus stapling. J Pediatr Orthop. 2008;28(5):549-54.
111. Stevens PM, Maguire M, Dales MD, Robins AJ. Physeal stapling for idiopathic genu valgum. J Pediatr Orthop. 1999;19(5):645-9.
112. Mielke CH, Stevens PM. Hemiepiphyseal stapling for knee deformities in children younger than 10 years: a preliminary report. J Pediatr Orthop. 1996;16(4):423-9.
113. Aykut US, Yazici M, Kandemir U, Gedikoglu G, Aksoy MC, Cil A, et al. The effect of temporary hemiepiphyseal stapling on the growth plate: a radiologic and immunohistochemical study in rabbits. J Pediatr Orthop. 2005;25(3):336-41.
114. Degreef I, Moens P, Fabry G. Temporary epiphysiodesis with Blount stapling for treatment of idiopathic genua valga in children. Acta Orthop Belg. 2003;69(5):426-32.
115. Burghardt RD, Herzenberg JE, Standard SC, Paley D. Temporary hemiepiphyseal arrest using a screw and plate device to treat knee and ankle deformities in children: a preliminary report. J Child Orthop. 2008;2(3):187-97.
116. Morein G, Gassner S, Kaplan I. Bone growth alterations resulting from application of CO2 laser beam to the epiphyseal growth plates. An experimental study in rabbits. Acta Orthop Scand. 1978;49(3):244-8.
117. Schroerlucke S, Bertrand S, Clapp J, Bundy J, Gregg FO. Failure of Orthofix eight-Plate for the treatment of Blount disease. J Pediatr Orthop. 2009;29(1):57-60.
118. Waris E, Ashammakhi N, Kelly CP, Andrus L, Waris T, Jackson IT. Transphyseal bioabsorbable screws cause temporary growth retardation in rabbit femur. J Pediatr Orthop. 2005;25(3):342-5.
119. Wiemann JMt, Tryon C, Szalay EA. Physeal stapling versus 8-plate hemiepiphysiodesis for guided correction of angular deformity about the knee. J Pediatr Orthop. 2009;29(5):481-5.

120. Ballal MS, Bruce CE, Nayagam S. Correcting genu varum and genu valgum in children by guided growth: temporary hemiepiphysiodesis using tension band plates. J Bone Joint Surg Br. 2010;92(2):273-6.
121. Ghanem I, Karam JA, Widmann RF. Surgical epiphysiodesis indications and techniques: update. Curr Opin Pediatr. 2011;23(1):53-9.
122. Rosen MA, Beer KJ, Wiater JP, Davidson DD. Epiphysiodesis by electrocautery in the rabbit and dog. Clin Orthop Relat Res. 1990(256):244-53.
123. Bisland SK, Johnson C, Diab M, Wilson BC, Burch S. A new technique for physiodesis using photodynamic therapy. Clin Orthop Relat Res. 2007;461:153-61.
124. Lee MC, Bier AD, Nickisch F, Eberson CP, Ehrlich MG, Chen Q. Epiphysiodesis with infusion of stromal cell-derived factor-1 in rabbit growth plates. J Bone Joint Surg Am. 2007;89(1):102-13.
125. Herring JA. Tachdjian's Pediatric Orthopaedics: From the Texas Scottish Rite Hospital for Children. 5th Edition ed: Saunders, an imprint of Elsevier Inc; 2014.
126. Gyuyatt G. Evidence-based medicine
. ACP J Club 1991:114:A-16.
127. Daly J. Evidence Based Medicine and the Search for a Science of Clinical Care. 1 ed: University of California Press; 2005.
128. Daly J, Lumley J. Evidence and context. Aust N Z J Public Health. 2005;29(6):503.
129. Daly S, Ferma M. The unique role of nurses in bridging evidence-practice gaps. Aust J Adv Nurs. 2005;23(2):6-7.
130. Feinstein AR. Beyond statistics: what is really important in medicine? Cleve Clin J Med. 1997;64(3):127-8.
131. Feinstein AR, Horwitz RI. Problems in the "evidence" of "evidence-based medicine". Am J Med. 1997;103(6):529-35.
132. Oxman AD, Sackett DL, Guyatt GH. Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group. JAMA. 1993;270(17):2093-5.
133. Sackett D, Straus S, Richardson W, Rosenberg W, Haynes R. Evidence- Based Medicine: How to Practice and Teach EBM. 2nd ed. ed. Edinburgh, UK: Churchill Living- stone; 2000.
134. Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ. 1996;312(7040):1215-8.
135. Glasziou P, Vandenbroucke JP, Chalmers I. Assessing the quality of research. BMJ. 2004;328(7430):39-41.
136. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology. 2007;18(6):805-35.
137. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.
138. Crowther MA, Cook DJ. Trials and tribulations of systematic reviews and meta-analyses. Hematology Am Soc Hematol Educ Program. 2007:493-7.
139. Sackett D, Richardson, WS., Rosenburg, W., Haynes, RB. How to practice and teach evidence based medicine. 2nd ed. ed: Churchill Livingstone; 1997.
140. Wright RW, Brand RA, Dunn W, Spindler KP. How to write a systematic review. Clin Orthop Relat Res. 2007;455:23-9.

141. Joanna Briggs Institute Reviewers' Manual. 2014 edition ed. Aromataris E, Munn Z, editors. Adelaide, Australia: The Joanna Briggs Institute; 2014.
142. Pearson A. Evidence synthesis and its role in evidence-based health care. Nurs Clin North Am. 2014;49(4):453-60.
143. Manchikanti L. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management, part I: introduction and general considerations. Pain Physician. 2008;11(2):161-86.
144. Manchikanti L, Hirsch JA, Smith HS. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: Part 2: Randomized controlled trials. Pain Physician. 2008;11(6):717-73.
145. Cain M, Stephenson M, Umapathysivam K, Williams N, Ianunzio J. Effectiveness of different minimally invasive epiphysiodesis techniques in the management of pediatric leg length discrepancies: a systematic review protocol. JBI database of systematic reviews and implementation reports. 2016;14(12):14-24.
146. Wood M, Ross-Kerr, JC. From question to proposal. Basic steps in planning nursing research. 7th ed ed: Jones and Bartlett Publishers; 2006.
147. Hulley S, Cummings, SR., Browner, WS., Grady, DG., Newman, TB. . Designing clinical research. 3rd ed ed: Lippincott Williams and Wilkins; 2007.
148. Aslam S, Emmanuel P. Formulating a researchable question: A critical step for facilitating good clinical research. Indian J Sex Transm Dis. 2010;31(1):47-50.
149. Sackett DL. Evidence-based medicine. Semin Perinatol. 1997;21(1):3-5.
150. Thabane L, Thomas T, Ye C, Paul J. Posing the research question: not so simple. Can J Anaesth. 2009;56(1):71-9.
151. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg. 2011;128(1):305-10.
152. Godfrey C, Harrison, MB. Systematic Review Resource Package. The Joanna Briggs Institute Method for Systematic Review Research Quick Reference Guide. In: Collaboration QJB, editor. 4 ed: Joanna Briggs Institute; 2015.
153. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
154. Benyi E, Berner M, Bjernekull I, Boman A, Chrysis D, Nilsson O, et al. Efficacy and Safety of Percutaneous Epiphysiodesis Operation around the Knee to Reduce Adult Height in Extremely Tall Adolescent Girls and Boys. International journal of pediatric endocrinology. 2010;2010:740629.
155. Inan M, Chan G, Bowen JR. The correction of leg-length discrepancy after treatment in developmental dysplasia of the hip by using a percutaneous epiphysiodesis. Journal of pediatric orthopedics Part B. 2008;17(1):43-6.
156. Odink RJ, Gerver WJ, Heeg M, Rouwe CW, van Waarde WM, Sauer PJ. Reduction of excessive height in boys by bilateral percutaneous epiphysiodesis around the knee. Eur J Pediatr. 2006;165(1):50-4.
157. Raab P, Wild A, Seller K, Krauspe R. Correction of length discrepancies and angular deformities of the leg by Blount's epiphyseal stapling. European Journal of Pediatrics. 2001;160(11):668-74.
158. Caskey PM, Baird GO, Tompkins BJ, Foley RP. Single-Incision Percutaneous Epiphysiodesis of the Lower Extremity. Operative Techniques in Orthopaedics. 2009;19(1):31-5.

159. Gottliebsen M, Møller-Madsen B, Stødkilde-Jørgensen H, Rahbek O. Controlled longitudinal bone growth by temporary tension band plating: An experimental study. Bone and Joint Journal. 2013;95 B(6):855-60.
160. Saghieh S. Percutaneous epiphysiodesis. Operative Dictations in Orthopedic Surgery: Springer New York; 2013. p. 27-9.
161. Shabtai L, Herzenberg JE. Limits of Growth Modulation Using Tension Band Plates in the Lower Extremities. J Am Acad Orthop Surg. 2016;24(10):691-701.
162. Babu LV, Evans O, Sankar A, Davies AG, Jones S, Fernandes JA. Epiphysiodesis for limb length discrepancy: a comparison of two methods. Strategies in trauma and limb reconstruction (Online). 2014;9(1):1-3.
163. Bayhan IA, Karatas AF, Rogers KJ, Bowen JR, Thacker MM. Comparing Percutaneous Physeal Epiphysiodesis and Eight-Plate Epiphysiodesis for the Treatment of Limb Length Discrepancy. J Pediatr Orthop. 2017;37(5):323-7.
164. Lykissas MG, Jain VV, Manickam V, Nathan S, Eismann EA, McCarthy JJ. Guided growth for the treatment of limb length discrepancy: a comparative study of the three most commonly used surgical techniques. Journal of pediatric orthopedics Part B. 2013;22(4):311-7.
165. Siedhoff M, Ridderbusch K, Breyer S, Stucker R, Rupprecht M. Temporary epiphyseodesis for limb-length discrepancy. 8- to 15-year follow-up of 34 children. Acta Orthop. 2014;85(6):626-32.
166. Horn J, Gunderson RB, Wensaas A, Steen H. Percutaneous epiphysiodesis in the proximal tibia by a single-portal approach: evaluation by radiostereometric analysis. J Child Orthop. 2013;7(4):295-300.
167. Kemnitz S, Moens P, Fabry G. Percutaneous epiphysiodesis for leg length discrepancy. Journal of pediatric orthopedics Part B. 2003;12(1):69-71.
168. Lauge-Pedersen H, Hagglund G. Eight plate should not be used for treating leg length discrepancy. J Child Orthop. 2013;7(4):285-8.
169. Monier BC, Aronsson DD, Sun M. Percutaneous epiphysiodesis using transphyseal screws for limb-length discrepancies: high variability among growth predictor models. J Child Orthop. 2015;9(5):403-10.
170. Pendleton AM, Stevens PM, Hung M. Guided growth for the treatment of moderate leg-length discrepancy. Orthopedics. 2013;36(5):e575-80.
171. Song MH, Choi ES, Park MS, Yoo WJ, Chung CY, Choi IH, et al. Percutaneous epiphysiodesis using transphyseal screws in the management of leg length discrepancy: optimal operation timing and techniques to avoid complications. J Pediatr Orthop. 2015;35(1):89-93.
172. Institute JB. New JBI Levels of Evidence2014 28th December 2017. Available from: http://www.joannabriggs.org/assets/docs/approach/JBI-Levels-of-evidence_2014.pdf.
173. Moola S MZ, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. . Chapter 7: Systematic reviews of etiology and risk. . In: Aromataris E MZ, editor. Joanna Briggs Institute Reviewer's Manual: The Joanna Briggs Institute; 2017.
174. Dekkers OM, Egger M, Altman DG, Vandenbroucke JP. Distinguishing case series from cohort studies. Ann Intern Med. 2012;156(1 Pt 1):37-40.
175. Popay H, Roberts H, A. S. Guidance on the Conduct of Narrative Synthesis in Systematic Reviews: Final Report 2006.
176. Achana F, Hubbard S, Sutton A, Kendrick D, Cooper N. An exploration of synthesis methods in public health evaluations of interventions concludes that the use of modern statistical methods would be beneficial. J Clin Epidemiol. 2014;67(4):376-90.

177. McDonald PJ, Kulkarni AV, Farrokhyar F, Bhandari M. Ethical issues in surgical research. Canadian journal of surgery Journal canadien de chirurgie. 2010;53(2):133-6.
178. Lovett B, Sawyer W, Houghton J, Taylor I. Systematic review of the methodological quality of randomized controlled trials of the surgical excision of cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2000;26:840.
179. Parikh D, Johnson M, Chagla L, Lowe D, McCulloch P. D2 gastrectomy: lessons from a prospective audit of the learning curve. Br J Surg. 1996;83(11):1595-9.
180. Testori A, Bartolomei M, Grana C, Mezzetti M, Chinol M, Mazzarol G, et al. Sentinel node localization in primary melanoma: learning curve and results. Melanoma Res. 1999;9(6):587-93.
181. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. BMJ. 2002;324(7351):1448-51.
182. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012;28(2):138-44.
183. Subramonian K, Muir G. The 'learning curve' in surgery: what is it, how do we measure it and can we influence it? BJU Int. 2004;93(9):1173-4.
184. Montori VM, Swiontkowski MF, Cook DJ. Methodologic issues in systematic reviews and meta-analyses. Clin Orthop Relat Res. 2003(413):43-54.
185. Ernst E, Resch KL. Reviewer bias: a blinded experimental study. J Lab Clin Med. 1994;124(2):178-82.
186. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ. 2003;326(7400):1167-70.
187. Dodwell E, Uppstrom T, Heyworth B. Protocol for the PEDS trial: percutaneous epiphysiodesis drill vs screws: a randomized controlled trial. BMJ. 2017;Open.