SURGICAL ACCURACY OF PATIENT-SPECIFIC INSTRUMENTS IN HIGH TIBIAL OSTEOTOMY AND DISTAL FEMORAL OSTEOTOMY: AN ALIGNMENT STUDY OF THE LOWER-LIMBS, PELVIS AND LUMBAR SPINE

by Hugo Wiggins, BSc

Principal supervisor: Dr Dane Turner (Dabirrahmani)

Assistant supervisors: Dr Joseph Cadman and Associate Professor Richard Appleyard

A thesis submitted in candidature for the degree of
Master of Research

Macquarie Medical School

Faculty of Medicine, Health and Human Sciences

Macquarie University

25th March 2022

Keywords/Phrases

Varus, valgus, osteoarthritis, osteotomy, conservative treatment, surgical treatment, high tibial osteotomy, distal femoral osteotomy, opening-wedge, patient-specific instruments, EOS, long-leg X-ray, hip-knee-ankle angle, functional leg length, anatomical femur length, anatomical tibia length, mechanical medial proximal tibial angle, mechanical lateral distal femoral angle, knee joint line convergence angle, pelvic obliquity, lumbar scoliosis, tibial slope, knee flexion angle, sacral slope, pelvic tilt, lumbar lordosis.

List of Abbreviations

AFL – anatomical femur length

ATL – anatomical tibia length

CV – coefficient of variation

DFO – distal femoral osteotomy

FLL – functional leg length

HKA – hip-knee-ankle angle

HTO – high tibial osteotomy

KFA – knee flexion angle

KJLCA – knee joint line convergence angle

KOA – knee osteoarthritis

LL – lumbar lordosis

LS – lumbar scoliosis

mLDFA – mechanical lateral distal femoral angle

mMPTA – mechanical medial proximal tibial angle

OA – osteoarthritis

PO – pelvic obliquity

PSI – patient-specific instruments

PT – pelvic tilt

SS – sacral slope

TKR – total knee replacement

TS – tibial slope

UKOA – unicompartmental knee osteoarthritis

VV – varus/valgus

Table of Contents

Abstract

Introduction: The high tibial osteotomy (HTO) and distal femoral osteotomy (DFO) are common surgical procedures for the treatment of unicompartmental knee osteoarthritis in combination with varus/valgus knee malalignment. Patient-specific instruments (PSI) are novel 3D-printed surgical guides that aim to improve the coronal and sagittal plane accuracy of these procedures, which are important factors for patient outcomes. Investigation of PSI accuracy in HTO/DFO is ongoing, as different PSI designs could determine the accuracy of the corrections. Furthermore, pelvic/spinal alignment changes following HTO/DFO has received limited attention, despite studies demonstrating correlations between change in lower-limb anatomy and alignment of the pelvis/spine. ***Methods:*** X-ray and EOS radiographic images were analysed in a retrospective single-centre clinical study to compare the planned HTO/DFO surgical corrections to post-operative measurements of the hip-knee-ankle angle (HKA) and tibial slope (TS). Secondary observational measurements included the functional leg length (FLL), anatomical tibia and femur length, mechanical medial proximal tibial angle, mechanical lateral distal femoral angle, knee joint line convergence angle and knee flexion angle. Pelvic and spinal parameters included pelvic obliquity (PO), pelvic tilt, sacral slope, lumbar scoliosis and lumbar lordosis. Intra/inter-observer and methodological (inter-image) reliability were investigated to identify potential sources of measurement error – analysed using coefficient of variation (CV), with an acceptable variability threshold of 30%. ***Results:*** HKA error – the difference between the planned HKA and post-op measured HKA – was -2.05° ± 3.03 for HTO and 0.50° ± 2.90 for DFO. TS error was -0.97° ± 1.46. FLL change was 4.4 mm ± 4.7, and PO change was 1.33° ± 1.26 on the operative sides. HKA measurements showed acceptable variability (CV=5.17–26.76%). TS measurements showed acceptable variability for intra-observer reliability (CV=25.64%), but unacceptable variability for inter-observer and inter-image reliability (CV=179.18% and 45.88%, respectively). All inter-image measurements except for HKA showed unacceptable variability (CV=42.55–118.26%). ***Conclusion:*** This study indicated that performing HTO/DFO using PSI can result in accurate corrections of varus/valgus knee malalignment. However, intra/inter-observer and inter-image reliability data of the two-dimensional methods utilised in this study showed measurement variability that limits the confidence in our findings. Three-dimensional surgical planning and post-operative evaluation of HTO/DFO using weight-bearing computed tomography or sterEOS™ software should be investigated, as these are likely to address the limitations of this study and provide more accurate results on surgical accuracy and post-operative alignment changes.

List of Figures

List of Tables

Statement of Original Authorship

The work presented in this thesis has not been submitted as part of another degree at any university or institution. All sections of this thesis were the product of Mr Hugo Wiggins, and all relevant research is referenced where necessary.

The research undertaken to form this thesis was approved by the Macquarie University Human Research Ethics Committee on 08/06/2021, reference number: 52021982328611

Signature:

Date: 25/03/2022

COVID-19 and Supervision Statement

Macquarie University statement

Dear Examiner,

Many of our HDR candidates have had to make changes to their research due to the impact of COVID-19. Below you will find a statement from the candidate, approved by their Supervisory Panel, that indicates how their original research plan has been affected by COVID-19 restrictions. Relevant ongoing restrictions in place caused by COVID-19 will also be detailed by the candidate.

Candidate statement

The presence of the COVID-19 pandemic caused major changes to the way in which this form of clinical research would normally have been conducted. The impact in the first five months of this study was minor as University campus research and clinic visitation was permitted, which meant communication with patients and the clinicians was possible. However, the following five months and onwards presented significant challenges with the implementation of lockdown restrictions which limited or prevented face-to-face engagement with the surgical team and patients. This influenced the pace at which the research could be conducted as communication shifted to online means. In addition, the surgeries analysed in this research are classified as elective procedures and are thus less likely to be performed during periods of high COVID-19 prevalence, contributing to a lower number of eligible participants than projected and a reduction in the statistical power of analyses in the study.

Research supervision was also impacted for over half of this study. At the onset of lockdown restrictions, the primary supervisor had to reduce her weekly allocation to this project as a result of work-related changes. This meant that reduced assistance with the project and general daily communication compounded the effects of COVID-19.

Acknowledgements

To my principal supervisor, Dr Dane Turner, thank you for providing me with a research project that aligned so well with my knowledge and interests, yet challenged me in an area I had no previous experience in. I have grown more as a student and person this year than any other year in my memory, which I attribute to the experiences this project allowed me to have. Of course, your expertise and guidance along the way was invaluable.

To my assistant supervisors, Dr Joseph Cadman and Associate Professor Richard Appleyard, thank you for your individual and collaborative contributions to my work. You helped to mitigate the influences of COVID-19 on an already-challenging clinical study, and I appreciated having you both involved.

To the surgeons who set the foundation for this research, Dr Mustafa Alttahir and Professor Munjed Al Muderis, I acknowledge the years of dedication you have given to your specialty and the expertise you provided throughout my project. Thank you Dr William Lu for your clinical research assistance.

To the participants in this study, thank you for seeing value in my research and volunteering your time to contribute useful information to the current knee osteotomy body of knowledge. Without such involvement, surgical medicine would be unable to advance as quickly as it does.

To my friends, I appreciate all of you for adding value and joy to my life in your own unique ways.

To my family, your love and support throughout a Master's degree almost entirely completed online due to the impact of COVID-19 was incredible.

Chapter 1: Introduction

Varus and valgus knee malalignment presents significant risk for unicompartmental knee osteoarthritis (UKOA) development (1, 2). Conservative treatment of UKOA can relieve symptomatology, but the long-term efficacy and safety of these methods has limitations (3-15). The high tibial osteotomy (HTO) and distal femoral osteotomy (DFO) have been performed to surgically treat UKOA with knee malalignment since 1961 (16), with excellent results shown in the following decades (17, 18). However, the most accurate HTO/DFO technique for achieving the planned coronal and sagittal plane corrections remains unclear.

Patient-specific instruments (PSI) are novel 3D-printed surgical guides that are constructed based on pre-operative high-resolution computed tomography scans of patient anatomy, and were first reported in HTO/DFO in 2013 (19). PSI allow HTO/DFO procedures to be tailored to each patient, with the aim of improving accuracy and reducing complications/revisions (20). To our knowledge, an Australian study of PSI use in HTO/DFO has not been conducted. Given the heterogeneity in PSI designs/manufacturers and the novelty of the technique in HTO/DFO, ongoing research on the accuracy of PSI corrections is important. Furthermore, the influences of HTO/DFO on pelvic/spinal alignment has received limited attention, despite the known correlation between lower-limb anatomy and spinal alignment (21-33).

This thesis presents a retrospective single-centre clinical study of variables related to lower-limb and pelvic/spinal alignment, measured from long-leg X-ray and EOS (EOS Imaging, Paris France) radiographic images in combination with InteleViewer^{TM} software (Intelerad, Quebec, Canada).

Chapter 2 covers background concepts and HTO/DFO-specific research that guided the selection of our measurements and formed the research aims. Chapter 3 outlines the Materials and Methods from the clinical study, which is separated into pre-operative clinical management and applied research methods to differentiate the involvement of surgeons/engineers and researchers in the study. Chapter 4 provides the results, primarily displaying the post-operative changes observed across the procedures due to the clinical relevance of this information – raw pre/post-operative data is tabulated at the end of each Section for additional statistical analysis. Chapter 5 discusses the results of this study in relation to the literature, with challenges and limitations highlighted to guide future research on the variables investigated in this thesis. Chapter 6 gives a concluding statement on the findings from the study.

Chapter 2: Literature Review

From Section 2.1 to 2.5, this literature review will cover background concepts necessary to understanding research-specific concepts relevant to the clinical study conducted to form this thesis. Section 2.6 to 2.10 will cover seminal high tibial osteotomy (HTO)/distal femoral osteotomy (DFO) research to provide a historical perspective, as well as contemporary research that has formed the current understanding in HTO/DFO research and its relevant considerations. Section 2.11 summarises the findings of the literature review by clarifying gaps in the current body of knowledge to rationalise the conduction of further research, concluding with the provision of aims for our study.

2.1 LOWER-LIMB ALIGNMENT AND VARUS/VALGUS DEFORMITY AT THE KNEE

When viewing anteroposterior (AP) radiographic images of anatomically normal lower-limbs in a weight-bearing (WB) position, a straight line drawn from the centre of the hip to the centre of the ankle will pass directly through the centre of the knee joint (34). Referred to as the mechanical axis (MA) of each lower-limb (Figure 2.1), this line indicates the distribution of force through the two (lateral and medial) compartments of the knee (Figure 2.2), which must be evenly distributed to allow optimal biomechanics and prevent overloading of a single compartment (35). However, lateral or medial deviation of the knee joint away from the MA can occur as a result of congenital deformity (36), obesity (37), trauma (38), or osteoarthritic pathology (35). When this occurs, lateral deviation of the knee is known as varus malalignment – aka ‘bowed legs’ – and medial deviation of the knee is known as valgus malalignment – aka ‘knock-knees’ (Figure 2.3a & 2.3b, respectively) (39).

A measurement to objectify lower-limb deformities of this kind is the hip-knee-ankle angle (HKA), which involves a three-point line through the centres of the hip, knee and ankle, often measured from the medial side of the knee (Figure 2.4) (40). Hence, an HKA that traces the MA will equal 180º, which is the normal value for the HKA (41), and represents no varus/valgus (VV) malalignment. Typically, an HKA that deviates ±<3º from 180º is considered clinically insignificant and is unlikely to cause premature pathology in the knee joint due to preservation of even weight distribution across the joint compartments (34). However, VV knee malalignment can overload the medial and lateral joint compartments, respectively, by more than three times their normal WB forces at 10° of deformity (35, 42, 43). This significant unicompartmental load increase can lead to accelerated cartilage wear and catalyse development of unicompartmental

knee osteoarthritis (UKOA) – explained in Section 2.3 – which can decrease joint functionality and quality of life (QoL) as the anatomical deformity and pain increase (1, 2). Hence, early diagnosis and treatment of VV knee deformity is crucial in order to prevent UKOA development/progression and for knee replacement to be delayed or even avoided entirely (44). However, the complexity of VV knee treatment will be made evident throughout this Chapter.

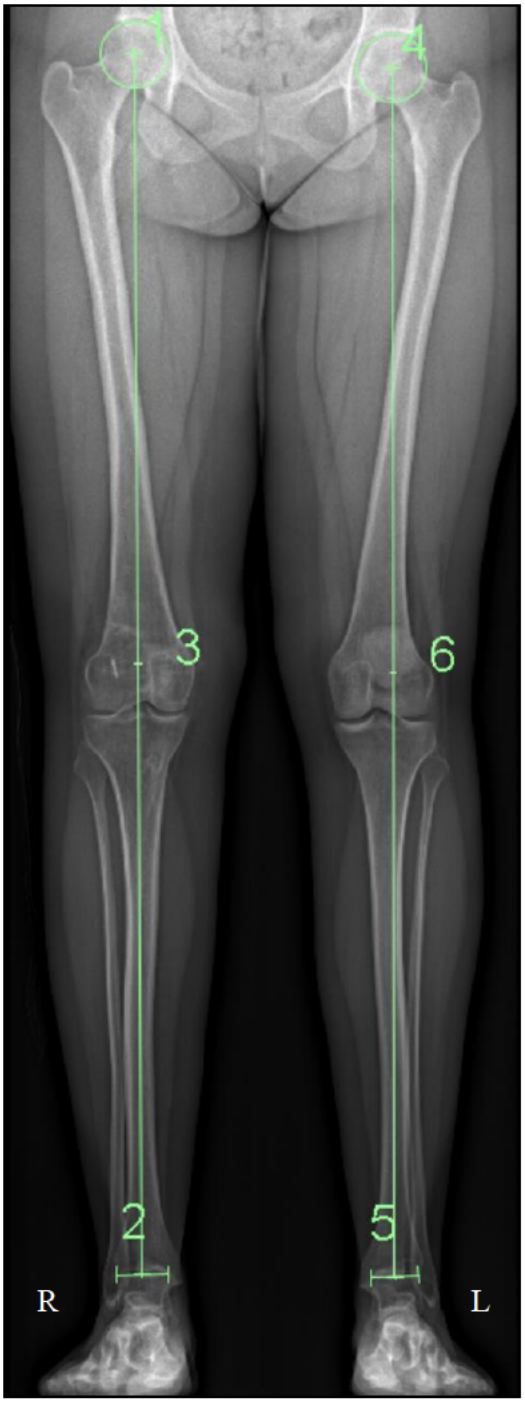


Figure 2.1 Mechanical axis of normal alignment versus valgus malalignment
Long-leg X-ray where Line 3 can be seen passing through the tibial spines at the centre of the knee, whereas Line 6 can be seen passing lateral to the tibial spines, indicating valgus malalignment of the left knee

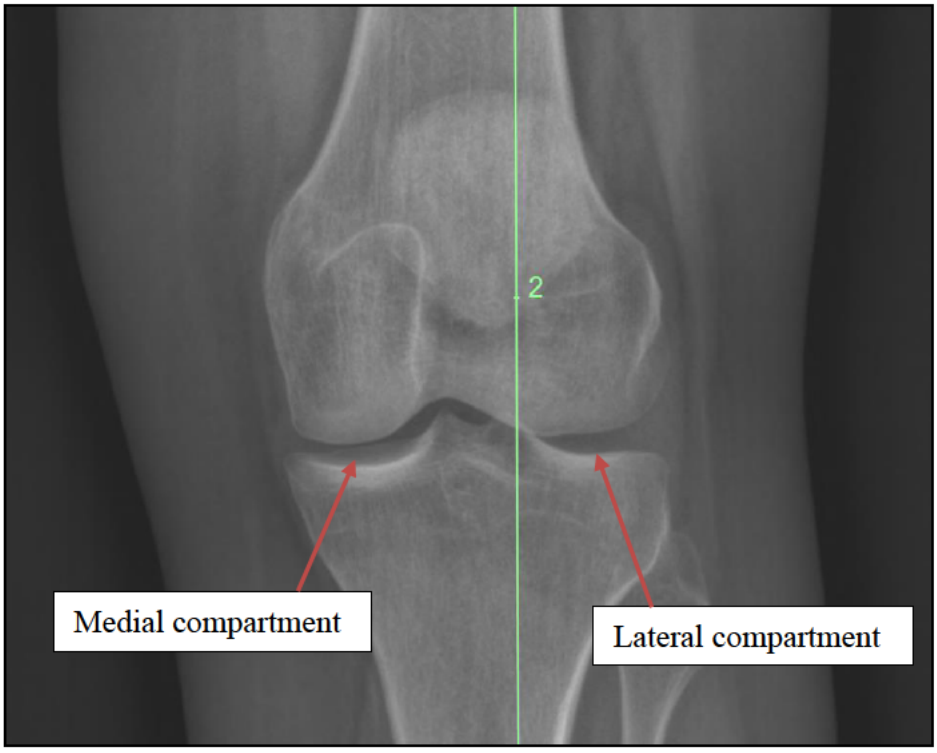


Figure 2.2 Medial and lateral knee joint compartments

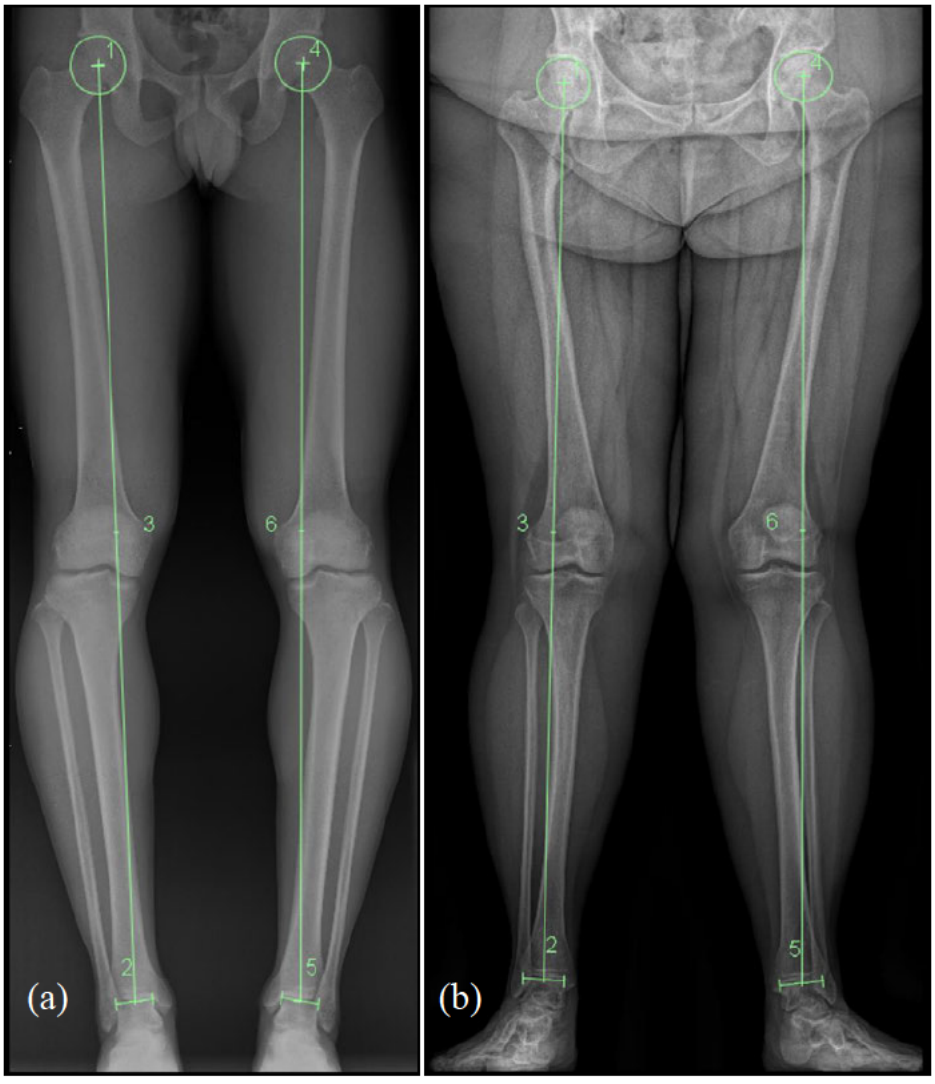


Figure 2.3 Bilateral varus (a) and bilateral valgus (b) knee malalignment

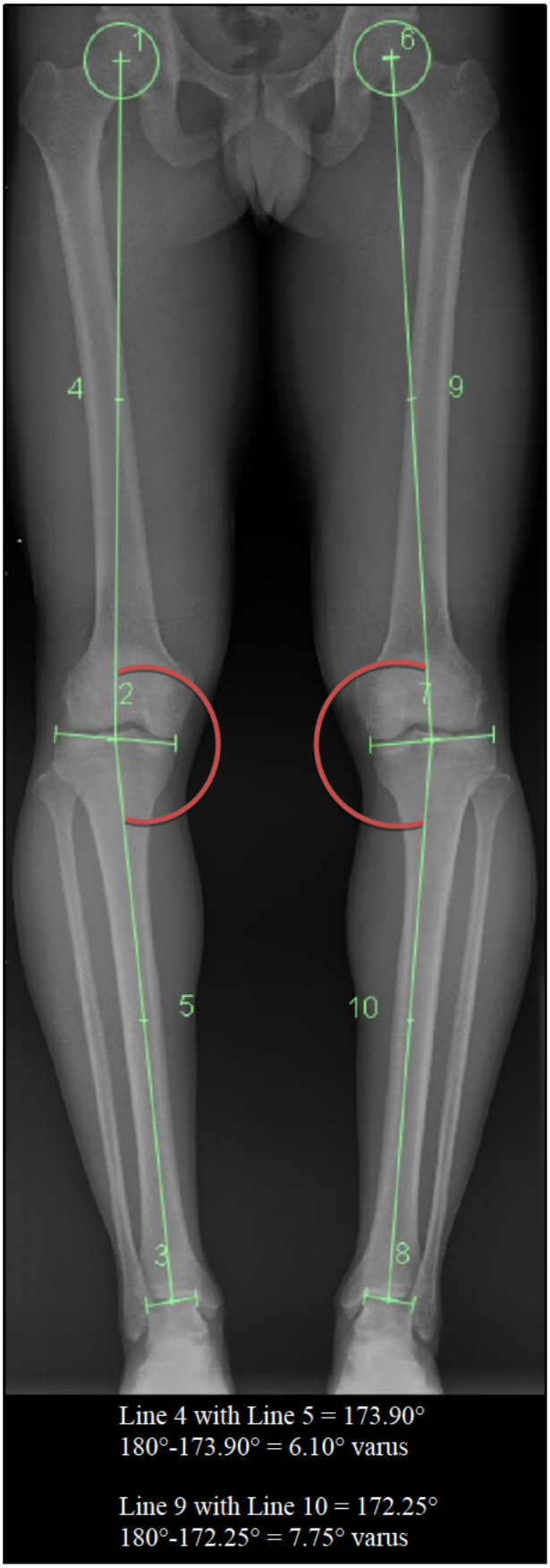


Figure 2.4 Example hip-knee-ankle angle measurement

2.2 RADIOGRAPHIC MODALITIES FOR OBSERVING VARUS/VALGUS DEFORMITY

At all stages of patient management, accurate radiographic analysis is a major determinant of patient outcome (45, 46). Long-leg X-ray (LLXR) has been the gold standard for lower-limb malalignment measurement for many decades (47), and the capability of this imaging modality has thus been proven. These setups are cost-efficient, simplistic, emit low levels of radiation and enable detailed images of bone morphology (48, 49), making them an attractive option for imaging centres worldwide (47). Typically, LLXR is single-planar, meaning only one image can be taken at a time (47). This means coronal and sagittal (front and side) plane images must be taken separately, which is unideal when needing to analyse malalignment in both planes due to patient stance inevitably changing between images even if strict protocols are applied. Bi-planar X-ray machines offer an advantage over single-plane, as they can acquire coronal and sagittal images simultaneously, providing clinicians with a more complete view of patient malalignment, albeit at the expense of an increased radiation dose (50).

Whilst LLXR is sufficient for measuring skeletal alignment, advancements have been made over the last 15 years in the form of EOS machines (EOS Imaging, Paris, France) which benefit the clinician and the patient. EOS machines (Figure 2.5a) can visualise malalignment of not just the lower-limbs, but the entire skeletal system in a single image (51), which is made possible through two mobile X-ray sources that travel vertically and capture orthogonal views in the coronal and sagittal planes (Figure 2.5b & 2.5c). This mechanism of horizontal X-ray projection allows for the quality of EOS images to be enhanced compared to standard LLXR and may reduce the chance of radiographic artifacts (52). EOS machines are reported to emit around 10-times less radiation per-scan compared to LLXR (53), making EOS use more suitable for longitudinal monitoring of patients due to the minimisation of radiation exposure over repeated scans. Although EOS machines offer numerous advantages over LLXR, they are far less common, with only 400 installed worldwide across 40 countries – 23 located in Australia. This low prevalence EOS is likely attributed to the higher cost of the machines and their relatively new status (54).

Macquarie Medical Imaging (MMI) – the imaging facility located at Macquarie University Hospital (MUH) – houses the only EOSedge^{TM} (shown in Figure 2.5a) machine in Australia, which will be utilised during our clinical study on high tibial osteotomy/distal femoral osteotomy surgical accuracy, presented in Chapter 3.

Figure 2.5 EOS machine (a) and resulting coronal (b) and sagittal (c) images EOSedge™ model from surgicom.com.au

2.3 OSTEOARTHRITIS AND ITS BURDEN IN THE KNEE

Osteoarthritis (OA) is a progressive joint disease primarily affecting bone and articular cartilage which can cause individuals severe pain, inflammation and reduced QoL (55). In recent years, OA has been reported as a leading cause of disability worldwide (56-58), with 300 million individuals estimated to have lived with the condition in the year 2020 (59), causing approximately a $303 billion burden per annum on the United States healthcare system alone (60). Knee OA (KOA) is the most common form of OA (61), and UKOA is a prevalent form of KOA (62). Lastly, UKOA of the medial tibiofemoral compartment is more common than in the lateral compartment, which is due to ~60% of force being transmitted through the medial compartment of normally aligned knees during ambulation (63, 64). From this epidemiological and biomechanical data, it can be appreciated that UKOA – particularly of the medial tibiofemoral joint – represents a significant proportion of OA burden, which has made treatment for this condition a topic of great interest across conservative and surgical specialties since the pathophysiological mechanisms of OA have been somewhat understood (65-68).

Reinforcement of the pathophysiology and gross anatomical deformity associated with various stages of KOA is necessary before covering the current treatment options and their benefits/limitations in Section 2.4. There are four predominant features that may be present in typical KOA cases at an intra-articular level, which can be summarised by the acronym 'L.O.S.S.': loss of cartilage; osteophyte formation; subchondral sclerosis; subchondral cysts (69). Loss of cartilage – the primary OA mechanism – describes the degradation of articular cartilage that

provides smooth joint functionality and shock absorption, eventuating in progressive joint space narrowing (JSN) between the femur and tibia (Figure 2.6) as the disease progresses (70). It should be noted here that UKOA is not solely a consequence of VV deformity, but UKOA can also cause VV deformity to develop as a result of JSN i.e. UKOA and VV can be caused by each other (71). Osteophyte formation involves protrusions of bone that disrupt the function of the joint and can cause 'locking' or 'catching' of the knee when these protrusions interfere with the articular surface range of motion (ROM) (72). Subchondral sclerosis refers to the hardening of bone below articular cartilage, which can lead to pain and decreased shock-absorptive properties associated with healthy cartilage (8). Subchondral cysts are fluid-filled sacs that protrude from either the femur or tibia into the synovial cavity, causing discomfort and risk of infection if ruptured (73). These pathologies are the target in KOA treatment (detailed explanation of conservative treatments in Sub-Section 2.4.1, and surgical treatments in Sub-Section 2.4.2), with each treatment presenting different benefits and limitations of joint function recovery depending on the location and stage of the disease progression.

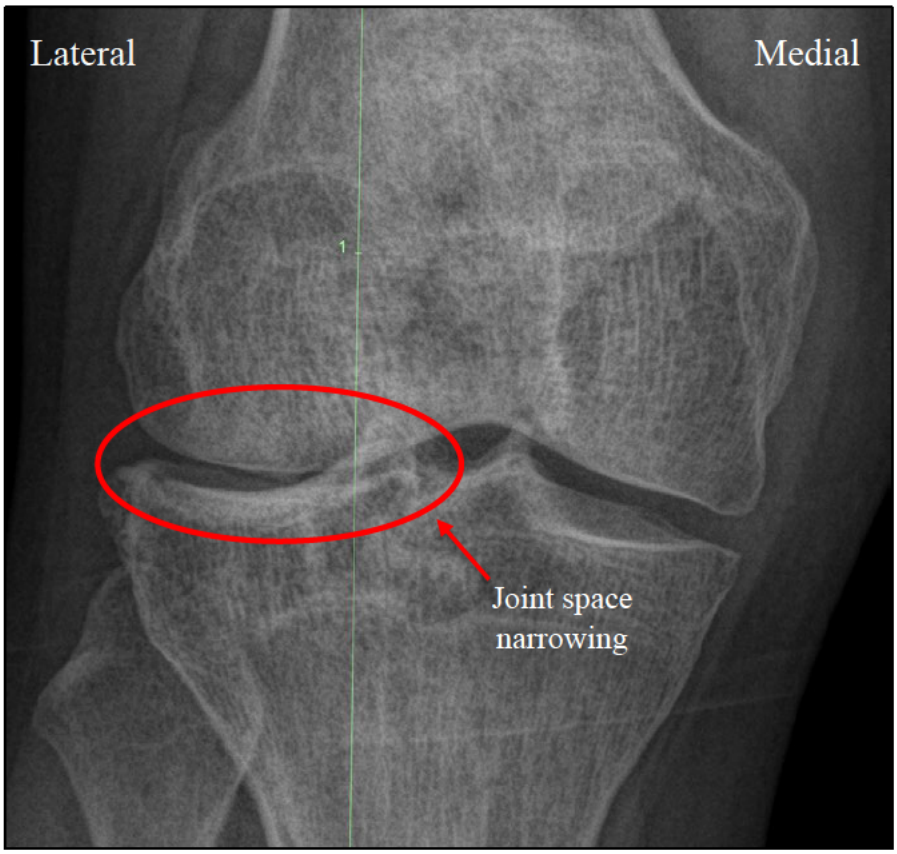


Figure 2.6 Example of lateral knee joint space narrowing from valgus malalignment

2.4 THE CURRENT KNEE OSTEOARTHRITIS TREATMENT SPECTRUM

Despite extensive research over recent years providing evidence for and against various conservative and surgical KOA treatment approaches, as of the year 2020, a comprehensive disease-modifying treatment has not been established, nor has consensus been reached regarding the best short and long-term options for reducing pain and improving QoL (74). This Section provides evidence of various conservative and surgical approaches, identifying the benefits and limitations of each treatment in addressing KOA symptomatology.

2.4.1 Conservative treatment

As the initial treatment for KOA, conservative treatments can be defined as medical, orthotic or rehabilitative techniques that do not involve surgical intervention (75). Before surgical intervention is considered, it is recommended individuals attempt conservative treatment for relief of their condition. The first category of conservative treatment is non-pharmaceutical interventions (Table 2.1), with these typically being the first form of treatment a patient will be recommended by their consulting physician when suffering KOA symptomatology (76). Obesity has a high correlation with WB joint OA onset/progression (37), and OA has been reported as the second-most financially burdensome obesity-related pathology (77). Hence, the relationship between KOA and obesity is evident, and indirect treatment in the form of weight loss has been shown to reduce symptoms and facilitate regeneration of cartilage in KOA sufferers (78). Weight loss may be a viable option for younger, early-stage KOA sufferers without knee malalignment, but the prognosis of a weight-loss approach in the absence of such demographics is likely to be unfavourable (79, 80). Another non-pharmaceutical option for KOA treatment is physiotherapy and associated techniques applied by physiotherapists, described by Page et al. in a 2011 review article (81): manual therapy – to release of musculotendinous tension around the knee; exercise prescription – for restoration of knee strength lost through disuse atrophy of surrounding musculature; taping – typically used for altering patellofemoral joint tracking; leg bracing – shifting WB to the more-preserved knee compartment in the case of UKOA; insoles and shoe alteration – for leg-length discrepancy and shifting WB through the ankle and knee. These techniques are often classified as palliative as opposed to disease-modifying, and have even been known to cause additional discomfort, such as taping irritation and knee brace skin/nerve compression (82). This makes the long-term efficacy of this treatment form unfavourable and often unsustainable.

Pharmaceutical management is the other category in the conservative KOA treatment dichotomy (Table 2.2), which can be defined as any oral, topical or injectable substance aiming to address joint pain, inflammation and/or slow/reverse the disease pathogenesis (83). Paracetamol

(acetaminophen in the United States) is commonly recommended as the first-line analgesic for pain relief in KOA sufferers (84). This may be a suitable option for managing intermittent flare-ups in early-stage KOA sufferers, but the mild strength of paracetamol substances limits its long-term efficacy as the disease pathogenesis progresses and symptomatology worsens (5). Chronic long-term use of the maximum daily dose of paracetamol has also been linked with liver failure (85), so it is unadvisable to rely on paracetamol for OA treatment in the case of more severe symptomatology requiring excessive supplementation for pain management. Individuals may also elect to use topically-applied nonsteroidal anti-inflammatory drugs (NSAIDs) as an alternative, such as the well-known Nurofen or Voltaren, which will elicit a more localised treatment to the symptomatic region compared to the systemic approach of paracetamol (4, 86). Understandably, the typical side-effects from a topically applied treatment are minimal, such as skin irritation in hypersensitive or allergic individuals (87). However, a limiting factor associated with topically-applied substances is individual variations in skin permeability, which may inhibit the analgesic efficacy of topical pharmaceutical substances (12). Another topical treatment similar to topical NSAIDs is capsaicin – a chilli pepper-derived chemical that causes a warmth sensation to the area it is applied (67) – which has been shown to provide OA symptom relief (88). It is believed that this relief is physiologically derived from the local depletion of substance P from nerve fibres, which reduces pain perception (89). However, this supposed mechanism is juxtaposed by reports of capsaicin causing unbearable burning sensations, rendering it as an unusable treatment for some sensitive individuals (10, 90). NSAIDs may also be administered orally in tablet form, such as Aspirin or ibuprofen-containing alternatives, but often require simultaneous prescription of proton pump inhibitors (PPIs) to avoid gastrointestinal tract ulceration from the excess acid production caused by NSAID intake (91). PPIs also carry their own side-effects – most notably enteric infection (92) – making the potential domino effect of NSAID prescription one to avoid, if possible (93).

Intra-articular injectable treatments are common towards the latter-stages of conservative pharmaceutical treatment prescription, one of which may be glucocorticoids (GC) (94). GC are powerful steroidal anti-inflammatory drugs that locally reduce pain around the site of injection through downregulation of nuclear factor kappa B (NFκB) – a protein that inhibits the production of inflammatory cytokines (95). Numerous studies have demonstrated the efficacy of GC injections at reducing OA symptomatology (96-99), but the consequences of long-term GC use must be considered before prescription. It is known that immunosuppression occurs as a result of GC use due to inhibiting inflammatory cytokines (100), which can leave individuals susceptible to local and systemic infection. Furthermore, GC cause a cascade of hormonal changes that can ultimately lead to osteocyte apoptosis and increased osteoclast activity, resulting in osteoporosis

(101). Interestingly, the risk of bone fracture appears to be elevated only in the first few months of GC intake, with this risk attenuating thereafter (102). Increased fluid retention and development of Cushing's syndrome is the final long-term side-effect that is typically discussed as the most concerning in the literature, which occurs as a result of synthetic GC acting as an aldosterone-like substance within the circulatory system (103). Thus, weight gain, high blood pressure and diabetes – known consequences in Cushing's syndrome (104, 105) – are potential outcomes stemming from GC injection. For these reasons, it is unadvisable to prescribe GC for more than a number of months, as the chances of developing side-effects has been suggested to increase with age, dose and duration (106). The other main injectable treatment for OA is hyaluronic acid (HA), also known as hyaluronan (107). HA is a naturally-occurring substance that constitutes part of normal synovial fluid makeup, contributing to the shock-absorptive and lubricative properties necessary for optimal joint function (108, 109). Hence, viscosupplementation – the term given to injection of synthetically-produced HA – has been shown to reduce OA symptomatology, presumably by restoring a degree of shock-absorption and lubrication within the synovial cavity (110). The patient-reported efficacy and safety of HA appears to be exceptional, with a 2018 systematic review of 27 studies on HA for KOA treatment revealing a 55% reduction in pain with no serious adverse events reported (111). However, HA injection has not been shown to slow or reverse the progression of OA pathophysiology (15), which classifies this treatment as palliative rather than disease-modifying. Nevertheless, the absence of adverse events in the literature may suggest that this is the most recommendable injection for managing KOA symptomatology whilst avoiding severe side-effects, which is an important factor during the prescription process.

The theme that can be noticed with conservative treatments is that they lack the ability to modify anatomy/pathophysiology, and are not likely to be suitable options for more severe OA over extended time periods. Until advancements are made in the non-pharmaceutical and pharmaceutical conservative OA treatment domains, the current value of these options is management of symptomatology and delaying surgical intervention.

Table 2.1 Conservative non-pharmaceutical knee osteoarthritis treatments

Non-pharmaceutical treatment				
Treatment name	**Original report as osteoarthritis treatment**	**Benefits**	**Limitations**	**Time before symptom relief**
Weight loss	1900 (112)	Natural, controllable and sustainable effects with reduced risk of developing weight-related comorbidities (113)	Effect is slow (if weight is lost at a healthy rate) and physical activity is needed in order to lose weight, which may aggravate osteoarthritis (11)	Months (114)
Manual therapy	1893 (115)	Natural and controllable with potential immediate and prolonged symptomatology relief from loosening of musculotendinous tissue (116)	Must be consistently performed to maintain benefits, as effects will reverse when tissue naturally tightens (14)	Minutes (to days if delayed-onset muscle soreness occurs) (117)
Strength training	1992 (118)	Natural and controllable, with evidence to suggest attenuated joint space narrowing by strengthening the surrounding structures (119)	May exacerbate osteoarthritis initially due to increased movement and potential weight-bearing through joint (6)	Weeks to months (120)
Taping	1976 (121)	Potential immediate relief from patellofemoral osteoarthritis (122, 123)	Must be re-applied and may cause individuals discomfort from compression or skin irritation (7)	Immediate with potential ongoing benefits (122)
Bracing	1970 (124)	Immediate relief from unicompartmental knee osteoarthritis due to shifting weight-bearing to healthy compartment (125)	Adds weight/bulk, elicits pressure on skin, and may also be considered cosmetically unpleasing when the knee is exposed (3)	Immediate with potential ongoing benefits (125)
Orthotic/shoe alterations	1965 (126)	Possible relief from pedal pathology caused by knee malalignment, with subsequent changes to knee weight-bearing (127)	Adds weight/bulk and not compatible with all shoe types	Immediate with potential ongoing benefits (128)

Table 2.2 Conservative pharmaceutical knee osteoarthritis treatments

Pharmaceutical treatment				
Treatment name	**Original report as osteoarthritis treatment**	**Benefits**	**Limitations**	**Time before symptom relief**
Paracetamol (acetaminophen)	1960 (129)	Quick-acting relief from early-stage osteoarthritis symptomatology with minimal side-effects in moderate doses (84)	Not effective for severe symptomatology due to mild strength and dangers associated with large-dose consumption (5)	Minutes to an hour (130)
Topical nonsteroidal anti-inflammatories (NSAIDs)	1989 (131)	Quick-acting, localised relief from mild symptoms without the side-effects associated with its oral counterpart (86)	Not suitable for moderate/severe symptoms, and variations in skin permeability may inhibit efficacy (12)	Hours to days or even weeks (132)
Capsaicin	1990 (133)	Quick-acting, localised relief from mild symptoms without systemic side-effects (10)	May cause cutaneous burning sensation and discomfort (10)	Hours (133)
Oral NSAIDs	1963 (134)	Strong systemic pain relief (135)	High-dosage and/or long-term use are associated with many severe side-effects (4)	Hours (4)
Glucocorticoids	1950 (136)	Consistent evidence to suggest efficacy against osteoarthritis symptomatology (96-99)	Severe cascade of local and systemic side-effects from long-term use (13)	Days (137)
Hyaluronic acid	1971 (138)	Symptom relief with no adverse side-effects recently reported (111)	Has not been shown to modify disease pathophysiology (15)	Days to weeks (139)

2.4.2 Surgical treatment

Whilst the aforementioned conservative treatments may provide symptom relief, given the progressive nature of OA, it is often inevitable that symptoms will progress, and surgical treatment may become the focus of discussion between clinicians and patients. In addition, if VV knee malalignment is present, patients are placed in a difficult situation where choosing conservative treatments will not address this malalignment, and the prognosis with continued conservative treatment is likely to be poor. Hence, once conservative measures have been exhausted, a patient may choose to explore surgical options, outlined from least-to-most invasive in Table 2.3 after each surgery has been explained. As with all invasive general anaesthetic surgical procedures, there is risk of infection, local or systemic complications and rare occurrence of death (140, 141), which means careful consideration of patient demographics and assessment of morbidity is necessary before a decision is made to proceed with surgery. However, the reported correlation between chronic OA and worsening mental health (142-144) makes such intervention warranted to alleviate symptoms and improve QoL.

Beginning with arthroscopy, this technique is a keyhole-based surgery typically involving two or three portals (depending on physician preference) to observe and manipulate the intra-articular structure of the knee joint (145). The basic principle of this procedure is to restore as-close-to-normal joint architecture by removing or repairing potential irritants that may be causing individuals discomfort, executed by the surgeon using a small shaver and scissors inserted through one of the portals. Irritants can include loose bodies (bone or cartilage that has broken away from the surface and is allowed to move freely throughout the synovial cavity), meniscal tears, rough cartilage/bone or inflamed synovial tissue (146). Lavage may also be performed simultaneously, which is rinsing of the synovial cavity with a saline solution to cleanse damaged tissue and restore a homeostatic environment (147). Whilst the aims of arthroscopy are logical, the presence of OA within the knee joint can be a predictor of knee arthroscopy being inefficacious (148). This is because osteoarthritic bone can continue to degrade and cause damage to surrounding anatomy, returning the patient to their pre-arthroscopic state in the months/years following the procedure. Hence, if individuals with KOA do elect to undergo arthroscopy, short-term efficacy (if any) should be considered.

The next surgical OA treatment commonly documented in the literature is cartilage microfracture (MFx) – synonymously referred to as bone marrow stimulation. It involves arthroscopic shaving of damaged cartilage, followed by drilling perforations in the subchondral bone to promote a regenerative process that forms new cartilage (149). This regenerative process is caused by the passage of autologous mesenchymal stem cells from bone marrow through the subchondral bone perforations to form a blood clot along the surface of the cartilage lesion (150).

Thus, a healing cascade is initiated, and the area of cartilage responsible for symptomatology undergoes reformation. The indications for MFx are younger individuals (aged <40) with very early stage OA, minimal HKA malalignment and chondral defects of approximately two centimetres in diameter (150). Because of these indications, MFx is more commonly used for the treatment of focal traumatic cartilage injuries in the hope of preventing/slowing the progression of OA than the direct treatment of OA (151). According to contemporary literature, if MFx is efficacious, five years post-op appears to be the time at which the procedure can be expected to fail (152). Hence, the limitations to this technique are evident, as the demographics it is typically applied to represents a very small proportion of the total KOA population.

Unicompartmental knee replacement (UKR) (also referred to as unicondylar/partial knee replacement) is the first of the major surgical interventions for KOA that will be discussed in this Chapter. As the name suggests, UKR is the replacement of only the medial or lateral tibiofemoral joint compartment that is affected with OA (153), completely preserving the opposite compartment. This is achieved through the surgical removal of diseased articular cartilage and bone, and insertion of artificial titanium/polyethylene components to restore function and alleviate pain. Although UKOA is a common condition (62), UKR is less commonly used to surgically treat patients. A recent systematic review of 3037 surgeons by Klasan et al. revealed only 5-10% of knee replacement surgeries were UKR throughout this cohort (154). The presence of osteotomy corrections (Section 2.5) in the UKOA surgical treatment sphere could play a role in this statistic, due to achieving a similar outcome whilst preserving the natural architecture of the joint (155). Nevertheless, UKR is a suitable UKOA treatment option for older (aged >60) individuals with a BMI <30, who are less active and have lower expectations of the procedure in terms of their lifestyle or exercise preferences (156). However, individuals have been reported as approximately five times more likely to require a revision UKR than a revision total knee replacement (TKR) (157), and revision UKR is also suggested to have worse outcomes than primary TKR (158). Physicians consider such findings when determining whether UKR is the best mid-to-long-term option for the patient, and if performing a TKR would be more suitable.

TKR has been a common surgical intervention for KOA for many decades, increasing in popularity as patient outcome and implant survival continue to show improvements (150, 159). Unlike UKR, TKR involves replacing all three articular compartments of the knee, removing the osteoarthritic joint surfaces and forming an entirely new joint (160). Similarly, however, titanium/polyethylene componentry are used, with the only difference being the size and shape to fit the entire knee anatomy. With the right indications, the success of TKR surgeries has continued to improve since being pioneered in 1968 (161), to the point where a minimum of 10 years implant survival is expected (162) and more than 20 years of survival is becoming more common (163).

Despite this success, patient dissatisfaction rates have been reported at 25% for reasons of unnatural joint function or pain/discomfort (164), yet, the reason for poor TKR outcome remains unclear (165). What is clear, however, is that older patients (aged >65) with lower physical demands and expectations of the procedure experience the best outcomes from TKR (166). For these reasons, delaying TKR as long as possible is regarded as the best approach for individuals with KOA (166, 167), which provides a rationale for osteotomy corrections, as explained in the following Section.

2.5 OSTEOTOMY CORRECTIONS AROUND THE KNEE

From Greek origins, the word 'osteon' means 'bone', and the suffix 'otomy' means 'to cut'. Therefore, an osteotomy is defined as either the partial or complete surgical cutting of a bone for the purposes of shortening, lengthening or changing its alignment (168). Osteotomy corrections are a unique form of surgical intervention for KOA, as they are classified as an extra-articular procedure, unlike the previously mentioned techniques, which are all intra-articular. This means that the walls of the synovial cavity are not breached, and the entire procedure occurs outside of the knee joint. Osteotomies aim to realign the positioning of the ankle relative to the hip and knee, such that WB through the knee is shifted from the arthritic compartment to the more-preserved compartment. The typical indications for an osteotomy correction of VV malalignment with UKOA are younger individuals (<65) with moderate UKOA (Kellgren-Lawrence Grade ≤3), good ROM (~100°), a body-mass index (BMI) <30 and an active lifestyle (35). Contraindications include a flexion contracture/recurvatum of >10° and bicompartmental/tricompartmental KOA (169). Age and weight are often the two most flexible factors when determining suitability for an osteotomy over an arthroplasty, as individuals aged >65 or with a BMI >30 can still have successful outcomes from the procedure (170).

2.5.1 High tibial osteotomy (HTO)

The HTO (also referred to as proximal tibial osteotomy/superior tibial osteotomy) is the realignment procedure typically used to treat medial KOA with varus deformity (171). It involves making an incomplete cut through the medial aspect of the superior tibia towards the lateral cortex near the fibular head (Figure 2.7), spreading the cut to form an opening-wedge, and securing the wedge with hardware and bone grafting (Figure 2.8). By doing this, the position of the ankle relative to the knee is altered, changing the alignment of the lower-limb (visible in Figure 2.9), and shifting WB from the osteoarthritic medial compartment to the more-preserved lateral compartment. Thus, pain is hoped to be alleviated and QoL improved. HTO can also be performed using a closing-wedge on the lateral side, but it is most commonly performed on the medial aspect of the superior tibia as an opening-wedge osteotomy (64), and the rationale for this will be detailed

in Sub-Section 2.7.1. Patient outcomes following HTO have been subject to controversy over recent decades, with topics such as the ideal HKA correction angle, location of the osteotomy, surgical technique and internal fixation types all being suggested to influence the success of the procedure – these are discussed in more detail in the following Sections.

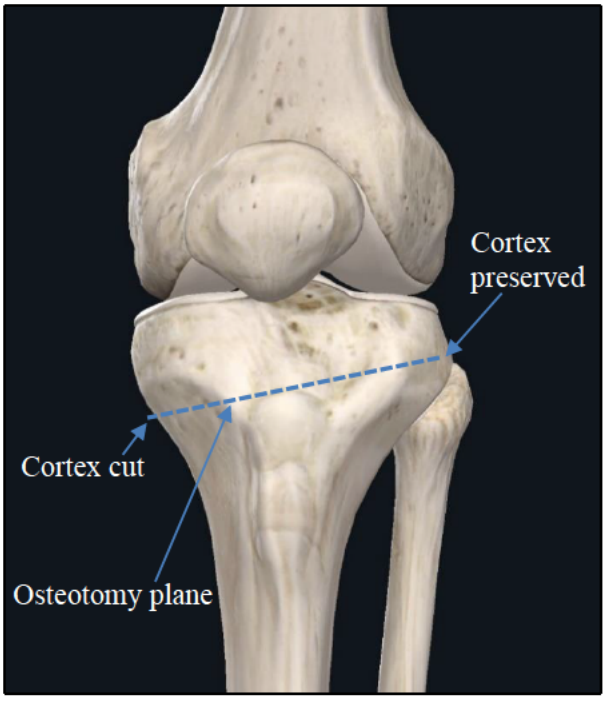


Figure 2.7 3D model of high tibial osteotomy positioning before wedge opening
Model from Complete Anatomy 2021 (3D4Medical, Dublin, Ireland)

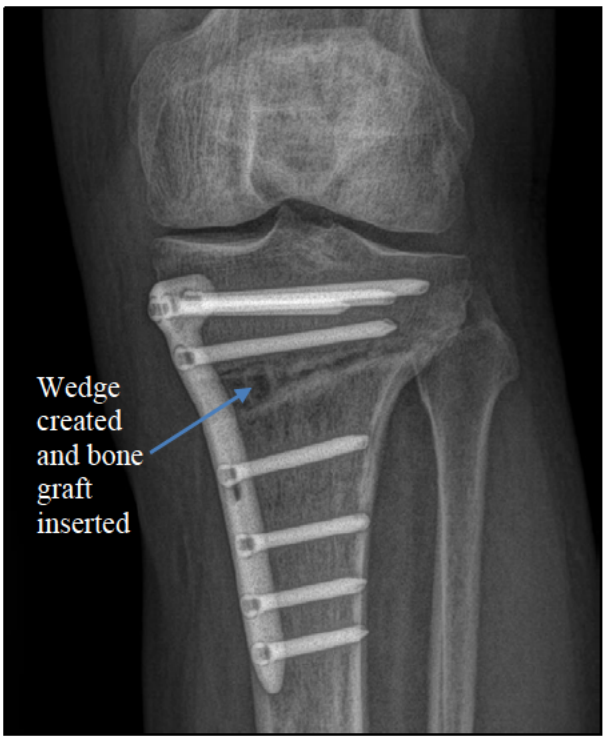


Figure 2.8 High tibial osteotomy radiograph with internal fixation

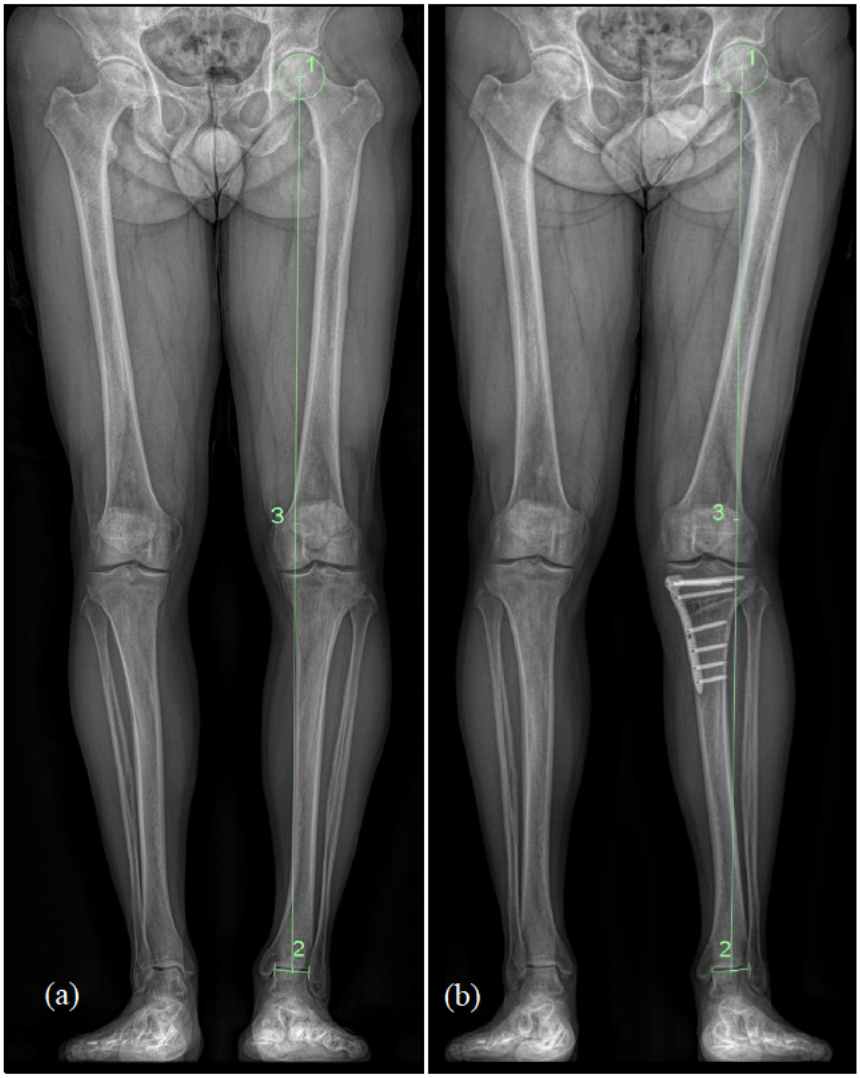


Figure 2.9 Pre-op versus post-op mechanical axes after high tibial osteotomy
(a) Pre-operative varus malalignment with the mechanical axis passing through the medial compartment versus **(b)** post-operative valgus alignment with the mechanical axis repositioned to pass through the lateral compartment

2.5.2 Distal femoral osteotomy (DFO)

As an opposite to HTO, the DFO is most commonly used to treat lateral KOA with valgus deformity (172). An incomplete cut is made at the lateral aspect of the distal femur towards the adductor tubercle (Figure 2.10), followed by forming an opening-wedge, inserting a bone graft and internally fixating the realignment (Figure 2.11). The procedure aims to change the position of the ankle relative to the knee (Figure 2.12), such that WB through the knee is shifted to the medial compartment away from the osteoarthritic lateral compartment (172). In modern orthopaedics, the DFO is typically performed on the lateral aspect of the distal femur as an opening-wedge osteotomy, but can also take the form of a closing-wedge at the medial aspect of the distal femur (173). The internal fixation used in DFO is different in shape and screw length compared to that used in HTO to accommodate the morphology of the distal femur.

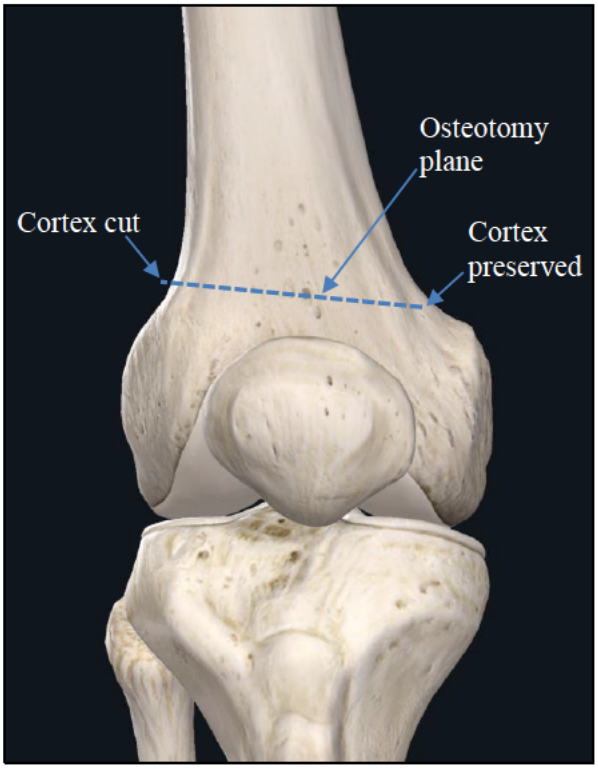


Figure 2.10 3D model of distal femoral osteotomy positioning before wedge opening Model from Complete Anatomy 2021

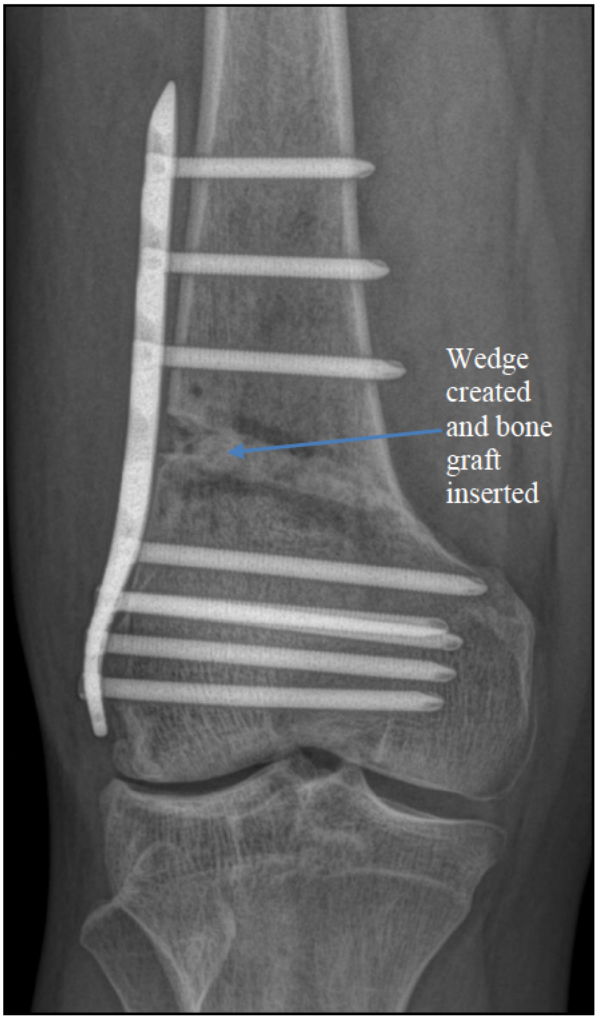


Figure 2.11 Distal femoral osteotomy radiograph with internal fixation

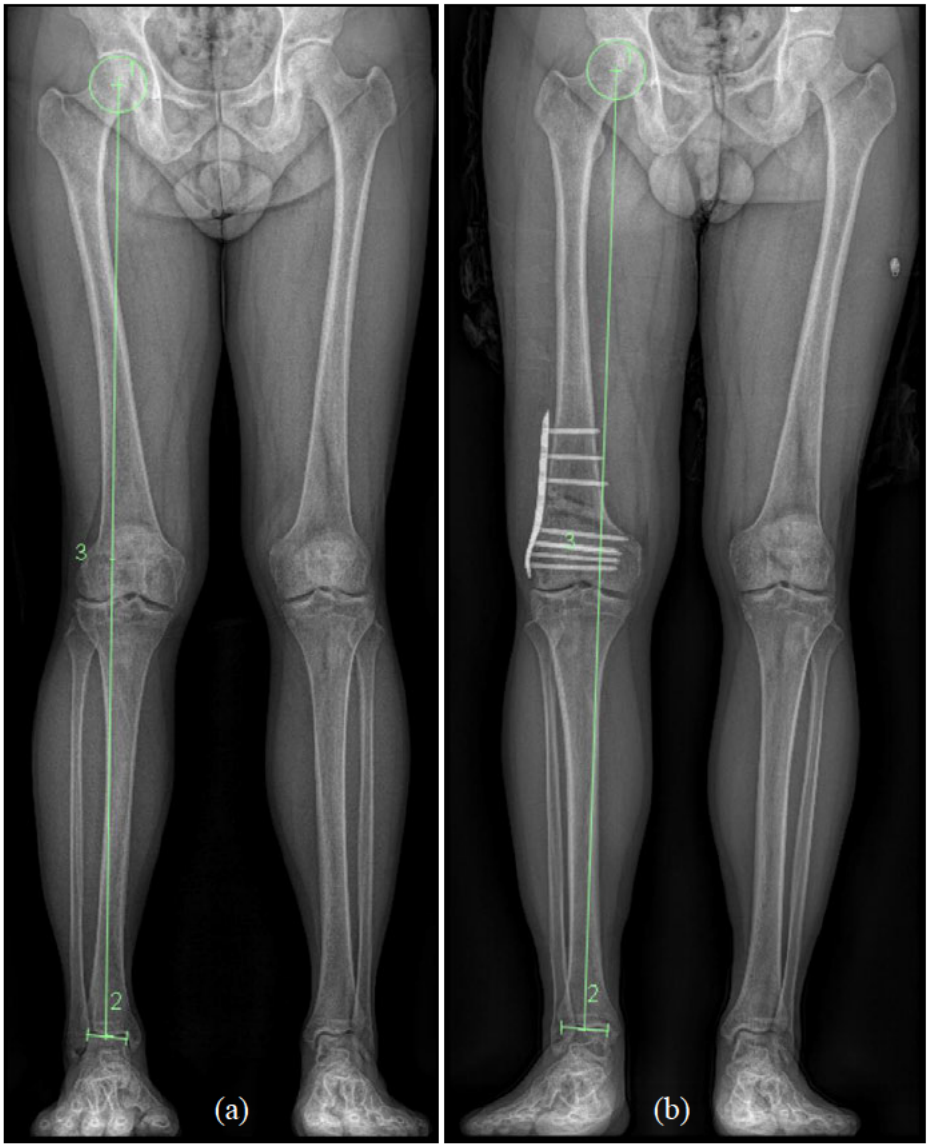


Figure 2.12 Pre-op versus post-op mechanical axes after distal femoral osteotomy
(a) Pre-operative valgus malalignment with the mechanical axis passing through the lateral compartment versus **(b)** post-operative varus alignment with the mechanical axis repositioned to pass through the medial compartment

Table 2.3 Surgical knee osteoarthritis treatments

Surgical treatment				
Treatment name	**Original report as osteoarthritis treatment**	**Benefits**	**Limitations**	**Time before symptom relief**
Arthroscopic debridement and lavage	1931 (174)	Removes potential sources of irritation and returns synovial cavity to homeostasis (146, 147)	Mostly palliative, with presence of osteoarthritis likely to reverse benefits of the procedure in months/years (148)	~6 weeks (175)
Microfracture	1980 (149)	Preserves the natural architecture of the joint and uniquely targets regeneration of cartilage, unlike most other conservative and surgical treatments (150)	Requires very specific indications for surgery that excludes a large proportion of osteoarthritis patients (176)	>8 weeks (150)
High tibial osteotomy (HTO) or Distal femoral osteotomy (DFO)	1961 (16)	Preserves the natural joint, enables high-impact physical activities and can delay the need for total knee replacement (TKR) by >15 years (35).	High planning and surgical complexity, and an increased risk of revision TKR following HTO/DFO (177)	>8 weeks (178)
Unicompartmental knee replacement (UKR)	1982 (179)	Replaces osteoarthritic compartment but preserves half of the natural knee to maintain relatively normal knee feeling and function (153)	Reported five times greater risk of revision UKR compared to revision TKR (157), with revision UKR having worse outcomes than primary total knee replacement (158)	~6 weeks (180)
TKR	1968 (161)	Removes all osteoarthritic articular bone and can provide 10 to 20 years of improved knee function (162, 163)	Has a dissatisfaction rate of 25% (164) and entirely removes the natural architecture of the joint (160)	~6 weeks (181)

2.6 SURGICAL CORRECTION TARGET

The optimal HKA to achieve post-operatively for positive long-term patient outcome has been a controversial topic since Jackson first published his results of 10 tibial osteotomy procedures for varus and valgus correction in 1961 (16). He stated in this paper that the intra-operative aim was for the leg to 'look straight', with the hope of restoring a 180º HKA to match the MA of the lower limb. This highlights the arbitrary nature of early osteotomy corrections with minimal pre-operative planning and intra-operative assurance of correction accuracy. Despite this, all patients reported that their pain had significantly or entirely reduced at 6–72-months follow-up, which may suggest even slight unloading of the osteoarthritic compartment can provide alleviation of pain for a substantial time period. Understandably, this is a primitive example of osteotomy findings in comparison to contemporary evidence, but it serves as a baseline indicator of the capability of the procedure to improve UKOA symptoms.

Fujisawa published an arthroscopic study of 54 patients in 1979 that identified individuals with varus deformity and medial compartment OA whose MA was corrected to approximately 62.5% of the tibial plateau width (TPW) (concept shown in Figure 3.1) through a valgising HTO demonstrated cartilage regeneration in the medial compartment between 1 and 2 years post-op (17). This was a promising finding that indicated reversibility of OA pathophysiology and potential for a more positive prognosis of UKOA through an unloading osteotomy. However, it was unclear whether similar findings had been achieved at alternative MA locations across the TPW, and more studies were needed to confirm intra-articular changes following various degrees of correction to confirm the superiority of a post-operative MA located at 62.5% TPW (approximately 3–6º valgus) – later termed the Fujisawa point.

Naturally, advancements in osteotomy research in the form of larger sample sizes and longer follow-up occurred in the decade following Fujisawa's findings, of which Hernigou et al. reported on a 93-person cohort who underwent HTO for varus correction (18). This cohort all underwent valgising HTO with the aim of achieving 3–6º valgus post-operatively. With an average follow-up of 11.5 years, the results of this study showed that most individuals who were under-corrected (<3º valgus) showed progression of their medial compartment OA and had worse long-term outcomes. Contrastingly, the individuals who were overcorrected (>6º valgus) all developed lateral compartment OA after approximately 5 years. Finally, the 20 individuals who achieved the intended 3–6º valgus claimed no progression of medial symptoms nor developed lateral symptoms, suggesting this approach could give the best long-term patient outcome. This study also corroborated the findings of Brinkman et al. 6 years prior, which concluded that failure to meet the intended post-operative HKA was the most common determinant of poor patient outcome (45).

Emphasising accuracy at all stages of osteotomy planning and execution was the conclusion from Hernigou et al.'s study.

More recent literature shows that the concepts formed in the previous studies have maintained their relevance in modern osteotomy procedures, except for some contrasting suggestions from different authors. The method described by Fujisawa – shifting the mechanical axis to 62.5% of the total TPW – is still employed by many surgeons across the world. A 2021 systematic review by Tawy et al. analysed 39 studies from 2005 to 2019 where the Fujisawa point was targeted (182). This study observed 4 patient-reported outcome measures (PROMs) – explained in Section 2.10 – that are commonly used to determine patient outcome in the orthopaedics field, and analysed the correlation between these PROMs and post-operative HKA correction accuracy. The visual analogue scale (VAS) score, Oxford Knee Score (OKS), Knee Osteoarthritis Outcome Score (KOOS) and EQ-5D improved significantly post-operatively, despite inconsistent surgical accuracy with an average post-op alignment of 2.3º ± 1.7 valgus. Hence, Tawy et al.'s serendipitous finding was that the supposed 3–6º valgus needed for optimal patient outcome may indeed be more forgiving after seeing positive results from valgus outside of the traditional values. This study also highlighted the frequency of under-correction in HTO, which could be a source of unfavourable outcomes or revision surgery in extreme cases.

As a middle ground to the aforementioned studies, some authors have suggested the MA should cross at 55% of TPW due to providing sufficient medial unloading and avoiding lateral overloading, combining to supposedly give the best long-term outcome (183-185). Van Genechten et al. commented on these papers in 2020, advocating a multifactorial approach for determining the degree of correction (41). Van Genechten et al. suggested OA severity, other knee pathologies, pre-operative malalignment and the contralateral limb should be factors in determining a patient-specific post-operative alignment target. He also suggested that greater consideration should be given to the mechanical medial proximal tibial angle (mMTPA) and mechanical lateral distal femoral angle (mLDFA), as well as the joint line convergence angle (JLCA) – all displayed in Sub-Section 3.2.4 – as these can play a role in determining the force distribution through the knee joint (20, 48, 186). This is a non-exhaustive list of examples that have led to the outdating of a fixed alignment target in knee osteotomy procedures, and allows surgeons to customise their surgery to match each unique case.

Upon reviewing the literature, it is evident that the degree of correction can be an individualistic consideration, determined by patient demographics and pathology. Hence, tailoring the correction angle in HTO/DFO to the needs of each patient has become normalised and aims to maximise the benefits from the procedures. Another debate relevant to this is the HTO/DFO techniques that facilitate the most safe and accurate corrections, which will be discussed in the following Section.

2.7 OSTEOTOMY TYPES AND SURGICAL TECHNIQUES

Whilst the general concept behind all varising or valgising osteotomies around the knee is the same, there are various intra-operative techniques for achieving the desired correction. However, for reasons of complication rates, procedure complexity, biomechanical consequences, long-term survival and reported surgical accuracy, there has been a movement towards using opening-wedges in HTO/DFO surgeries, especially over the last two decades.

2.7.1 Movement from closing-wedge to opening-wedge and consideration of osteotomy location

Several decades ago, the closing-wedge was considered the most popular approach for HTO/DFO procedures (187). As the name suggests, it involves making two cuts to create a wedge, followed by closing of the wedge to alter alignment and internal fixation for stability during bone healing. An obvious advantage of this technique is the absence of bone grafting, which simplifies the procedure compared to an opening-wedge – where invasiveness of autografts or potential rejection of allografts are immediate disadvantages (188). In addition, closing-wedges have been suggested to have lower early complication rates compared to opening-wedges according to Duivenvoorden et al. in 2014 (189). Their study showed lower rates of wound infection, non-union, tibial plateau fracture and under-correction in closing-wedge procedures compared to opening-wedges. However, the same study revealed a 21% conversion to TKR following closing-wedge HTO compared to 6% in opening-wedge over a 6-year period in the cohorts of 47 and 45 patients, respectively. This indicates closing-wedges may be the inferior approach for long-term patient outcome, but may cause less complications intra-operatively and within 12 months post-op.

Even if this was statistically evident, there are some severe complications associated with a closing-wedge approach on the lateral aspect of the tibia. Palsy of the peroneal nerve occurred in 1 participant in Duivenvoorden et al.'s closing-wedge cohort, which is a form of potentially irreversible and disabling complication that can be mitigated by changing the location of the osteotomy to the medial aspect of the tibia and using an opening-wedge approach (190). Another disadvantage of closing wedges in the tibia for varus correction is the presence of the fibula on the

lateral side. This inevitably means that the fibula must undergo shortening to match the alteration to the tibia, with failure to execute this accurately being a potential source of complications. Performing a simultaneous osteotomy of the fibula also means the chances of complications are increased due to more osteotomies and complexity of osteosynthesis positioning (191). This increased post-operative morbidity may also reduce mobility in patients and predispose them to development of deep vein thrombosis (192). For these reasons, closing-wedges appear far less common in the interest of avoiding severe complications and maximising procedure survival.

2.7.2 Manual/conventional osteotomy

Conducting HTO/DFO using a manual approach (also referred to as the 'conventional' approach) was the initial technique used in knee realignment osteotomies (16). As the name suggests, the manual technique relies heavily on the pre-operative planning and employs a 'freehand' approach to correcting the alignment of the limb based on the planned osteotomy location and wedge dimensions (48) – explained in Sub-Section 3.1.1. Hence, the image intensifier (II) is used for locating the surgical site and monitoring the accuracy of each stage of the procedure, with the diathermy cable or lead-impregnated grid line methods often used to confirm the repositioned WBL intra-operatively (193). The internal fixation is then positioned based on the decision of the surgeon. This technique can be performed accurately, but systematic review of the literature has demonstrated reduced consistency of manual HTO in achieving the planned post-operative alignment in both the coronal and sagittal planes, when compared to alternative techniques (194). Contemporary literature comparing manual HTO/DFO to other surgical techniques is becoming sparse, likely due to a reducing number of surgeons using the manual method in high-volume centres. Despite technological advancement over recent decades to improve surgical accuracy/consistency and reduce complications, the manual technique is still used by some surgeons due to preference, reluctancy to adopt new technology or financial circumstances of their surgical facility. However, manually performing HTO/DFO is likely to be progressively phased out as a new generation of surgeons and research can rationalise an increased transition to computer-assisted/navigated surgery or patient-specific instruments – explained in the following Sub-Sections – that may allow better surgical accuracy and patient outcome.

2.7.3 Navigated/computer-assisted osteotomy

Navigated/computer-assisted osteotomy was a significant advancement from the manual technique. It involves the use of intracortical pins housing spherical optical targets that are inserted percutaneously to the femur and tibia, which are calibrated using infrared sensors to register the location of the limb/s in three-dimensional (3D) space (195). Thus, the degree of surgical correction and final limb alignment in the coronal, sagittal and axial planes can be measured continuously throughout the procedure. This provides a significant advantage over conventional intra-operative measurement methods using 2D fluoroscopic images to determine accuracy, which are only momentary single-plane indications of alignment that are subject to parallax error (196). An obvious disadvantage of percutaneous intracortical fixation of hardware is the increased invasiveness and surgery-associated morbidity, albeit minor. The first study to identify the navigation method as providing increased accuracy to conventional methods was published in 2005 by Saragaglia et al. (196). This case-controlled study of 28 navigated and conventional surgeries found 96% of navigated procedures resulted in ±2° of the targeted post-operative alignment compared to only 71% in the conventional group. Many studies have since corroborated the findings of Saragaglia et al. and have reinforced the benefit of navigated osteotomies compared to the conventional approach.

The most recent and comprehensive study comparing these techniques appears to be the 2016 systematic review by Yan et al., where 34 studies from 2005 to 2016 comparing navigated and conventional opening-wedge HTO accuracy and PROM data were collated (197). Across a total of 1608 navigated and 608 conventional HTO surgeries, navigated osteotomies showed more statistically accurate correction for HKA and tibial slope. Whilst there was also an improvement in PROM data for the navigated group, this difference was not statistically significant, which may demonstrate the heterogeneity in PROM outcomes depending on pre-operative condition and patient expectation (198). Furthermore, the mean procedure time was increased by approximately 10 minutes in the navigation group compared to the conventional group due to equipment setup and calibration, which is a minor disadvantage with navigation. These points aside, the increased accuracy seen in the navigation group suggests navigation has strong potential to reduce the incidence of over or under-correction, which may prevent revision or rapid conversion to TKR.

2.7.4 Patient-specific instrument osteotomy

As evidenced throughout the literature review so far, all aspects of HTO/DFO require precision in order to be effective, and the margin for error is minimal (199). The osteotomy, as well as drilling holes for screw insertion and internal fixation need to be executed accurately for the patient to have the best chance of a successful outcome. Hence, patient-specific instruments (PSI) aim to improve the accuracy and reliability of the procedure whilst reducing the operative time and complication rates (20). PSI are 3D-printed surgical guides that are manufactured for each patient based on computer-aided design (CAD) modelling of the patient's anatomy from a high-resolution computed tomography (CT) scan (19). The details of how PSI are constructed and used intra-operatively are covered in the 'Materials and Methods' Chapter – Sub-Section 3.1.2 and 3.1.3, but an example of PSI is presented below in Figure 2.13.

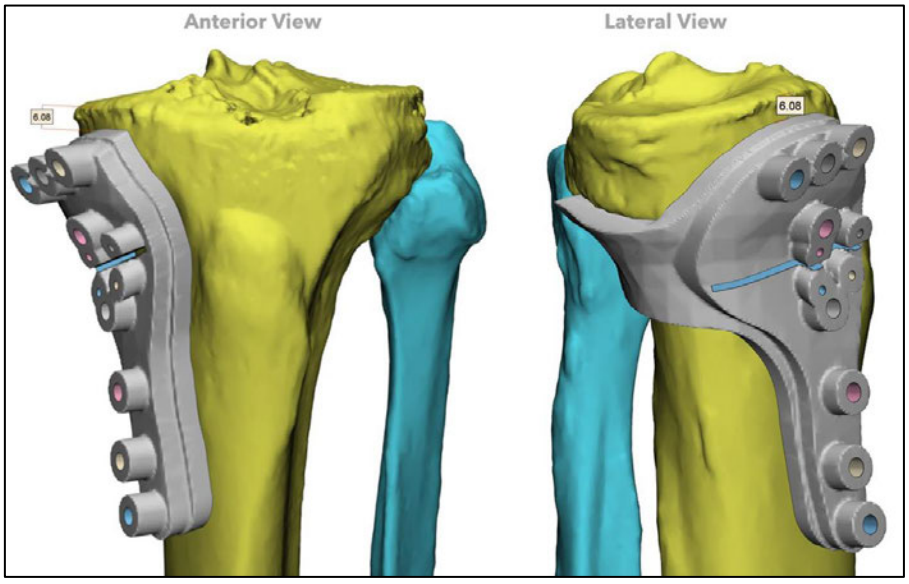


Figure 2.13 Example of patient-specific instruments in high tibial osteotomy
Patient-specific instruments (PSI) are visible in grey, where holes represent drilling/screw insertion and the slot is the osteotomy location

The use of PSI was first pioneered in maxillofacial surgery in 2003 (200). PSI were then used in orthopaedics, first in trauma (201) and spine (202) surgery, then upper limb osteotomies in 2008 (203) and hip arthroplasty in 2010 (204). Billings et al. 2000 could be classified as the first use of surgical guides for osteotomy procedures (205), but this represents a primitive example of the concept. Finally, contemporary PSI were proven as a feasible concept for knee osteotomies in 2013 as the first primary research publication on a patient cohort (19).

Given the novelty of the technique, a thorough systematic search of Google Scholar, PubMed and Macquarie University's institutional proxy server was conducted in May 2021 by HW and SM, identifying 14 primary research articles – summarised in Table 2.4 – investigating the use of PSI in HTO or DFO procedures, including the initial proof-of-concept in 2013.

Table 2.4 Study information of patient-specific instrument osteotomy articles

Author	**Year**	**Country**	**Knees**	**% Male**	**Mean age**	**Mean patient BMI**	**Internal fixation**	**Bone void filler**	**Mean accuracy error (mean ± SD, unless otherwise indicated)**	**Complications**
Victor and Premanathan (19)	2013	Belgium	14	57	44	N/A	TomoFix	None	HKA 0.3° ± 0.75	1 delayed union in smoker
Perez-Mananes et al. (206)	2016	Spain	8	N/A	44	N/A	TomoFix	Autograft	HKA 0.5° (range 0-1.2°)	None
Arnal-Burro et al. (173)	2017	Spain	12	35	44	N/A	TomoFix	Autograft	HKA 0.28° (range 0-1°)	N/A
Munier et al. (207)	2017	France	10	N/A	46	29	Activmotion	Synthetic	HKA 0.12° (range -1.7–1.8°)	1 haematoma
Yang et al. (208)	2018	Taiwan	10	40	67	N/A	TomoFix	None	WBL 4.90%	None
Chaouche et al. (40)	2019	France	100	59	44	N/A	Activmotion	None, allograft or synthetic	HKA 1° ± 0.9	18 minor hinge fractures, 9 haematomas, 2 graft osteolysis, 6 major hinge fractures, 3

Author	Year	Country	Knees	% Male	Mean age	Mean patient BMI	Internal fixation	Bone void filler	Mean accuracy error (mean ± SD, unless otherwise indicated)	Complications
										wound infections, 1 non-union
Jacquet et al. (209)	2019	France	21	38	45	24	Activmotion	Allograft or synthetic	HKA 0.43° ± 0.50	None
Shi et al. (210)*	2019	China	12	33	44	24	Best® locked conformed plate	None	WBL 4.90% (range 2-11%)	N/A
Fucentese et al. (211)	2020	Switzerland	23	70	45	31	TomoFix	None	HKA 0.8° ± 1.5	2 impaired wound healing, 1 infection
Jacquet et al. (212)	2020	France	71	44	44	N/A	Activmotion	Synthetic	HKA 1.0° ± 1.0	N/A
Mao et al. (48)	2020	China	18	22	44	26	N/A	Allograft (autograft for wedge openings >10mm)	mFTA 0.2° ± 0.6	1 DVT, 1 infection

Author	Year	Country	Knees	% Male	Mean age	Mean patient BMI	Internal fixation	Bone void filler	Mean accuracy error (mean ± SD, unless otherwise indicated)	Complications
Van Genechten et al. (41)	2020	Belgium	10	60	47	N/A	TomoFix	Allograft	mFTA 0.9° ± 0.6	1 minor and 1 major hinge fracture
Predescu et al. (213)	2021	Romania	25	N/A	N/A	N/A	Activmotion	3 synthetic, 7 no void filler	HKA all within ±2° of plan	2 major hinge fractures, 1 delayed union in smoker
Savov et al. (214)	2021	Germany	19	68	43	N/A	Activmotion	None	HKA 1.45° ± 1.16	None

Abbreviations: N/A = variable not found in study, HKA = hip-knee-ankle angle, SD = standard deviation, WBL = weight-bearing line (mechanical axis position along tibial plateau width), BMI = body mass index, * = closing-wedge technique analysed in study, DVT = deep vein thrombosis, mFTA = mechanical femorotibial angle (uses mechanical axes of the femur and tibia to measure alignment, as opposed to HKA which uses centres of the hip, knee and ankle)

Across the studies presented in Table 2.4, it can be observed that majority of the coronal plane correction accuracy using PSI in HTO/DFO falls within ±2° of the planned correction. Van Genechten et al. supported this finding, suggesting that 'good' accuracy can be classified as ±2° from the planned correction and 'excellent' accuracy as ±1.5° (41). It also appears that over-corrections are more common than under-corrections in the Table 2.4 studies, which is a questionable finding as we identified one study that reported both over and under-corrections as positive values instead of negative values for under-corrections. It could not be determined whether the same misleading data presentation was in other studies from Table 2.4 due to the omission of a case-by-case display of pre/target/post-op data.

Regarding accuracy, a computer-simulated study by Jud et al. showed that mal-positioning of the PSI intra-operatively may have minimal effect on the coronal accuracy of the procedure (215), which may strengthen the rationale for PSI use. Of course, the applicability of these findings to in vivo surgeries cannot be guaranteed due to the computerised nature of Jud et al.'s study, but the mathematics of the study should be theoretically generalisable, depending on the morphology of the bone and design of the PSI. The sagittal plane was suggested to be the more sensitive to change as a result of incorrect PSI positioning, which stresses the importance of correct positioning to avoid iatrogenic change to the tibial slope.

Aside from enhanced correction accuracy, other potential benefits of PSI use were identified by authors in Table 2.4. In relation to operative time, Perez-Mananes et al. found that operative time was reduced by 33% using PSI compared to those using the conventional method (206). In addition, they recorded 6.9 times less intra-operative fluoroscopy use in the PSI group compared to the conventional. Arnal-Burro et al. found PSI surgeries to be 32 minutes shorter and use 59 less fluoroscopic images (173). Shi et al. found PSI surgeries to be approximately 19 minutes shorter and use 80% less fluoroscopic images compared to a conventional group (210). Mao et al.'s PSI cohort had 17-minute shorter surgeries with around 3 times less fluoroscopic exposure compared to a conventional group (48). Jacquet el al. suggest that after a learning curve of approximately 10 and 9 surgeries using PSI, the operative time and fluoroscopic use, respectively, can be progressively reduced (212). It should be kept in-mind that Savov et al. demonstrated reducing fluoroscopic use too far can lead to decreased accuracy due to fluoroscopy being important for monitoring stages of the procedure, which may suggest a minimum amount of fluoroscopy use per surgery (214). Nevertheless, reduced general anaesthetic and radiation exposure to the patient is a clear benefit of PSI use. Finally, Arnal-Burro et al. identified that the cost of surgery was €412 less in a PSI group compared to a conventional group (173), but this may vary greatly between centres depending on their logistics. Variation aside, cost is a worthy consideration to justify a transition to PSI use in surgical centres with lower financial capacity.

Intra and peri-operative complications in HTO/DFO surgeries have remained a concern for patient and surgeon alike throughout the lifespan of the procedure. Hinge fracture has been reported as the most common complication of opening-wedge HTO in numerous studies (40, 213, 216-219), and is an ongoing complication seen with PSI use, as evidenced in Table 2.4. Whilst PSI do aim to prevent hinge fractures by controlling the depth and orientation of the bone saw, hinge fractures can still occur during passive varisation/valgisation by the surgical team, while using osteotomes or during post-operative weight-bearing. Hence, such complications are only intra-operatively mitigated using PSI. Han et al. studied the 'safe zone' for avoiding hinge fractures in cadaveric specimen (220), which provided recommendation for the positioning of the osteotomy to avoid hinge fractures. All other HTO/DFO-associated complications such as DVT, infections or non/malunion, should remain unaffected by PSI use.

Tampere et al.'s 2018 review commented on the lack of homogeneity in PSI HTO/DFO studies in terms of their outcome data (49). We also noticed this throughout our literature search, observable in HKA, mechanical femorotibial angle (mFTA) and weight-bearing line (WBL) measurements used by different authors for pre-operative planning and determination of accuracy. Although the overall findings of these studies can be understood, different metrics make systematic review and corroboration of findings difficult. Understandably, different surgeons are used to various pre-operative planning/measurement methods, and if surgical accuracy is consistent, there is no need for change. However, metrical uniformity throughout the literature would be an improvement to the HTO/DFO research sphere.

2.8 OSTEOTOMY INTERNAL FIXATION AND BONE VOID FILLERS

There is a plethora of internal fixation options available for HTO/DFO surgeries, which range in size, shape and screw mechanism. Recent systematic review of 7 HTO internal fixation plate models was conducted by Diffo Kaze et al., concluding that T-shaped plates with wider proximal ends positioned on the anteromedial aspect of the tibia provide the best mechanical strength and post-operative stability (221). Hence, plates such as the TomoFix Medial High Tibial Plate (Depuy Synthes, MA, USA) are ideal for use in HTO procedures. It appears that similar investigation of DFO internal fixation has not been conducted, but the concepts identified in Diffo Kaze's study are likely translatable to femoral anatomy, except for the standard positioning of the plate on the lateral aspect.

It should be noted here that hardware irritation is common in opening-wedge osteotomy patients, often resulting in early hardware removal once bone healing is complete (222, 223). Of course, treating the KOA symptomatology and malalignment is the primary goal of the procedures, but avoidance of hardware irritation is ideal. With this in-mind, thinner plates have been shown to

reduce early hardware removal frequency (224), which is a worthy consideration for manufacturers, as well as surgeons when selecting hardware to be used for each patient.

Opening-wedge bone void filling in HTO/DFO, or lack thereof, has also received attention across recent years. Slevin et al. systematically reviewed this topic in 2016 (225). Their study analysed the difference between autograft, allograft, synthetic bone substitute or no void filler on the bone union rates across 1421 surgeries in 22 articles. Whilst it was concluded that no significant advantage is offered by any void-filling choice, it was clear that autografts performed better than allografts in terms of bone union and maintenance of the correction. Furthermore, autografts and allografts performed better than synthetic bone substitute. It was also identified that opening-wedge gaps of less than 10 mm can successfully heal without the use of a void filler, but healing times may increase with bigger wedge sizes, and wedge gaps more than 14 mm are recommended to involve a void filler to minimise chances of non-union.

2.9 THE RELATIONSHIP BETWEEN LOWER-LIMB ANATOMY AND PELVIC/SPINAL ALIGNMENT

Since the pelvis and spine sit upon the lower limbs, it is logical that lower limb deformity can have a collateral effect on pelvic and spinal alignment in all three planes that may cause pathology if unaddressed.

Regarding coronal plane considerations, a functional leg length discrepancy (LLD) of any magnitude will inevitably change the force distribution through the acetabulofemoral joints in a neutral weight-bearing stance i.e. the longer leg will absorb more force through the hip (226). Consequently, there will be an increased risk of osteoarthritic changes in the hip joint over time, with a tendency to push the pelvis into an oblique position (227). As a consequence of pelvic obliquity, lumbar scoliosis can be a compensatory mechanism to facilitate even weight distribution through the left and right halves of the body (228). Uneven load distribution through the intervertebral discs is a consequence of scoliosis, which may predispose individuals to disc herniation or lateral OA of the vertebrae (229). A dedicated review by Murray et al. in 2015 on the interrelatedness between LLD and OA of the knee, hip and spine attempted to clarify this relationship (27). They concluded that a sufficient amount of literature exists on the link between LLD and KOA, with less literature, surprisingly, on the link between LLD and hip OA. It was also evident that limited experimental attention has been given to the relationship of LLD and OA in the intervertebral discs and facet joints. Hence, ongoing longitudinal research is needed to objectify these relationships amongst various population groups. For these reasons, more attention should be given to LLD in HTO/DFO studies, and this can be rationalised by the apparent changes in functional leg length (FLL) that were identified in a 2019 systematic review and meta-analysis

of opening and closing-wedge osteotomies by Lee et al. (230). This study analysed 125 opening and 175 closing-wedge osteotomies, identifying an average FLL change of 6.96 mm and -1.95 mm, respectively. The degree of HKA correction was correlated with the increase/decrease in FLL, but closing-wedges appeared to elicit a smaller change in FLL than the 'clinically concerning' difference observed in opening-wedges. To avoid iatrogenic development of pelvic/spinal malalignment following any form of opening or closing-wedge osteotomy in the tibia or femur, pre-operative alignment measurements and detailed planning/execution should be ensured such that pathological change to FLL is minimised post-operatively.

For sagittal plane considerations, knee flexion angle (KFA) and tibial slope (TS) are two related lower-limb parameters that can subsequently affect sagittal pelvic and spinal alignment. The concept of knee-spine syndrome explains the relationship between KFA and lumbar lordosis (LL) angle, detailed by Murata et al. in 2003 (22). This paper showed that an increase in knee flexion had a correlation with reduced LL, leading to elevated pressure on the anterior surface of the intervertebral discs. Similarly, increased sacral slope (SS) has also been shown to correlate with reduced LL (231). Continuing from this, recent studies have demonstrated that higher TS is known to cause individuals to develop a decreased KFA due to the alteration of the tibial plateau's orientation relative to the ground – termed the 'parallel mechanism' (232). Described by Mochizuki et al., this biomechanical phenomenon explains that compensatory changes may occur superiorly and inferiorly to the knee to maintain ambulatory balance in the case of an increased TS. Furthermore, increased TS has been shown by Brandon et al. to increase the incidence of anterior cruciate ligament (ACL) rupture due to the tibia having a greater tendency to slide anteriorly during ambulation, placing more tensile stress on the ACL (233). The results of this study were that ACL-insufficient males and females both had a significantly increased TS than healthy controls with intact ACL architecture. Hence, during HTO procedures, it is crucial that the TS remains unchanged, or that any deliberate change does not negatively impact the biomechanics of the patient or predispose them to ligamentous damage during physical activity. It should be noted here that a flexion contracture more than 10–15° has been established as a contraindication to HTO procedures, as post-operative function and outcome is likely to be poor (169).

Despite a wide range of evidence on lower-limb anatomy setting the foundation for normal pelvic/spinal alignment, to our knowledge, only one study has been published on the effects of HTO on pelvic/spinal changes. Conducted by Kim et al. in 2016 (29), their study looked at the gait patterns of an HTO cohort 1-week before and 1-year after surgery compared to healthy controls. All pelvic and spinal parameters improved post-operatively towards the healthy control group, suggesting that restoration of lower-limb alignment can provide benefits to individuals beyond the immediate aims of the surgery. Hence, it is important to expand on these findings by assessing the

reliability of results across different research methods, and determining whether the same effect will apply to DFO procedures as well.

2.10 PATIENT-REPORTED OUTCOME MEASURES

Patient-reported outcome measures (PROMs) are short questionnaires given to individuals in a clinical or research setting that aim to acquire data on their physical function and QoL relating to specific symptomatology and/or general life (234-236). In the case of surgical intervention, these questionnaires are often given to the patient during pre-operative clinical consultation and/or post-operatively – either as a one-time completion or repeated during longitudinal investigation (237). PROMs are particularly valuable when used alongside surgeries that have specific pre-operatively planned targets (such as HTO/DFO), as the accuracy of the procedures can be correlated with the outcome scores of completed PROMs to determine if surgical accuracy can predict outcome. Knee research utilises a plethora of PROMs that all have their own strengths and limitations regarding their question diversity and response type e.g. written or Likert scale responses (238, 239). PROMs that cover a wide range of the health dimensions - such as physical, social and emotional – offer the most value from a research perspective, as they allow a deeper understanding of the patient beyond simply physical symptoms. This can give insight regarding certain responses in the questionnaires, such as the presence of psychological comorbidities having an influence on patient expectation (239). Hence, we reviewed the literature to select a PROM set suitable for use in our HTO/DFO clinical study.

A 2021 systematic review by Tawy et al. on the correlation between HTO accuracy and knee-related PROMs served as a starting point for understanding the contemporary use of PROMs in knee osteotomy research (182). Out of 39 studies included in the review, 22 studies used the Visual Analogue Scale (VAS), 10 used the Knee Injury and Osteoarthritis Outcome Score (KOOS), and 9 used the Oxford Knee Score (OKS). The VAS is a simplistic 0 to 10 Likert scale PROM on the level of pain experienced over a certain timeframe or at the time of questionnaire completion (240). Despite its popularity, the VAS only gives an indication of overall pain symptomatology, omitting investigation of any activity-dependent fluctuation in pain. Shorter PROMs like this have been suggested as favourable due to eliminating the risk of respondent fatigue (241), but the VAS offers very restricted research value. The KOOS (242), however, is a comprehensive 42-item Likert scale PROM that covers 5 domains of patient health – pain, symptoms, activities of daily living, sport and recreation function and knee-related QoL. It was initially validated from cohorts undergoing surgical procedures for knee pain (243), meaning the KOOS is highly suited for use in clinical studies on surgical outcomes. The OKS is another evidently popular PROM used in knee osteotomy research (244). The 12-item Likert scale form is

answered based on the patient's experience in the four weeks prior to completion. Whilst this does offer more research value than the VAS, it only involves a limited timeframe that is considered in responses. The questions also do not take into account lifestyle modifications that the patient may have made in order to avoid symptom exacerbation (245). For these reasons, the KOOS appears to provide the most research value from the PROMs covered in Tawy et al.'s systematic review. A limitation of this paper is that only United Kingdom Knee Osteotomy Registry-recommended PROMs were considered for inclusion, excluding other PROMs commonly used in orthopaedic research.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is another PROM commonly utilised throughout the literature (246). The KOOS was developed as an extended version of the WOMAC, meaning the entire 17-item WOMAC is situated within the KOOS question set in the same 0 to 4 Likert scale format. The aim of extending the WOMAC was to increase the question diversity and timeframe considered throughout the PROM. The WOMAC can still be used as a standalone PROM in OA-related studies with permission, but many researchers would elect to use the KOOS for its broader scope, albeit at the expense of a longer completion time for the participant.

Another PROM comparable to the KOOS is the Short Form 36 (SF-36) (247). This is a 36-item, 0 to 4 Likert scale questionnaire covering numerous dimensions of health, including physical, social and emotional wellbeing. Throughout the SF-36, respondents are asked to consider their current health, as well as their health over the last four weeks. There is also a question asking respondents to rate their health at the time of answering compared to one-year prior, which gives perspective on the overall health perception the patient has surrounding the outcome of their surgery.

It was evident throughout our PROM review that use of more than one PROM to assess the effect of an intervention is common practice, as the reliability and scope of findings can be increased. However, as mentioned previously, the likelihood of respondent fatigue should be considered when providing participants with multiple PROMs to be completed in succession. Although we did not identify research on recommended PROM completion time, it should be kept as short as possible to minimise respondent fatigue – a maximum time of around 15–20 minutes seems acceptable based on the number of PROMs used in various studies and the time taken to complete each form.

2.11 RESEARCH GAP AND AIMS OF THIS STUDY

From this literature review, there is sufficient evidence indicating that opening-wedge high tibial osteotomy (HTO)/distal femoral osteotomy (DFO) using PSI in combination with autograft or allograft and internal fixation is a highly capable method for accurately correcting knee malalignment in combination with unicompartmental knee osteoarthritis. However, the significant heterogeneity we observed between PSI designs means that homogeneity between study results cannot be assumed, and accuracy must be confirmed for each PSI model that is manufactured. In light of this, to our knowledge, a study of HTO/DFO using PSI has not been conducted in Australia, providing a clear rationale for our research. It was also evident that changes in the pelvis and spine following HTO/DFO surgeries has received limited attention.

Hence, the aim for this clinical study is to perform X-ray and EOS radiographic measurements to:

- Determine the accuracy of PSI in HTO/DFO procedures by comparing the planned alignment (as pre-operatively defined by the engineering/surgical team from Macquarie University Hospital) to post-operative measurements of the hip-knee-ankle angle (HKA) and tibial slope (TS).
- Observe the influence of HTO/DFO on secondary alignment measurements, including functional leg length (FLL), anatomical femur/tibia length (AFL/ATL), mechanical medial proximal tibial angle (mMPTA), mechanical lateral distal femoral angle (mLDFA), knee joint line convergence angle (KJLCA), pelvic obliquity (PO), lumbar scoliosis (LS), knee flexion angle (KFA), sacral slope (SS), pelvic tilt (PT) and lumbar lordosis (LL).
- Compare surgical accuracy to PROM data from before and/or after the procedures to establish correlation between accuracy and patient outcomes.
- Conduct an intra and inter-observer reliability investigation, quantifying human error that may be present throughout results.
- Identify methodological (inter-image) error that may be present throughout results by measuring un-operated anatomy i.e. control variables that should theoretically not change between pre and post-operative images.

Chapter 3: Materials and Methods

To analyse the accuracy of HTO/DFO using PSI, as well as pelvic/spinal alignment changes following the procedures, we conducted a retrospective single-centre study on a patient cohort from Macquarie Limb Reconstruction Centre (MLRC), operating at Macquarie University Hospital (MUH). The lead surgeon at this MLRC (MAM) is a Professor in orthopaedic surgery with over 10 years of realignment osteotomy experience prior to this study, mainly using the navigated technique explained in Sub-Section 2.7.3. However, the transition to patient-specific instrument (PSI) use in his high tibial osteotomy (HTO)/distal femoral osteotomy (DFO) procedures began in August 2020, marking the beginning of our patient cohort. Section 3.1 details the clinical and surgical patient management that precedes our direct research involvement. Section 3.2 outlines the study design and applied methodological approach, which is supported with reference to prior studies.

3.1 CLINICAL MANAGEMENT AND SURGICAL PLANNING

3.1.1 Defining the surgical correction

All patients who present at MLRC with suspected osteoarthritis (OA) pathology of the knee are sent for a series of non-weight-bearing and weight-bearing (WB) images from anteroposterior (AP), lateral, Rosenburg and Skyline views, including either a long-leg X-ray (LLXR) or EOS scan (EOS Imaging, Paris, France). During the LLXR and EOS scans, patients stand with the feet approximately shoulder-width apart, knees and hips in full-extension, patellae facing anteriorly and the spine erect. This standardised protocol allows for visualisation of pathology and consistent quantification of malalignment that may have developed as a result of OA, which enables the patient's symptoms to be potentially matched with radiographic evidence. If these images are sufficient to make a diagnosis, management can be discussed from conservative or surgical approaches. If an HTO/DFO is indicated and decided as a suitable treatment, the pre-operative LLXR/EOS is used to begin the pre-operative planning of the procedure. This starts with a measurement of the HKA to quantify the degree of deformity that may be present (as described previously in Figure 2.4). Using this measurement, the desired degree of surgical correction will be determined based on a myriad of factors such as the degree of pre-operative malalignment, condition of the more-preserved knee compartment, alignment of the contralateral limb or the body mass index (BMI) of the patient – these may indicate a smaller or larger correction angle.

Calculating opening-wedge dimensions: The Dugdale method

There are several methods for pre-operative wedge dimension planning in HTO/DFO, which is a necessary step in constructing PSI – explained in the following Sub-Section. One popular approach for this wedge calculation is the Dugdale method, described by Dugdale et al. in 1992 (248). This method (displayed for an HTO in Figure 3.1) – conducted from whole-limb radiographs – uses the desired post-operative lower-limb mechanical axis (MA) location through the tibial plateau width (TPW) and compares that with the pre-operative alignment to establish a difference between these measurements. This, in combination with a measurement of the width of the tibia along the osteotomy plane, creates an accurate wedge size that is replicated intra-operatively to achieve the intended post-operative limb alignment.

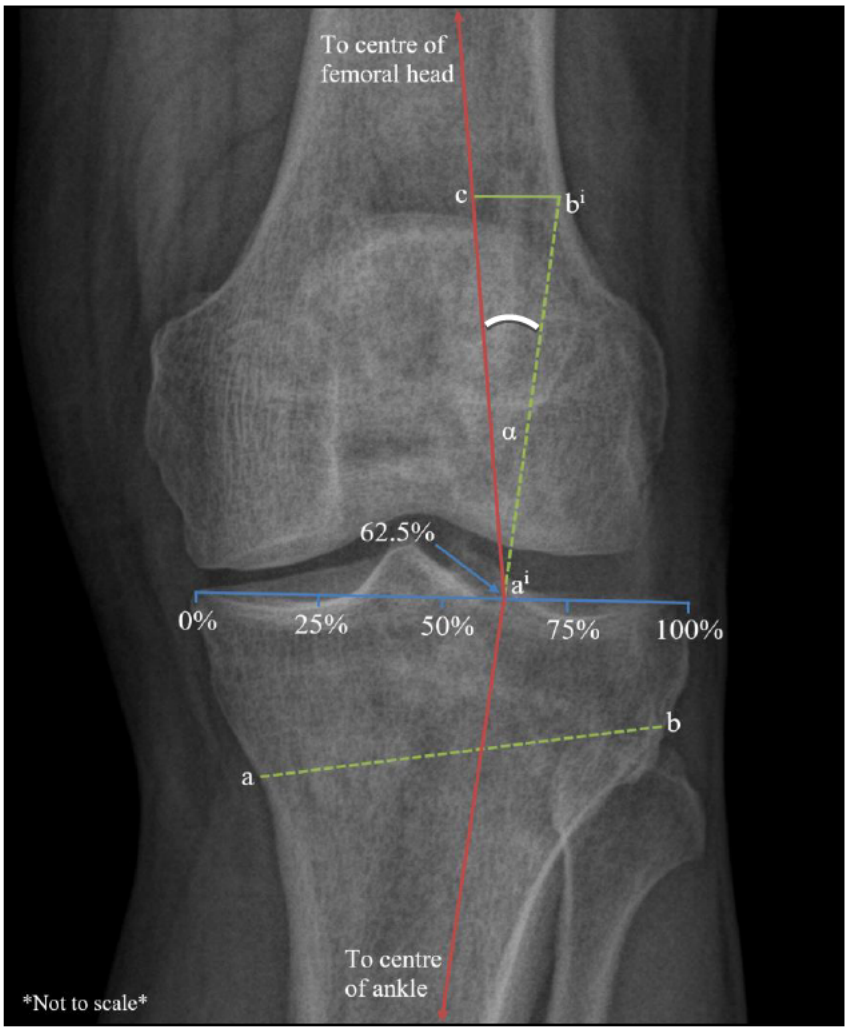


Figure 3.1 Dugdale method for calculating opening-wedge dimensions
Distance **point a** to **point b** is the length of the osteotomy plane. **Point a^i** is positioned at the Fujisawa point 62.5% of the tibial plateau width (or any other targeted position, as determined by the surgeons), and **point a^i** to **point b^i** (a continuation of the line from the centre of the ankle) is equal in length to **point a** to **point b. Angle α** is the opening-wedge distraction angle to be replicated intra-operatively, with **point b^i** to **point c** representing the desired opening-wedge distraction distance. The triangle formed by **point a^i**, **point b^i** and **point c** is the complete wedge dimensions, which is used to simulate the procedure within a 3D modelling software and create PSI, explained in Sub-Section 3.1.2

3.1.2 Constructing patient-specific instruments (PSI)

To manufacture a PSI for HTO/DFO procedures based on pre-operative radiographic planning, a high-resolution computed tomography (CT) scan must be taken of either the tibia or femur. This is followed by a series of computer-aided design (CAD) processes that create digital and 3D-printed replicas of patient bone morphology and the PSI that are used for the surgery. The logistics of this process (using HTO as the exemplar) was as follows:

1. High-resolution CT scan (0.625 mm slices) DICOM (digital image and communication in medicine) file/s accessed on PACS (picture archiving and communication system) and downloaded.
2. DICOM file imported to radiological post-processing software for segmentation – Mimics (Materialise, Leuven, Belgium).
3. Model formed and surfaces smoothed for accurate 3D-printing.

4. Model exported to 3D modelling software – 3Matic (Materialise, Leuven, Belgium) – where a PSI is created and fitted to the model of the tibia to simulate desired surgical positioning (Figure 3.2).

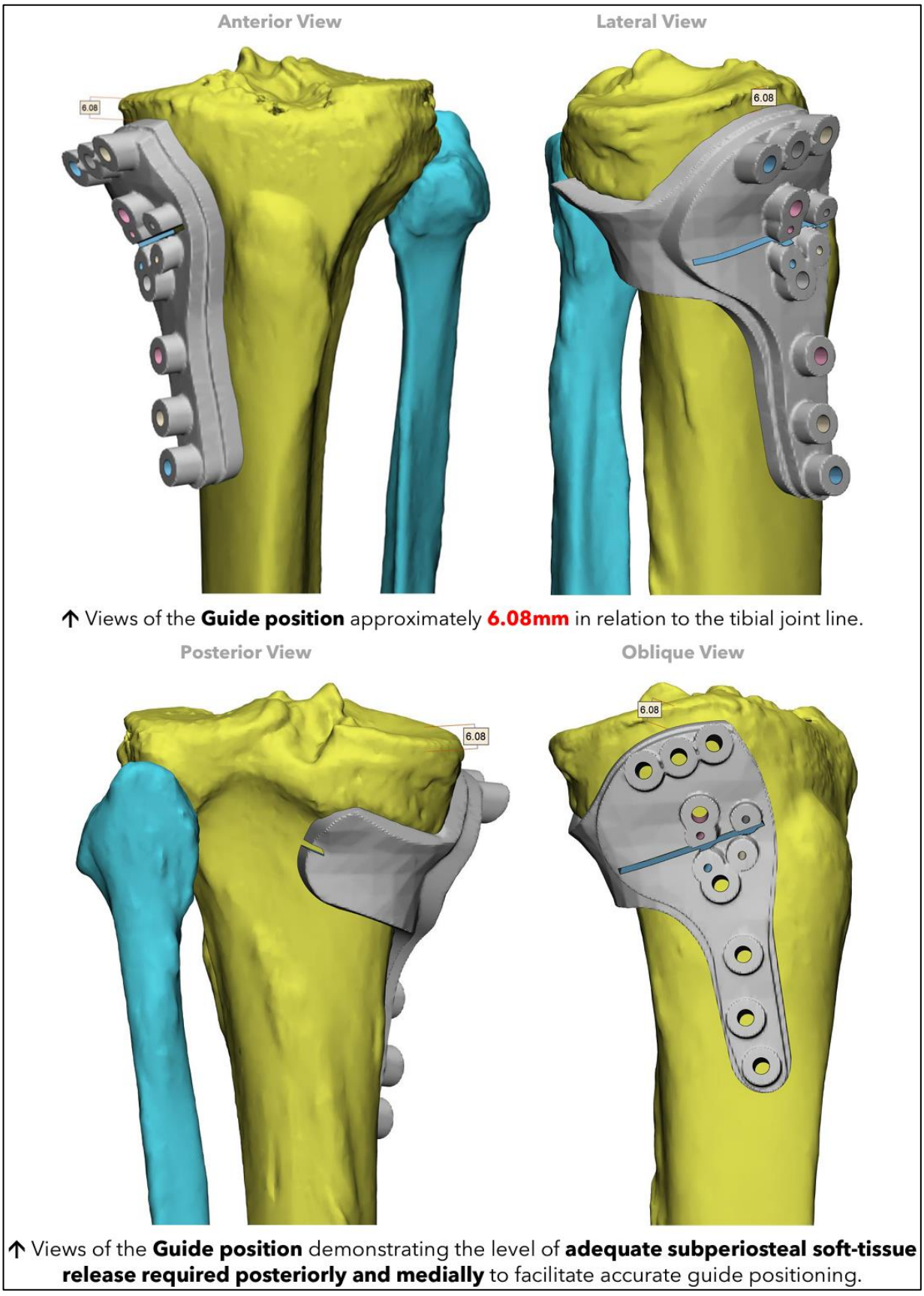


Figure 3.2 3D models of bone with patient-specific instrument inserted

5. Planned Kirschner wire (K-wire) positioning and osteotomy plane (Figure 3.3).

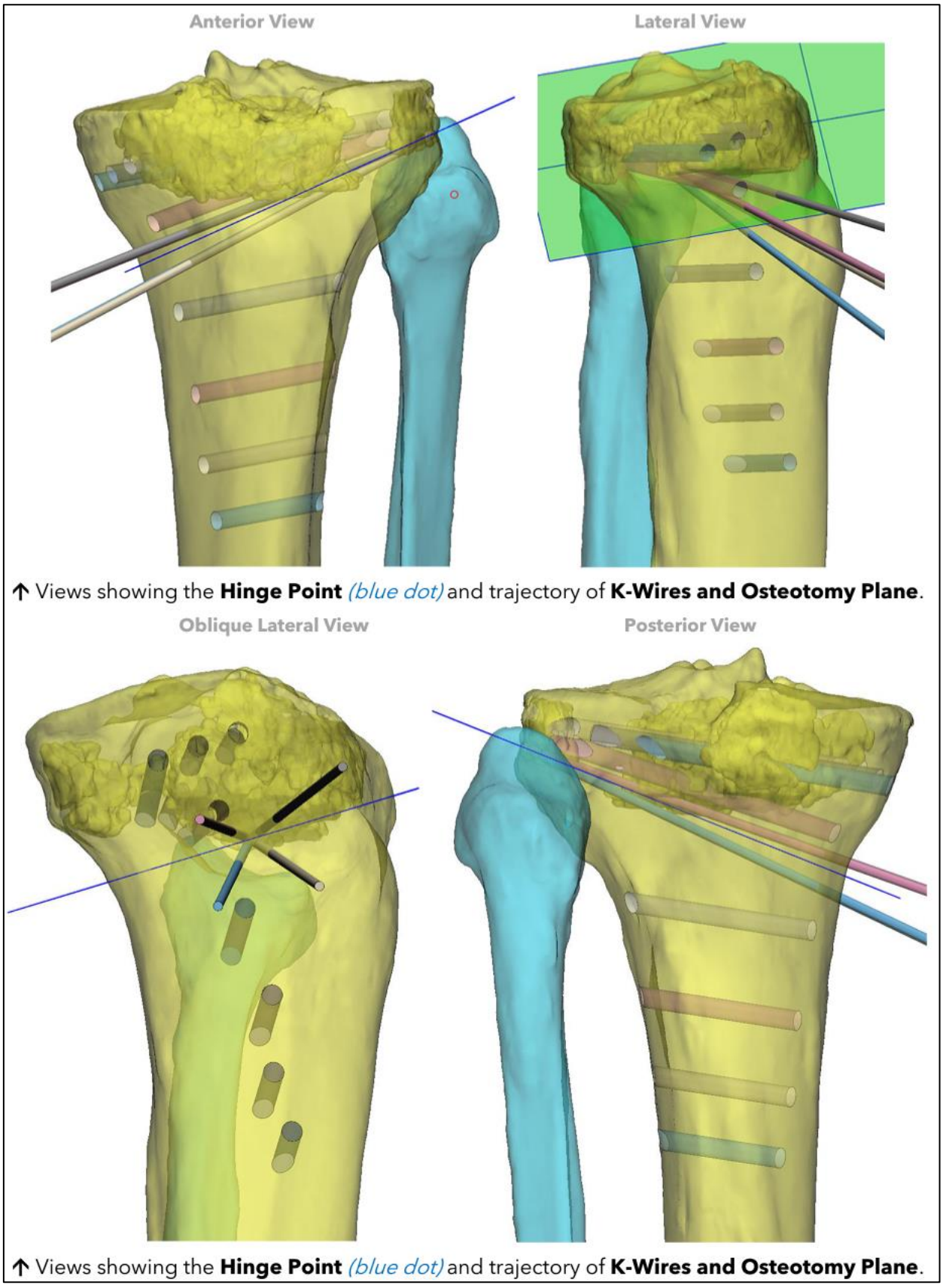


Figure 3.3 Kirschner wire positioning and osteotomy plane simulation

6. Simulation of the procedure is performed by creating an opening-wedge, indicating the screw length/orientation and internal fixation positioning (Figure 3.4).

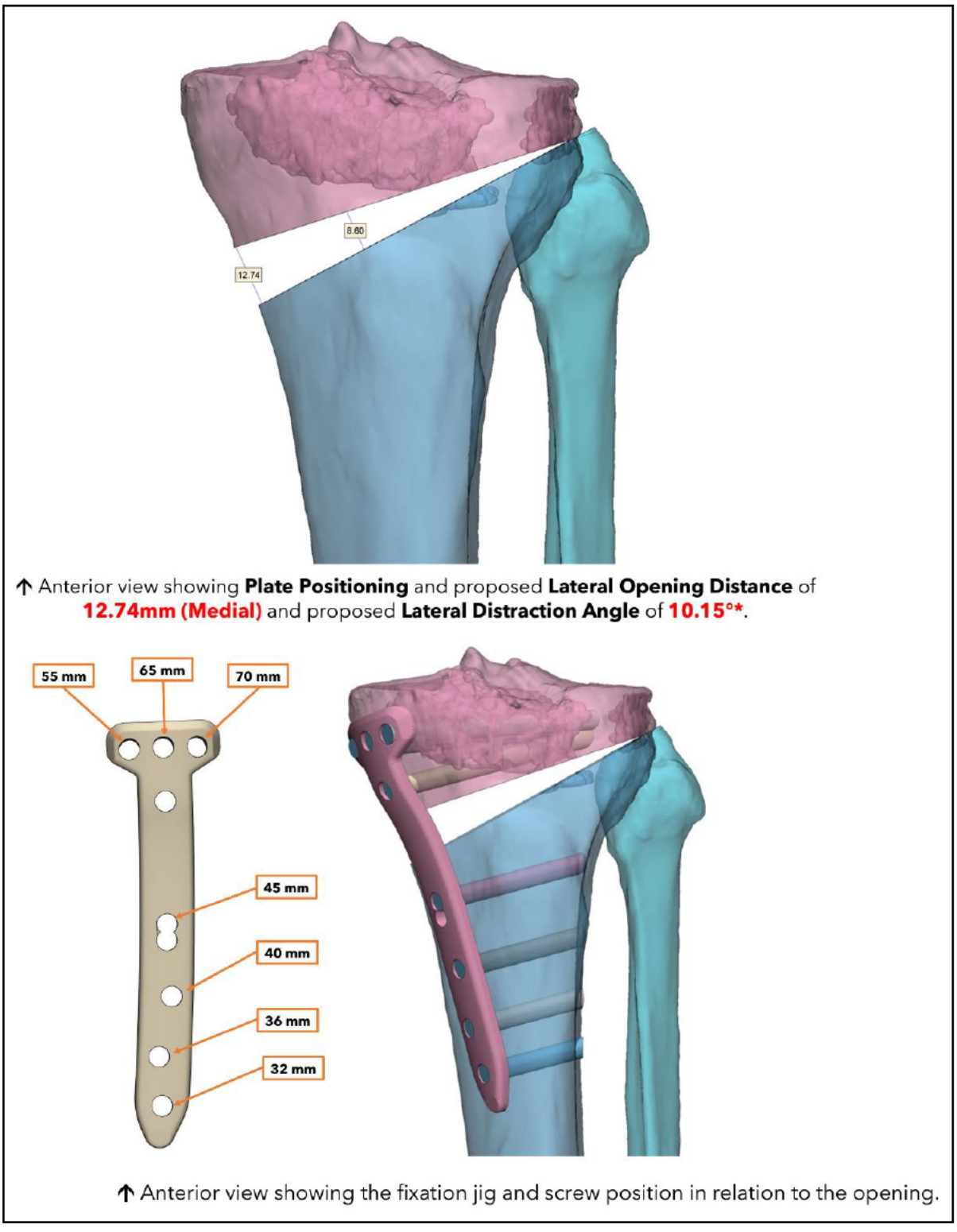


Figure 3.4 Opening-wedge simulation and hardware positioning

7. STL (Standard Triangle Language) files of the tibia and PSI exported, then sent to manufacturers for 3D-printing.

3.1.3 Surgical procedures

The surgical technique for patients undergoing HTO/DFO using PSI with MLRC is described here. In some cases, simultaneous procedures may be performed if they are indicated (such as a tibial tubercle osteotomy or soft-tissue release), but these will not be described as they exceed the scope of this study and will not affect our alignment measurements. Individuals who undergo simultaneous procedures that would affect results are excluded from the study, as specified in our exclusion criteria in Sub-Section 3.2.2.

Arthroscopy (if applicable)

1. Observe the condition of all three knee compartments for any contraindications, determining whether the procedure should be performed i.e. the condition of the more-preserved compartment and patellofemoral joint is checked for OA that may predict poor outcome or rapid conversion to total knee replacement (TKR).
2. Debridement of joint pathology, removal of loose bodies and smoothening of articular surfaces.
3. If viable, proceed to HTO/DFO.

HTO technique

1. Patient positioned supine with a non-sterile inflatable torniquet, followed by prep and drape as per hospital protocol.
2. Anteromedial vertical incision over the pes anserinus region, with subcutaneous layers incised to the bone. Neurovascular structures are retracted posteriorly.
3. PSI tested for fit on a 3D-printed model of the patient's superior tibia, before positioning the PSI on the patient.
4. Four K-wires inserted through holes in the PSI and checked under image intensifier (II) for correct positioning.
5. Osteotomy made using a bone saw, followed by adjustments to the osteotomy using an osteotome to preserve the lateral cortex.
6. Removal of K-wires and PSI.
7. Osteotomy completed with osteotome under direction vision.
8. Laminar spreader used to distract the opening-wedge to the desired size, assisted by a valgus force carefully provided by another member of the surgical team.

9. Internal fixation plate inserted and secured using screws pre-measured to the patient's tibia width on 3Matic software.
10. Wedge allograft compacted to fill opening-wedge space.
11. Bone grafting checked under II for sufficient filling of opening-wedge.
12. All soft-tissue layers (including periosteum) closed from deep-to-superficial to minimise risk of infection.

DFO technique

1. Patient positioned supine with a non-sterile inflatable torniquet, followed by prep and drape as per hospital protocol.
2. Lateral vertical incision posterior to the vastus lateralis muscle at the distal femur.
3. Dissection performed until vastus lateralis can be located and retracted anteriorly for desired osteotomy site visualisation, followed by incising soft-tissue layers to the bone. Care is taken to avoid damage neurovascular structures.
4. PSI tested for fit on a 3D-printed model of the patient's distal femur, before positioning the PSI on the patient.
5. Four K-wires inserted through holes in the PSI and checked under II for correct positioning.
6. Osteotomy made using a bone saw, followed by adjustments to the osteotomy using an osteotome to preserve the medial cortex.
7. Removal of K-wires and PSI.
8. Osteotomy completed with osteotome under direct vision.
9. Laminar spreader used to distract the opening-wedge to the desired size, assisted by a varus force carefully provided by another member of the surgical team.
10. Internal fixation plate inserted and secured using screws pre-measured to the patient's femur width on 3Matic software.
11. Wedge allograft compacted to fill opening-wedge space.
12. Bone grafting checked under II for sufficient filling of opening-wedge.
13. All soft-tissue layers (including periosteum) closed from deep-to-superficial to minimise risk of infection.

3.2 APPLIED METHODS

3.2.1 Ethical approval

This study received ethical approval from the Macquarie University Human Research Ethics Committee on the 8th of June 2021 (RE: 52021982328611) – approval letter in Appendix A. This approval included a patient information and consent form (PICF) with the details of the study (Appendix B), as well as a questionnaire form for participants to complete for subjective outcome measurements (Appendix C).

3.2.2 Participants and recruitment logistics

HTO/DFO procedures under MLRC between August 2020 and July 2021 were included in a shortlist of potential procedures to be analysed in this study (n=71), with recruitment logistics graphically displayed in Figure 3.5.

Exclusions were applied to surgeries involving the following criteria (n=18):

- Initial HTO/DFO surgeries that required revision.
- Individuals aged <18 and >65.
- Individuals with joint dysplasia of the hip, knee or ankle.
- Simultaneous procedures on the tibia or femur that would affect results (e.g. bone lengthening or derotation osteotomies).

After 4 more individuals were excluded due to inaccessible patient management system profiles, 49 patients were eligible for analysis. These individuals were contacted (between 18/06/21 and 27/07/21) via telephone numbers provided on their admission forms at MLRC, where the details and purpose of the study were briefly explained after confirming patient identity. If individuals agreed to be sent the PICF and questionnaires, these were sent via e-mail or postage services. This documentation gave more specific details of the study and enabled written informed consent to be received prior to inclusion. If individuals did not answer phone calls after three attempts on separate days, they were sent a different e-mail containing the details that were included in the telephone call script, such that they could understand the study and choose to participate without direct verbal communication – contact details were included for any enquiries. 42 patients answered phone calls and agreed to be sent further information via e-mail, leaving 7 patients who did not answer calls. A further 2 individuals elected not to participate after being informed of the study details (total exclusions n=24), bringing the final number of eligible participants to 47 after all recruitment processes had concluded.

20 patients (demographics outlined in Table 3.1) returned the PICF and questionnaires to become participants in the study, with 27 patients unresponsive at the participation cut-off date (13/08/21) after reminder phone calls/e-mails. This is a participation percentage of 43% across eligible patients.

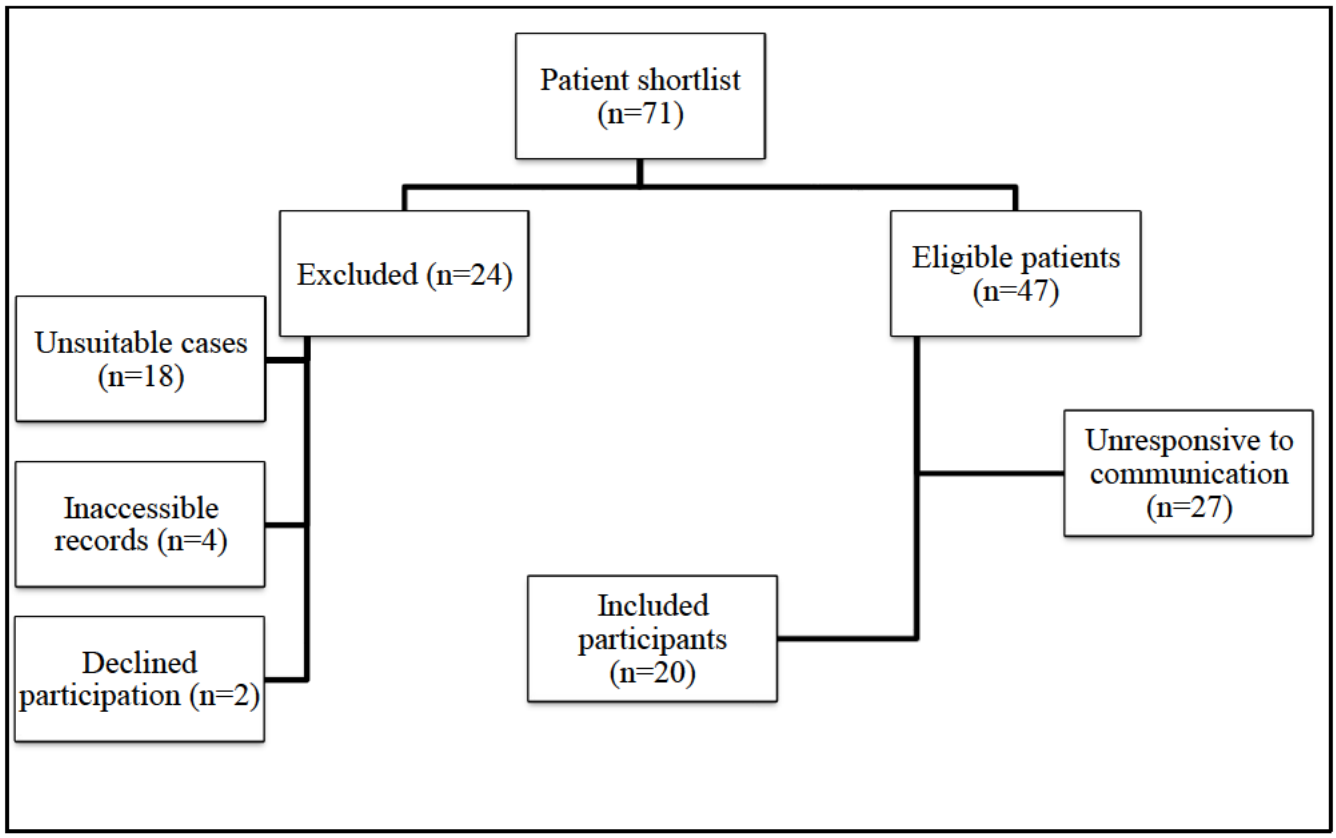


Figure 3.5 Participant selection flowchart

Table 3.1 Clinical study participant demographics

Surgery date	Case	HTO/DFO	Side	Sex	Age at surgery	Height (m)	Weight (kg)	BMI	Background	Previous related surgery
19/08/2020	1	DFO	Left	Female	20	1.60	71	27.73	Australian	Contralateral DFO
26/09/2020	2	HTO	Bilateral	Male	26	1.75	75	24.49	Taiwanese	None
12/10/2020	3	HTO	Left	Male	45	1.93	115	30.87	Australian	Right total hip replacement
19/10/2020	4	HTO	Left	Male	46	1.72	87	29.41	Australian	None
19/10/2020	5	HTO	Right	Male	50	1.72	100	33.80	Greek	None
9/11/2020	6	HTO	Left	Male	55	1.82	125	37.74	Not provided	None
16/11/2020	7	HTO	Left	Male	65	1.80	98	30.13	Croatian	None
18/11/2020	8	HTO	Bilateral	Male	45	1.83	110	32.85	Australian	None
7/12/2020	9	HTO	Right	Male	60	1.69	63	22.06	Australian	Contralateral HTO
20/01/2021	10	DFO revision	Right	Male	48	1.83	135	40.31	Australian	Right DFO
25/01/2021	11	HTO	Right	Male	65	1.60	80	31.25	Australian	None
10/02/2021	12	DFO	Bilateral	Female	41	1.56	79	32.46	Australian	None

Surgery date	Case	HTO/DFO	Side	Sex	Age at surgery	Height (m)	Weight (kg)	BMI	Background	Previous related surgery
17/02/2021	13	HTO revision	Right	Male	60	1.76	104	33.57	Australian	None
3/03/2021	14	HTO	Right	Male	38	1.78	80	25.25	Australian	None
3/03/2021	15	DFO	Right	Male	41	1.75	80	26.12	Indonesian	None
7/04/2021	16	DFO	Left	Female	37	1.65	95	34.89	Australian	None
21/04/2021	17	HTO revision	Left	Male	55	1.77	74	23.62	Australian	Right above knee amputation
28/04/2021	18	HTO	Left	Male	57	1.76	86	27.76	Australian	None
12/05/2021	19	HTO revision	Left	Male	53	1.72	96	32.45	Not provided	Left HTO
31/05/2021	20	HTO revision	Right	Male	55	1.74	95	31.38	Latin	Right HTO and left HTO
				Range	20–65	1.56–1.93	63–135	22.06–40.31		
				Mean	48.10	1.74	92.40	30.41		
				SD	11.99	0.09	18.67	4.71		

Abbreviations: High tibial osteotomy (HTO), distal femoral osteotomy (DFO), body mass index (BMI), standard deviation (SD)

3.2.3 Measurement software

For all measurements, InteleViewer^{TM} (Intelerad, Quebec, Canada) Version 4-17-1 was used to analyse pre-operative and post-operative X-ray and EOS images. This platform is a PACS used by MLRC for the purposes of storing/accessing medical images and quantifying pathology. Both X-ray and EOS imaging modalities are facilitated and are visible on a 2D interface, with 6 forms of calibrated measurements available for each image frame (demonstrated in Figure 3.6):

1. Linear measurement – a two-point line providing a measurement in centimetres (cm) to two decimal places (DP)
2. Cobb angle measurement – two lines positioned in any orientation throughout the interface, with the angle of these lines relative to each other measured from 0-180.00 degrees (°)
3. Circular measurement – a circular region of interest with a centre-point marking and volume measurement in cm^2 to two DP
4. Freehand measurement – a sketchable area measurement given in cm^2 to two DP
5. Simple angle measurement – a three-point line giving an angle from 0-180.00°
6. Orthogonal measurement – a linear measurement automatically generating a bisecting equal-length orthogonal measurement, given in cm to two DP

All measurements were conducted on a Dell U2720Q 27-inch Ultra High Definition monitor (Dell, Texas, United States) with a native pixel resolution of 3840x2160 (aspect ratio of 16:9). This provided excellent image fidelity for visualisation of anatomical landmarks on each radiograph to ensure measurements were as accurate as possible. Each radiograph can be zoomed up to 44,850% true size, aiding accurate and repeatable line positioning – an important function when measuring small changes in alignment.

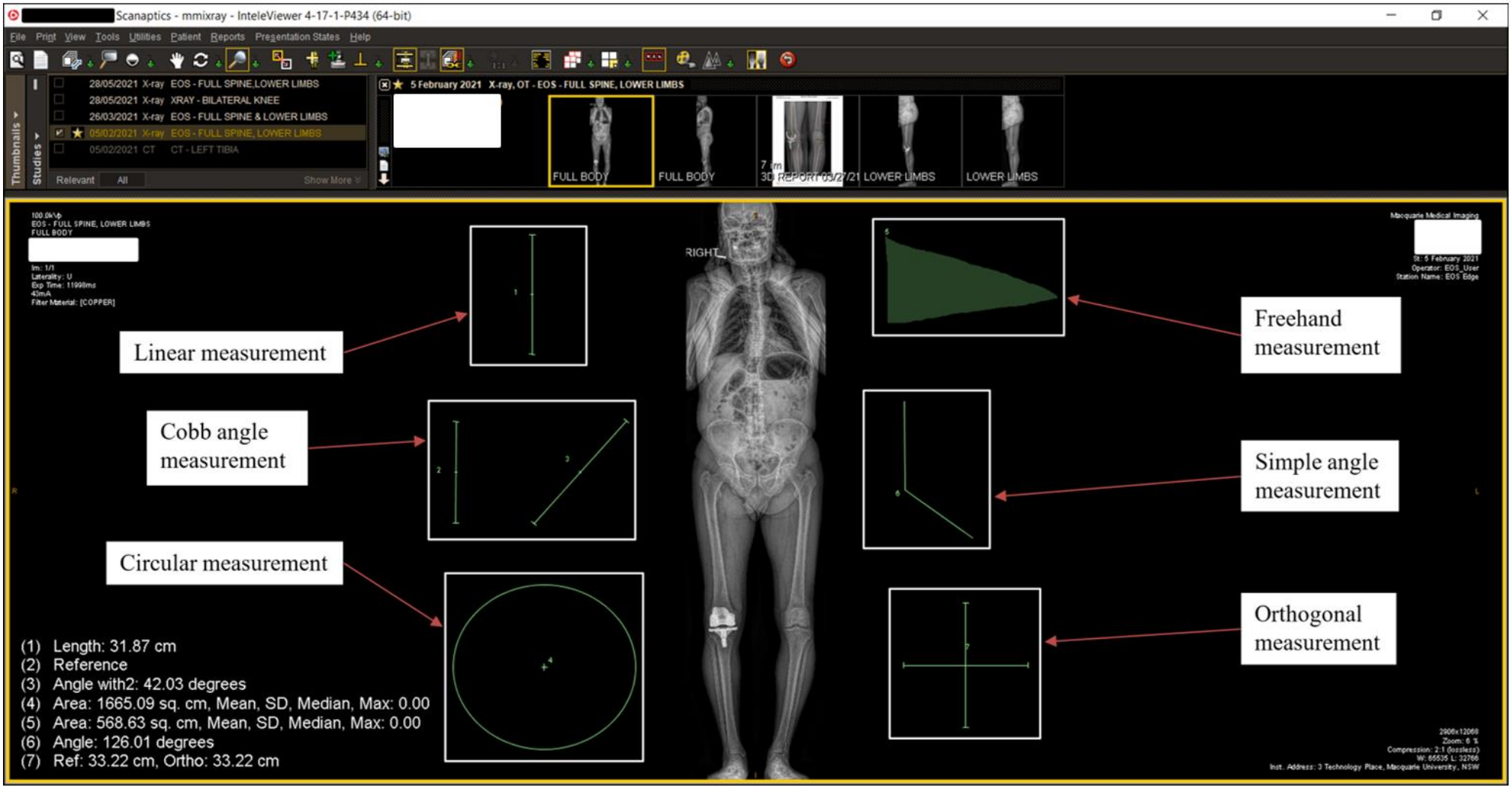


Figure 3.6 InteleViewer^{TM} image interface and measurement tools

3.2.4 Measurement methodology

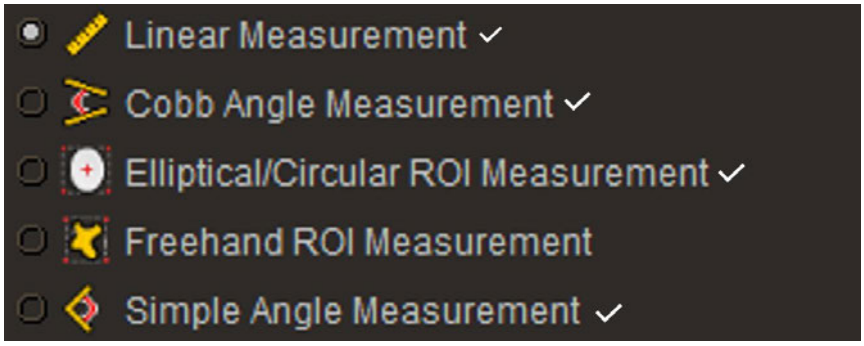
Coronal measurements

1. Hip-knee-ankle angle (HKA)
2. Functional leg length (FLL)
3. Anatomical femur length (AFL)
4. Anatomical tibia length (ATL)
5. Mechanical medial proximal tibial angle (mMPTA)
6. Mechanical lateral distal femoral angle (mLDFA)
7. Knee joint line convergence angle (KJLCA)
8. Pelvic obliquity (PO)
9. Lumbar scoliosis (LS) – Full-spine EOS images only

Sagittal measurements

10. Tibial slope (TS)
11. Knee flexion angle (KFA)
12. Sacral slope (SS)
13. Pelvic tilt (PT)
14. Lumbar lordosis (LL) – Full-spine EOS images only

List of measurement tools used



This Sub-Section details how each of the aforementioned variables were measured within the InteleViewer™ software. A single full-page Figure is provided for each measurement for the purposes of clarity and discernment of line positioning/anatomical landmark definition. This Sub-Section also references literature to support each specific measurement technique, as well as normal values for each measurement. Each measurement technique was further reviewed and approved by an orthopaedic surgeon from MLRC (MA).

Coronal measurements

Measurement 1: HKA (34, 40, 63, 249) – normal value 180°±<3° (182)

1. Elliptical measurement – centre of the femoral head
2. Linear measurement – centre of the tibial plateau, using the lateral borders of the superior tibia as the boundary points, but excluding any osteophytes that would significantly medialise or lateralise the measurement
3. Linear measurement – centre of the talus
4. Cobb angle measurement – centre of the femoral head to centre of the tibial plateau
5. Cobb angle measurement – centre of the tibial plateau to the centre of the talus
6. Final HKA (Figure 3.7) is given by Step 4 & 5, measured from the medial side (i.e. obtuse angles = varus, reflex angles = valgus)

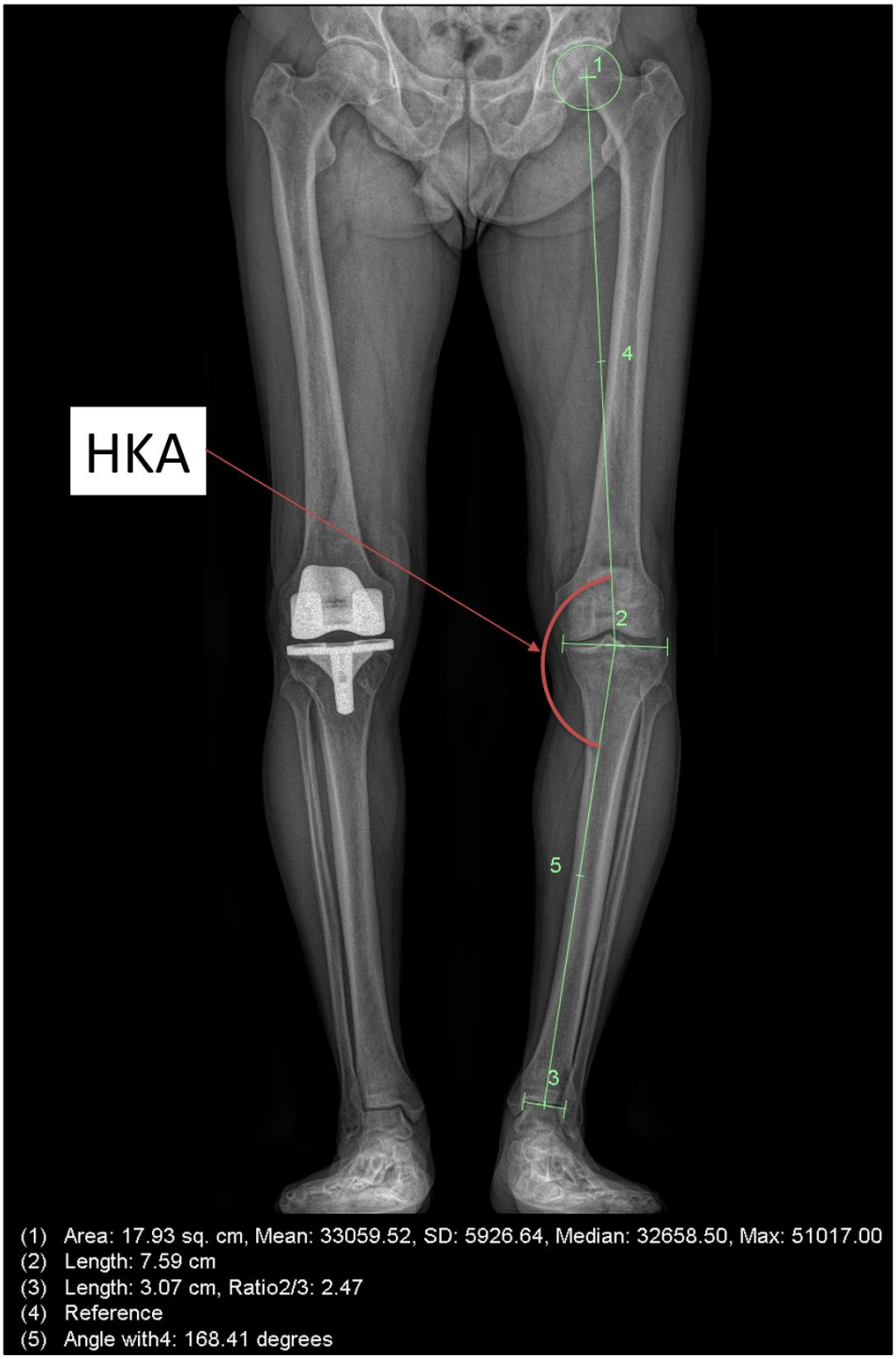


Figure 3.7 Hip-knee-ankle angle (HKA) measurement

Measurement 2: FLL (250)

1. Linear measurement – centre of the tibial plafond
2. Linear measurement – connect the centre of the tibial plafond with the most proximal surface of the femoral head
3. Final FLL (Figure 3.8) given by Step 2

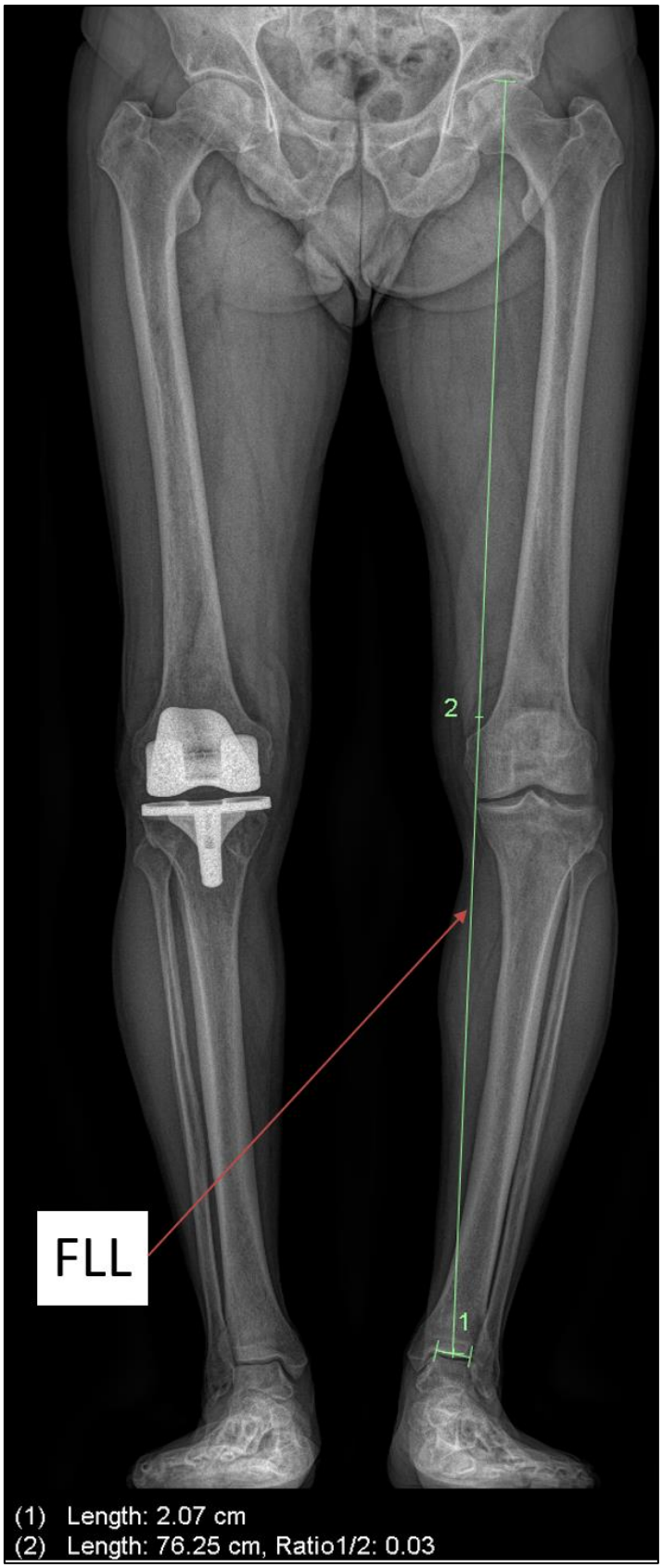


Figure 3.8 Functional leg-length (FLL) measurement

Measurement 3: AFL (251, 252)

1. Linear measurement – most proximal surface of the femoral head to the intercondylar notch
2. Final AFL (Figure 3.9) given by Step 1

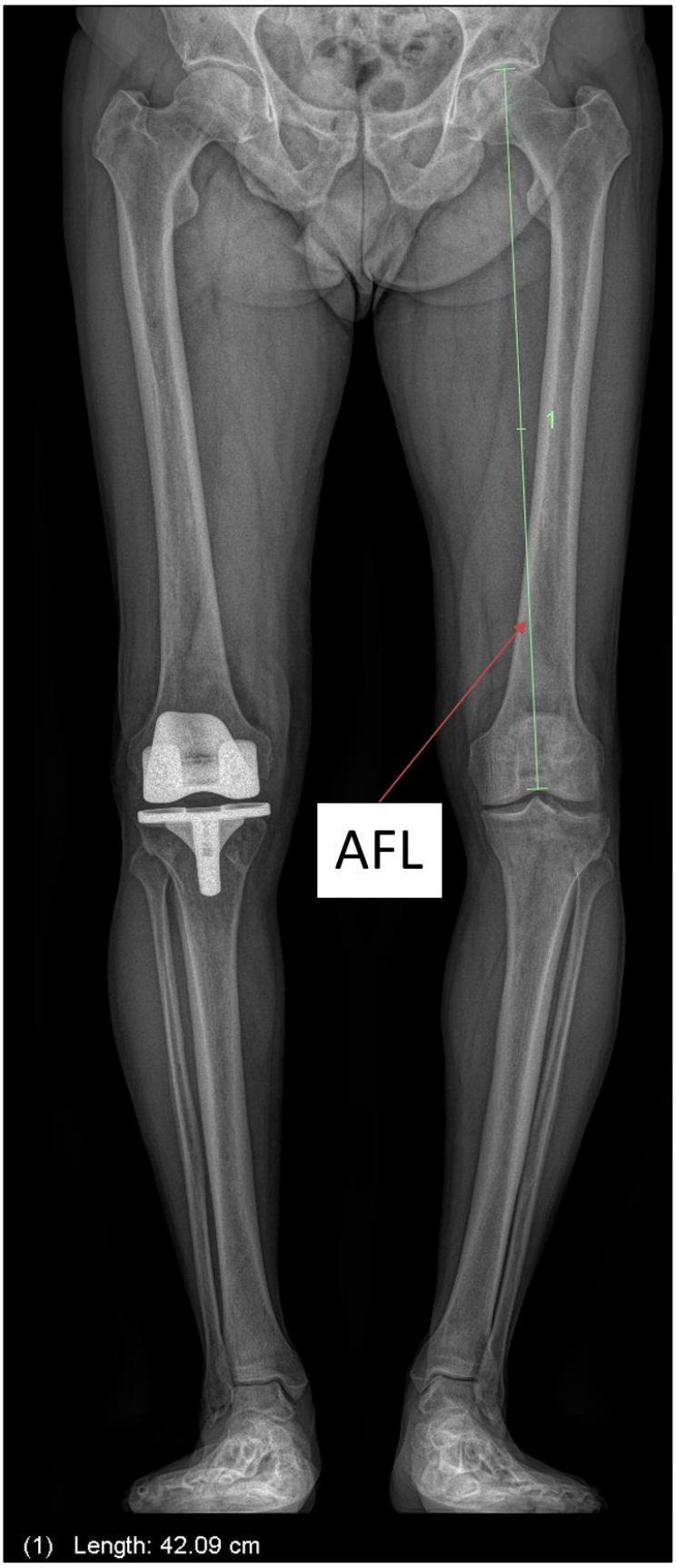


Figure 3.9 Anatomical femur length (AFL) measurement

Measurement 4: ATL (253)

1. Linear measurement – centre of the tibial plateau
2. Linear measurement – centre of the tibial plafond
3. Linear measurement – connect the centre of the tibial plateau with the centre of the tibial plafond
4. Final ATL (Figure 3.10) given by Step 3

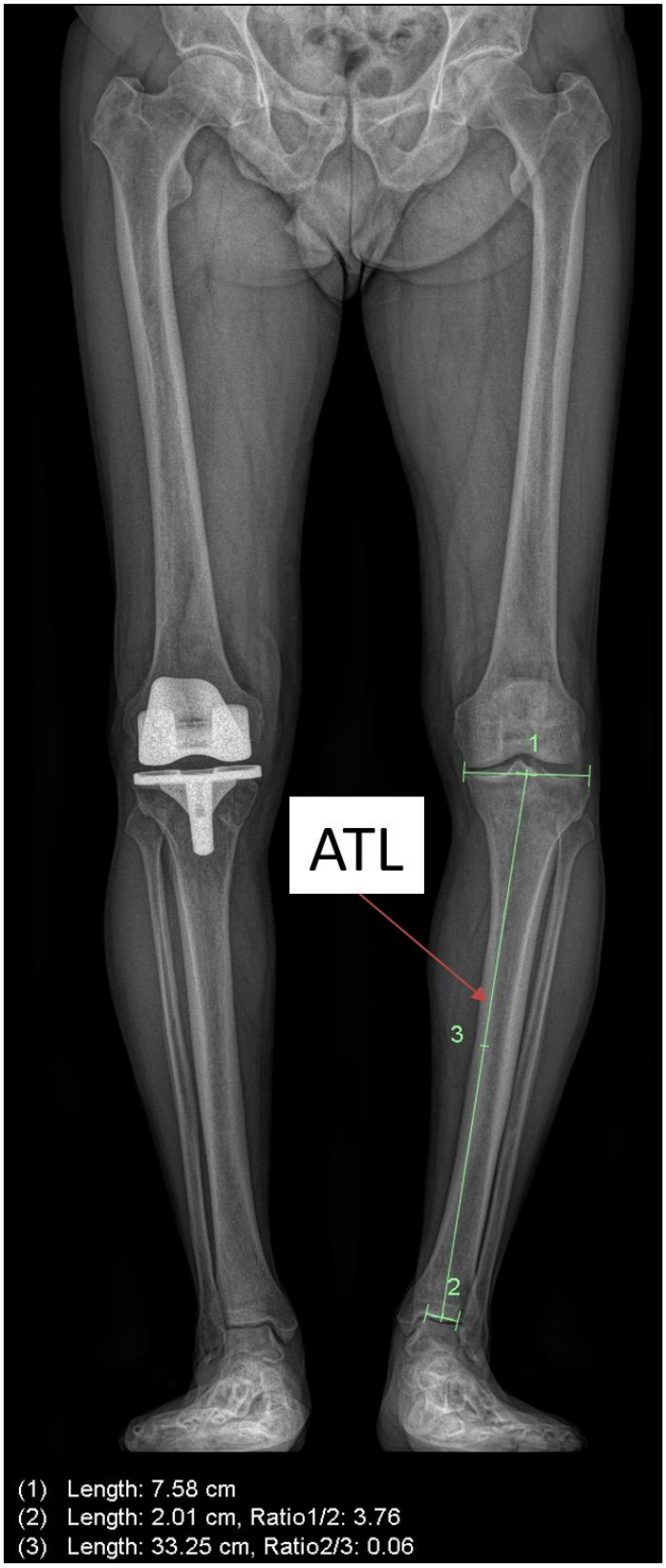


Figure 3.10 Anatomical tibia length (ATL) measurement

Measurement 5: mMPTA (250, 251, 254-256) – normal value ~87° (257)

1. Linear measurement – centre of the tibial spines
2. Linear measurement – centre of the tibial plafond
3. Cobb angle measurement – tibial mechanical axis as a line from the centre of the tibial spines to the centre of the tibial plafond
4. Cobb angle measurement – line tangential to the tibial joint line
5. Final mMPTA (Figure 3.11) as the medial angle given by Step 3 & 4

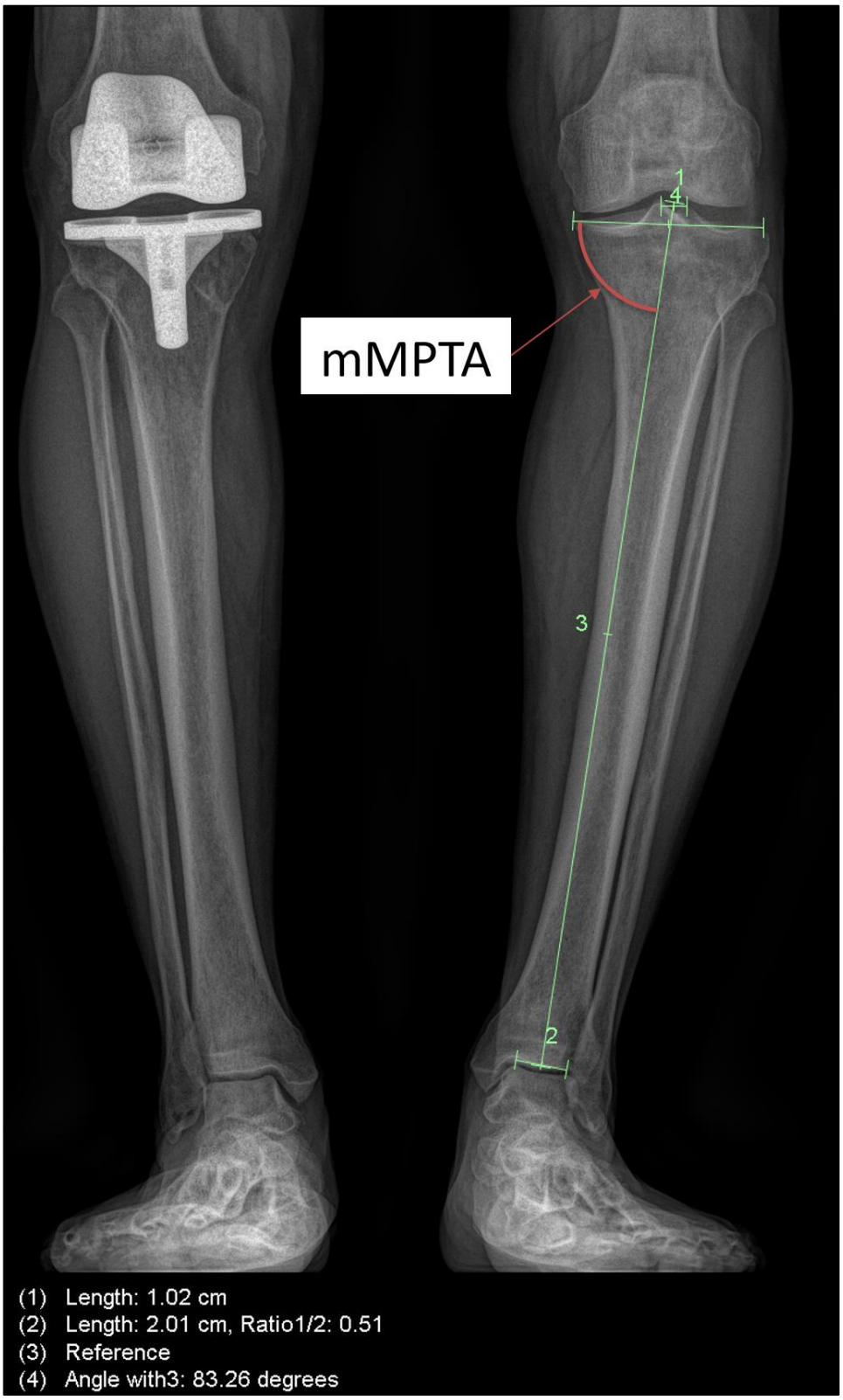


Figure 3.11 Mechanical medial proximal tibial angle (mMPTA) measurement

Measurement 6: mLDFA (250, 251) – normal value ~87° (34)

1. Elliptical measurement – centre of the femoral head
2. Cobb angle measurement – femoral mechanical axis as a line from the centre of the femoral head through the intercondylar notch
3. Cobb angle measurement – line tangential to the femoral condyles
4. Final mLDFA (Figure 3.12) as the lateral angle given by Step 3 & 4

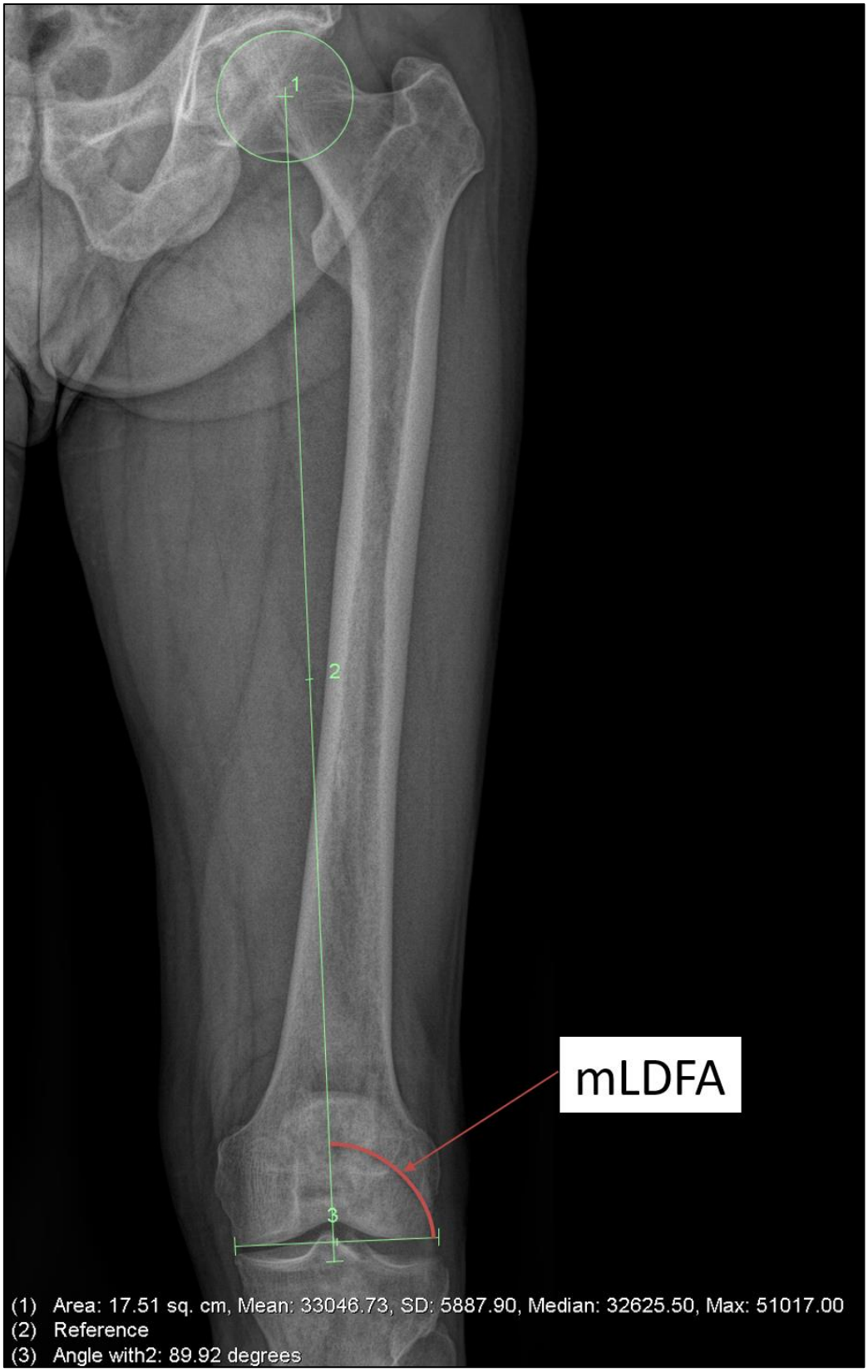


Figure 3.12 Mechanical lateral distal femoral angle (mLDFA) measurement

Measurement 7: KJLCA (186, 258) – normal value 0-2° (186, 259)

1. Cobb angle measurement – line tangential to the femoral condyles
2. Cobb angle measurement – line tangential to the tibial plateau
3. Final KJLCA (Figure 3.13) given by Step 1 & 2

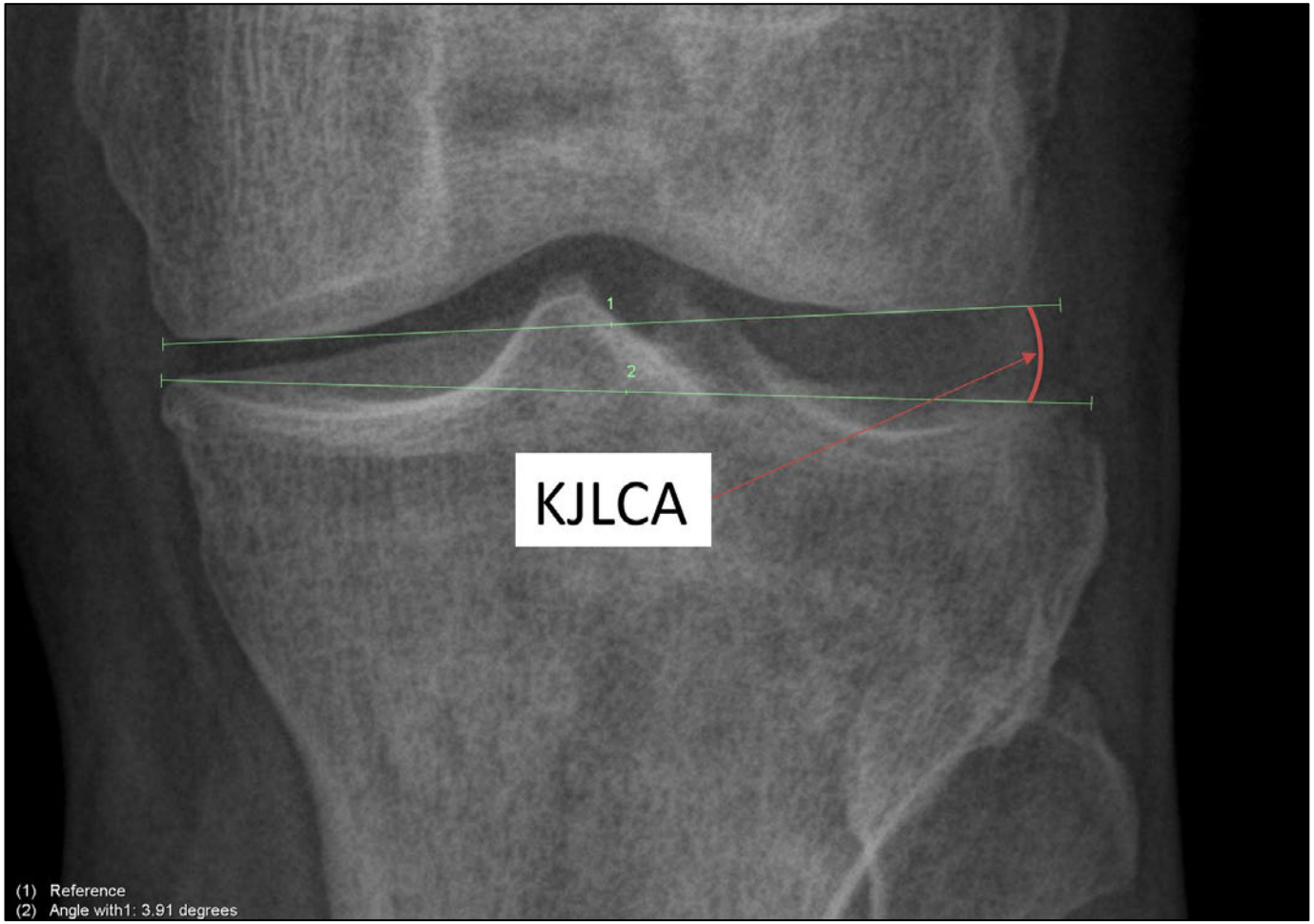


Figure 3.13 Knee joint line convergence angle (KJLCA) measurement

Measurement 8: PO (260, 261) – normal value 0°
InteleViewer™ does not have a function whereby a Cobb angle measurement that is parallel with the X or Y axes can be generated. As such, improvisation is needed to conduct certain analyses that require a vertical or horizontal reference line to establish the anatomical alignment of a certain bone/s. This is done through using the image window borders – which are assumed to be perpendicular – as a guide for placing Cobb angle lines in their necessary positions.

1. Black/white invert is turned on, such that the image background is white and the image window borders can be visualised (seen in Figure 3.14a)
2. Cobb angle measurement – FIRST line parallel to the vertical border of the image window (present in Figure 3.14a, but more clearly visible in Figure 3.14b)
3. Cobb angle measurement – SECOND line parallel to the horizontal border of the image window (present in Figure 3.14a, but more clearly visible in Figure 3.14b), such that Lines 1 & 2 are perpendicular, with this horizontal axis (Line 2) as the reference line for Step 4
4. Cobb angle measurement – line tangential to the rooves of the acetabula (Figure 3.15)
5. Final PO (Figure 3.15) given by Step 3 and 4

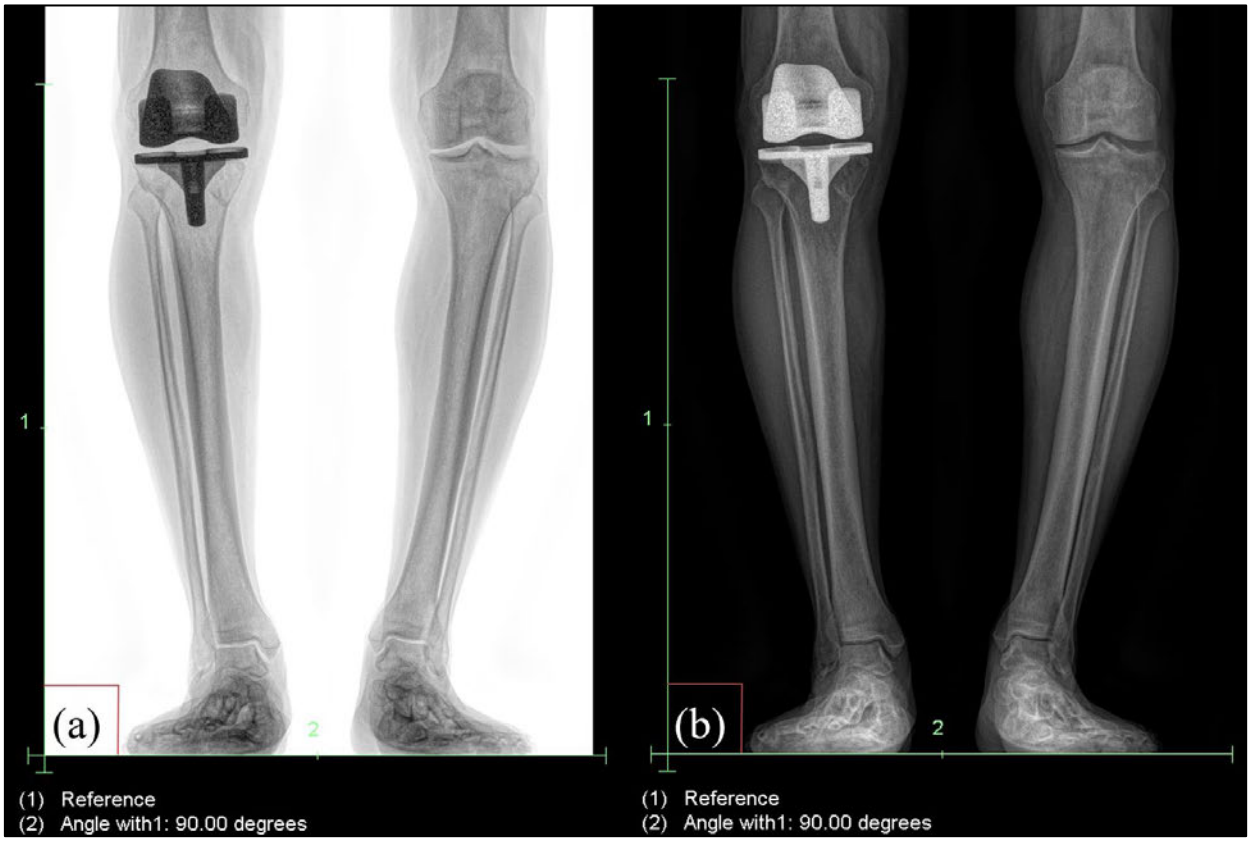


Figure 3.14 Using the image window borders to create X and Y axes

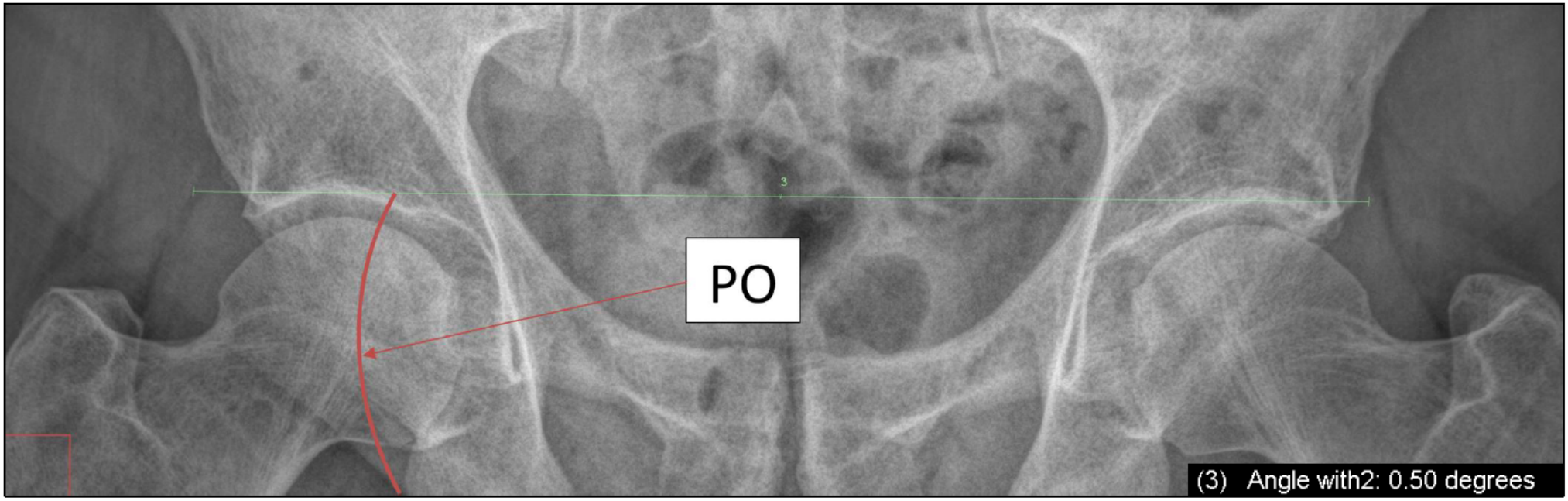


Figure 3.15 Pelvic obliquity (PO) measurement

Measurement 9: LS (262, 263) – normal value <10° (262)

1. Cobb angle measurement – line tangential to the lateral borders of the superior articular surface of the L1 vertebral body
2. Cobb angle measurement – line tangential to the lateral borders of the inferior articular surface of the L5 vertebral body
3. Final LS (Figure 3.16) given by Step 1 and 2

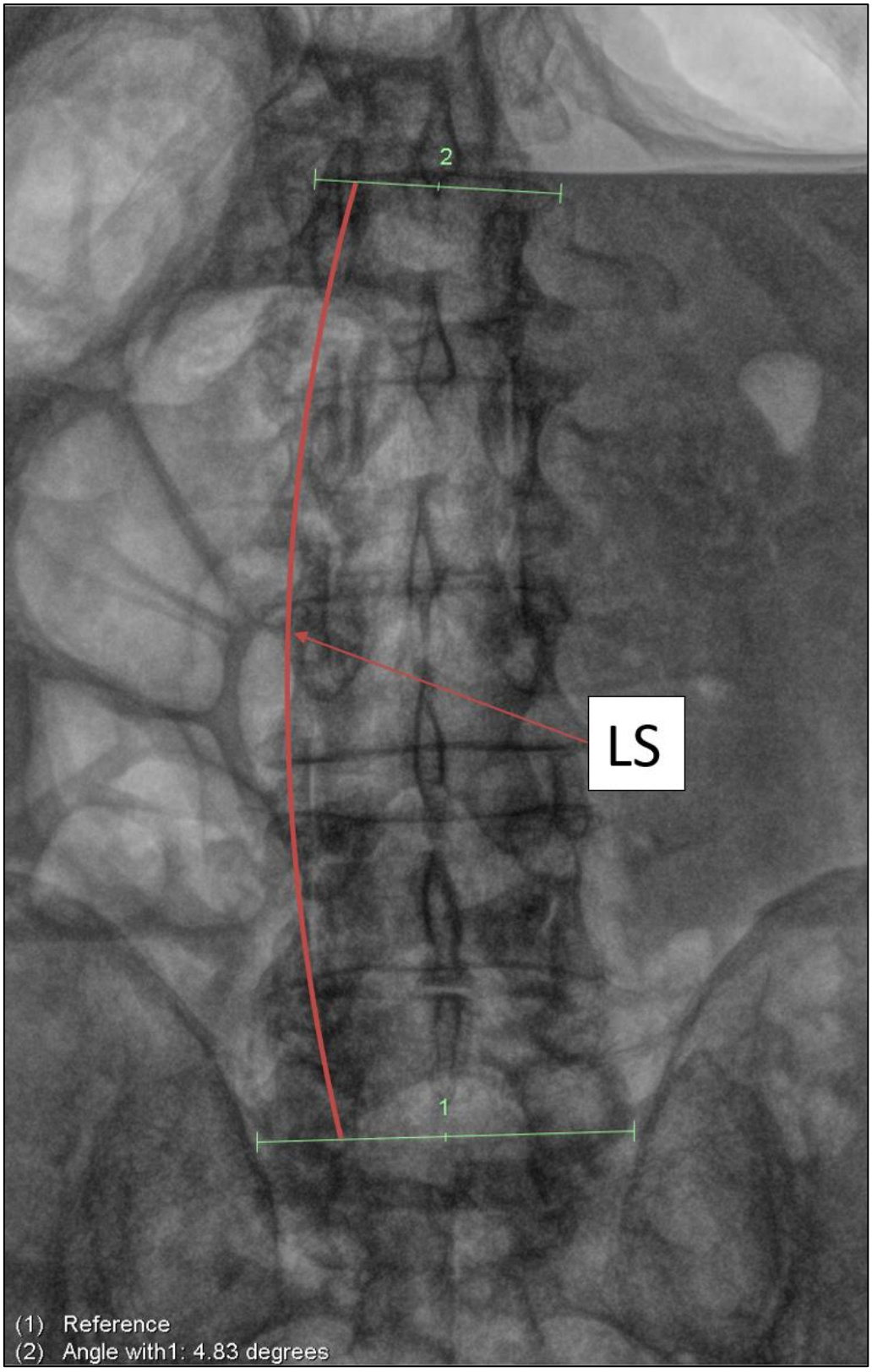


Figure 3.16 Lumbar scoliosis (LS) measurement

Sagittal measurements

Measurement 10: TS (264, 265) – normal value ~80°±4° (266)

1. Linear measurement – line from anterior and posterior-most points between the medial and lateral tibial plateau to determine centre
2. Linear measurement – establish the centre of the tibial plafond using the anterior and posterior-most points of the articular surface as the boundaries. Ensure this line is tangential to the superior-most point of the tibial plafond articular surface. Perpendicular guide lines are used for accurate positioning of this measurement
3. Cobb angle measurement – connect centre of tibial plafond to centre of tibial plateau to establish sagittal mechanical axis of the tibia
4. Cobb angle measurement – line tangential to the anterior and posterior-most points of the medial tibial plateau
5. TS (Figure 3.17) given by Step 3 and 4

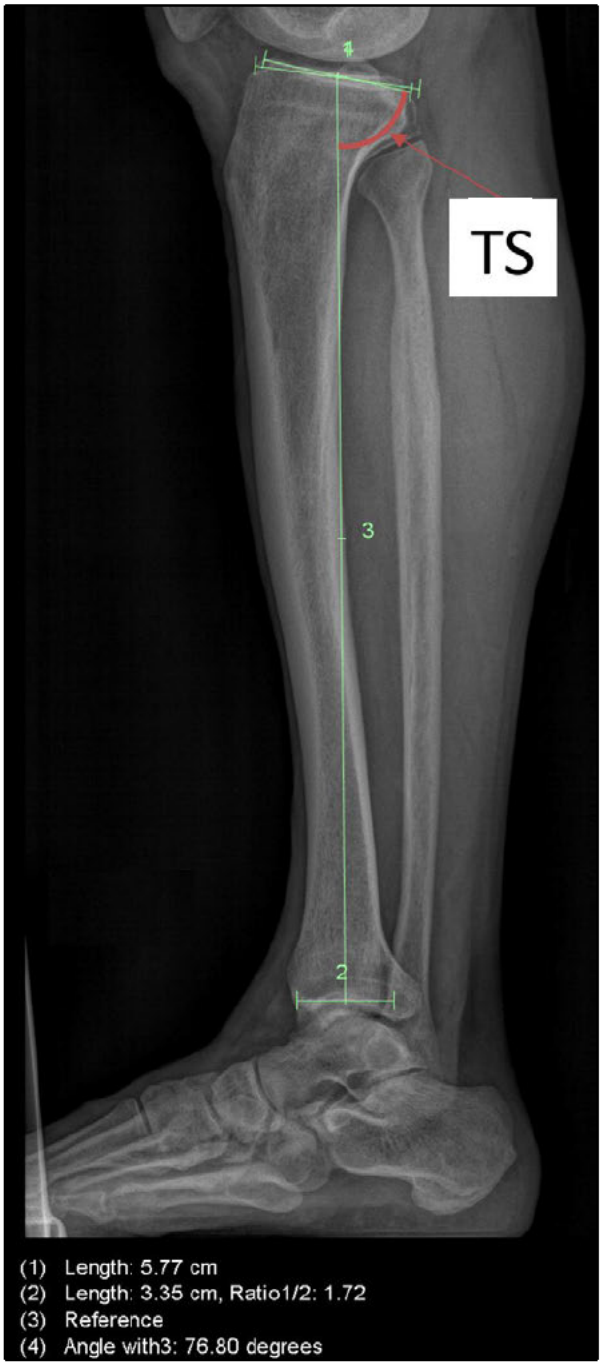


Figure 3.17 Tibial slope (TS) measurement

Measurement 11: KFA (31, 267) – normal value 180° (267)

1. Elliptical measurement – centre of femoral head
2. Simple angle measurement – from **a)** centre of femoral head to **b)** centre of tibial plateau to **c)** centre of tibial plafond
3. KFA (Figure 3.18) given by Step 2

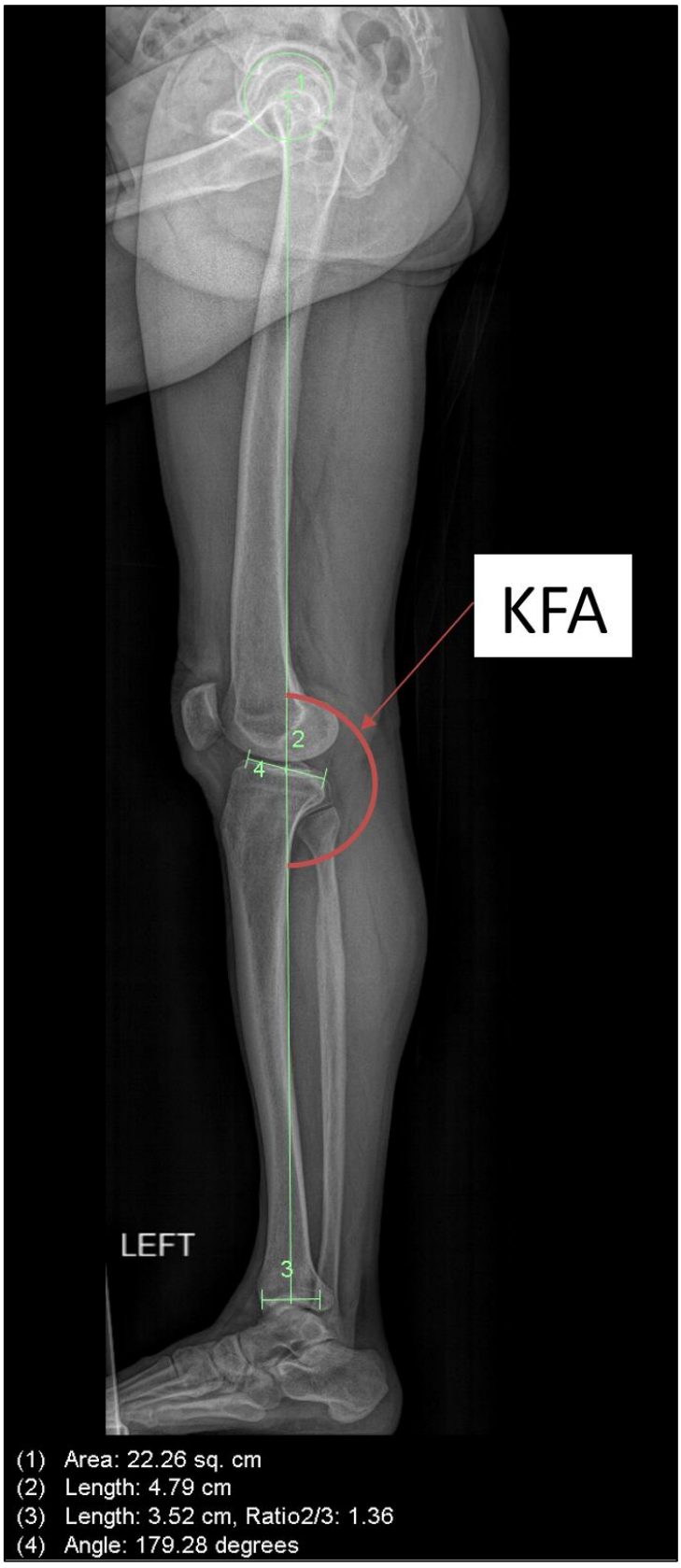


Figure 3.18 Knee flexion angle (KFA) measurement

Measurement 12: SS (268) – normal value ~35° (269)

1. Cobb angle tool – image contrast turned on to visualise window borders, then FIRST reference line at the left-hand border and SECOND reference line at the bottom border (same technique as applied to Measurement 8 – PO)
2. Cobb angle tool – line tangential to the superior articular surface of S1.
3. SS (Figure 3.19) given by Step 1 and 2

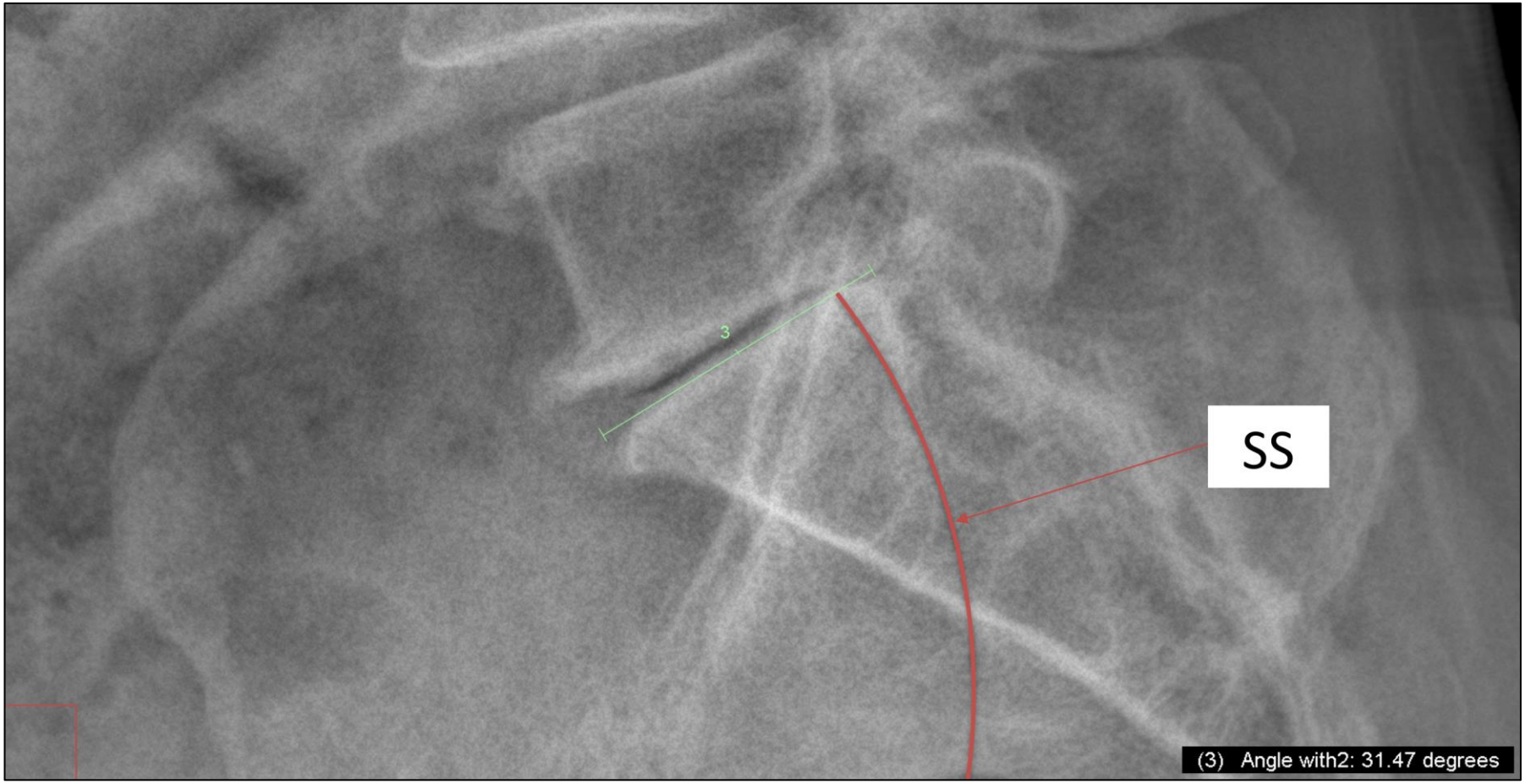


Figure 3.19 Sacral slope (SS) measurement

Measurement 13: PT (270) – normal value ~15° (270)

1. Elliptical measurement – find centre of femoral heads
2. Linear measurement – line connecting the centre of the femoral heads
3. Linear measurement – establish the centre of the superior articular surface of S1
4. Image contrast turned on to visualise image borders (as per PO and SS)
5. Cobb angle measurement – reference line parallel to left image window border
6. Cobb angle tool – vertical bisector through the mid-point between the centre of the femoral heads
7. Cobb angle measurement – line from the mid-point between the centre of femoral head to centre of superior articular surface of S1
8. Final PT (Figure 3.20) given by Step 6 and 7

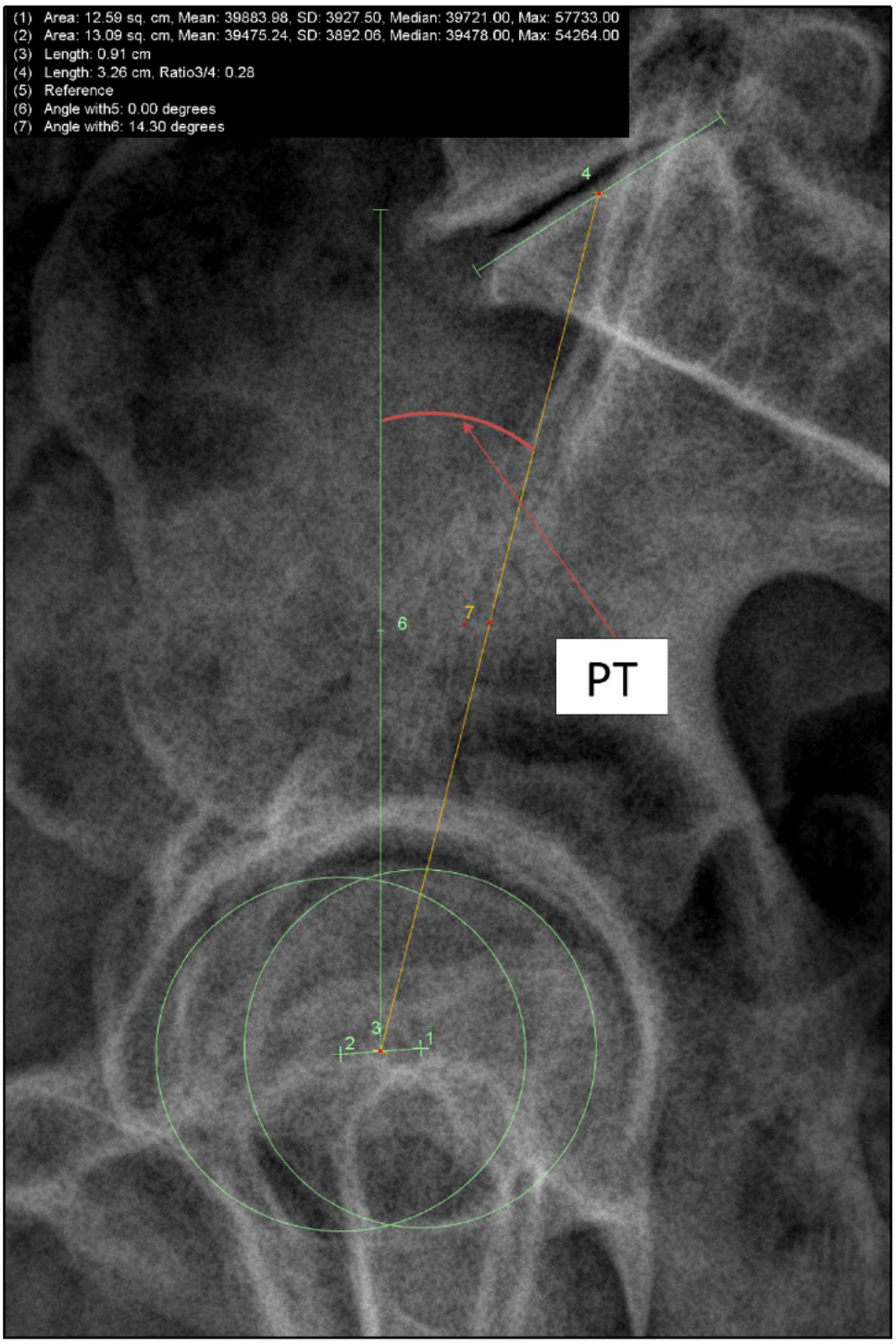


Figure 3.20 Pelvic tilt (PT) measurement

Measurement 14: LL (271) – normal value 20-45° (231)

1. Cobb angle measurement – line tangential to the superior articular surface of the L1 vertebral body
2. Cobb angle measurement – line tangential to the inferior articular surface of the L5 vertebral body
3. LL (Figure 3.21) given by Step 1 and 2

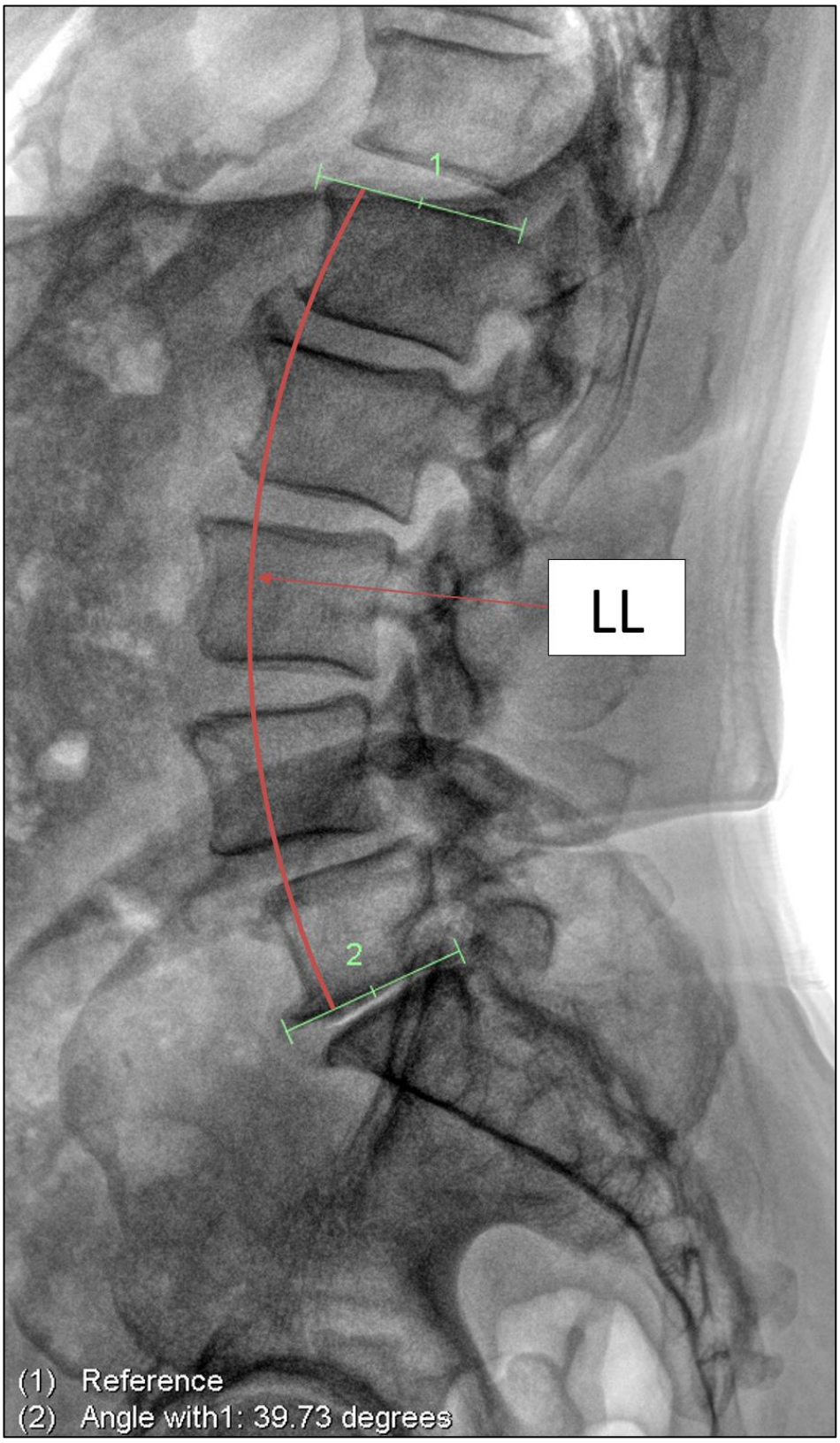


Figure 3.21 Lumbar lordosis (LL) measurement

3.2.5 Patient-reported outcome measures

After recruitment of each participant via a PICF, a questionnaire form was completed. This form included patient-reported outcome measures (PROM) that were chosen based on our literature review and those routinely used at MLRC, described below.

Knee Injury and Osteoarthritis Outcome Score (KOOS) (242)

42-item form covering 5 domains:

- Pain – 9 items
- Symptoms – 7 items
- Activities of daily living – 17 items
- Sport and recreation function – 5 items
- Knee-related quality of life – 4 items

Each item is scored from 0-4 (least to worst impact), with a maximum possible score of 168. Participant scores were calculated as a percentage of the maximum possible score e.g., a score of 84/168 = 50%.

Short-Form 36 (SF-36) (247)

36-item form covering physical, social and emotional domains over current and previous-four-week time frames.

Each item is scored from 0-100 (least to worst impact), with a maximum possible score of 3600. Participant scores were also calculated as a percentage of the maximum possible score for this PROM.

3.2.6 Measurement data collection/categorisation and analysis

Data set 1 – Primary measurements

Depending on the available images, pre-operative and post-operative measurements on the left and right leg were taken of the 14 variables (from Sub-Section 3.2.4) of interest on all participants (taken by HW). Hence, from these measurements, data of un-operated anatomy was separated out to form Data set 4, explained on the next page.

Surgery-specific data was considered from the following categories:

- HTO/DFO procedures
- Different internal fixation plates for HTO, labelled Plate A and Plate B (Figure 3.22).

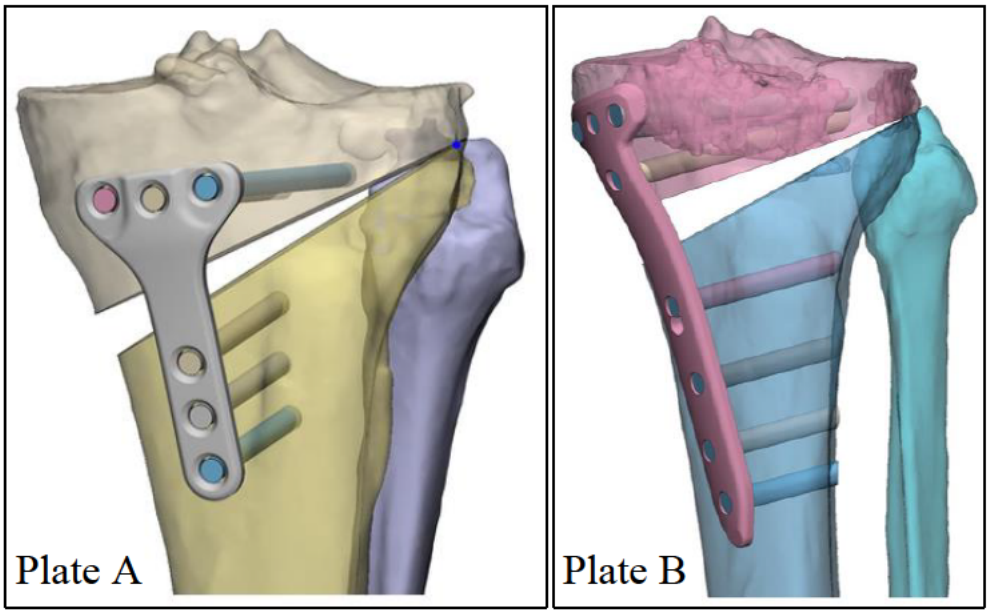


Figure 3.22 High tibial osteotomy Plate A and Plate B
3Matic (Materialise, Leuven, Belgium) modelling of superior tibia, osteotomy simulation and Plate A/Plate B. Plate B has larger dimensions and uses two more screws than Plate A.

Data set 2 – Intra-observer reliability

Measurements of HKA, ATL, PO and TS were repeated two more times after the initial Data set 1 measurement round (three times total), separated by two weeks between each repetition of measurements to eliminate bias. These four variables were chosen due their availability across most image sets, high clinical relevance and/or greater perceived difficulty during the measurement process.

Data set 3 – Inter-observer reliability

An orthopaedic registrar from MLRC (GO – Observer 2) was chosen to assist with an inter-observer reliability investigation. This involved a single measurement of HKA, PO and TS (chosen for the same reasons as Data set 2) on all pre-operative and post-operative images for the left and right leg. These were then compared to Data set 1 from HW.

Data set 4 – Methodological (inter-image) error

Measurements from Data set 1 that should theoretically not have changed between pre and post-op images (i.e. measurements of anatomy that was not operated on) were separated out to establish control measurements that identify inter-image error that may have been present throughout the study. For example, a left-sided HTO patient should have identical left-sided mLDFA measurements in pre and post-op images, as their femur is not surgically altered. Similarly, this patient should have very similar, if not identical right leg HKA in pre and post-op images (under the assumption that imaging protocols were adhered to). These assumptions should be met if standard imaging protocols were adhered to.

Data analysis

Data analysis was performed in Microsoft Excel (Microsoft, Washington, United States) and SPSS Statistics 27 (IBM, New York, United States). This analysis involved calculation of mean and standard deviation (SD) for post-operative change data (post-op data minus pre-op data), as well as raw data. P-values were calculated from raw data using paired T-tests with a significance level of <0.05 and a hypothesis of $H_0=H_1$.

Coefficient of variation (CV) was calculated to determine the variability for intra/inter-observer reliability and methodological (inter-image) error data, using the following equation: $CV\% = \frac{s \times 100}{\bar{x}}$ where s = sample SD and $\bar{x}$ = sample mean. The acceptable variability threshold for CV was set at 30% (272). Statistically outlying data was included in analyses to accurately represent potential variability.

Chapter 4: Results

Measurements made within InteleViewer™ (Intelerad, Quebec, Canada) software are presented in this Section. Data was separated into pre-operative bone morphology/malalignment, post-operative bone morphology/alignment change and patient-reported outcome measures (PROMs). Intra/inter-observer reliability and methodological (inter-image) error were then investigated to determine measurement error that may have been present throughout the study. At all stages of measurement conduction, the senior orthopaedic surgeons in this study were provided screenshot records for review to ensure the work had been done in-line with standard clinical protocols. Most Figures are displayed as the difference between pre and post-operative measurements, such that the changes following HTO/DFO are clear – these changes are presented as mean ± standard deviation (SD). Raw pre/post-operative data descriptive statistics and P-values/coefficient of variation (CV) are tabulated at the end of each Section, where applicable.

4.1 PRE-OPERATIVE BONE MORPHOLOGY AND MALALIGNMENT

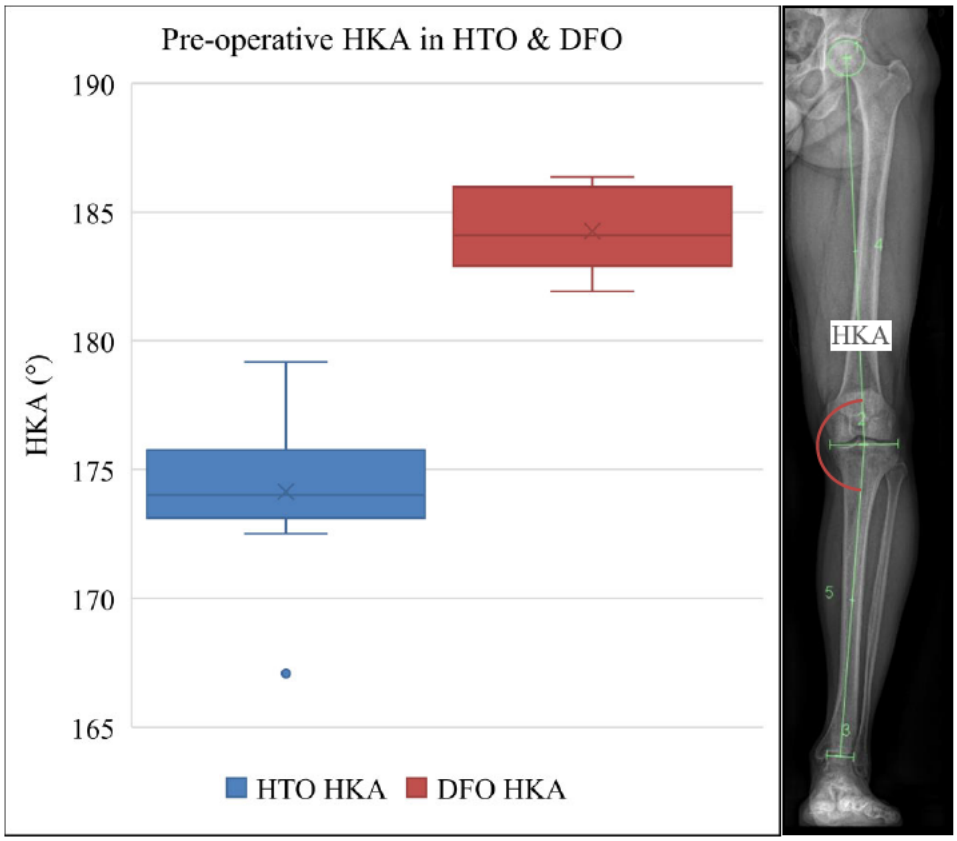


Figure 4.1 Pre-operative varus or valgus malalignment
Normal values 180°. Hip-knee-ankle angle (HKA), high tibial osteotomy (HTO), distal femoral osteotomy (DFO). HTO HKA (n=14), varus 174.14° ± 2.76. DFO HKA (n=6), valgus 184.26° ± 1.70.

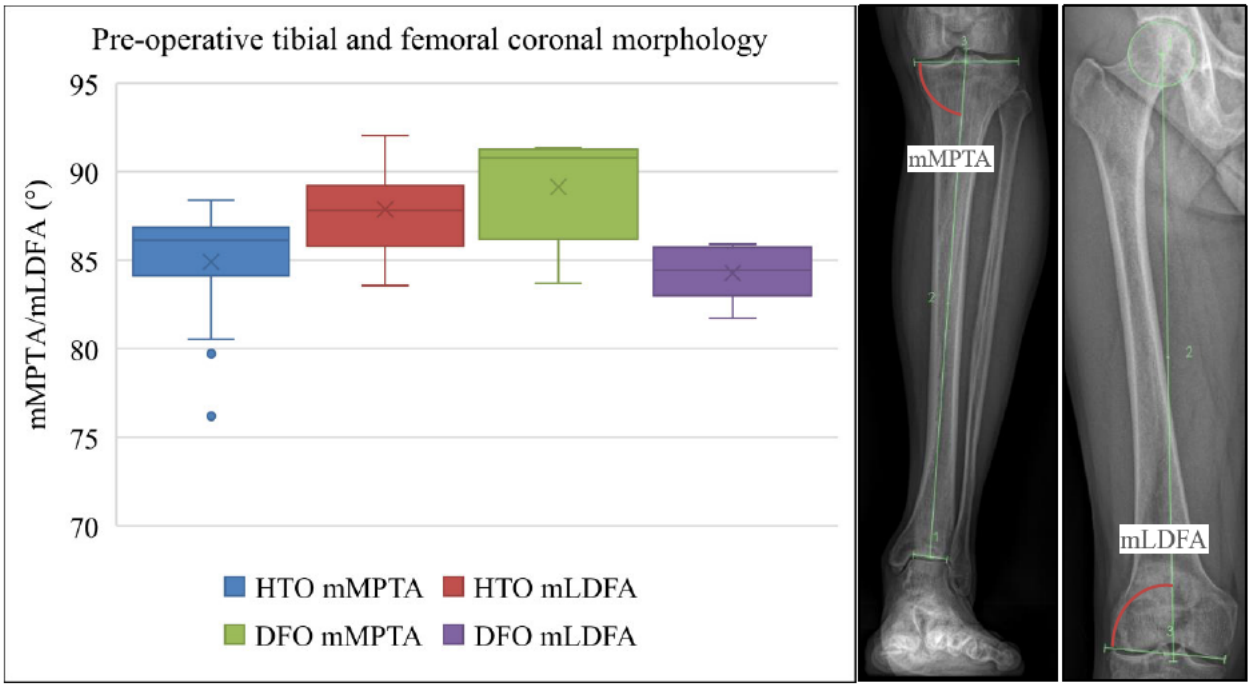


Figure 4.2 Pre-operative tibial and femoral coronal morphology
Normal values 87°. High tibial osteotomy (HTO), distal femoral osteotomy (DFO), mechanical medial proximal tibial angle (mMPTA), mechanical lateral distal femoral angle (mLDFA). HTO mMPTA (n=14), 84.91° ± 3.53. HTO mLDFA (n=14), 87.87° ± 2.33. DFO mMPTA (n=6), 89.14° ± 3.12. DFO mLDFA (n=6), 84.27° ± 1.63.

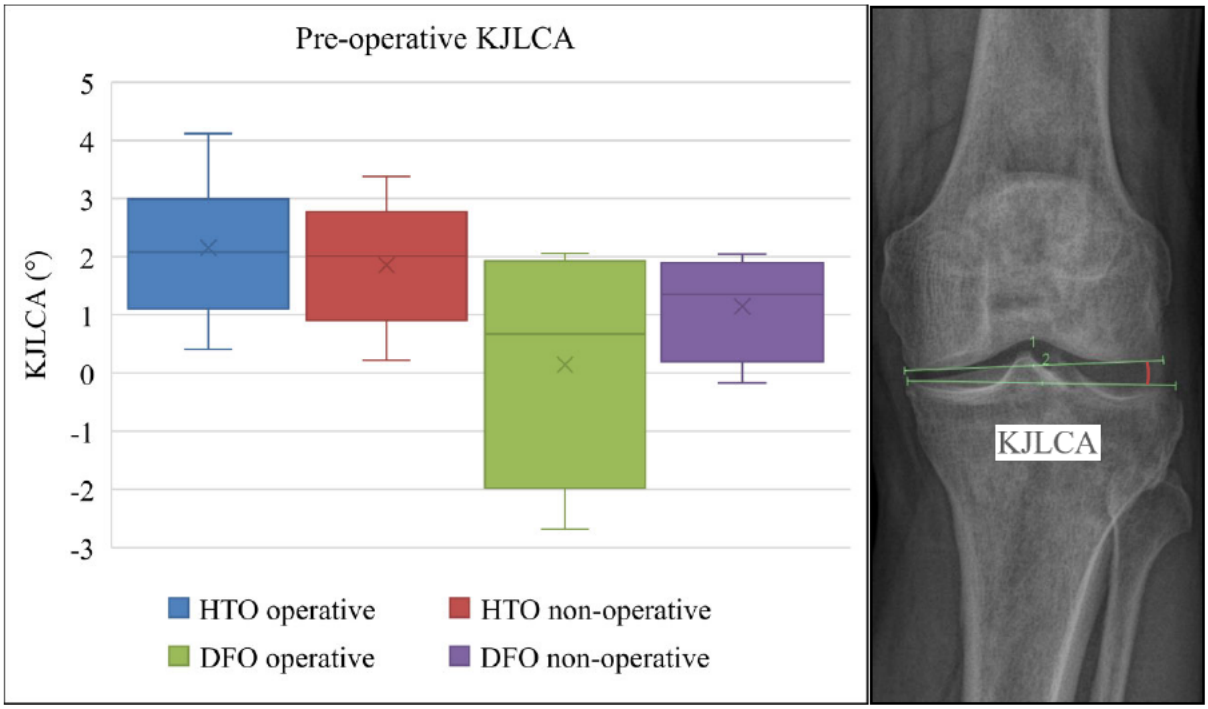


Figure 4.3 Pre-operative knee joint line convergence angle
Knee joint line convergence angle (KJLCA), high tibial osteotomy (HTO), distal femoral osteotomy (DFO). Positive values represent medially-narrowed KJLCA. HTO operative side (n=15), KJLCA 2.15° ± 1.16. HTO non-operative side (n=12), KJLCA 1.86° ± 1.07. DFO operative side (n=6), KJLCA 0.14° ± 1.95. DFO non-operative side (n=4), KJLCA 1.15° ± 0.94.

4.2 POST-OPERATIVE BONE MORPHOLOGY AND ALIGNMENT CHANGE

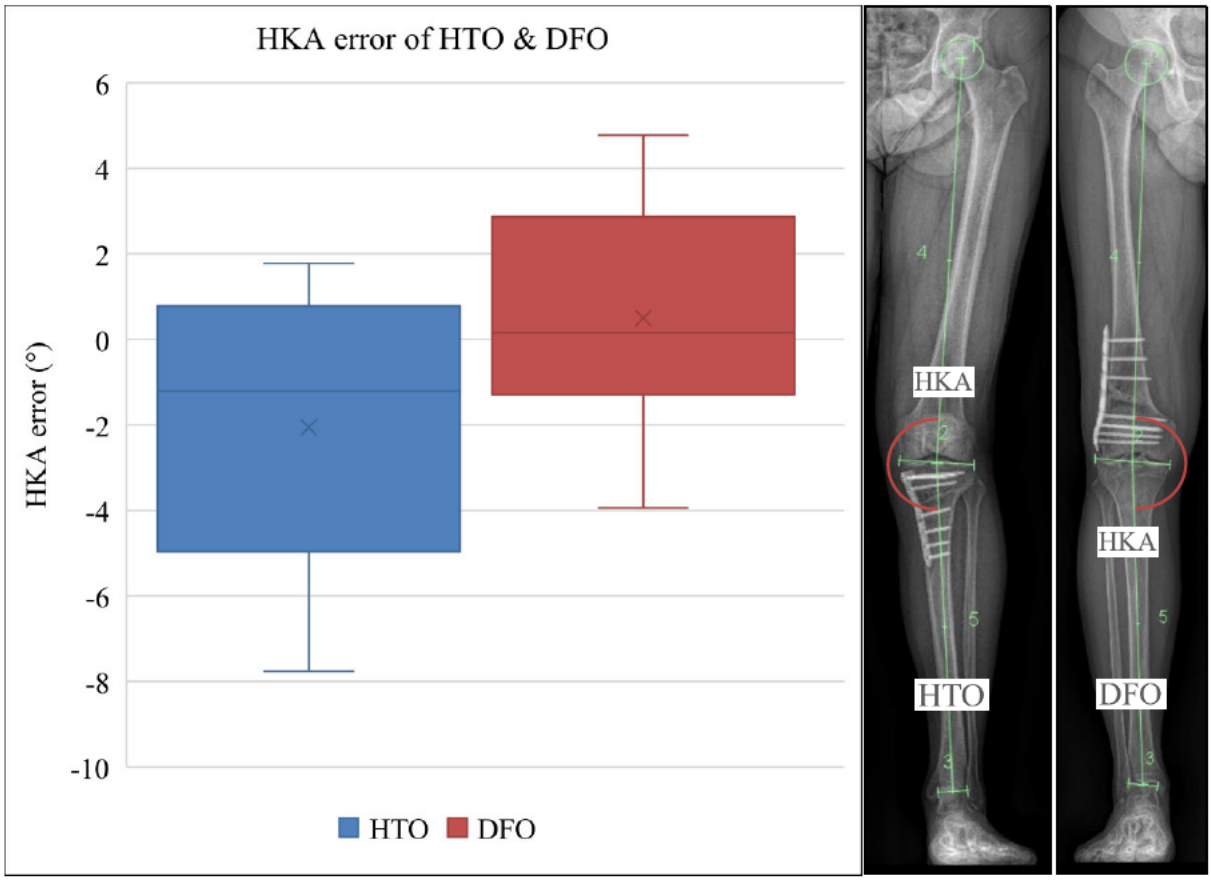


Figure 4.4 Post-operative hip-knee-ankle angle error
Hip-knee-ankle angle (HKA), high tibial osteotomy (HTO), distal femoral osteotomy (DFO). HKA error, calculated as the post-operative HKA measurement minus the targeted HKA i.e. negative values represent under-correction. HTO (n=14), raw error -2.05° ± 3.03, percentage error -28.64% ± 47.35. DFO (n=6), raw error 0.50° ± 2.90, percentage error 0.87% ± 57.61.

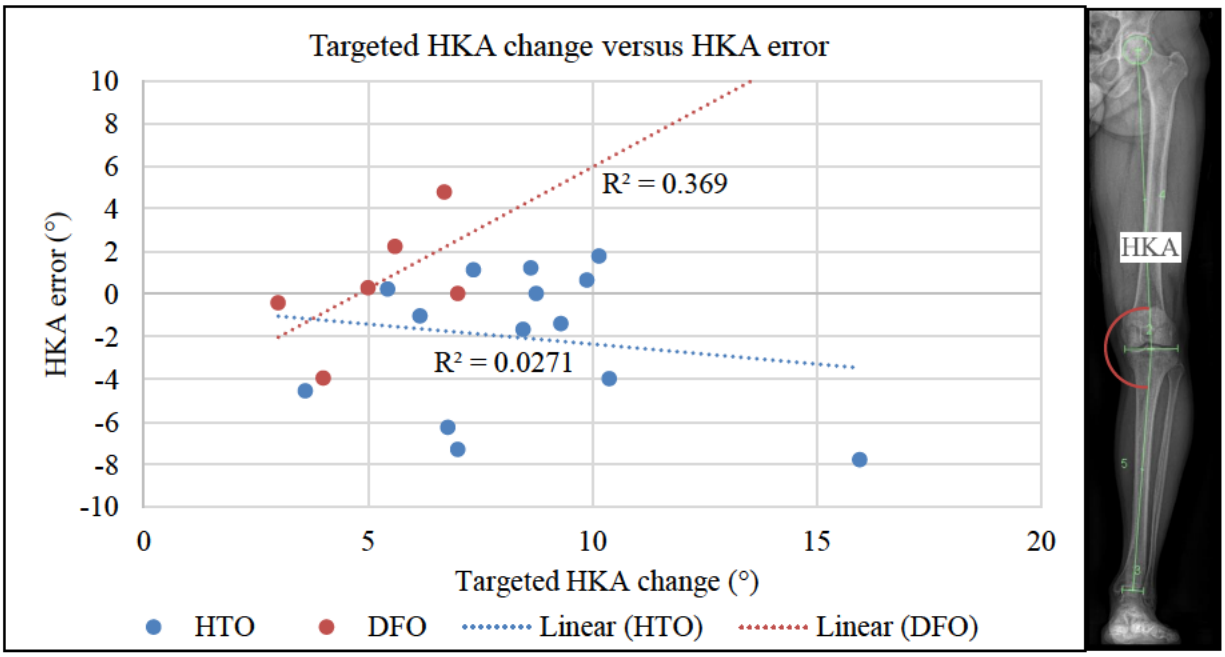


Figure 4.5 Correlation between targeted alignment change and hip-knee-ankle angle error
Targeted hip-knee-ankle angle (HKA) change is the planned degree of surgical alteration to the HKA. High tibial osteotomy (HTO) R^2=-0.03, distal femoral osteotomy (DFO) R^2=0.37.

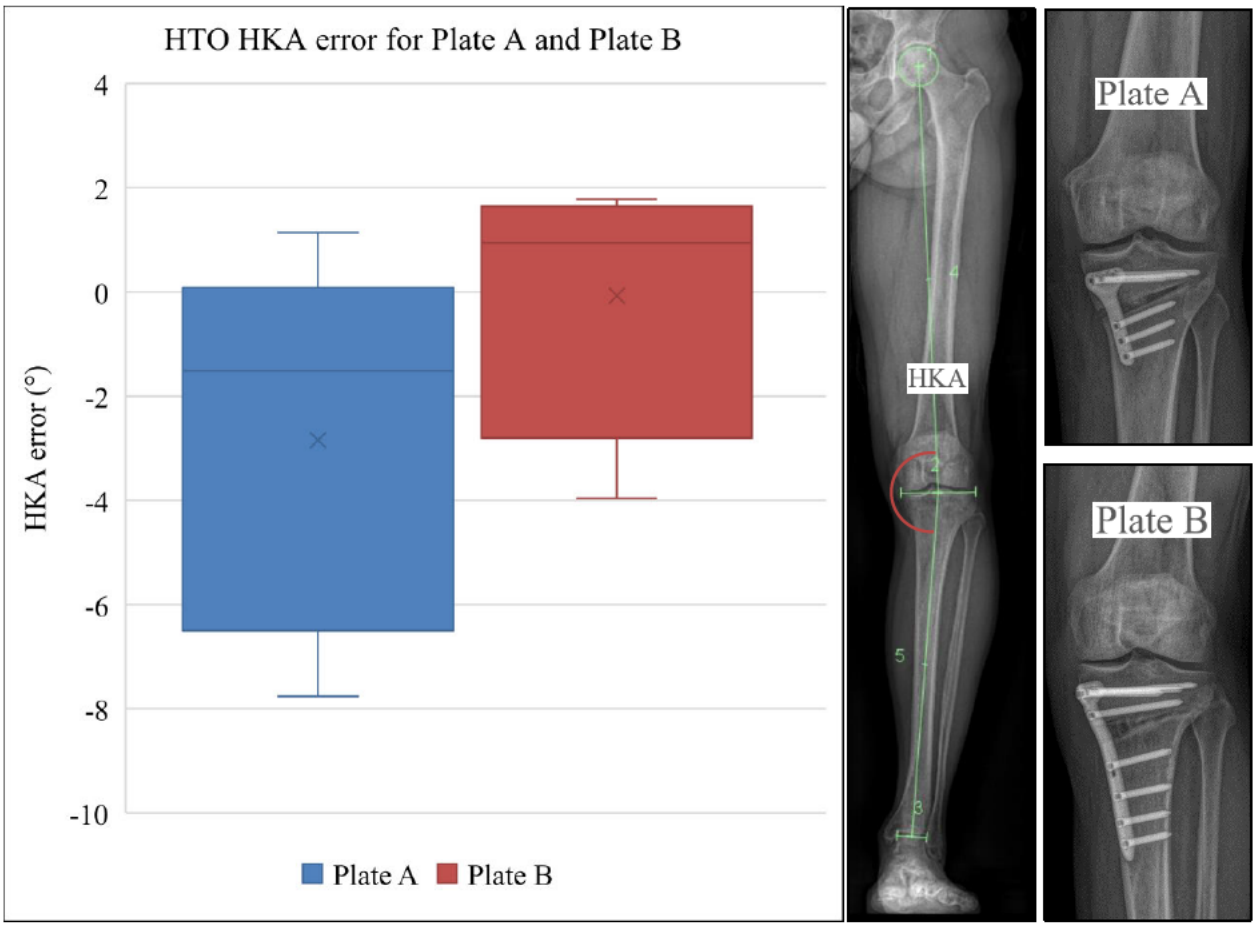


Figure 4.6 Plate A versus Plate B hip-knee-ankle angle error
High tibial osteotomy (HTO), hip-knee-ankle angle (HKA). HKA error, calculated as the post-operative HKA measurement minus the targeted HKA i.e. negative values represent under-correction. Plate B has larger dimensions and uses 2 more screws than Plate A. Plate A (n=10), HKA error -2.85° ± 3.31. Plate B (n=4), HKA error -0.07° ± 2.63.

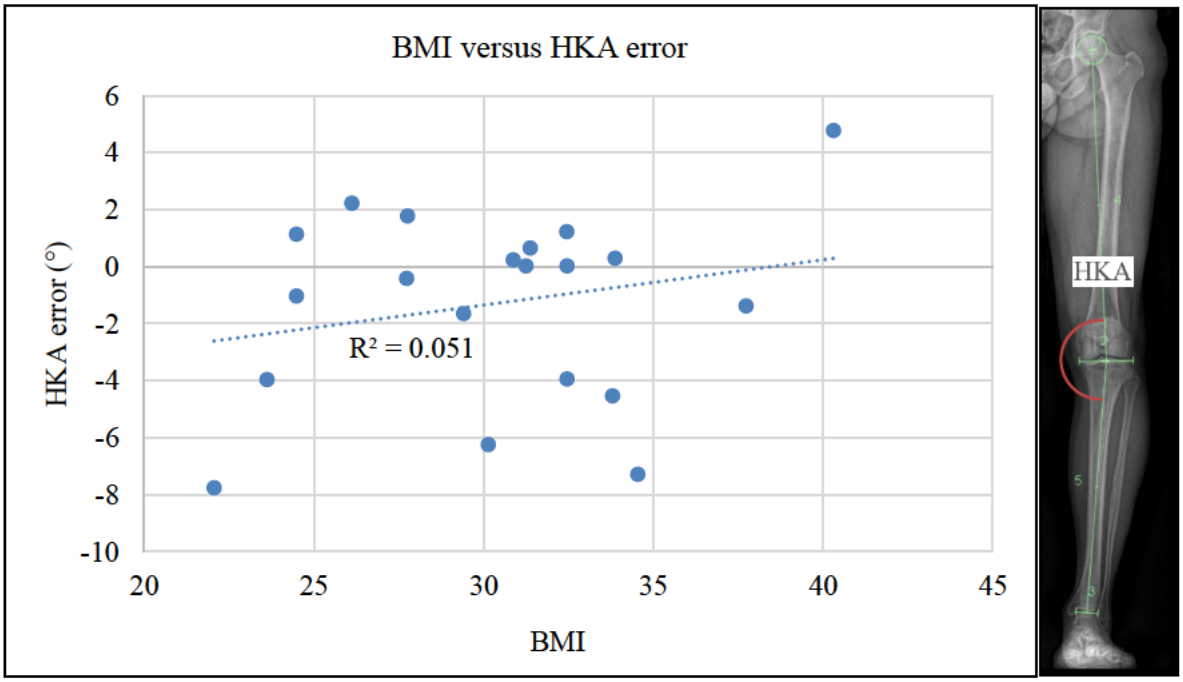


Figure 4.7 Correlation between patient Body Mass Index and hip-knee-ankle angle error
Body mass index (BMI), hip-knee-ankle angle (HKA). R^2=0.05

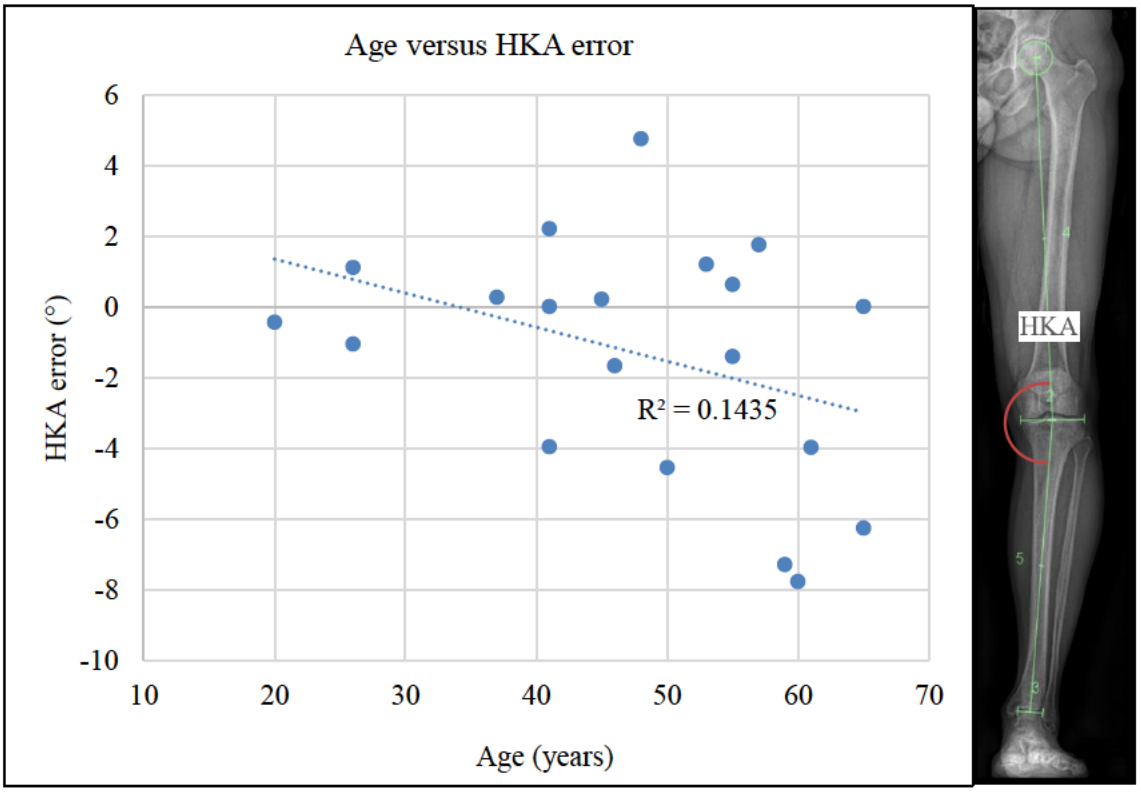


Figure 4.8 Correlation between patient age and hip-knee-ankle angle error
Hip-knee-ankle angle (HKA). HKA error, calculated as the post-operative HKA measurement minus the targeted HKA i.e. negative values represent under-correction. R^2=-0.14

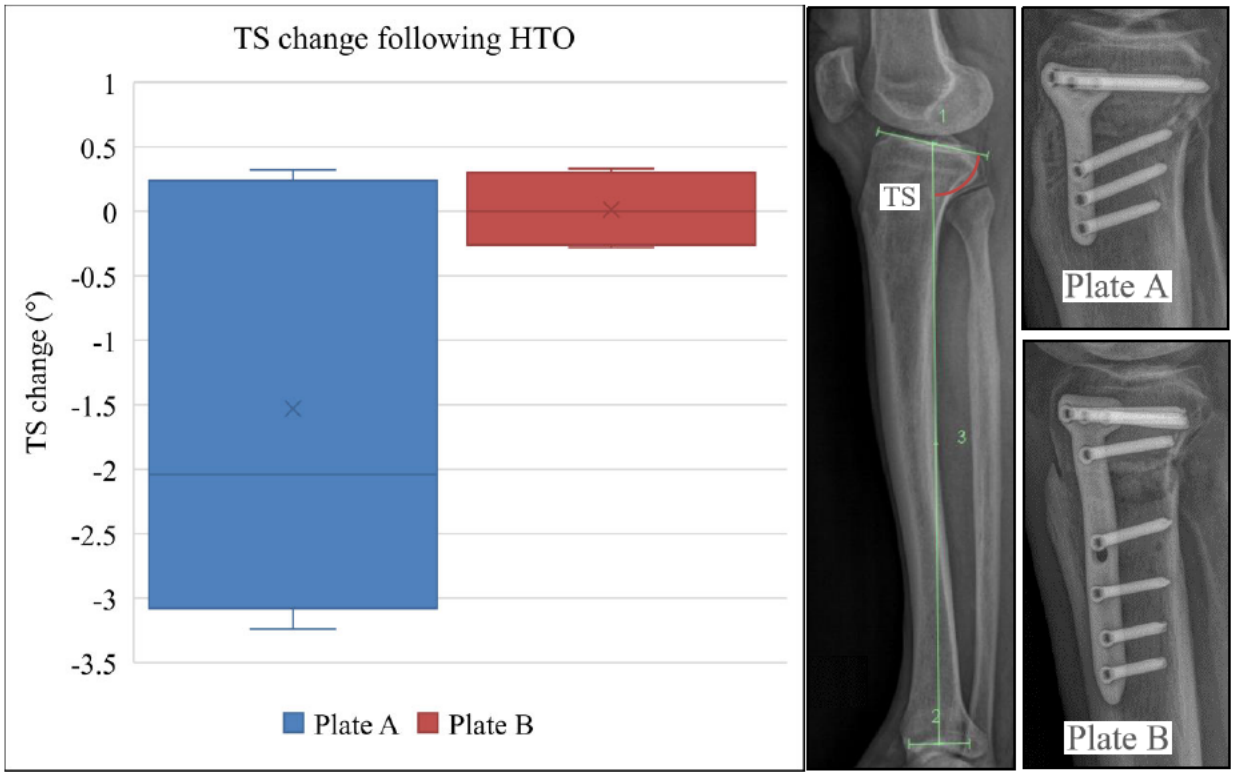


Figure 4.9 Post-operative change in tibial slope following high tibial osteotomy
Tibial slope (TS), high tibial osteotomy (HTO). Plate B has larger dimensions and uses 2 more screws than Plate A. All surgeries aimed to maintain the pre-operative TS angle. Negative values represent an increase in TS. Plate A (n=7), TS change -1.53° ± 1.58. Plate B (n=4), TS change 0.01° ± 0.30.

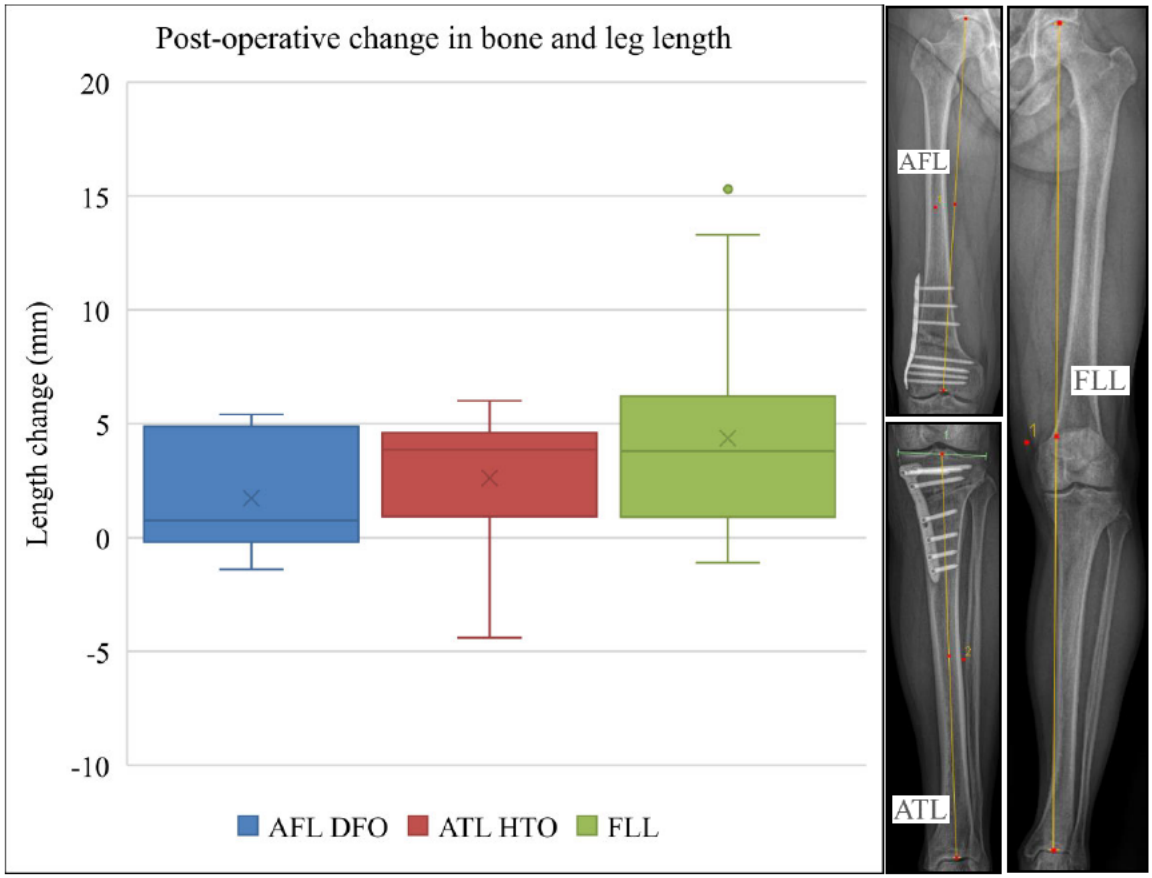


Figure 4.10 Post-operative change in bone and functional leg length
Anatomical femur length (AFL), distal femoral osteotomy (DFO), anatomical tibia length (ATL), high tibial osteotomy (HTO)functional leg length (FLL). Femurs (n=6), AFL change 1.73 mm ± 2.70. Tibias (n=12), ATL change 2.61 mm ± 2.84. Functional leg length (n=18), FLL change 4.36 mm ± 4.66.

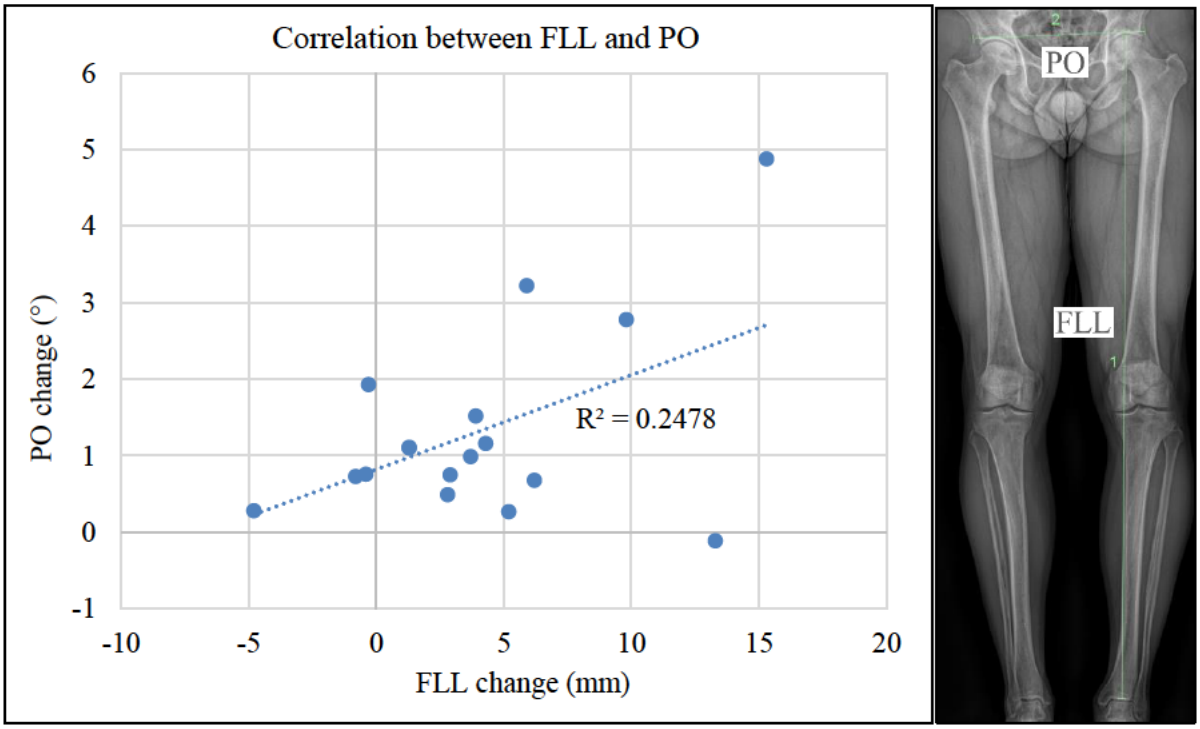


Figure 4.11 Correlation between change in functional leg length and pelvic obliquity
Functional leg length (FLL), pelvic obliquity (PO). N=17, FLL change 4.09 mm ± 5.08. PO change 1.33° ± 1.22. R^2=0.25

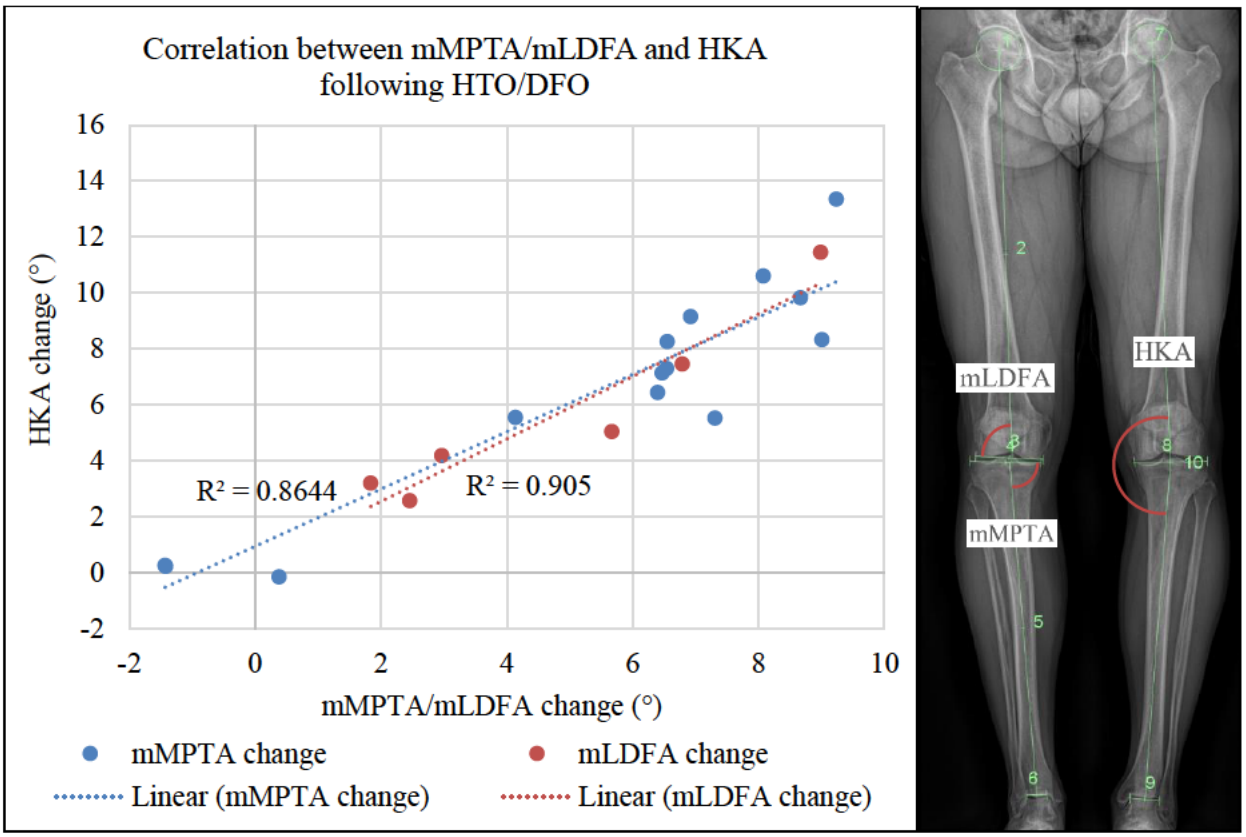


Figure 4.12 Correlation between change in mechanical medial proximal tibial angle/mechanical lateral distal femoral angle and hip-knee-ankle angle
Mechanical medial proximal tibial angle (mMPTA), mechanical lateral distal femoral angle (mLDFA), hip-knee-ankle angle (HKA), high tibial osteotomy (HTO), distal femoral osteotomy (DFO). mMPTA versus HKA in HTO (n=14), R^2=0.86. mLDFA versus HKA in DFO (n=6), R^2=0.91.

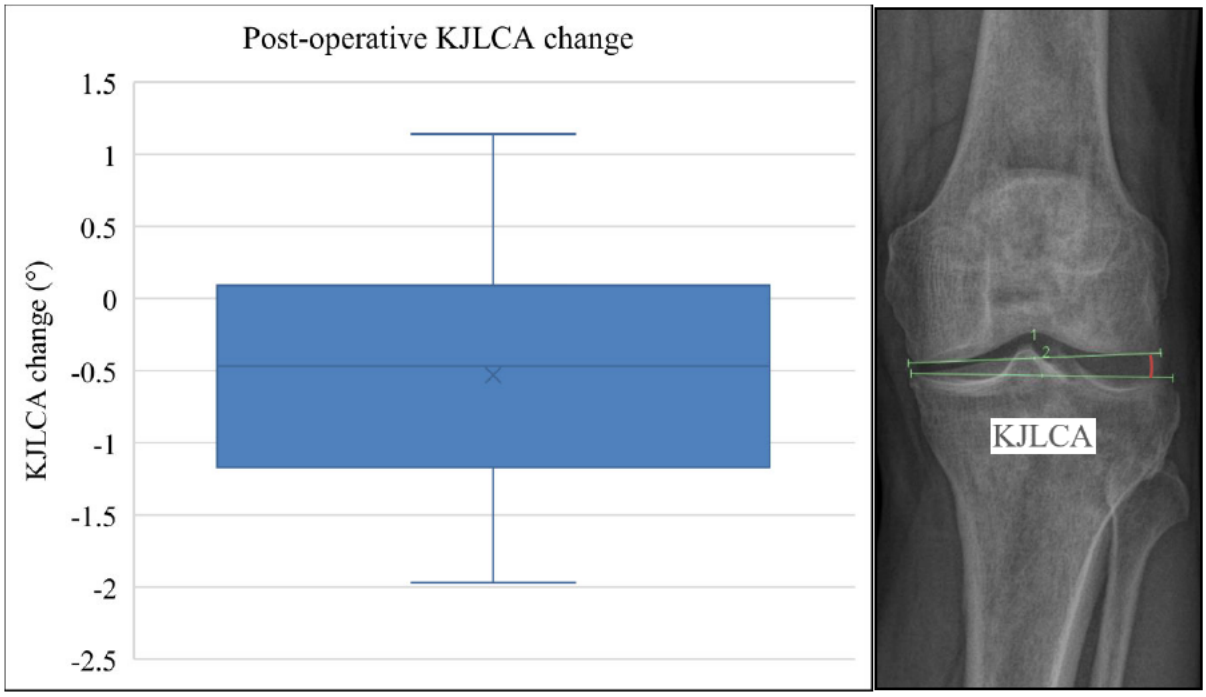


Figure 4.13 Post-operative knee joint line convergence angle change
Knee joint line convergence angle (KJLCA). Negative values represent a transition towards parallel joint line convergence. N=20, KJLCA change -0.53° ± 0.84.

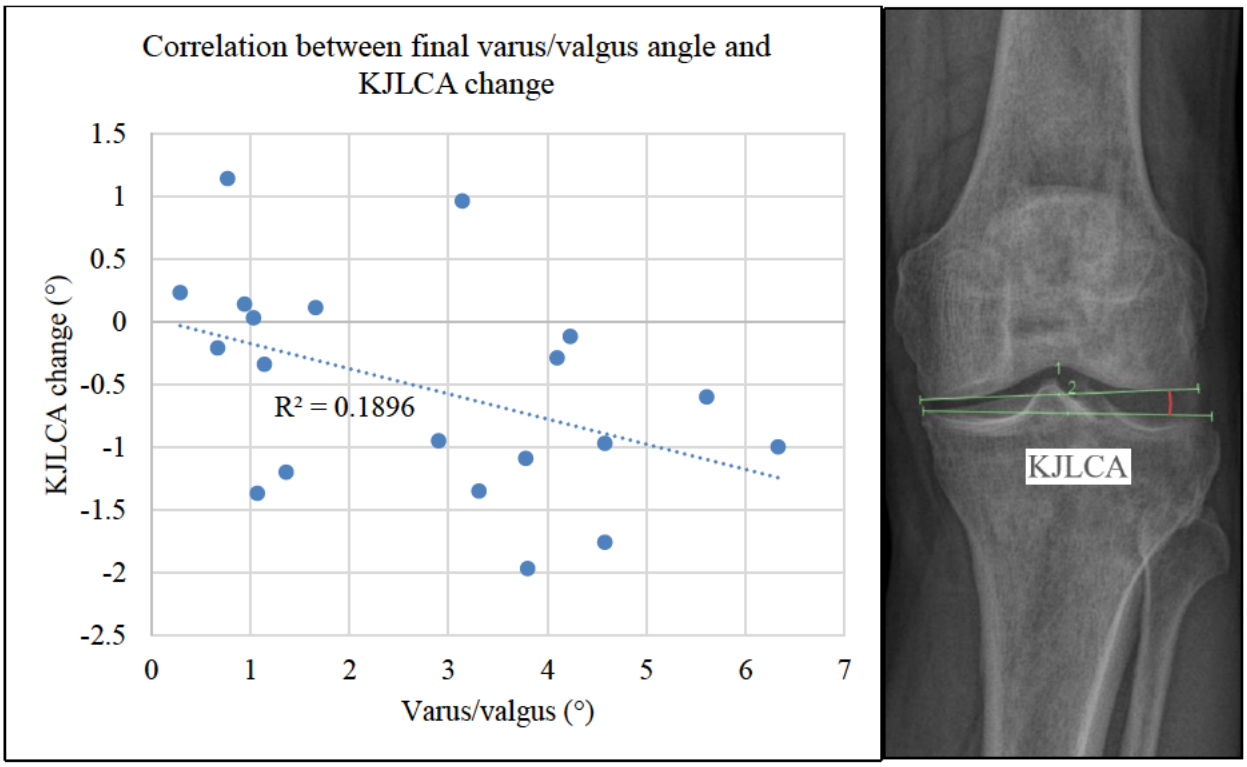


Figure 4.14 Correlation between post-operative varus/valgus and knee joint line convergence angle change
Knee joint line convergence angle (KJLCA). R^2=-0.19

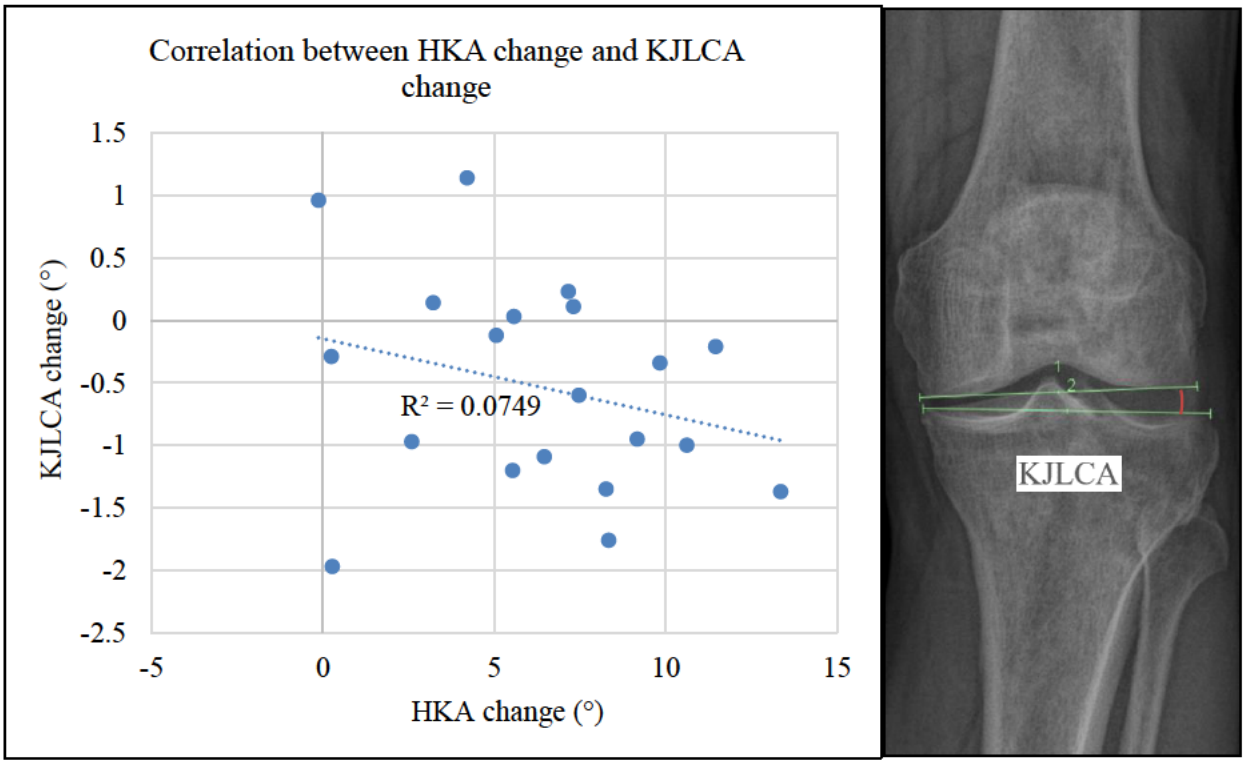


Figure 4.15 Correlation between change in hip-knee-ankle angle and knee joint line convergence angle
Hip-knee-ankle angle (HKA), knee joint line convergence angle (KJLCA). R^2=-0.07

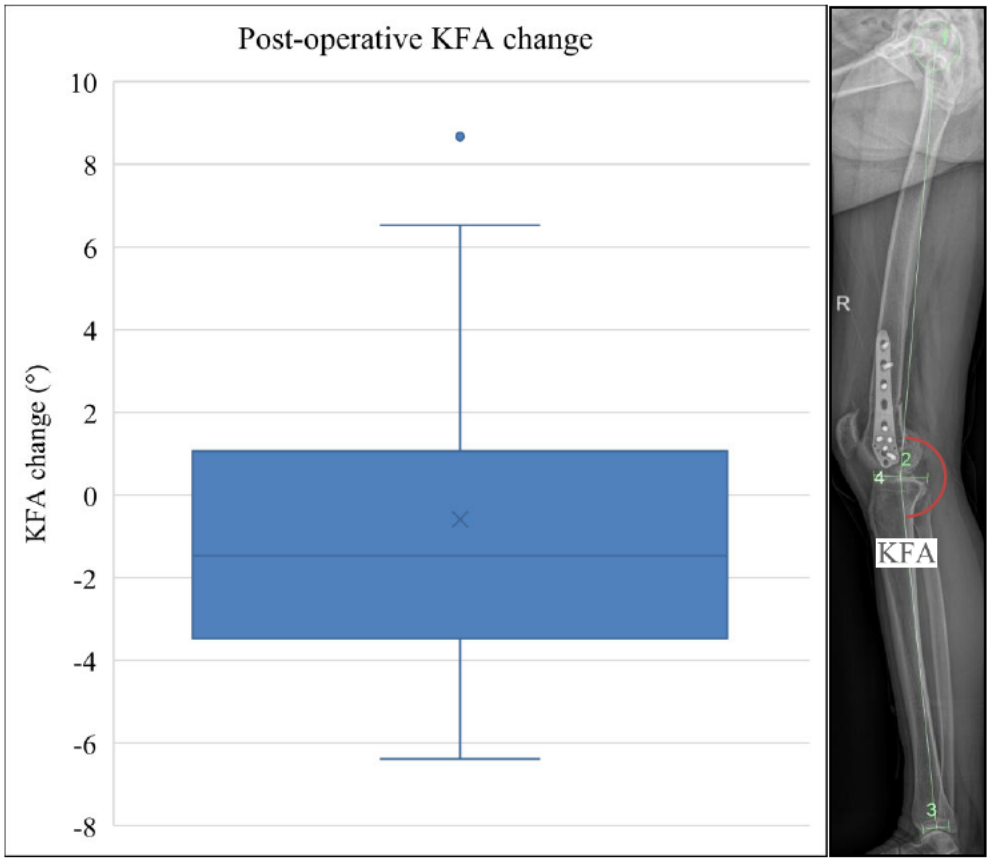


Figure 4.16 Post-operative change in knee flexion
Knee flexion angle (KFA). Negative values represent a post-operative increase in knee flexion. N=15, change -0.59° ± 4.17.

Table 4.1 Pre-operative versus post-operative data analysis

Measurement	Target/Pre-op/Post-op	Mean ± SD	P-value
HTO HKA error	Target	182.63° ± 1.15	0.0548
	Post	180.68° ± 3.39	
DFO HKA error	Target	179.08° ± 0.64	0.6985
	Post	178.60° ± 3.11	
HTO HKA error Plate A	Target	182.47° ± 1.34	0.0237
	Post	179.63° ± 3.02	
HTO HKA error Plate B	Target	183.02° ± 0.11	0.8568
	Post	183.32° ± 3.06	
FLL	Pre	82.34 cm ± 6.68	0.0010
	Post	82.77 cm ± 6.83	
AFL	Pre	42.92 cm ± 3.78	0.1762
	Post	43.09 cm ± 3.95	
ATL	Pre	36.69 cm ± 2.85	0.0088
	Post	36.95 cm ± 2.78	
HTO mMPTA	Pre	84.91° ± 3.53	0.0001
	Post	90.40° ± 3.91	
DFO mLDFA	Pre	84.27° ± 1.63	0.0089
	Post	89.06° ± 2.04	
KJLCA	Pre	2.00° ± 1.11	0.0133
	Post	1.48° ± 0.97	
TS	Pre	83.09° ± 2.61	0.0517
	Post	82.12° ± 2.69	
KFA	Pre	176.55° ± 6.59	0.5911
	Post	175.96° ± 5.64	

4.3 PATIENT-REPORTED OUTCOME MEASURES

Data from the two PROMs completed by participants are presented here, and are compared with other variables that have been suggested as influencing factors for procedure success.

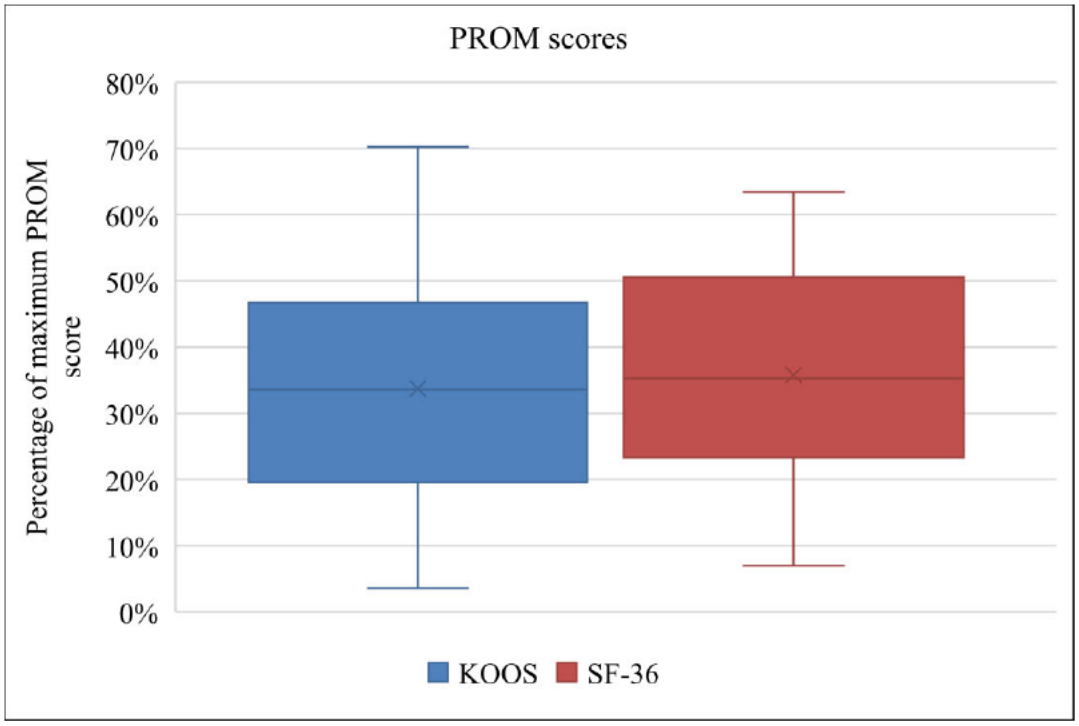


Figure 4.17 Patient-reported outcome measure scores
Patient-reported outcome measure (PROM) 0-100% (least to most affected by knee symptomatology). Knee Injury and Osteoarthritis Outcome Score (KOOS), Short Form 36 (SF-36). KOOS (n=18) 33.72% ± 19.07. SF-36 (n=18), 35.81% ± 17.82. There was no statistically significant difference between KOOS and SF-36 scores (p=0.2477).

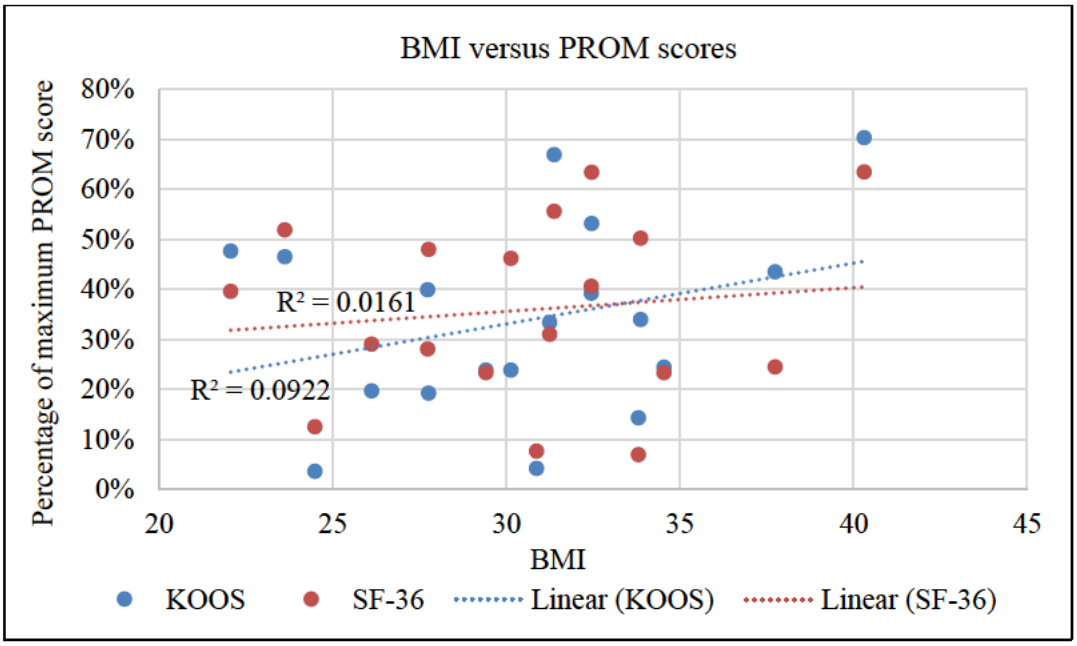


Figure 4.18 Correlation between patient Body Mass Index and patient-reported outcome measure scores
Body Mass Index (BMI). Patient-reported outcome measure (PROM) 0-100% (least to most affected by knee symptomatology). KOOS R^2=0.09, SF-36 R^2=0.02.

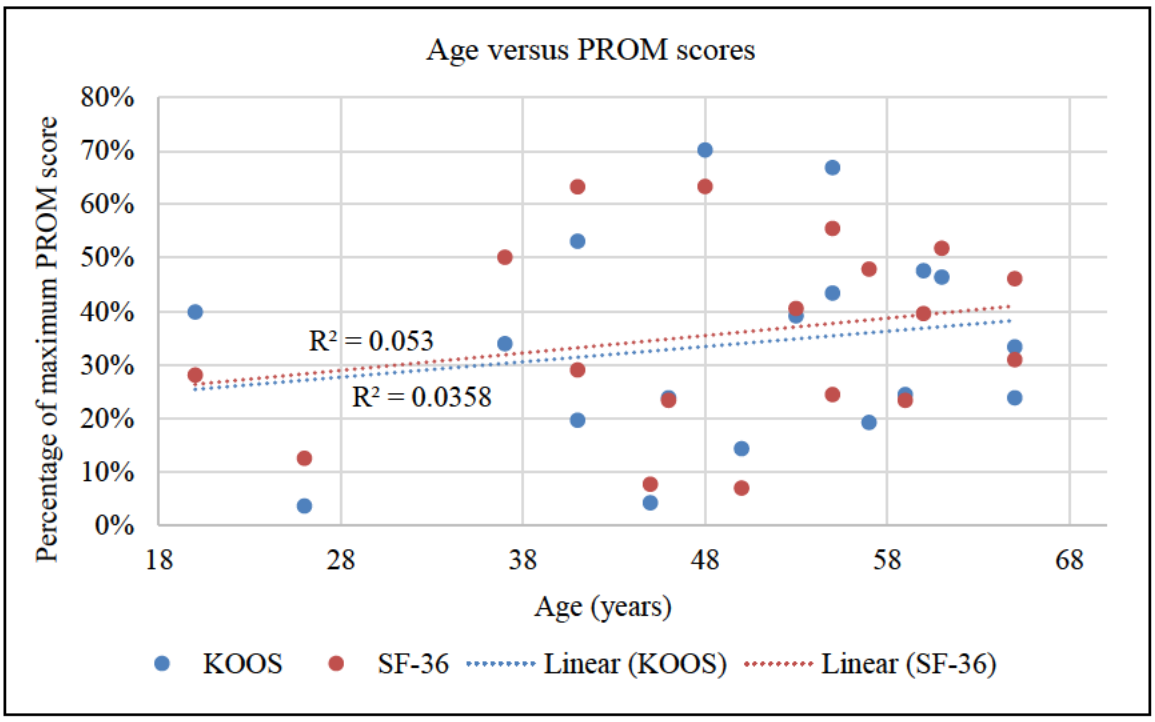


Figure 4.19 Correlation between patient age and patient-reported outcome measure scores
Patient-reported outcome measure (PROM) 0-100% (least to most affected by knee symptomatology). KOOS R^2=0.04, SF-36 R^2=0.05.

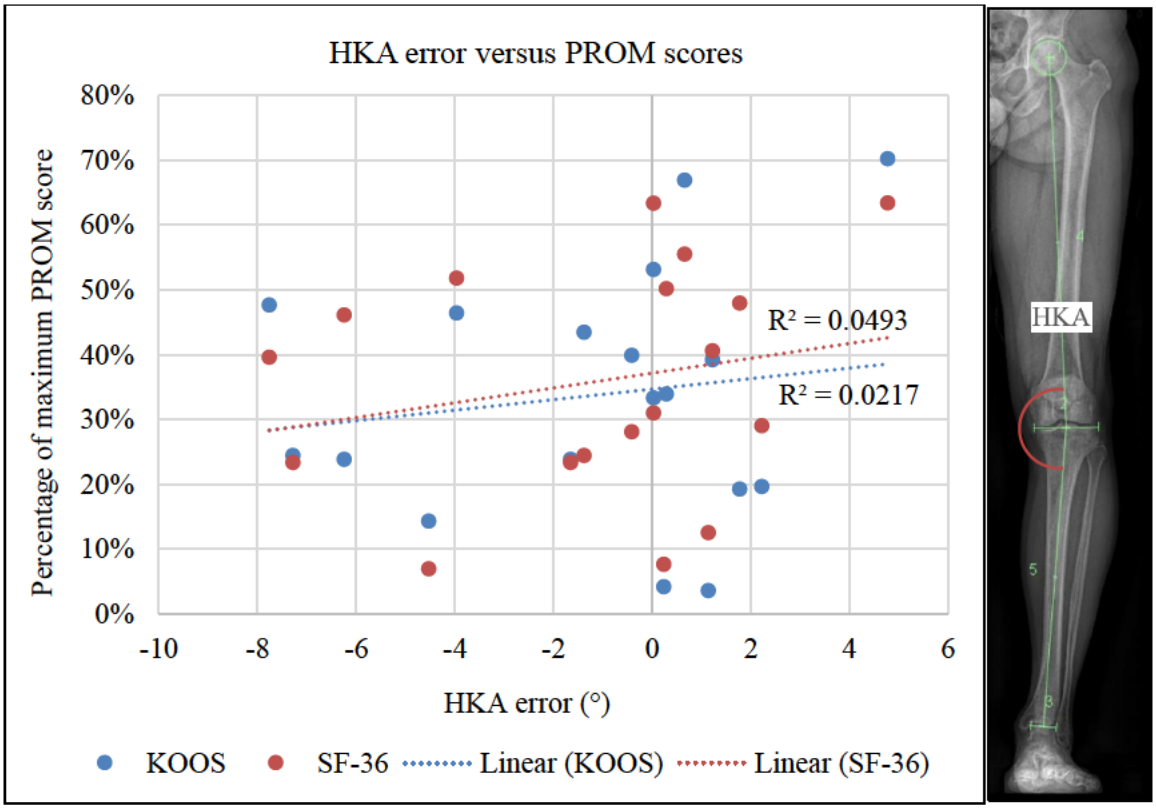


Figure 4.20 Correlation between post-operative alignment error and patient-reported outcome measure scores
Hip-knee-ankle angle (HKA) error, calculated as the post-operative HKA measurement minus the targeted HKA. Patient-reported outcome measure (PROM) 0-100% (least to most affected by knee symptomatology). KOOS R^2=0.02, SF-36 R^2=0.05.

4.4 POTENTIAL SOURCES OF MEASUREMENT ERROR

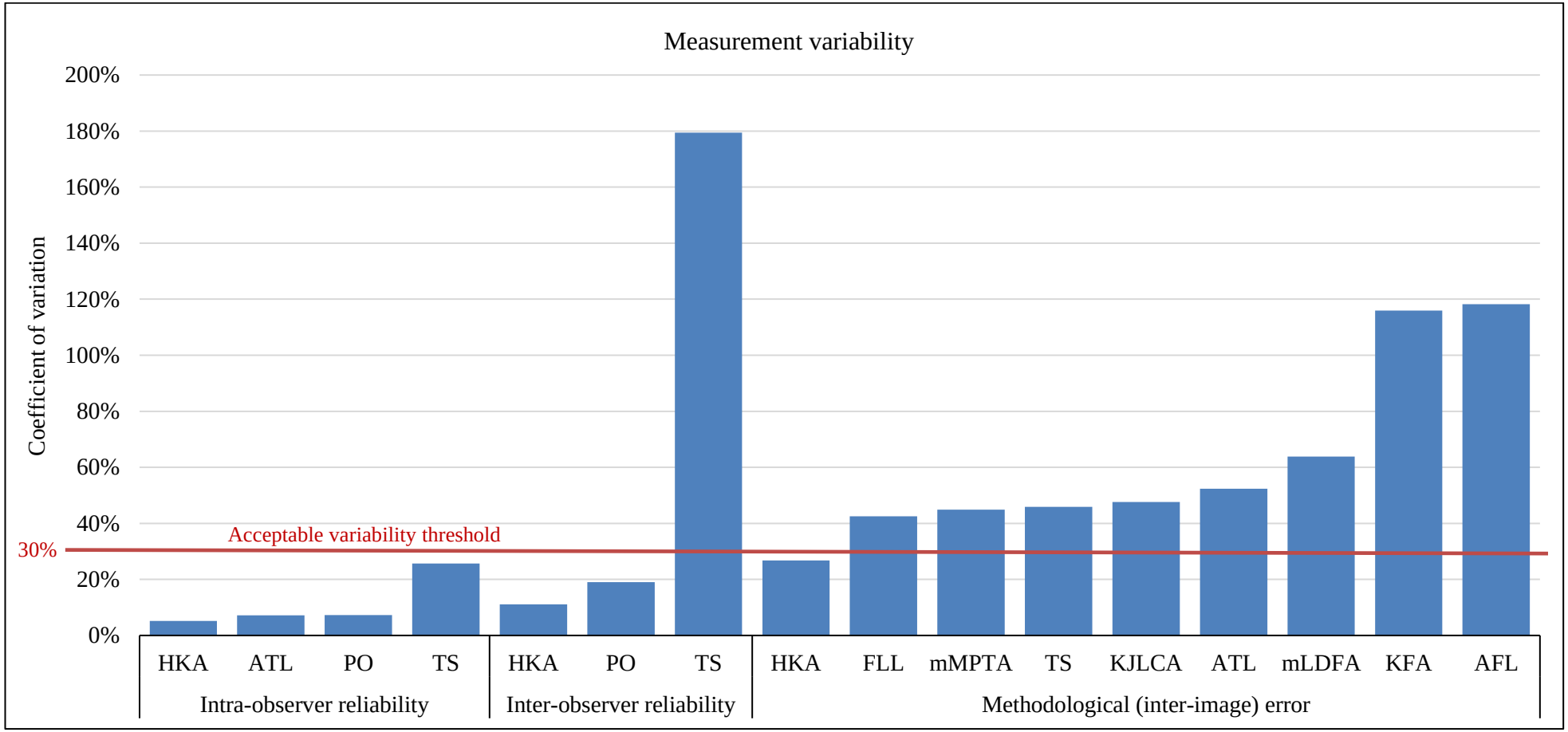


Figure 4.21 Measurement variability summary
Hip-knee-ankle angle (HKA), anatomical tibia length (ATL), pelvic obliquity (PO), tibial slope (TS), functional leg length (FLL), mechanical medial proximal tibial angle (mMPTA), knee joint line convergence angle (KJLCA), mechanical lateral distal femoral angle (mLDFA), knee flexion angle (KFA), anatomical femur length (AFL). Acceptable variability threshold set at 30% based on Hussein et al. (272)

Intra-observer reliability

Table 4.2 Intra-observer reliability data analysis

Measurement	N=	Round	Mean ± SD of raw data	Mean ± SD of ranges across repeat measurements rounds	Variation coefficient (%)
HKA	74	1	177.63° ± 3.92	0.15° ± 0.09	5.17
		2	177.60° ± 3.91		
		3	177.60° ± 3.90		
PO	36	1	0.76° ± 2.49	0.11° ± 0.06	7.24
		2	0.77° ± 2.47		
		3	0.80° ± 2.44		
TS	64	1	83.31° ± 2.80	0.35° ± 0.21	25.64
		2	83.32° ± 2.75		
		3	83.32° ± 2.80		
ATL	74	1	36.51 cm ± 2.85	0.4 mm ± 0.3	7.22
		2	36.52 cm ± 2.85		
		3	36.53 cm ± 2.85		

Inter-observer reliability

Table 4.3 Inter-observer reliability data analysis

Measurement	N=	Observer	Mean ± SD of raw data (°)	Mean ± SD of differences between observers (°)	Variation coefficient (%)
HKA	71	1	177.39 ± 3.80	-0.04 ± 0.28	11.08
		2	177.43 ± 3.79		
PO	34	1	0.53 ± 2.18	-0.05 ± 0.24	19.02
		2	0.58 ± 2.12		
TS	59	1	83.34 ± 2.82	-0.02 ± 2.13	179.39
		2	83.36 ± 3.20		

Methodological (inter-image) error

Table 4.4 Methodological error data analysis

Measurement	N=	Pre/Post-op	Mean ± SD for raw data	Mean ± SD of differences between pre and post-op images	Variation coefficient (%)
HKA	15	Pre	176.75° ± 2.38	-0.17° ± 0.71	26.76
		Post	176.64° ± 2.65		
mMPTA	21	Pre	87.18° ± 2.66	-0.04° ± 0.57	44.87
		Post	87.14° ± 2.81		
mLDFA	29	Pre	87.60° ± 2.01	0.07° ± 0.80	63.80
		Post	87.67° ± 1.88		
KJLCA	15	Pre	1.67° ± 1.09	-0.06° ± 0.64	47.62
		Post	1.61° ± 1.44		
TS	19	Pre	83.81° ± 2.95	0.09° ± 0.55	45.88
		Post	83.90° ± 2.80		
KFA	11	Pre	178.10° ± 7.13	2.26° ± 1.98	115.98
		Post	180.36° ± 6.58		
FLL	15	Pre	83.93 cm ± 6.02	2.07 mm ± 4.78	42.55
		Post	84.13 cm ± 6.13		
AFL	29	Pre	46.19 cm ± 3.04	0.09 mm ± 7.86	118.26
		Post	46.20 cm ± 3.27		
ATL	21	Pre	35.99 cm ± 2.81	1.18 mm ± 2.45	52.39
		Post	36.11 cm ± 2.87		

Chapter 5: Discussion

From Section 5.1 to 5.4, this Chapter covers the findings of our study and compares those to existing literature. In the interest of avoiding repetition, Section 5.5 addresses recurring challenges and limitations present throughout the study. Section 5.6 concludes this Chapter with recommendations for future research in the knee osteotomy sphere.

5.1 PRE-OPERATIVE BONE MORPHOLOGY AND MALALIGNMENT

All high tibial osteotomy (HTO) and distal femoral osteotomy (DFO) patients had pre-operative malalignment below 13° varus and 7° valgus, respectively (Figure 4.1). This represents suitable malalignment to correct with a single-level opening-wedge osteotomy and expect good patient outcome – more than 15° varus/valgus is suggested to be the contraindication to single-level osteotomy and an indication for double-level osteotomy (273). Furthermore, mechanical medial proximal tibial angles (mMPTA) and mechanical lateral distal femoral angles (mLDFA) fell within 11° and 6° of the normal 87° for HTO and DFO patients, respectively, which are suitable for a single-level opening-wedge correction.

HTO patients appeared to have much greater deformity in the tibia compared to the femoral deformity in DFO patients i.e. DFO patients had lower-limb valgus deformity from the femur and tibia combined, whereas HTO patient's varus originated more from solely the tibia. Of course, sample-size disparity of 14 and 6 for HTO and DFO, respectively, should be kept in-mind here. There was greater presence of medially-narrowed knee joint line convergence angle (KJLCA) in varus malaligned individuals compared to laterally-narrowed KJLCA in the valgus malaligned. This implies that some DFO surgeries may have been shifting weight bearing towards medial compartments with comparatively less preserved cartilage volume than the lateral compartments (274). This is justified if the patient presents with lateral-sided joint pain, as the cartilage on the medial side may not have undergone symptomatic osteoarthritic change, even if it radiographically appears as narrowed. Finally, comparison of the operative knee to the non-operative knee revealed notable KJLCA symmetry, suggesting that the development of symptomatology on one side may be predictive of future contralateral symptomatology.

Overall, no concerning values were observed in the pre-operative measurements which could have warranted additional exclusions from the study, providing confidence in the suitability of our cohort to be used for post-operative change investigation.

5.2 POST-OPERATIVE BONE MORPHOLOGY AND ALIGNMENT CHANGE

Hip-knee-ankle angle (HKA)

As the primary objective for this study, the pre-operatively planned HKA alignment correction target was compared to our post-operative HKA measurement, with the difference between these values labelled as 'HKA error'. Discrepancy between these target and the post-op measurements was objectified in Figure 4.4 as a box plot quantifying the HKA error for HTO/DFO. Our data reflected an HKA error of -2.05° ± 3.03 for 14 HTO procedures, and 0.50° ± 2.90 for 6 DFO procedures. There was no statistically significant difference between target HKA values and post-operative measurements for HTO ($p=0.0548$) or DFO ($p=0.6985$). This indicates that HTO/DFO performed with patient-specific instruments (PSI) can result in accurate surgical corrections of varus/valgus deformity of the knee.

Comparing our results to previous studies of PSI accuracy in HTO/DFO, our HKA error appears more varied than those reported by other authors. Summarised in Table 2.4 of the Literature Review Chapter, the 'Mean accuracy error' column displayed the findings from 14 studies of PSI use in HTO/DFO in terms of their 'HKA error' equivalent (19, 40, 41, 48, 173, 206-214), depending on the various metrics used to measure knee alignment. Due to heterogeneity in these metrics, summary statistics cannot be generated, but it can be discerned that our mean and standard deviation (SD) for HKA error showed more variation than the identified literature. Possible causation of this disparity is likely to be a combination of radiographic and methodological influences, which will be elucidated in Section 5.5.1. We also calculated these results as percentage error, which provides further description on the apparent surgical accuracy, since it calculates HKA error as a percentage of the planned correction angle, rather than a raw value e.g. an HKA error of -2° from a planned correction angle of 4° is an HKA percentage error of -50%, meaning the procedure was under-corrected by half of the planned correction. Our data from Figure 4.4 showed HKA percentage error of -28.64% ± 47.35 for HTO and 0.87% ± 57.61 for DFO. Raw values are typically reported due to their clinical relevance, but presentation of both raw and percentage error would be a welcome addition to osteotomy research if it were to become standard practice.

Figure 4.5 showed no correlation between the size of the planned HKA correction angle and HKA error for the 14 HTO procedures with an R^2 of -0.03. There was weak correlation for DFO procedures with an R^2 of 0.37, but this was calculated from a comparatively small sample of 6.

There was notable difference between HTO secured with Plate A and Plate B in terms of HKA error in Figure 4.6, with Plate B reducing the incidence of under-corrections and tightening the SD (HKA error 0.07° ± 2.63) compared to Plate A (HKA error -2.28° ± 3.07). Sample sizes of

10 and 4 for Plate A and Plate B, respectively, could be a cause of this difference, but the results from Plate B were promising even with less than half of the sample size. This also supported the conclusion from Diffo Kaze et al.'s systematic review of osteosyntheses that larger T-shaped plates may facilitate more accurate corrections (221), which is a design characteristic of Plate B. No correlation was seen between body mass index (BMI) and HKA error, nor between patient age and HKA error. This data was unsurprising since BMI and age are suggested to be reasonably forgiving factors in terms of their influence on HTO/DFO outcome (170, 198), as mentioned in the surgical indications from Section 2.5.

The final analysis was correlating change in mMPTA and mLDFA with the change in HKA, which showed $R^2 = 0.86$ for mMPTA and $R^2 = 0.91$ for mLDFA. These very strong correlations provide confidence that mMPTA, mLDFA and HKA measurements were all conducted accurately, as there should be a strong correlation between change in these variables (48, 181).

Tibial slope (TS)

Regarding TS change following HTO procedures (shown in Figure 4.9), we observed a TS increase of 0.97° ± 1.46 across 11 procedures. This aligns with the 2016 meta-analysis of 27 studies indicating an expected TS increase of ~2° following medial opening-wedge HTO (275). In our study, the 7 osteotomies fixed with Plate A appeared to show more TS change (increased by 1.53° ± 1.58) than the 4 osteotomies fixed with Plate B (decreased by 0.01° ± 0.30), which may suggest superior post-operative stability and wedge-opening maintenance of Plate B. This stability is likely attributed to the increased surface area that Plate B covers, as well as the use of 2 more screws compared to Plate A (221).

Another consideration regarding TS change is the positioning of internal fixation. Visible in Plate A from Figure 3.22 and supported in Diffo Kaze et al.'s systematic review of HTO osteosyntheses (221), positioning of fixation on the anteromedial aspect of the superior tibia should logically provide more stability to the anterior portion of the wedge. If this were to be the case, then the expectation of increased TS following opening-wedge HTO could be related to reduced support at the posterior portion of the wedge, leading to posterior closure of the wedge during ossification and a subsequent increase in TS. Figure 3.22, however, shows Plate B positioned more towards the medial aspect of the superior tibia, which may give more even support to the anterior and posterior sections of the wedge to maintain TS. According to the team of engineers who assisted in planning the surgeries in our study, plate positioning is often determined by facilitating a suitable 'plate-to-bone' distance at the superior and inferior osteotomy level – calculated on 3Matic software.

Luites et al. conducted a radiostereometric analysis (RSA) study of 20 TomoFix-secured opening-wedge HTO procedures at 6-weeks post-op, which showed ~0.5° dorsal tilting of the tibial plateau relative to inferior bone (276). RSA should give an excellent indication of tibial plateau movement, and although Luites et al. did not use standard radiographic TS measurement (as used in our study), it provides strong evidence that a slight increase in TS is a likely post-operative outcome. Our speculation on TS increase being caused by a weight-bearing induced posterior closure of the opening-wedge was also mentioned by Luites et al., but there appears to be no consensus on what causes TS increase. It is likely that there are many causes, and isolation of these causes to determine their influence on TS change would be very difficult.

Anatomical femur length (AFL), anatomical tibia length (ATL) and functional leg length (FLL)

In an attempt to identify the source of coronal pelvic alignment change, bone length measurements were taken in the form of AFL, ATL and FLL. As expected with an opening-wedge approach, a slight increase in bone length was mostly seen. AFL saw a change of 1.7 mm ± 2.7 with no obvious outliers, and ATL saw a change of 2.61 mm ± 2.84 after two clear outliers (which showed ~25 mm decrease in ATL) were removed relating to radiographic issues (Section 5.5.1). Similar observations were seen in FLL with regards to a slight post-operative increase of 4.36 mm ± 4.66 after exclusion of the same two outlier measurements from ATL.

This aligns with Lee et al.'s 2016 systematic review indicating an average 6.96 mm increase in leg length across 127 opening-wedge HTO procedures (230). Whilst Lee et al. described this change as clinically concerning, the pre-operative condition of the patient is the ultimate determinant in whether such an increase in FLL will negatively impact biomechanics. A leg-length discrepancy (LLD) of more than 15 mm has been suggested as the threshold at which clinical concern is introduced (277, 278). Hence, FLL change following HTO/DFO may only be clinically concerning if the surgery results in an LLD of more than 15 mm. In many instances, HTO/DFO may actually restore leg-length equality that was caused by varus/valgus malalignment i.e. malalignment can cause a shortened FLL. Pre-operative assessment of patient FLL in combination with surgical planning/simulation could determine whether or not a concerning change can be expected. Even if an LLD of more than 15 mm has been described as concerning and has shown correlation with hip OA (278), an expected post-operative LLD of more than 15 mm may not be a contraindication to HTO/DFO, as individuals could receive many years of improved knee function and QoL from these surgeries, and hip OA development may not be guaranteed.

Our final comment on FLL change is that bigger opening-wedge sizes do not always result in a greater FLL change. Although wedge dimensions were not recorded in this study, it was noticed that patients who went from varus into valgus, or vice versa, often showed very minor FLL

increase, or even shortening. This is because neutral HKA alignment gives the largest FLL value. Hence, surpassing neutral HKA alignment can result in no change or shortening of FLL.

Pelvic obliquity (PO)

Directly related to FLL, pelvic obliquity (PO) was the measurement for quantifying coronal pelvic alignment change post-surgery. Although PO is often measured as a millimetre distance between two horizontal lines tangential to the rooves of the acetabula (279), we elected to use an angle measurement – FLL already gives a very strong indication of millimetre offset between the acetabula on 2D radiographic images. PO change was 1.33° ± 1.26, with this value being related to the operative side i.e. a positive value means that the pelvis shifted superiorly on the operative side. In the case of bilateral surgeries, the smaller FLL change value was subtracted from the larger FLL change value, and then compared to PO change on the side that demonstrated the larger FLL value – a potential limitation for these data points. Correlation between change in FLL and PO was weak at R^2=0.25, but incorrect patient stance and/or knee flexion during image acquisition are likely reasons for this correlation not being stronger (see Section 5.5.1). Nevertheless, our results showed the relationship between FLL and PO.

Akin to the possible effect of FLL change on the hip joint, whether PO change is sufficient to cause symptomatic scoliosis in the spine will depend on the pre-operative condition of the patient alongside any existing spinal symptoms/pathology. A notable finding from revisiting the literature is that LLD of more than 20 mm is suggested to be when significant spinal malalignment can begin to develop (25), which would correspond to a PO threshold of approximately 3.75° based on our measurements. For the same reasons previously mentioned regarding FLL change and hip OA, minor predicted spinal malalignment may not be a contraindication to HTO/DFO, and perhaps spinal measurements and clinical monitoring may only be warranted if the procedures cause LLD/PO of more than 20 mm/3.75°, respectively.

Knee flexion angle (KFA)

To delineate the cause of sagittal pelvic alignment change following HTO/DFO, KFA needed to be investigated, as this correlates strongly with inter-related parameters like sacral slope, pelvic tilt and lumbar lordosis (22, 231, 232). Our data showed post-operative KFA change of -0.59° ± 4.17 (negative values represent an increase in knee flexion), which was more change than anticipated. Section 5.4 will demonstrate the variability observed in control measurements of KFA.

We believe that KFA measurement using the full single-leg lateral/sagittal protocols currently in-place at imaging facilities may not be suitable for taking this measurement on some individuals. Patients are typically asked to stand on one leg fully extended/hyperextended, with the other foot placed on a small block in-front and hands placed on shoulders. This protocol

suffices for standard clinical observations of the surgical site, but the research value must be questioned. Whether this protocol is applied before or after surgery, in cohorts where knee pain and osteoarthritic change is present, asking patients to weight-bear on one leg in full extension is a biomechanically demanding task that may not be entirely complied with due to physical limitations or avoidance of discomfort. Hence, when these images are taken post-operatively, it is possible that patients are still regaining confidence in full-extension weight bearing and could flex their knee to compensate, resulting in an invalid measurement of true KFA.

No existing literature was found on knee flexion change following HTO/DFO, nor could data on the accuracy of single-leg sagittal radiographs for KFA measurement be found. Understandably, KFA is not a measurement that is typically discussed in relation to HTO/DFO procedures, so this omission in the literature was unsurprising. However, if a comprehensive study on change in sagittal pelvic/spinal alignment following HTO/DFO were to be conducted, it would require precise measurement of KFA in a bipedal stance to eliminate the possible influences of current unipedal imaging protocol. A bipedal stance would also be required to validly measure pelvic/spinal parameters, as taking these measurements with the patient standing on one leg is likely to not be valid. With these factors in-mind, the possibility of executing this type of protocol using X-ray is questionable, as some form of 3D reconstruction would likely be necessary to differentiate the two limbs since they would inevitably overlap in a standard sagittal radiograph using this approach.

It would also be useful to determine what degree of flexion change comes from bone morphological change versus knee joint/surrounding musculoligamentous structure influence. For example, a change in TS following HTO could logically change the position of the ankle relative to the knee, and induce a minor degree of recurvatum/procurvatum in the tibia. Hence, if no change is seen in the sagittal morphology of the tibia, (if KFA is validly measured) then it may be reasonable to conclude that flexion change could have originated around the knee itself. Ultimately, the message we are trying to convey is that confirming sagittal pelvic/spinal alignment change as a consequence of HTO/DFO procedures would be extremely difficult and has a plethora of influencing factors to navigate.

Sagittal pelvic/spinal parameters

We intended to gather sacral slope (SS), pelvic tilt (PT), lumbar lordosis (LL) and lumbar scoliosis (LS) data, as these could have been correlated with any change in FLL/KFA and linked back to the HTO/DFO procedures performed. However, these sagittal measurements often could not be taken from the available images, which will be detailed in Sub-Section 5.5.1.

In addition, most of the participants underwent unilateral surgeries, which is ideal for observing coronal pelvic and spinal alignment change, but sagittal alignment presents more considerations – the literature on correlation between sagittal lower-limb alignment and pelvic/spinal alignment typically involves symmetrical lower-limb alignment change causing pelvic/spinal alignment change (as explained in Section 2.9). Hence, another consideration for any future study on pelvic/spinal alignment change following HTO/DFO would be to control for unilateral versus bilateral surgeries. Furthermore, axial plane alignment of the pelvis should be investigated since asymmetrical change to sagittal lower-limb alignment can cause compensatory truncal kinematics change, as indicated in gait analysis study (23). EOS image (EOS Imaging, Paris, France) 3D reconstructions using sterEOS^{TM} software (Biospace Med, Paris, France) can facilitate axial pelvic alignment measurement, but a recent study demonstrated the difficulty of acquiring reliable results (280).

Sensitivity of sagittal pelvic/spinal measurements to change based on patient stance, such as SS, PT and LL, also presents great difficulty in achieving accurate results relating to HTO/DFO (22). These three measurements are difficult to standardise as they are dynamic depending on posture/stance variation during image acquisition (281), meaning any observed change may not be directly related to HTO/DFO. These factors further exemplify the difficulty in confirming the effect of HTO/DFO on sagittal pelvic/spinal alignment changes.

KJLCA

When the alignment of the lower-limb changes as a result of HTO/DFO, cartilage pressure can be reduced in the arthritic compartment and increased in the more preserved compartment (183, 274). KJLCA is said to be an indicator of cartilage pressure, so this measurement was conducted bilaterally on all patients in our study.

We hoped to see a shift towards parallel KJLCA (0°) post-operatively, as this could indicate reduced pressure in the arthritic compartment. This was seen as a KJLCA change towards parallel of 0.53° ± 0.84, with ~75% of patients demonstrating a post-operative shift towards parallel.

These results align with Na et al.'s recent KJLCA study in HTO (282), which showed that patients with pre-operative KJLCA of less than 4° typically did not demonstrate more than 2° of post-operative KJLCA change, which was also seen in our pre and post-op data from Figures 4.3 and 4.13, respectively. However, Na et al. observed larger post-operative change in patients with pre-operative KJLCA of >4°. Hence, the conclusion from their study was that additional consideration of soft-tissue correction should be given to patients with pre-operative KJLCA greater than 4°, as post-operative KJLCA change greater than 2° can negatively impact correction accuracy. Very weak negative correlation was seen in our data between change in HKA and

KJLCA at R^2=-0.07, with a weak negative correlation seen between final HKA deviation from neutral alignment (degrees of varus/valgus) and KJLCA change at R^2=-0.19.

5.3 PATIENT-REPORTED OUTCOME MEASURES

The patient-reported outcome measure (PROM) data gathered during this study has limitations. Our participant cohort ended up being entirely retrospective due to the date of study commencement, as well as the onset of COVID-19 lockdown restrictions shortly after commencement. As a result, completion of PROMs was only done post-operatively. Hence, data from these questionnaires is a standalone indication of knee-related symptomatology at the time of completion, with no pre-operative results to determine whether the patient's perceived condition had improved or worsened following surgery. Furthermore, the retrospective nature of this study meant that participant recruitment was conducted at different stages of post-operative recovery e.g. some patients may have completed forms at 12-weeks post-op whereas others at 16-weeks post-op. This could have impacted PROM responses, as the stage of post-op recovery and return to normal daily activities may have differed throughout the cohort.

If the research was prospectively conducted, participants would be given a short PROM to be completed before/after clinic visitation at pre-defined time points, which would greatly enhance the findings related to each surgery. PROM data showed no statistically significant difference (p=0.2477) between scores of 33.72% ± 19.07 for the Knee Injury and Osteoarthritis Outcome Score (KOOS), and 35.81% ± 17.82 for Short Form 36 (SF-36), demonstrating similarity between these PROMs and indicating that participants completed the forms accurately. PROM scores showed very weak correlation with patient BMI (R^2=0.09 for KOOS, R^2=0.02 for SF-36) and very weak correlation with patient age (R^2=0.04 for KOOS, R^2=0.05 for SF-36). Finally, PROM scores showed very weak correlation with HKA error (R^2=0.02 for KOOS, R^2=0.05 for SF-36). Other studies have identified a stronger correlation between PROM scores and HKA error (182), which highlights the limitations in our PROM data.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) data was collected, but was removed from the study due to the KOOS covering the questions offered by WOMAC.

5.4 POTENTIAL SOURCES OF MEASUREMENT ERROR

<u>Intra-observer reliability</u>

Investigation of possible human error in measurements was performed to enhance the findings from this project. This was done in the form of 3 repeat measurements (two additional measurements after the initial 'Data set 1' round, separated by two weeks in between rounds) of

HKA, PO, ATL and TS for all 20 participants in pre and post-operative images on the left and right sides. The measurements in this investigation were chosen due to their availability across most image sets, high clinical relevance and/or greater perceived difficulty during the measurement process. Given the heterogeneity between image quality and patient stance seen throughout the study, we decided that 3 repeat measurements across a wide range of images/patients would provide more value than a greater number of repeated measurements across less images.

Figure 4.21 showed coefficient of variation (CV) results of 5.17% for HKA, 7.22% for ATL, 7.24% for PO and 25.64% for TS. The more varied TS results were unsurprising given the known difficulty of radiographic TS measurement and the greater sensitivity to change even with small alterations to line positioning along the tibial plateau (283). Nevertheless, all data showed acceptable levels of variability with CV values below the acceptability threshold of 30%.

Inter-observer reliability

In tandem with intra-observer analysis was inter-observer analysis involving an orthopaedic registrar from Macquarie Limb Reconstruction Centre (GO – Observer 2). Observer 2 conducted a single measurement of HKA, PO and TS for all 20 participants in pre and post-operative images on the left and right sides. Measurement data was entered into a blank spreadsheet by Observer 2 with no prior knowledge of the measurement values already acquired in the study. Only a single measurement was requested for this analysis in the interest of Observer 2's available time alongside clinic/hospital duties. Given the various techniques for HKA, PO and TS measurement, Observer 2 was provided a copy of the detailed protocol (from Section 3.2.4) that was applied by the primary observer, such that valid comparisons could be made.

CV data showed acceptable results of 11.08% for HKA and 19.02% for PO. TS results, however, had a CV of 179.39%, which falls far beyond the defined acceptability threshold. After the three largest outlier measurements of >5° disparity were excluded, CV was still unacceptable at 148.13%. Observer 2's results were also compared with the primary observer's results in terms of raw difference (seen in Table 4.3), calculated as the primary observer measurement values minus the values obtained by Observer 2. This showed a raw difference of -0.02° ± 2.13, with 50% of Observer 2's measurements lying within ±~1.2° of the primary observer's measurements, providing some evidence that TS measurement can be very accurate between observers. However, there is potential for large variability in measurements, which is unsurprising given the difficulty in TS measurement from 2D images and the high level of radiographic interpretation and measurement precision required to acquire accurate data. Another consideration is the level of experience and background between the primary observer and Observer 2 – a research student and

orthopaedic registrar, respectively. In any case, the similarity in data between intra-observer and inter-observer measurements suggests that these results provide good evidence of the potential measurement variation that can occur.

Methodological error

It is well appreciated in the literature that 2D radiographic measurements are susceptible to error if patients are not positioned correctly during image acquisition, or if individuals have rotational deformities that disrupt standard imaging protocols (284-288). With the aim of analysing methodological error, we chose to investigate variables that should theoretically not change between the pre-operative images and the post-operative images e.g. tibial measurements should not change following a DFO surgery. By doing so, any change that is identified can be indicative of methodological error that may be present throughout the study, under the assumption that imaging protocols were strictly adhered to. There is also an assumption that imaging protocol is the same for the operative and non-operative leg i.e. if only the operative leg is instructed to have the patellae facing forward, then the non-operative leg is likely to have pre and post-op HKA measurement difference. According to the lead radiographer (KG) at Macquarie Medical Imaging (MMI), instructions should be the same for operative and non-operative sides as per standard imaging protocol.

The measurements that were included in this analysis were HKA, FLL, ATL, AFL, mMPTA, mLDFA, KJLCA, TS and KFA (Figure 4.21). HKA was the only measurement that fell under the CV acceptability threshold at 26.76%, providing good evidence that 2D radiographs facilitate repeatable measurements of varus/valgus lower-limb deformity. However, the CV showed unacceptable variability for all other measurements in this methodological analysis, ranging from 42.55% to 118.26%. The likely cause of differences in these measurements is the same as previously mentioned i.e. knee flexion/hyperextension, femoral version or rotational deformities. However, another possible cause of measurement difference particularly relevant to this analysis is uneven weight distribution between the left and right leg between images, such as compensatory change to avoid pain in the operated knee post-surgery. This could cause stretch of the medial/lateral collateral ligaments or a change in cartilage pressure to elicit different measurements pre versus post-op. Since post-op images were taken ≥8-weeks after the procedures, such compensatory stance is unlikely, but this methodological data indicates that changes to measurements other than HKA may have unacceptable levels of measurement error.

5.5 CHALLENGES AND LIMITATIONS

5.5.1 Radiographs and Methodology

The majority of the radiographs analysed in this work appeared to be excellently captured and the methodology could be executed according to our measurement protocol from Sub-Section 3.2.4. However, some radiographs from the five different imaging facilities accessed during this study proved very difficult, or even impossible to conduct the necessary measurements from. The first issue was the image exposure of some lateral single-leg X-rays. Whilst this issue was rarely present in coronal long-leg X-rays (LLXR) and could be resolved by altering the brightness, invert and contrast settings within InteleViewer^{TM}, a number of lateral X-rays could not be used for certain analyses. Typically, the visibility of the ankle, tibia and distal section of the femur was sufficient, but the femoral head could occasionally not be identified – KFA could not be measured as a result. It is unclear whether these lateral images were not intending to capture the femoral head, and were rather aiming to capture the knee joint for general clinical observation pre/post-operatively. Regardless, it should be standard protocol to capture the entire limb from around the ilium down, such that the radiographs are suitable for KFA measurements in clinical and research contexts. However, as mentioned in Section 5.2, single-leg stance could be problematic for KFA measurements. TS measurements were also difficult to perform as a result of image penetration, which was mentioned by Observer 2 in feedback following the analysis. If the penetration was insufficient to clearly differentiate the medial and lateral tibial plateau, the confidence in measurement position was reduced and variability in results subsequently occurred, evidenced in our intra/inter-observer and methodological (inter-image) error data (Figure 4.21). No EOS images involved the same penetration insufficiency, which could suggest an increased consistency of the EOS technology. A Figure demonstrating penetration issues is not included, as single-frame screenshots would only be static representations of problematic radiographs, as they are unable to demonstrate thorough manipulation of brightness/contrast settings within InteleViewer^{TM}.

Another significant issue with the radiographs appeared to be patient stance during image acquisition. There is a standardised protocol applied to each coronal LLXR/EOS scan for pre/post-op knee osteotomy analysis. This involves the patient standing with even weight distribution, feet shoulder-width apart, knees and hips in full extension, the patellae facing anteriorly and the spine erect. Most images appeared to follow this protocol closely, but some images may have deviated from this. A common observation was difference in femoral anteversion/retroversion (active rotation of the femur) between pre and post-op images (Figure 5.1). Even if these differences are minor, they can cause large differences in measurement values (286). It is therefore not possible to confirm whether the source of HKA error from Figure 4.4 is surgical or methodological, which places a limitation on the confidence in the findings.

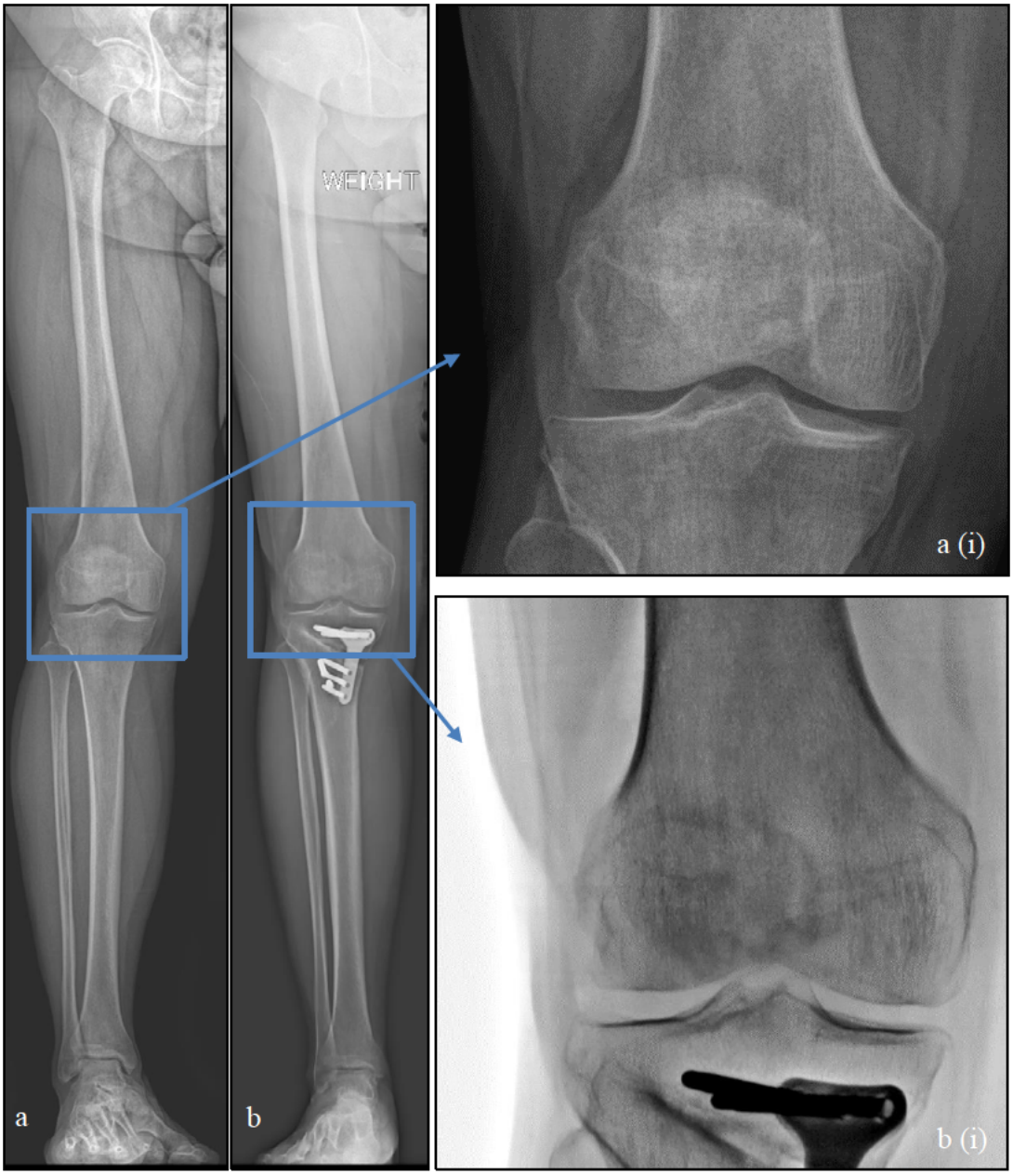


Figure 5.1 Example of difference in femoral version between images
a Pre-op image versus **b** post-op image, with **a (i)** demonstrating centralised patella and **b (i)** a lateralised patella, indicating possible femoral retroversion in the post-operative image, which gives an impression of greater varus and a subsequent under-correction. Foot positioning can also be seen as different between each image, which can suggest difference in femoral version.

Torsional bone deformities – long bone axial rotation of proximal segments relative to distal segments – in the femur or tibia also presented a known challenge to acquiring accurate varus/valgus measurements (289), as observed throughout the study. Patients with significant femoral and/or tibial torsion create additional consideration for radiographers, as often two images should be taken – an image with the feet parallel facing anteriorly and an image with the patellae facing anteriorly. For example, the radiograph from Figure 5.1a was taken correctly, even though the foot appears to be turned inward. Whilst taking two images is a useful solution for rotational deformities, a recent paper by Nguyen et al. on LLXR standardisation considered the issue of

patella mal-tracking prevalence in KOA patient (290). Hence, the patellae of some individuals may be naturally off-centre in coronal radiographs when standing in the correct position. A possible way to navigate this may be to determine patella tracking and femoral/tibial axial rotation prior to pre-operative imaging, to determine how the patient should be positioned in the images used for surgical planning.

The final radiograph-related challenge encountered during this study was the availability of full-spine EOS scans. Part of the secondary aims for the study was to observe post-operative change to lordosis and scoliosis in the lumbar spine, which can only be visualised in EOS scans capturing the entire spine. Hence, in order to measure post-operative change in these variables, a patient must have undergone a pre and post-operative full-spine EOS scan. Only one participant with scoliosis in our cohort had these images available, yet, the usability of the images was questioned due to the sagittal malalignment of the femoral heads. The reason for low numbers of full-spine EOS scans presumably relates to the traditional prescription of pelvis-down scans for individuals with knee malalignment, as the image window of LLXR cannot capture the spine in a single-image. Furthermore, the consideration of the spine in HTO/DFO patients exceeds the scope of surgical management which orthopaedic surgeons offer – debilitating or symptomatic spinal pathology is managed by spine surgeons. For these reasons, despite the availability of an EOS machine at MMI, prescription of a spinal EOS scan for HTO/DFO patients is not currently standard practice. To conduct a comprehensive study on post-operative spinal alignment change, clinicians would be required to prescribe full-spine EOS scans to all patients where an HTO/DFO may be indicated, such that research can be retrospectively/prospectively facilitated. Of course, this would result in a slightly increased radiation dose, but the lower radiation of EOS would assist in rationalising spinal investigation (53). It should also be noted that static measurement of spinal alignment parameters would provide a limited perspective on post-operative change, and gait analysis (or other related methods) would be required in combination to investigate any dynamic consequences of spinal alignment change following the procedures.

5.5.2 Participation

The number of participants for this study fell short of the projected numbers, which may have a myriad of causation. Being an entirely retrospective cohort and with the presence of COVID-19 restrictions, the majority of the patients were not seen by the research team at any stage, and were simply recruited via a telephone call or e-mail.

Whilst literature on this topic could not be found, it would be assumed that a greater percentage of patients would have elected to participate in the study if they were seen in-person by the researcher/s and had the research explained to them/questions answered in a clinical setting. Instead, a phone call or e-mail was mostly the means of communication, which may have made individuals more hesitant consenting to research involvement.

Furthermore, documentation to be completed by patients was predominantly sent and returned via e-mail, which created some technological barriers to participation, as indicated by some participants who raised concerns about their ability to be involved based on their available technology e.g. lack of a tablet/computer or printer/scanner. Whilst the methods for document completion was made as flexible as possible in digital form to facilitate maximum participation, for those who were incapable of digital document completion/return, the COVID-19 circumstances prevented some individuals from visiting post offices to send hard copies of the documents. In future, we would elect to use an online survey tool to simplify the completion of documents and eliminate some barriers to research involvement that patients faced.

Finally, the quantity of documentation required from each participant would be reduced in future projects. Participants were asked to complete PROMs that were multiple pages long – albeit in multiple-choice format – which may have caused patients to decide not to complete the forms. In addition, patients who did begin completion of the forms may have realised that a number of questions overlapped in content, which is a result of similar PROM design to cover a number of important symptom and general health-related measures. Hence, respondent fatigue may have been a factor in non-completion of PROMs (291). Despite our use of multiple detailed PROMs to potentially enhance the research and broaden the applicability of the findings, the use of a single PROM, or avoiding repetitive questioning throughout multiple shorter PROMs, may benefit participation rates in future work.

5.6 FUTURE DIRECTIONS FOR KNEE OSTEOTOMY RESEARCH

Several recommendations can be made following our study to guide and enhance future HTO/DFO research:

1. Refinement of the methodological approach used to determine accuracy of the PSI correction. Radiographic measurement of HKA error has a number of influencing factors that may not give a true indication of the correction executed by the PSI – i.e. the HKA could be impacted by the stability of internal fixation or radiographic measurement error (as covered in Section 5.5.1). Hence, to confirm the accuracy of coronal and sagittal plane correction with PSI, cadaveric studies may be the most appropriate as they allow the PSI corrections to be isolated from potential confounds. A cadaveric study would also allow pre and post-op CT analysis without the concerns of excessive radiation in a patient study. Miao et al. recently published a similar study (292), but each PSI should be investigated separately due to differences in design. If the PSI corrections were seen to be accurate in-vitro, then the source HKA error in-vivo could be more-closely linked to internal fixation or radiographic error.

2. To investigate weight-bearing computed tomography (CT) for pre/post-op analysis. Most identified studies used long-leg radiographs for planning the correction and measuring accuracy, as this has been the gold standard for decades. Despite this method being used in many HTO/DFO studies reporting excellent surgical accuracy, there are potential sources of error associated with radiographs for alignment measurements, as observed in our study. We identified three studies that used standard CT scanning to plan and analyse osteotomy procedures. Victor and Premanathan used supine full-leg CT scans, allowing bilateral 3D reconstructions of the lower-limbs (19). Shi et al. and Jacquet et al. applied a similar method, but used supine CT scans of the femoral head, knee and ankle to create 3D reconstructions of lower limb segments for operative planning with a reduced radiation exposure (210, 212). However, we did not identify an HTO/DFO study using CT scanning in a weight-bearing position, which is a logical progression for future research.

3. Surgical planning and evaluation of HTO/DFO procedures from EOS images in combination with sterEOS^{TM} software could also be investigated, as this allows 3D reconstructions of lower-limb anatomy based on coronal and sagittal images. This may allow comparable alignment measurement accuracy to CT scanning at a reduced radiation dosage.

4. Radiostereometric analysis (RSA) of various internal fixation types and their influence on varus/valgus correction accuracy and tibial slope maintenance would provide valuable information on opening-wedge movement throughout ossification. Luites et al. conducted an RSA study in an HTO cohort in 2009 (276), but updated HTO and DFO research on revised internal fixation models would establish a more contemporary perspective on choice of hardware.

Chapter 6: Conclusion

This thesis demonstrated that high tibial osteotomy (HTO) and distal femoral osteotomy (DFO) using patient-specific instruments (PSI) is a capable method for accurately correcting varus/valgus malalignment of the knee. Slight tibial slope increase can be expected from HTO, but larger internal fixation designs appear to provide better opening-wedge stability and limit such change. Single-bone and functional leg length increase following HTO/DFO is minor and may only negatively impact coronal pelvic/spinal alignment in cases where the procedures would exacerbate pre-existing malalignment. Change towards parallel knee joint line convergence was seen, and indicated successful unloading of the arthritic compartments. Analysing HTO/DFO influence on sagittal pelvic/spinal alignment is difficult and would require revised imaging protocols to validate such correlation.

Analysis of intra-observer, inter-observer and methodological (inter-image) reliability of the two-dimensional radiographic methods utilised in this study revealed measurement variation that limits the confidence in our primary findings. In light of this, we recommend that complete three-dimensional (3D) pre-operative planning and post-operative evaluation, such as with weight-bearing computed tomography (CT), is investigated in HTO/DFO procedures. Successful implementation of such an approach is likely to provide a more accurate indication of surgical accuracy and post-operative alignment change as a step towards further individualised treatment plans. EOS image 3D reconstructions using sterEOS^{TM} software could also facilitate more accurate analysis at a comparatively reduced radiation dose to CT scans, with the added potential of incorporating simultaneous spinal alignment measurements. Machine learning implementation to clinical research would complement improved and more complex analysis methodologies and may uncover new considerations for knee osteotomy procedures.

References

1. Katz JN. Total joint replacement in osteoarthritis. Best Practice & Research Clinical Rheumatology. 2006;20(1):145-53.
2. Leitch K. Biomechanical investigations of medial opening wedge high tibial osteotomy: gait analysis, materials testing and dynamic radiography. 2014.
3. Anderson E, Frank P, Henshaw J, Rae H. Clinical assessment of a new weight-relieving brace. The Journal of bone and joint surgery British volume. 1977;59(4):439-45.
4. Argoff CE. Recent developments in the treatment of osteoarthritis with NSAIDs. Current medical research and opinion. 2011;27(7):1315-27.
5. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. Osteoarthritis and cartilage. 2007;15(8):957-65.
6. Birchfield PC. Osteoarthritis overview. Geriatric Nursing. 2001;22(3):124-31.
7. Castrogiovanni P, Di Giunta A, Guglielmino C, Roggio F, Romeo D, Fidone F, et al. The effects of exercise and kinesio tape on physical limitations in patients with knee osteoarthritis. Journal of Functional Morphology and Kinesiology. 2016;1(4):355-68.
8. Felson D, Anderson J, Naimark A, Kannel W, Meenan R. The prevalence of chondrocalcinosis in the elderly and its association with knee osteoarthritis: the Framingham Study. The Journal of rheumatology. 1989;16(9):1241-5.
9. Huurman WW, Jacobsen FS, Anderson JC, Chu W. Limb-length discrepancy measured with computerized axial tomographic equipment. The Journal of bone and joint surgery American volume. 1987;69(5):699-705.
10. Kosuwon W, Sirichatiwapee W, Wisanuyotin T, Jeeravipoolvarn P, Laupattarakasem W. Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin versus placebo. Medical journal of the Medical Association of Thailand. 2010;93(10):1188.
11. Messier SP. Obesity and osteoarthritis: disease genesis and nonpharmacologic weight management. Rheumatic Disease Clinics of North America. 2008;34(3):713-29.
12. Stanos SP. Topical agents for the management of musculoskeletal pain. Journal of pain and symptom management. 2007;33(3):342-55.
13. Stout A, Friedly J, Standaert CJ. Systemic absorption and side effects of locally injected glucocorticoids. PM&R. 2019;11(4):409-19.
14. Weerapong P, Hume PA, Kolt GS. The mechanisms of massage and effects on performance, muscle recovery and injury prevention. Sports medicine. 2005;35(3):235-56.
15. Alvarez-Flores M, Pazelli G, DeOcesano-Pereira C, Souza J, Chudzinski-Tavassi A. Development of a high content screening assay for the screening of proteins and peptides in a model of osteoarthritis. Osteoarthritis and Cartilage. 2019;27:S200.
16. Jackson J, Waugh W. Tibial osteotomy for osteoarthritis of the knee. The Journal of bone and joint surgery British volume. 1961;43(4):746-51.
17. Fujisawa Y, Masuhara K, Shiomi S. The effect of high tibial osteotomy on osteoarthritis of the knee. An arthroscopic study of 54 knee joints. The Orthopedic clinics of North America. 1979;10(3):585-608.
18. Hernigou P, Medevielle D, Debeyre J, Goutallier D. Proximal tibial osteotomy for osteoarthritis with varus deformity. A ten to thirteen-year follow-up study. The Journal of bone and joint surgery American volume. 1987;69(3):332-54.
19. Victor J, Premanathan A. Virtual 3D planning and patient specific surgical guides for osteotomies around the knee: a feasibility and proof-of-concept study. The bone & joint journal. 2013;95(11_Supple_A):153-8.
20. Cerciello S, Ollivier M, Corona K, Kaocoglu B, Seil R. CAS and PSI increase coronal alignment accuracy and reduce outliers when compared to traditional technique of medial open

wedge high tibial osteotomy: a meta-analysis. Knee Surgery, Sports Traumatology, Arthroscopy. 2020:1-12.
21. Bejjani F, Gross C, Pugh J. Model for static lifting: relationship of loads on the spine and the knee. Journal of biomechanics. 1984;17(4):281-6.
22. Murata Y, Takahashi K, Yamagata M, Hanaoka E, Moriya H. The knee-spine syndrome: association between lumbar lordosis and extension of the knee. The Journal of bone and joint surgery British volume. 2003;85(1):95-9.
23. Harato K, Nagura T, Matsumoto H, Otani T, Toyama Y, Suda Y. A gait analysis of simulated knee flexion contracture to elucidate knee-spine syndrome. Gait & Posture. 2008;28(4):687-92.
24. Schwab F, Patel A, Ungar B, Farcy J-P, Lafage V. Adult spinal deformity—postoperative standing imbalance: how much can you tolerate? An overview of key parameters in assessing alignment and planning corrective surgery. Spine. 2010;35(25):2224-31.
25. Betsch M, Rapp W, Przibylla A, Jungbluth P, Hakimi M, Schneppendahl J, et al. Determination of the amount of leg length inequality that alters spinal posture in healthy subjects using rasterstereography. European Spine Journal. 2013;22(6):1354-61.
26. Lee CS, Park SJ, Chung SS, Lee KH. The effect of simulated knee flexion on sagittal spinal alignment: novel interpretation of spinopelvic alignment. European Spine Journal. 2013;22(5):1059-65.
27. Murray KJ, Azari MF. Leg length discrepancy and osteoarthritis in the knee, hip and lumbar spine. The Journal of the Canadian Chiropractic Association. 2015;59(3):226.
28. Yanagisawa S, Sato N, Shimizu M, Saito K, Yamamoto A, Takagishi K. Relation among the knee, sagittal spinal alignment, and the spinal range of motion: Investigation in local medical check-ups using the SpinalMouse. Asia-Pacific journal of sports medicine, arthroscopy, rehabilitation and technology. 2015;2(2):68-71.
29. Kim YH, Dorj A, Han A, Kim K, Nha KW. Improvements in spinal alignment after high tibial osteotomy in patients with medial compartment knee osteoarthritis. Gait & posture. 2016;48:131-6.
30. Betsch M, Michalik R, Graber M, Wild M, Krauspe R, Zilkens C. Influence of leg length inequalities on pelvis and spine in patients with total hip arthroplasty. PloS one. 2019;14(8):e0221695.
31. Kim SC, Kim JS, Choi HG, Kim TW, Lee YS. Spinal Flexibility Is an Important Factor for Improvement in Spinal and Knee Alignment after Total Knee Arthroplasty: Evaluation Using a Whole Body EOS System. Journal of clinical medicine. 2020;9(11):3498.
32. Vigdorchik JM, Sharma AK, Feder OI, Buckland AJ, Mayman DJ, Carroll KM, et al. Stiffness after total knee arthroplasty: is it a result of spinal deformity? The Journal of arthroplasty. 2020;35(6):S330-S5.
33. Vigdorchik JM, Sharma AK, Buckland AJ, Elbuluk AM, Eftekhary N, Mayman DJ, et al. 2021 Otto Aufranc Award: A simple Hip-Spine Classification for total hip arthroplasty: validation and a large multicentre series. The Bone & Joint Journal. 2021;103(7 Supple B):17-24.
34. Thienpont E, Schwab P-E, Cornu O, Bellemans J, Victor J. Bone morphotypes of the varus and valgus knee. Archives of orthopaedic and trauma surgery. 2017;137(3):393-400.
35. Sharma L, Song J, Dunlop D, Felson D, Lewis CE, Segal N, et al. Varus and valgus alignment and incident and progressive knee osteoarthritis. Annals of the rheumatic diseases. 2010;69(11):1940-5.
36. Talarico V, Baserga M, Fuiano L, Mattace F, Mastria G, Arcuri V. Evaluation of the varus-valgus knee in a group of Calabrian children. La Pediatria medica e chirurgica: Medical and surgical pediatrics. 2011;33(2):80-4.
37. Coggon D, Reading I, Croft P, McLaren M, Barrett D, Cooper C. Knee osteoarthritis and obesity. International journal of obesity. 2001;25(5):622-7.
38. Inoue M, McGurk-Burleson E, Hollis JM, Woo SL-Y. Treatment of the medial collateral ligament injury: I: The importance of anterior cruciate ligament on the varus-valgus knee laxity. The American journal of sports medicine. 1987;15(1):15-21.

39. Bleck E. Developmental orthopaedics. III: Toddlers. Developmental medicine and child neurology. 1982;24(4):533-55.
40. Chaouche S, Jacquet C, Fabre-Aubrespy M, Sharma A, Argenson J-N, Parratte S, et al. Patient-specific cutting guides for open-wedge high tibial osteotomy: safety and accuracy analysis of a hundred patients continuous cohort. International orthopaedics. 2019;43(12):2757-65.
41. Van Genechten W, Van Tilborg W, Van den Bempt M, Van Haver A, Verdonk P. Feasibility and 3D Planning of a Novel Patient-Specific Instrumentation Technique in Medial Opening-Wedge High Tibial Osteotomy. The Journal of Knee Surgery. 2020.
42. Vandekerckhove P-JT, Matlovich N, Teeter MG, MacDonald SJ, Howard JL, Lanting BA. The relationship between constitutional alignment and varus osteoarthritis of the knee. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(9):2873-9.
43. Mootanah R, Imhauser CW, Reisse F, Carpanen D, Walker RW, Koff MF, et al. Development and validation of a computational model of the knee joint for the evaluation of surgical treatments for osteoarthritis. Computer methods in biomechanics and biomedical engineering. 2014;17(13):1502-17.
44. Cameron JI, McCauley JC, Kermanshahi AY, Bugbee WD. Lateral opening-wedge distal femoral osteotomy: pain relief, functional improvement, and survivorship at 5 years. Clinical Orthopaedics and Related Research®. 2015;473(6):2009-15.
45. Brinkman J-M, Lobenhoffer P, Agneskirchner J, Staubli A, Wymenga A, Van Heerwaarden R. Osteotomies around the knee: patient selection, stability of fixation and bone healing in high tibial osteotomies. The Journal of bone and joint surgery British volume. 2008;90(12):1548-57.
46. Landauer F, Huber G, Paulmichl K, O'Malley G, Mangge H, Weghuber D. Timely diagnosis of malalignment of the distal extremities is crucial in morbidly obese juveniles. Obesity facts. 2013;6(6):542-51.
47. Zampogna B, Vasta S, Amendola A, Marbach BU-E, Gao Y, Papalia R, et al. Assessing lower limb alignment: comparison of standard knee xray vs long leg view. The Iowa orthopaedic journal. 2015;35:49.
48. Mao Y, Xiong Y, Li Q, Chen G, Fu W, Tang X, et al. 3D-Printed Patient-Specific Instrumentation Technique Vs. Conventional Technique in Medial Open Wedge High Tibial Osteotomy: A Prospective Comparative Study. BioMed Research International. 2020;2020.
49. Tampere T, Donnez M, Jacquet C, Berton P, Ollivier M, Parratte S. Patient-Specific Instrumentation (PSI) for High Tibial Osteotomy (HTO). Osteotomy About the Knee: Springer; 2020. p. 221-32.
50. Guggenberger R, Pfirrmann CW, Koch PP, Buck FM. Assessment of lower limb length and alignment by biplanar linear radiography: comparison with supine CT and upright full-length radiography. American Journal of Roentgenology. 2014;202(2):W161-W7.
51. 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. Bulletin de l'Academie nationale de medecine. 2005;189(2):287-97; discussion 97.
52. Masserat V, Ebrahimi HS, Eil N, Mollashahi J, Naebi M. Evaluation of frequency of periapical radiographic errors in Dental Radiology Department in Zahedan in 2014-2015. Sch J App Med Sci. 2017;5:112-15.
53. Kalifa G, Charpak Y, Maccia C, Fery-Lemonnier E, Bloch J, Boussard J-M, et al. Evaluation of a new low-dose digital x-ray device: first dosimetric and clinical results in children. Pediatric radiology. 1998;28(7):557-61.
54. Faria R, McKenna C, Wade R, Yang H, Woolacott N, Sculpher M. The EOS 2D/3D X-ray imaging system: a cost-effectiveness analysis quantifying the health benefits from reduced radiation exposure. European journal of radiology. 2013;82(8):e342-e9.
55. Lespasio MJ, Piuzzi NS, Husni ME, Muschler GF, Guarino A, Mont MA. Knee osteoarthritis: a primer. The Permanente Journal. 2017;21.

56. Gao Y-H, Zhao C-W, Liu B, Dong N, Ding L, Li Y-R, et al. An update on the association between metabolic syndrome and osteoarthritis and on the potential role of leptin in osteoarthritis. Cytokine. 2020;129:155043.
57. O'Neill TW, McCabe PS, McBeth J. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. Best practice & research Clinical rheumatology. 2018;32(2):312-26.
58. Vina ER, Kwoh CK. Epidemiology of osteoarthritis: literature update. Current opinion in rheumatology. 2018;30(2):160.
59. Abramoff B, Caldera FE. Osteoarthritis: pathology, diagnosis, and treatment options. Medical Clinics. 2020;104(2):293-311.
60. Murphy LB, Cisternas MG, Pasta DJ, Helmick CG, Yelin EH. Medical expenditures and earnings losses among US adults with arthritis in 2013. Arthritis care & research. 2018;70(6):869-76.
61. Rahimzadeh P, Imani F, Faiz SHR, Entezary SR, Nasiri AA, Ziaeefard M. Investigation the efficacy of intra-articular prolotherapy with erythropoietin and dextrose and intra-articular pulsed radiofrequency on pain level reduction and range of motion improvement in primary osteoarthritis of knee. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2014;19(8):696.
62. Armengol M. Correlating material properties to matrix constitution on porcine tibial plateaux: University of Oxford; 2014.
63. Hsu R, Himeno S, Coventry MB, Chao E. Normal axial alignment of the lower extremity and load-bearing distribution at the knee. Clinical orthopaedics and related research. 1990(255):215-27.
64. McNamara I, Birmingham T, Fowler P, Giffin J. High tibial osteotomy: evolution of research and clinical applications—a Canadian experience. Knee Surgery, Sports Traumatology, Arthroscopy. 2013;21(1):23-31.
65. Egloff C, Hügle T, Valderrabano V. Biomechanics and pathomechanisms of osteoarthritis. Swiss medical weekly. 2012;142(2930).
66. de l'Escalopier N, Anract P, Biau D. Surgical treatments for osteoarthritis. Annals of physical and rehabilitation medicine. 2016;59(3):227-33.
67. Kon E, Filardo G, Drobnic M, Madry H, Jelic M, van Dijk N, et al. Non-surgical management of early knee osteoarthritis. Knee Surgery, Sports Traumatology, Arthroscopy. 2012;20(3):436-49.
68. Hunter DJ, Lo GH. The management of osteoarthritis: an overview and call to appropriate conservative treatment. Medical Clinics of North America. 2009;93(1):127-43.
69. Walker JA. Osteoarthritis: pathogenesis, clinical features and management. Nursing standard. 2009;24(1):35-41.
70. Ding C, Garnero P, Cicuttini F, Scott F, Cooley H, Jones G. Knee cartilage defects: association with early radiographic osteoarthritis, decreased cartilage volume, increased joint surface area and type II collagen breakdown. Osteoarthritis and cartilage. 2005;13(3):198-205.
71. Brouwer G, Tol AV, Bergink A, Belo J, Bernsen R, Reijman M, et al. Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. Arthritis & rheumatism. 2007;56(4):1204-11.
72. Felson D, Gale D, Elon Gale M, Niu J, Hunter D, Goggins J, et al. Osteophytes and progression of knee osteoarthritis. Rheumatology. 2005;44(1):100-4.
73. Tanamas SK, Wluka AE, Pelletier J-P, Martel-Pelletier J, Abram F, Wang Y, et al. The association between subchondral bone cysts and tibial cartilage volume and risk of joint replacement in people with knee osteoarthritis: a longitudinal study. Arthritis research & therapy. 2010;12(2):1-7.
74. de Campos GC, Tieppo AM, de Almeida Jr CS, Hamdan PC, Alves WM, de Rezende MU. Target-based approach for osteoarthritis treatment. World journal of orthopedics. 2020;11(6):278.
75. Crawford DC, Miller LE, Block JE. Conservative management of symptomatic knee osteoarthritis: a flawed strategy? Orthopedic reviews. 2013;5(1).

76. Arden NK, Perry TA, Bannuru RR, Bruyère O, Cooper C, Haugen IK, et al. Non-surgical management of knee osteoarthritis: comparison of ESCEO and OARSI 2019 guidelines. Nature Reviews Rheumatology. 2020:1-8.
77. Anandacoomarasamy A, Caterson I, Sambrook P, Fransen M, March L. The impact of obesity on the musculoskeletal system. International journal of obesity. 2008;32(2):211-22.
78. Huang MH, Chen CH, Chen TW, Weng MC, Wang WT, Wang YL. The effects of weight reduction on the rehabilitation of patients with knee osteoarthritis and obesity. Arthritis Care & Research. 2000;13(6):398-405.
79. Felson DT. Weight and osteoarthritis. The American journal of clinical nutrition. 1996;63(3):430S-2S.
80. Anderson AS, Loeser RF. Why is osteoarthritis an age-related disease? Best practice & research Clinical rheumatology. 2010;24(1):15-26.
81. Page CJ, Hinman RS, Bennell KL. Physiotherapy management of knee osteoarthritis. International Journal of Rheumatic Diseases. 2011;14(2):145-51.
82. Schurman DJ, Smith RL. Osteoarthritis: current treatment and future prospects for surgical, medical, and biologic intervention. Clinical Orthopaedics and Related Research®. 2004;427:S183-S9.
83. Cheng DS, Visco CJ. Pharmaceutical therapy for osteoarthritis. PM&R. 2012;4:S82-S8.
84. Leopoldino AO, Machado GC, Ferreira PH, Pinheiro MB, Day R, McLachlan AJ, et al. Paracetamol versus placebo for knee and hip osteoarthritis. Cochrane Database of Systematic Reviews. 2019(2).
85. Larsen FS, Wendon J. Understanding paracetamol-induced liver failure. Intensive care medicine. 2014;40(6):888-90.
86. Graham GG, Scott KF. Mechanism of action of paracetamol. American journal of therapeutics. 2005;12(1):46-55.
87. McPherson ML, Cimino NM. Topical NSAID formulations. Pain Medicine. 2013;14(suppl_1):S35-S9.
88. Schnitzer TJ, Pelletier J-P, Haselwood DM, Ellison WT, Ervin JE, Gordon RD, et al. Civamide cream 0.075% in patients with osteoarthritis of the knee: a 12-week randomized controlled clinical trial with a longterm extension. The Journal of rheumatology. 2012;39(3):610-20.
89. Harvey WF, Hunter DJ. The role of analgesics and intra-articular injections in disease management. Rheumatic Disease Clinics of NOrth America. 2008;34(3):777-88.
90. Yosipovitch G, Maibach HI, Rowbotham MC. E ect of EMLA pre-treatment on capsaicin-induced burning and hyperalgesia. Acta Derm Venereol. 1999;79:118-21.
91. Scheiman JM. The use of proton pump inhibitors in treating and preventing NSAID-induced mucosal damage. Arthritis research & therapy. 2013;15(3):1-6.
92. Abraham NS. Proton pump inhibitors: potential adverse effects. Current opinion in gastroenterology. 2012;28(6):615-20.
93. Haastrup PF, Thompson W, Søndergaard J, Jarbøl DE. Side effects of long-term proton pump inhibitor use: a review. Basic & clinical pharmacology & toxicology. 2018;123(2):114-21.
94. Dhawan A, Mather III RC, Karas V, Ellman MB, Young BB, Bach Jr BR, et al. An epidemiologic analysis of clinical practice guidelines for non-arthroplasty treatment of osteoarthritis of the knee. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2014;30(1):65-71.
95. Barnes PJ. Nuclear factor-κB. The international journal of biochemistry & cell biology. 1997;29(6):867-70.
96. van Middelkoop M, Arden N, Atchia I, Birrell F, Chao J, Rezende M, et al. The OA Trial Bank: meta-analysis of individual patient data from knee and hip osteoarthritis trials show that patients with severe pain exhibit greater benefit from intra-articular glucocorticoids. Osteoarthritis and cartilage. 2016;24(7):1143-52.

97. Johnston PC, Lansang MC, Chatterjee S, Kennedy L. Intra-articular glucocorticoid injections and their effect on hypothalamic–pituitary–adrenal (HPA)-axis function. Endocrine. 2015;48(2):410-6.
98. Young P, Homlar KC. Extreme postinjection flare in response to intra-articular triamcinolone acetonide (Kenalog). Am J Orthop (Belle Mead NJ). 2016;45(3):E108-E11.
99. Cooper C, Bardin T, Brandi M-L, Cacoub P, Caminis J, Civitelli R, et al. Balancing benefits and risks of glucocorticoids in rheumatic diseases and other inflammatory joint disorders: new insights from emerging data. An expert consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Aging clinical and experimental research. 2016;28(1):1-16.
100. Scheinman RI, Cogswell PC, Lofquist AK, Baldwin AS. Role of transcriptional activation of IκBα in mediation of immunosuppression by glucocorticoids. Science. 1995;270(5234):283-6.
101. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporosis International. 2007;18(10):1319-28.
102. Compston J. Glucocorticoid-induced osteoporosis: an update. Endocrine. 2018;61(1):7-16.
103. LIfton RP, Dluhy RG, Powers M, Rich GM, Cook S, Ulick S, et al. A chimaeric llβ-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature. 1992;355(6357):262-5.
104. Hopkins RL, Leinung MC. Exogenous Cushing's syndrome and glucocorticoid withdrawal. Endocrinology and Metabolism Clinics. 2005;34(2):371-84.
105. Mazziotti G, Gazzaruso C, Giustina A. Diabetes in Cushing syndrome: basic and clinical aspects. Trends in Endocrinology & Metabolism. 2011;22(12):499-506.
106. Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG. Prevention and management of glucocorticoid-induced side effects: a comprehensive review: a review of glucocorticoid pharmacology and bone health. Journal of the American Academy of Dermatology. 2017;76(1):1-9.
107. Gigante A, Callegari L. The role of intra-articular hyaluronan (Sinovial®) in the treatment of osteoarthritis. Rheumatology international. 2011;31(4):427-44.
108. Lin W, Liu Z, Kampf N, Klein J. The Role of Hyaluronic Acid in Cartilage Boundary Lubrication. Cells. 2020;9(7):1606.
109. Bowman S, Awad ME, Hamrick MW, Hunter M, Fulzele S. Recent advances in hyaluronic acid based therapy for osteoarthritis. Clinical and translational medicine. 2018;7(1):1-11.
110. Migliore A, Procopio S. Effectiveness and utility of hyaluronic acid in osteoarthritis. Clinical Cases in Mineral and Bone Metabolism. 2015;12(1):31.
111. Altman R, Hackel J, Niazi F, Shaw P, Nicholls M, editors. Efficacy and safety of repeated courses of hyaluronic acid injections for knee osteoarthritis: a systematic review. Seminars in arthritis and rheumatism; 2018: Elsevier.
112. Kitcat C, Schuster H, Canfield S. Curriculum for Dalcroze eurhythmics in the nursery school, kindergarten and grades I-VI; accepted by. 1900.
113. Ogunbode A, Fatiregun A, Ogunbode O. Health risks of obesity. Annals of Ibadan postgraduate medicine. 2009;7(2):22-5.
114. Heart N, Lung, Institute B, Diabetes NIo, Digestive, Diseases K. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report: National Heart, Lung, and Blood Institute; 1998.
115. Forsbrook WR. A Dissertation on Osteo-arthritis: Lewis; 1893.
116. Threlkeld AJ. The effects of manual therapy on connective tissue. Physical therapy. 1992;72(12):893-902.
117. Jay K, Sundstrup E, Søndergaard SD, Behm D, Brandt M, Særvoll CA, et al. Specific and cross over effects of massage for muscle soreness: randomized controlled trial. International journal of sports physical therapy. 2014;9(1):82.
118. Weber M, Laube KU, Best S. [Mobility of patients with coxarthrosis]. Z Orthop Ihre Grenzgeb. 1992;130(4):310-6.

119. Mikesky AE, Mazzuca SA, Brandt KD, Perkins SM, Damush T, Lane KA. Effects of strength training on the incidence and progression of knee osteoarthritis. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2006;55(5):690-9.
120. DeFreitas JM, Beck TW, Stock MS, Dillon MA, Kasishke PR. An examination of the time course of training-induced skeletal muscle hypertrophy. European journal of applied physiology. 2011;111(11):2785-90.
121. Goodfellow J, Hungerford D, Zindel M. Patello-femoral joint mechanics and pathology. 1. Functional anatomy of the patello-femoral joint. The Journal of bone and joint surgery British volume. 1976;58(3):287-90.
122. Hinman R, Bennell K, Crossley K, McConnell J. Immediate effects of adhesive tape on pain and disability in individuals with knee osteoarthritis. Rheumatology. 2003;42(7):865-9.
123. McCarthy C, Dieppe P. Taping the patella medially: a new treatment for osteoarthritis of the knee joint? Bmj. 1994;308(6931):753-5.
124. Smith EM, Juvinall RC, Corell EB, Nyboer VJ. Bracing the unstable arthritic knee. Arch Phys Med Rehabil. 1970;51(1):22-8 passim.
125. Rannou F, Poiraudeau S, Beaudreuil J. Role of bracing in the management of knee osteoarthritis. Current opinion in rheumatology. 2010;22(2):218-22.
126. Freeman M. Treatment of ruptures of the lateral ligament of the ankle. The Journal of bone and joint surgery British volume. 1965;47(4):661-8.
127. Brouwer RW, van Raaij TM, Jakma TT, Verhagen AP, Verhaar JA, Bierma-Zeinstra SM. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database of Systematic Reviews. 2005(1).
128. Maly MR, Culham EG, Costigan PA. Static and dynamic biomechanics of foot orthoses in people with medial compartment knee osteoarthritis. Clinical Biomechanics. 2002;17(8):603-10.
129. Hart FD. Analgesics in rheumatic disorders. British medical journal. 1960;1(5181):1265.
130. Burnett I, Schachtel B, Sanner K, Bey M, Grattan T, Littlejohn S. Onset of analgesia of a paracetamol tablet containing sodium bicarbonate: a double-blind, placebo-controlled study in adult patients with acute sore throat. Clinical therapeutics. 2006;28(9):1273-8.
131. Maloberti M, Ferrero M, Rossi G, Pepe C. Evaluation of the efficacy and tolerance of BPAA gel in 48 patients with extra-articular rheumatic diseases and in 52 patients with osteoarthritis in the painful phase. Open non-comparative study. La Clinica Terapeutica. 1989;130(5):249-54.
132. Derry S, Conaghan P, Da Silva JAP, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database of Systematic Reviews. 2016(4).
133. Partsch G, Matucci-Cerinic M. Effect of capsaicin on the release of substance P from rheumatoid arthritis and osteoarthritis synoviocytes in vitro. Annals of the rheumatic diseases. 1990;49(8):653.
134. Hart FD, Boardman P. Indomethacin: a new non-steroid anti-inflammatory agent. British medical journal. 1963;2(5363):965.
135. Nelson AE. Osteoarthritis year in review 2017: clinical. Osteoarthritis and cartilage. 2018;26(3):319-25.
136. Hench PS, Kendall EC, Slocumb CH, Polley HF. Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions: a study in clinical physiology. Archives of internal medicine. 1950;85(4):545-666.
137. Barnes EV, Edwards NL. Treatment of osteoarthritis. Southern medical journal. 2005;98(2):205-10.
138. Rydell N, Balazs EA. Effect of intra-articular injection of hyaluronic acid on the clinical symptoms of osteoarthritis and on granulation tissue formation. Clinical Orthopaedics and Related Research®. 1971;80:25-32.
139. Modawal A, Ferrer M, Choi HK, Castle JA. Hyaluronic acid injections relieve knee pain. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. 2005.

140. Arbous MS, Grobbee D, Van Kleef J, De Lange J, Spoormans H, Touw P, et al. Mortality associated with anaesthesia: a qualitative analysis to identify risk factors. Anaesthesia. 2001;56(12):1141-53.
141. Cheadle WG. Risk factors for surgical site infection. Surgical infections. 2006;7(S1):s7-s11.
142. Morin RT, Li Y, Mackin RS, Whooley MA, Conwell Y, Byers AL. Comorbidity profiles identified in older primary care patients who attempt suicide. Journal of the American Geriatrics Society. 2019;67(12):2553-9.
143. Jung JH, Seok H, Kim JH, Song GG, Choi SJ. Association between osteoarthritis and mental health in a Korean population: a nationwide study. International journal of rheumatic diseases. 2018;21(3):611-9.
144. Harris CM. Seasonal variations in depression and osteoarthritis. The Journal of the Royal College of General Practitioners. 1984;34(265):436-9.
145. Sledge SL. Microfracture techniques in the treatment of osteochondral injuries. Clinics in sports medicine. 2001;20(2):365-78.
146. Adelani MA, Harris AH, Bowe TR, Giori NJ. Arthroscopy for knee osteoarthritis has not decreased after a clinical trial. Clinical Orthopaedics and Related Research®. 2016;474(2):489-94.
147. Reichenbach S, Rutjes AW, Nüesch E, Trelle S, Jüni P. Joint lavage for osteoarthritis of the knee. Cochrane Database of Systematic Reviews. 2010(5).
148. Rönn K, Reischl N, Gautier E, Jacobi M. Current surgical treatment of knee osteoarthritis. Arthritis. 2011;2011.
149. Steadman JR, Rodkey WG, Briggs KK. Microfracture: its history and experience of the developing surgeon. Cartilage. 2010;1(2):78-86.
150. Yen Y-M, Cascio B, O'Brien L, Stalzer S, Millett P, Steadman J. Treatment of osteoarthritis of the knee with microfracture and rehabilitation. Medicine+ Science in Sports+ Exercise. 2008;40(2):200.
151. Strauss EJ, Barker JU, Kercher JS, Cole BJ, Mithoefer K. Augmentation strategies following the microfracture technique for repair of focal chondral defects. Cartilage. 2010;1(2):145-52.
152. Orth P, Gao L, Madry H. Microfracture for cartilage repair in the knee: a systematic review of the contemporary literature. Knee Surgery, Sports Traumatology, Arthroscopy. 2020;28(3):670-706.
153. Belsey J, Yasen SK, Jobson S, Faulkner J, Wilson AJ. Return to Physical Activity After High Tibial Osteotomy or Unicompartmental Knee Arthroplasty: A Systematic Review and Pooling Data Analysis. The American Journal of Sports Medicine. 2020:0363546520948861.
154. Klasan A, Parker DA, Lewis PL, Young SW. Low percentage of surgeons meet the minimum recommended unicompartmental knee arthroplasty usage thresholds: Analysis of 3037 Surgeons from Three National Joint Registries. Knee Surgery, Sports Traumatology, Arthroscopy. 2021:1-7.
155. Cao Z, Mai X, Wang J, Feng E, Huang Y. Unicompartmental knee arthroplasty vs high tibial osteotomy for knee osteoarthritis: a systematic review and meta-analysis. The Journal of arthroplasty. 2018;33(3):952-9.
156. Carlos Rodríguez-Merchán E, Gómez-Cardero P. Unicompartmental knee arthroplasty: current indications, technical issues and results. EFORT open reviews. 2018;3(6):363-73.
157. Burn E, Liddle AD, Hamilton TW, Pai S, Pandit HG, Murray DW, et al. Choosing between unicompartmental and total knee replacement: what can economic evaluations tell us? A systematic review. PharmacoEconomics-open. 2017;1(4):241-53.
158. Craik JD, El Shafie SA, Singh VK, Twyman RS. Revision of unicompartmental knee arthroplasty versus primary total knee arthroplasty. The Journal of arthroplasty. 2015;30(4):592-4.
159. Moran C, Horton T. Total knee replacement: the joint of the decade: A successful operation, for which there's a large unmet need. British Medical Journal Publishing Group; 2000.

160. Essner A, Herrera L, Hughes P, Kester M. The influence of material and design on total knee replacement wear. The journal of knee surgery. 2011;24(01):009-18.
161. Freeman M, Todd R, Bamert P, Day W. ICLH arthroplasty of the knee: 1968--1977. The Journal of bone and joint surgery British volume. 1978;60(3):339-44.
162. Dy CJ, Marx RG, Bozic KJ, Pan TJ, Padgett DE, Lyman S. Risk factors for revision within 10 years of total knee arthroplasty. Clinical Orthopaedics and Related Research®. 2014;472(4):1198-207.
163. Ritter M. The Anatomical Graduated Component total knee replacement: a long-term evaluation with 20-year survival analysis. The Journal of bone and joint surgery British volume. 2009;91(6):745-9.
164. Kahlenberg CA, Nwachukwu BU, McLawhorn AS, Cross MB, Cornell CN, Padgett DE. Patient satisfaction after total knee replacement: a systematic review. HSS Journal®. 2018;14(2):192-201.
165. L. Snell D, Hipango J, Sinnott KA, Dunn JA, Rothwell A, Hsieh CJ, et al. Rehabilitation after total joint replacement: a scoping study. Disability and rehabilitation. 2018;40(14):1718-31.
166. Julin J, Jämsen E, Puolakka T, Konttinen YT, Moilanen T. Younger age increases the risk of early prosthesis failure following primary total knee replacement for osteoarthritis: a follow-up study of 32,019 total knee replacements in the Finnish Arthroplasty Register. Acta orthopaedica. 2010;81(4):413-9.
167. Pilone C, Rosso F, Cottino U, Rossi R, Bonasia DE. Lateral opening wedge distal femoral osteotomy for lateral compartment arthrosis/overload. Clinics in sports medicine. 2019;38(3):351-9.
168. Teitge RA, Torga-Spak R. Skeletal malalignment and anterior knee pain: rationale, diagnosis, and management. Anterior knee pain and patellar instability: Springer; 2006. p. 185-99.
169. Gomoll AH. High tibial osteotomy for the treatment of unicompartmental knee osteoarthritis: a review of the literature, indications, and technique. The Physician and sportsmedicine. 2011;39(3):45-54.
170. Puddu G, Cipolla M, Cerullo G, Franco V, Giannì E. Which osteotomy for a valgus knee? International orthopaedics. 2010;34(2):239-47.
171. Van den Bempt M, Van Genechten W, Claes T, Claes S. How accurately does high tibial osteotomy correct the mechanical axis of an arthritic varus knee? A systematic review. Knee. 2016;23(6):925-35.
172. van Heerwaarden R, Najfeld M, Brinkman M, Seil R, Madry H, Pape D. Wedge volume and osteotomy surface depend on surgical technique for distal femoral osteotomy. Knee Surgery, Sports Traumatology, Arthroscopy. 2013;21(1):206-12.
173. Arnal-Burró J, Pérez-Mañanes R, Gallo-del-Valle E, Igualada-Blazquez C, Cuervas-Mons M, Vaquero-Martín J. Three dimensional-printed patient-specific cutting guides for femoral varization osteotomy: do it yourself. The Knee. 2017;24(6):1359-68.
174. Takagi K. Arthroscope. Clinical Orthopaedics and Related Research®. 1982;167:6-8.
175. Lubowitz JH, Ayala M, Appleby D. Return to activity after knee arthroscopy. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2008;24(1):58-61. e4.
176. Krill M, Early N, Everhart JS, Flanigan DC. Autologous chondrocyte implantation (ACI) for knee cartilage defects: a review of indications, technique, and outcomes. JBJS reviews. 2018;6(2):e5.
177. Chen X, Yang Z, Li H, Zhu S, Wang Y, Qian W. Higher risk of revision in total knee arthroplasty after high tibial osteotomy: a systematic review and updated meta-analysis. BMC musculoskeletal disorders. 2020;21(1):1-8.
178. Lee OS, Ahn S, Lee YS. Effect and safety of early weight-bearing on the outcome after open-wedge high tibial osteotomy: a systematic review and meta-analysis. Arch Orthop Trauma Surg. 2017;137(7):903-11.

179. Goodfellow J, Kershaw C, Benson M, O'Connor J. The Oxford Knee for unicompartmental osteoarthritis. The first 103 cases. The Journal of bone and joint surgery British volume. 1988;70(5):692-701.
180. Nerhus TK, Heir S, Svege I, Skråmm I, Jervidalo T, Madsen JE, et al. Time-dependent improvement in functional outcome following Oxford medial unicompartmental knee arthroplasty: A prospective longitudinal multicenter study involving 96 patients. Acta orthopaedica. 2012;83(1):46-52.
181. Wongsak S, Chulsomlee K, Jarungvittayakon C, Jaovisidha S, Sa-Ngasoongsong P. Is continuous locking suture with braided suture sufficient for arthrotomy repair in the conventional TKR? A randomized controlled trial study. Journal of Orthopaedics. 2021;24:47-53.
182. Tawy G, Shahbaz H, McNicholas M, Biant L. The Relationships between Coronal Plane Alignments and Patient-Reported Outcomes Following High Tibial Osteotomy: A Systematic Review. Cartilage. 2021:19476035211007903.
183. Martay JL, Palmer AJ, Bangerter NK, Clare S, Monk AP, Brown CP, et al. A preliminary modeling investigation into the safe correction zone for high tibial osteotomy. The Knee. 2018;25(2):286-95.
184. Stanley JC, Robinson KG, Devitt BM, Richmond AK, Webster KE, Whitehead TS, et al. Computer assisted alignment of opening wedge high tibial osteotomy provides limited improvement of radiographic outcomes compared to flouroscopic alignment. The Knee. 2016;23(2):289-94.
185. van de Pol GJ, Verdonschot N, van Kampen A. The value of the intra-operative clinical mechanical axis measurement in open-wedge valgus high tibial osteotomies. The Knee. 2012;19(6):933-8.
186. Tsuji M, Akamatsu Y, Kobayashi H, Mitsugi N, Inaba Y, Saito T. Joint line convergence angle predicts outliers of coronal alignment in navigated open-wedge high tibial osteotomy. Archives of orthopaedic and trauma surgery. 2020;140(6):707-15.
187. LOBENHOFFER P, DE SIMONI C, STAUBLI A. Open-wedge high-tibial osteotomy with rigid plate fixation. Techniques in Knee Surgery. 2002;1(2):93-105.
188. Kuremsky MA, Schaller TM, Hall CC, Roehr BA, Masonis JL. Comparison of autograft vs allograft in opening-wedge high tibial osteotomy. The Journal of arthroplasty. 2010;25(6):951-7.
189. Duivenvoorden T, Brouwer R, Baan A, Bos P, Reijman M, Bierma-Zeinstra S, et al. Comparison of closing-wedge and opening-wedge high tibial osteotomy for medial compartment osteoarthritis of the knee: a randomized controlled trial with a six-year follow-up. JBJS. 2014;96(17):1425-32.
190. Kirgis A, Albrecht S. Palsy of the deep peroneal nerve after proximal tibial osteotomy. An anatomical study. JBJS. 1992;74(8):1180-5.
191. Brouwer RW, Huizinga MR, Duivenvoorden T, van Raaij TM, Verhagen AP, Bierma-Zeinstra SM, et al. Osteotomy for treating knee osteoarthritis. Cochrane Database of Systematic Reviews. 2014(12).
192. Turner R, Griffiths H, Heatley F. The incidence of deep-vein thrombosis after upper tibial osteotomy. A venographic study. The Journal of bone and joint surgery British volume. 1993;75(6):942-4.
193. Sabharwal S, Zhao C. Assessment of lower limb alignment: supine fluoroscopy compared with a standing full-length radiograph. JBJS. 2008;90(1):43-51.
194. Hasan K, Rahman QA, Zalzal P. Navigation versus conventional high tibial osteotomy: systematic review. Springerplus. 2015;4:271.
195. Saragaglia D, Roberts J. Navigated osteotomies around the knee in 170 patients with osteoarthritis secondary to genu varum. SLACK Incorporated Thorofare, NJ; 2005. p. S1269-S74.
196. Hankemeier S, Hufner T, Wang G, Kendoff D, Zheng G, Richter M, et al. Navigated intraoperative analysis of lower limb alignment. Archives of orthopaedic and trauma surgery. 2005;125(8):531-5.

197. Yan J, Musahl V, Kay J, Khan M, Simunovic N, Ayeni OR. Outcome reporting following navigated high tibial osteotomy of the knee: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2016;24(11):3529-55.
198. Herbst M, Ahrend M-D, Grünwald L, Fischer C, Schröter S, Ihle C. Overweight patients benefit from high tibial osteotomy to the same extent as patients with normal weights but show inferior mid-term results. Knee Surgery, Sports Traumatology, Arthroscopy. 2021:1-11.
199. Jones GG, Jaere M, Clarke S, Cobb J. 3D printing and high tibial osteotomy. EFORT open reviews. 2018;3(5):254-9.
200. Sarment DP, Al-Shammari K, Kazor CE. Stereolithographic surgical templates for placement of dental implants in complex cases. International Journal of Periodontics and Restorative Dentistry. 2003;23(3):287-96.
201. Brown GA, Firoozbakhsh K, DeCoster TA, Reyna Jr JR, Moneim M. Rapid prototyping: the future of trauma surgery? JBJS. 2003;85(suppl_4):49-55.
202. Goffin J, Van Brussel K, Martens K, Vander Sloten J, Van Audekercke R, Smet M-H. Three-dimensional computed tomography-based, personalized drill guide for posterior cervical stabilization at C1–C2. Spine. 2001;26(12):1343-7.
203. Murase T, Oka K, Moritomo H, Goto A, Yoshikawa H, Sugamoto K. Three-dimensional corrective osteotomy of malunited fractures of the upper extremity with use of a computer simulation system. JBJS. 2008;90(11):2375-89.
204. Raaijmaakers M, Gelaude F, De Smedt K, Clijmans T, Dille J, Mulier M. A custom-made guide-wire positioning device for hip surface replacement arthroplasty: description and first results. BMC musculoskeletal disorders. 2010;11(1):1-7.
205. Billings A, Scott DF, Camargo MP, Hofmann AA. High tibial osteotomy with a calibrated osteotomy guide, rigid internal fixation, and early motion. Long-term follow-up. JBJS. 2000;82(1):70-9.
206. Pérez-Mañanes R, Burró JA, Manaute JR, Rodriguez FC, Martín JV. 3D Surgical Printing Cutting Guides for Open-Wedge High Tibial Osteotomy: Do It Yourself. J Knee Surg. 2016;29(8):690-5.
207. Munier M, Donnez M, Ollivier M, Flecher X, Chabrand P, Argenson J-N, et al. Can three-dimensional patient-specific cutting guides be used to achieve optimal correction for high tibial osteotomy? Pilot study. Orthopaedics & Traumatology: Surgery & Research. 2017;103(2):245-50.
208. Yang JC-S, Chen C-F, Luo C-A, Chang M-C, Lee OK, Huang Y, et al. Clinical experience using a 3D-printed patient-specific instrument for medial opening wedge high tibial osteotomy. BioMed research international. 2018;2018.
209. Jacquet C, Chan-Yu-Kin J, Sharma A, Argenson J-N, Parratte S, Ollivier M. "More accurate correction using "patient-specific" cutting guides in opening wedge distal femur varization osteotomies. International orthopaedics. 2019;43(10):2285-91.
210. Shi J, Lv W, Wang Y, Ma B, Cui W, Liu Z, et al. Three dimensional patient-specific printed cutting guides for closing-wedge distal femoral osteotomy. International orthopaedics. 2019;43(3):619-24.
211. Fucentese SF, Meier P, Jud L, Köchli G-L, Aichmair A, Vlachopoulos L, et al. Accuracy of 3D-planned patient specific instrumentation in high tibial open wedge valgisation osteotomy. Journal of experimental orthopaedics. 2020;7(1):1-7.
212. Jacquet C, Sharma A, Fabre M, Ehlinger M, Argenson J-N, Parratte S, et al. Patient-specific high-tibial osteotomy's 'cutting-guides' decrease operating time and the number of fluoroscopic images taken after a brief learning curve. Knee Surgery, Sports Traumatology, Arthroscopy. 2020;28(9):2854-62.
213. Predescu V, Grosu A-M, Gherman I, Prescura C, Hiohi V, Deleanu B. Early experience using patient-specific instrumentation in opening wedge high tibial osteotomy. International Orthopaedics. 2021:1-7.
214. Savov P, Hold M, Petri M, Horstmann H, von Falck C, Ettinger M. CT based PSI blocks for osteotomies around the knee provide accurate results when intraoperative imaging is used. Journal of Experimental Orthopaedics. 2021;8(1):1-9.

215. Jud L, Fürnstahl P, Vlachopoulos L, Götschi T, Leoty LC, Fucentese SF. Malpositioning of patient-specific instruments within the possible degrees of freedom in high-tibial osteotomy has no considerable influence on mechanical leg axis correction. Knee Surgery, Sports Traumatology, Arthroscopy. 2019:1-9.
216. Martin R, Birmingham TB, Willits K, Litchfield R, LeBel M-E, Giffin JR. Adverse event rates and classifications in medial opening wedge high tibial osteotomy. The American journal of sports medicine. 2014;42(5):1118-26.
217. Meidinger G, Imhoff AB, Paul J, Kirchhoff C, Sauerschnig M, Hinterwimmer S. May smokers and overweight patients be treated with a medial open-wedge HTO? Risk factors for non-union. Knee Surgery, Sports Traumatology, Arthroscopy. 2011;19(3):333-9.
218. Nelissen E, Van Langelaan E, Nelissen R. Stability of medial opening wedge high tibial osteotomy: a failure analysis. International orthopaedics. 2010;34(2):217-23.
219. Esenkaya I, Elmali N. Proximal tibia medial open-wedge osteotomy using plates with wedges: early results in 58 cases. Knee Surgery, Sports Traumatology, Arthroscopy. 2006;14(10):955-61.
220. Han SB, Lee DH, Shetty GM, Chae DJ, Song JG, Nha KW. A "safe zone" in medial open-wedge high tibia osteotomy to prevent lateral cortex fracture. Knee Surgery, Sports Traumatology, Arthroscopy. 2013;21(1):90-5.
221. Kaze AD, Maas S, Belsey J, Hoffmann A, Seil R, van Heerwaarden R, et al. Mechanical strength of a new plate compared to six previously tested opening wedge high tibial osteotomy implants. Journal of experimental orthopaedics. 2019;6(1):1-15.
222. Jacobi M, Wahl P, Bouaicha S, Jakob RP, Gautier E. Distal femoral varus osteotomy: problems associated with the lateral open-wedge technique. Archives of orthopaedic and trauma surgery. 2011;131(6):725-8.
223. Dean CS, Liechti DJ, Chahla J, Moatshe G, LaPrade RF. Clinical Outcomes of High Tibial Osteotomy for Knee Instability: A Systematic Review. Orthop J Sports Med. 2016;4(3):2325967116633419.
224. Brosset T, Pasquier G, Migaud H, Gougeon F. Opening wedge high tibial osteotomy performed without filling the defect but with locking plate fixation (TomoFix™) and early weight-bearing: prospective evaluation of bone union, precision and maintenance of correction in 51 cases. Orthopaedics & Traumatology: Surgery & Research. 2011;97(7):705-11.
225. Slevin O, Ayeni OR, Hinterwimmer S, Tischer T, Feucht MJ, Hirschmann MT. The role of bone void fillers in medial opening wedge high tibial osteotomy: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2016;24(11):3584-98.
226. Wretenberg P, Hugo A, Broström E. Hip joint load in relation to leg length discrepancy. Medical Devices (Auckland, NZ). 2008;1:13.
227. Resende RA, Kirkwood RN, Deluzio KJ, Morton AM, Fonseca ST. Mild leg length discrepancy affects lower limbs, pelvis and trunk biomechanics of individuals with knee osteoarthritis during gait. Clinical biomechanics. 2016;38:1-7.
228. Kahanovitz N, Duncan J. The role of scoliosis and pelvic obliquity on functional disability in myelomeningocele. Spine. 1981;6(5):494-7.
229. Li M, Shen Y, Gao Z-l, Fang X-t, Xie Y, Wang C-f, et al. Surgical treatment of adult idiopathic scoliosis: long-term clinical radiographic outcomes. Orthopedics. 2011;34(3).
230. Lee OS, Ahn S, Lee YS. Comparison of the Leg-Length Change between Opening- and Closing-Wedge High Tibial Osteotomy: A Systematic Review and Meta-Analysis. J Knee Surg. 2019;32(4):372-9.
231. Lin R, Jou I-M, Yu C-Y. Lumbar lordosis: normal adults. Journal of the Formosan Medical Association. 1992;91(3):329-33.
232. Mochizuki T, Tanifuji O, Koga Y, Sato T, Kobayashi K, Watanabe S, et al. Correlation between posterior tibial slope and sagittal alignment under weight-bearing conditions in osteoarthritic knees. PLoS One. 2018;13(9):e0202488.

233. Brandon ML, Haynes PT, Bonamo JR, Flynn MI, Barrett GR, Sherman MF. The association between posterior-inferior tibial slope and anterior cruciate ligament insufficiency. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2006;22(8):894-9.
234. Black N. Patient reported outcome measures could help transform healthcare. Bmj. 2013;346.
235. Black N, Jenkinson C. Measuring patients' experiences and outcomes. Bmj. 2009;339.
236. Rathert C, Huddleston N, Pak Y. Acute care patients discuss the patient role in patient safety. Health care management review. 2011;36(2):134-44.
237. Galea V, Rojanasopondist P, Ingelsrud L, Rubash H, Bragdon C, Huddleston Iii J, et al. Longitudinal changes in patient-reported outcome measures following total hip arthroplasty and predictors of deterioration during follow-up: a seven-year prospective international multicentre study. The bone & joint journal. 2019;101(7):768-78.
238. Gagnier JJ. Patient reported outcomes in orthopaedics. Journal of Orthopaedic Research. 2017;35(10):2098-108.
239. Jester R, Santy-Tomlinson J, Drozd M. The use of patient reported outcome measures (PROMs) in clinical assessment. 2018.
240. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain. 1983;16(1):87-101.
241. Young VN, Jordan KM, Schneider SL, Lazar A, Dwyer CD, Rosen CA. Laryngology Quality of Life Questionnaire Associations: Towards Reducing Survey Burden. The Laryngoscope. 2021;131(7):1561-5.
242. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure. Journal of Orthopaedic & Sports Physical Therapy. 1998;28(2):88-96.
243. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health and quality of life outcomes. 2003;1(1):1-8.
244. Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. The Journal of bone and joint surgery British volume. 1998;80(1):63-9.
245. Steultjens M, Dekker J, Bijlsma J. Avoidance of activity and disability in patients with osteoarthritis of the knee: the mediating role of muscle strength. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 2002;46(7):1784-8.
246. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. Journal of rheumatology. 1988.
247. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Medical care. 1992:473-83.
248. Dugdale TW, Noyes FR, Styer D. Preoperative planning for high tibial osteotomy. The effect of lateral tibiofemoral separation and tibiofemoral length. Clinical orthopaedics and related research. 1992(274):248-64.
249. Moreland JR, Bassett L, Hanker G. Radiographic analysis of the axial alignment of the lower extremity. The Journal of bone and joint surgery American volume. 1987;69(5):745-9.
250. Yoshioka Y, Siu D, Cooke T, Chir B. The anatomy and functional axes of the femur. J Bone Joint Surg Am. 1987;69(6):873-80.
251. Jingjit W, Poomcharoen P, Limmahakhun S, Klunklin K, Leerapun T, Rojanasthien S. Femoral mechanical-anatomical angle of osteoarthritic knees. J Med Assoc Thai. 2014;97(12):1314-8.
252. Wise KL, Kelly BJ, Agel J, Marette S, Macalena JA. Reliability of EOS compared to conventional radiographs for evaluation of lower extremity deformity in adult patients. Skeletal radiology. 2020;49(9):1423-30.

253. Oh S-M, Bin S-I, Lee B-S, Kim J-M. The entry point of intramedullary tibia cutting guide should vary according to the individual tibia morphology in TKA. Archives of orthopaedic and trauma surgery. 2020;140(3):391-400.
254. Meier M, Janssen D, Koeck FX, Thienpont E, Beckmann J, Best R. Variations in medial and lateral slope and medial proximal tibial angle. Knee surgery, sports traumatology, arthroscopy. 2021;29(3):939-46.
255. Jang K-M, Lee J-H, Cho IY, Park B-K, Han S-B. Intraoperative fluoroscopic assessment of limb alignment is a reliable predictor for postoperative limb alignment in biplanar medial opening-wedge high tibial osteotomy. The Journal of arthroplasty. 2017;32(3):756-60.
256. Cherian JJ, Kapadia BH, Banerjee S, Jauregui JJ, Issa K, Mont MA. Mechanical, anatomical, and kinematic axis in TKA: concepts and practical applications. Current reviews in musculoskeletal medicine. 2014;7(2):89-95.
257. Pornrattanamaneewong C, Narkbunnam R, Chareancholvanich K. Medial proximal tibial angle after medial opening wedge HTO: A retrospective diagnostic test study. Indian journal of orthopaedics. 2012;46:525-30.
258. Lin Y-H, Chang F-S, Chen K-H, Huang K-C, Su K-C. Mismatch between femur and tibia coronal alignment in the knee joint: classification of five lower limb types according to femoral and tibial mechanical alignment. BMC musculoskeletal disorders. 2018;19(1):1-9.
259. Paley D. Normal lower limb alignment and joint orientation. Principles of deformity correction: Springer; 2002. p. 1-18.
260. Kocabiyik A, Misir A, Kizkapan TB, Yildiz KI, Kaygusuz MA, Alpay Y, et al. Changes in hip, knee, and ankle coronal alignments after total hip arthroplasty with transverse femoral shortening osteotomy for unilateral crowe type IV developmental dysplasia of the hip. The Journal of arthroplasty. 2017;32(11):3449-56.
261. Chaibi Y, Cresson T, Aubert B, Hausselle J, Neyret P, Hauger O, et al. Fast 3D reconstruction of the lower limb using a parametric model and statistical inferences and clinical measurements calculation from biplanar X-rays. Computer methods in biomechanics and biomedical engineering. 2012;15(5):457-66.
262. Trobisch P, Suess O, Schwab F. Idiopathic scoliosis. Deutsches Ärzteblatt International. 2010;107(49):875.
263. Morrissy R, Goldsmith G, Hall E, Kehl D, Cowie G. Measurement of the Cobb angle on radiographs of patients who have scoliosis: Evaluation of intrinsic error. J Bone Joint Surg Am. 1990;72(3):320-7.
264. Julliard R, Genin P, Weil G, Palmkrantz P. The median functional slope of the tibia. Principle. Technique of measurement. Value. Interest. Revue de chirurgie orthopedique et reparatrice de l'appareil moteur. 1993;79(8):625-34.
265. Dean RS, DePhillipo NN, Chahla J, Larson CM, LaPrade RF. Posterior Tibial Slope Measurements Using the Anatomic Axis Are Significantly Increased Compared With Those That Use the Mechanical Axis. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2021;37(1):243-9.
266. Jiang C-C, Yip K, Liu T. Posterior slope angle of the medial tibial plateau. Journal of the Formosan Medical Association= Taiwan yi zhi. 1994;93(6):509-12.
267. Kuriyama S, Morimoto N, Shimoto T, Takemoto M, Nakamura S, Nishitani K, et al. Clinical efficacy of preoperative 3D planning for reducing surgical errors during open-wedge high tibial osteotomy. Journal of Orthopaedic Research®. 2019;37(4):898-907.
268. Jiang Y, Sun X, Peng X, Zhao J, Zhang K. Effect of sacral slope on the biomechanical behavior of the low lumbar spine. Experimental and therapeutic medicine. 2017;13(5):2203-10.
269. Legaye J. The femoro-sacral posterior angle: an anatomical sagittal pelvic parameter usable with dome-shaped sacrum. European Spine Journal. 2007;16(2):219-25.
270. Vialle R, Levassor N, Rillardon L, Templier A, Skalli W, Guigui P. Radiographic analysis of the sagittal alignment and balance of the spine in asymptomatic subjects. JBJS. 2005;87(2):260-7.

271. Polly Jr DW, Kilkelly FX, McHale KA, Asplund LM, Mulligan M, Chang AS. Measurement of lumbar lordosis: evaluation of intraobserver, interobserver, and technique variability. Spine. 1996;21(13):1530-5.
272. Hussein Al-Marshadi A, Aslam M, Abdullah A. Uncertainty-Based Trimmed Coefficient of Variation with Application. Journal of Mathematics. 2021;2021.
273. Sabzevari S, Ebrahimpour A, Roudi MK, Kachooei AR. High tibial osteotomy: a systematic review and current concept. Archives of Bone and Joint Surgery. 2016;4(3):204.
274. Park CH, Bae DK, Kim KI, Lee JW, Song SJ. Serial changes in the joint space width and joint line convergence angle after closed-wedge high tibial osteotomy. The American journal of sports medicine. 2017;45(14):3254-61.
275. Nha K-W, Kim H-J, Ahn H-S, Lee D-H. Change in posterior tibial slope after open-wedge and closed-wedge high tibial osteotomy: a meta-analysis. The American journal of sports medicine. 2016;44(11):3006-13.
276. Luites J, Brinkman J-M, Wymenga A, Van Heerwaarden R. Fixation stability of opening-versus closing-wedge high tibial osteotomy: a randomised clinical trial using radiostereometry. The Journal of bone and joint surgery British volume. 2009;91(11):1459-65.
277. Khamis S, Carmeli E. A new concept for measuring leg length discrepancy. Journal of orthopaedics. 2017;14(2):276.
278. Cibere J, Thorne A, Bellamy N, Greidanus N, Chalmers A, Mahomed N, et al. Reliability of the hip examination in osteoarthritis: effect of standardization. Arthritis Care & Research. 2008;59(3):373-81.
279. Ploumis A, Trivedi V, Shin J-H, Wood KB, Grottkau BE. Progression of idiopathic thoracic or thoracolumbar scoliosis and pelvic obliquity in adolescent patients with and without limb length discrepancy. Scoliosis and spinal disorders. 2018;13(1):1-7.
280. Guezou-Philippe A, Dardenne G, Dorniol M, Letissier H, Lefèvre C, Stindel E. Reliability of pelvic parameters measurement with sterEOS: preliminary results. EPiC Series in Health Sciences. 2019;3:157-60.
281. Le Huec J, Aunoble S, Philippe L, Nicolas P. Pelvic parameters: origin and significance. European Spine Journal. 2011;20(5):564-71.
282. Na YG, Lee BK, Choi JU, Lee BH, Sim JA. Change of joint-line convergence angle should be considered for accurate alignment correction in high tibial osteotomy. Knee surgery & related research. 2021;33(1):1-10.
283. Naendrup J-H, Drouven SF, Shaikh HS, Jaecker V, Offerhaus C, Shafizadeh ST, et al. High variability of tibial slope measurement methods in daily clinical practice: comparisons between measurements on lateral radiograph, magnetic resonance imaging, and computed tomography. The Knee. 2020;27(3):923-9.
284. Nelitz M. Femoral derotational osteotomies. Current reviews in musculoskeletal medicine. 2018;11(2):272-9.
285. Fouilleron N, Marchetti E, Autissier G, Gougeon F, Migaud H, Girard J. Proximal tibial derotation osteotomy for torsional tibial deformities generating patello-femoral disorders. Orthopaedics & Traumatology: Surgery & Research. 2010;96(7):785-92.
286. Krackow KA, Pepe CL, Galloway EJ. A mathematical analysis of the effect of flexion and rotation on apparent varus/valgus alignment at the knee. SLACK Incorporated Thorofare, NJ; 1990.
287. Moon H-S, Choi C-H, Jung M, Lee D-Y, Kim J-H, Kim S-H. The effect of knee joint rotation in the sagittal and axial plane on the measurement accuracy of coronal alignment of the lower limb. BMC Musculoskeletal Disorders. 2020;21(1):1-9.
288. Sorin G, Pasquier G, Drumez E, Arnould A, Migaud H, Putman S. Reproducibility of digital measurements of lower-limb deformity on plain radiographs and agreement with CT measurements. Orthopaedics & Traumatology: Surgery & Research. 2016;102(4):423-8.
289. Swanson KE, Stocks GW, Warren PD, Hazel MR, Janssen HF. Does axial limb rotation affect the alignment measurements in deformed limbs? Clinical Orthopaedics and Related Research®. 2000;371:246-52.

290. Nguyen HC, Gielis WP, van Egmond N, Weinans H, Slump CH, Sakkers RJ, et al. The Need for a Standardized Whole Leg Radiograph Guideline: The Effects of Knee Flexion, Leg Rotation, and X-ray Beam Height. Journal of Cartilage & Joint Preservation. 2021:100022.
291. Lavrakas PJ. Encyclopedia of survey research methods: Sage publications; 2008.
292. Miao Z, Li S, Luo D, Lu Q, Liu P. The validity and accuracy of 3D-printed patient-specific instruments for high tibial osteotomy: a cadaveric study. Journal of Orthopaedic Surgery and Research. 2022;17(1):1-8.

Appendix

Appendix A – Ethical Approval Letter

Medicine & Health Sciences Subcommittee
Macquarie University, North Ryde
NSW 2109, Australia

08/06/2021

Dear Dr Turner,

Reference No: 52021982328611
Project ID: 9823
Title: Assessment of lower limb, pelvic and spinal alignment following high tibial osteotomy (HTO) and distal femoral osteotomy (DFO)

Thank you for submitting the above application for ethical review. The Medicine & Health Sciences Subcommittee has considered your application.

I am pleased to advise that ethical approval has been granted for this project to be conducted by Dr Dane Turner, and other personnel: A/Prof Richard Appleyard, Dr Joseph Cadman, Prof Munjed Al Muderis, Dr Mustafa Alttahir, Dr William Lu, Mr. Hugo Wiggins.

This research meets the requirements set out in the National Statement on Ethical Conduct in Human Research 2007, (updated July 2018).

Standard Conditions of Approval:

1. Continuing compliance with the requirements of the National Statement, available from the following website: https://nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018.

2. This approval is valid for five (5) years, subject to the submission of annual reports. Please submit your reports on the anniversary of the approval for this protocol - 8 June (*yearly*). You will be sent an automatic reminder email one week from the due date to remind you of your reporting responsibilities.

Annual report 1 - FROM: 8 June 2022 TO: 8 June 2023

Annual report 2 - FROM: 8 June 2023 TO: 8 June 2024

Annual report 3 - FROM: 8 June 2024 TO: 8 June 2025

Annual report 4 - FROM: 8 June 2025 TO: 8 June 2026

Annual report 5 - FROM: 8 June 2026 TO: 8 June 2027

3. All adverse events, including unforeseen events, which might affect the continued ethical acceptability of the project, must be reported to the subcommittee within 72 hours.

4. All proposed changes to the project and associated documents must be submitted to the subcommittee for review and approval before implementation. Changes can be made via the Human Research Ethics Management System.

The HREC Terms of Reference and Standard Operating Procedures are available from the Research Services website: https://www.mq.edu.au/research/ethics-integrity-and-policies/ethics/human-ethics.

It is the responsibility of the Chief Investigator to retain a copy of all documentation related to this project and to forward a copy of this approval letter to all personnel listed on the project.

Should you have any queries regarding your project, please contact the Faculty Ethics Officer.

The Medicine & Health Sciences Subcommittee wishes you every success in your research.

Yours sincerely,

Dr Mark Butlin

Chair, Medicine & Health Sciences Subcommittee

The Faculty Ethics Subcommittees at Macquarie University operate in accordance with the National Statement on Ethical Conduct in Human Research 2007, (updated July 2018), [Section 5.2].

Appendix B – Participant Information and Consent Form (PICF)

Department of Biomedical Sciences, and
MQ Health Limb Reconstruction Clinic
Faculty of Medicine, Health and Human Sciences
MACQUARIE UNIVERSITY, NSW, 2109

MACQUARIE University
SYDNEY·AUSTRALIA

Participant Information and Consent Form

Name of Project: Assessment of lower limb, pelvic and spinal alignment following high tibial osteotomy (HTO) and distal femoral osteotomy (DFO)

Sponsor: Macquarie University

You are invited to participate in a study investigating the biomechanics and the subjective outcomes of your high tibial osteotomy (HTO) or distal femoral osteotomy (DFO). Your doctor would have described your procedure in detail.

This study is separate to the standard care provided by your clinicians and will not affect the outcome of your procedure in any way.

This study requires you to give permission to access digital copies of your medical images directly related to this procedure as well as the completion of a questionnaire regarding your knee function.

The aim of this study is to measure the lower limb alignment by comparing the postoperative correction with the pre-operative alignment plans and to see how this has improved your knee function. We would also like to measure the alignment of your pelvis and spine, before and after your surgery, to determine how these correlate with the surgical correction. These measurements will be made from your medical images (e.g. X-rays), which are already taken during the clinic's standard procedure. Although there are no direct benefits to you as a patient, the findings from this study will contribute to the current knowledge on HTO and DFO surgical techniques and how the level of alignment correction affects alignment in the pelvis and spine.

Please ensure the following study eligibility criteria applies to you:

- You are aged between 18 and 65.
- You are undergoing/ have undergone an HTO/DFO on one or both of your legs.
- You do not have joint dysplasia of any kind.

If you decide to participate, your pre-operative and post-operative (up to 3 months after your procedure) medical images will be acquired from your selected imaging facility and used to measure biomechanical angles. You will also be asked to complete three questionnaires relating to your knee function (e.g. Physical function, pain and joint stiffness) and quality of life. These will be completed once pre-operatively (if enrolled in the study at this time) and once post-operatively (~8 weeks after surgery). This study will not incur any cost to you.

If you wish to withdraw from the study at any time (even after the completion of your surgery and imaging sessions), you are free to do so without giving a reason, and there will be no consequences for your withdrawal.

This study should generally not cause any risks to you. There is, however, the inconvenience for you in completing some questionnaires. This should take no longer than 20 minutes to complete and will be provided to you when visiting the clinic for your appointments. Also, if you feel that any of the questions in the questionnaire cause distress, please make an appointment to see your GP.

This study is funded by Macquarie University and will be conducted by: Prof Munjed Al Muderis, Dr Mustafa Alttahir, Dr Tim O'Carrigan or Dr Razvan Stoita of the Department of Orthopaedics, Macquarie University Hospital; Dr Danè Turner (Senior research fellow) of the Department of Biomedical Sciences; Dr William Lu (Clinical Researcher); A/Prof Richard Appleyard (Clinical Skills Director) and Dr Joseph Cadman (Research fellow) of the Department of Biomedical Sciences; and Mr Hugo Wiggins (Masters student) of the Department of Biomedical Sciences at Macquarie University. This study will be undertaken as part of Mr Hugo Wiggins' requirement for the degree of Master of Research under the supervision of Dr Danè Turner.

You can contact either Dr Danè Turner on (02) 9850-2753 or email Daneh.Turner@mq.edu.au or Prof Munjed Al Muderis on (02) 9812-3605 or email Reception@almuderis.com.au.

All data and personal information collected throughout the study will be confidential, except as required by law. All data for this study will be coded and re-identifiable for purposes of follow-up. No individual will be identified in any publication of the results, which we aim to publish after its approximate 12 month duration. Data will be stored on password-protected network drives for 7 years after publication of the results and deleted thereafter. Access to the data will be strictly limited to the individuals directly involved in the investigation, who are listed on this form. A summary of the results of the data can be made available to you on request. Please email or call Dr Danè Turner (contact details above).

I _____ have read (or have been verbally informed of) and understand the proposed study, and answers to my questions (if any) were satisfactory. I consent to participate in this study and accept the potential for risks (if any) mentioned in this form. An identical physical or digital copy of this form was given to me by the research group to keep for my own records.

Participant's name: _____

Participant's signature: _____

Date: _____/_____/_____

Investigator's name: _____

Investigator's signature: _____

Date: _____/_____/_____

All ethical aspects of this study have been approved by the Macquarie University Human Research Ethics Committee and adhere to the National Health and Medical Research Council's Statement of Ethical Conduct in Human Research. If you wish to clarify any ethical concerns confidentially, please contact Macquarie University's Director of Research Ethics & Integrity on (02) 9850 7854, or via ethics@mq.edu.au.

The following section does NOT need to be completed for you to participate in this study. It will enable the results of this study, as well as information on future studies, to be communicated directly to you if they become available. Please circle the following:

YES / NO I would like to receive a copy of the study results if they become available.

YES / NO I would like to be informed of future research studies from the Faculty of Medicine, Health and Human Sciences at Macquarie University.

Please list one of the following if you selected **YES** for either of the options above:

Email (optional): _____

OR

Phone number (optional): _____

(Participant's OR investigator's copy)

Appendix C – Patient-reported outcome measure (PROM) form

MACQUARIE University
SYDNEY·AUSTRALIA

PARTICIPANT ID: | | | | |

MACQUARIE UNIVERSITY ORTHOPAEDIC RESEARCH

PARTICIPATION PROFILE BEFORE/AFTER HIGH TIBIAL OSTEOTOMY (HTO)/DISTAL FEMORAL OSTEOTOMY (DFO)

TODAY'S DATE: _____/_____/_____

PARTICIPANT FULL NAME: _____

DATE OF BIRTH: _____/_____/_____

WEIGHT (kg): _____

HEIGHT (cm): _____

SEX (Please tick): ☐ **Male** ☐ **Female**

ETHNICITY: _____

SIDE OF KNEE (Please tick affected side): ☐ **Left** ☐ **Right**

DATE OF KNEE SURGERY: _____/_____/_____

CONTACT NUMBER(S): MOBILE _____ **HOME** _____

SURGEON'S FULL NAME: _____

Welcome to Macquarie University Orthopaedic Research

Please fill in the following questionnaires to your best ability. The questionnaires are based around pain, stiffness, functionality and overall quality of life you experience due to your knee.

Macquarie University Orthopaedics Research wish to contact you before and/or 2-6 months after your surgery to see what progress you have made and how your knee has developed since your surgery. If you are happy to come in or be contacted over the phone or via e-mail, please write your name and sign the following section.

Consent Form

I, (Name) _____ agree to be contacted before and/or 2-6 months after my HTO/DFO surgery to answer and complete this questionnaire form.

I understand that this will be either on site (at Macquarie University), over the telephone or through e-mail (depending on your convenience).

Signature: _____

HTO/DFO Questionnaire Updated 06/05/2021

MACQUARIE University
SYDNEY·AUSTRALIA

PARTICIPANT ID: | | | | |

Questionnaire 1 – Knee Injury and Osteoarthritis Outcome Score (1/3)

Pain

P1	How often is your knee painful?	☐ Never	☐ Monthly	☐ Weekly	☐ Daily	☐ Always

What degree of pain have you experienced the last week when…?

P2	Twisting/pivoting on your knee	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P3	Straightening knee fully	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P4	Bending knee fully	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P5	Walking on flat surface	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P6	Going up or down stairs	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P7	At night while in bed	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P8	Sitting or lying	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P9	Standing upright	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Symptoms

Sy1	How severe is your knee stiffness after first wakening in the morning?	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sy2	How severe is your knee stiffness after sitting, lying, or resting later in the day?	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sy3	Do you have swelling in your knee?	☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Always
Sy4	Do you feel grinding, hear clicking or any other type of noise when your knee moves?	☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Always
Sy5	Does your knee catch or hang up when moving?	☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Always
Sy6	Can you straighten your knee fully?	☐ Always	☐ Often	☐ Sometimes	☐ Rarely	☐ Never
Sy7	Can you bend your knee fully?	☐ Always	☐ Often	☐ Sometimes	☐ Rarely	☐ Never

HTO/DFO Questionnaire Updated 06/05/2021

MACQUARIE University
SYDNEY·AUSTRALIA

PARTICIPANT ID: | | | | |

Questionnaire 1 – Knee Injury and Osteoarthritis Outcome Score (2/3)

Activities of daily living

What difficulty have you experienced the last week…?

A1 Descending	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A2 Ascending stairs	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A3 Rising from sitting	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A4 Standing	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A5 Bending to floor/picking up an object	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A6 Walking on flat surface	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A7 Getting in/out of car	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A8 Going shopping	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A9 Putting on socks/stockings	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A10 Rising from bed	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A11 Taking off socks/stockings	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A12 Lying in bed (turning over, maintaining knee position)	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A13 Getting in/out of bath	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A14 Sitting	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A15 Getting on/off toilet	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A16 Heavy domestic duties (shovelling, scrubbing floors, etc)	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A17 Light domestic duties (cooking, dusting, etc)	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Sport and recreation function

What difficulty have you experienced the last week…?

Sp1 Squatting	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp2 Running	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp3 Jumping	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp4 Turning/twisting on your injured knee	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp5 Kneeling	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

HTO/DFO Questionnaire Updated 06/05/2021

MACQUARIE University
SYDNEY·AUSTRALIA

PARTICIPANT ID: | | | | |

Questionnaire 1 – Knee Injury and Osteoarthritis Outcome Score (3/3)

Knee-related quality of life

Q1 How often are you aware of your knee problems?	☐ Never	☐ Monthly	☐ Weekly	☐ Daily	☐ Always
Q2 Have you modified your lifestyle to avoid potentially damaging activities to your knee?	☐ Not at all	☐ Mildly	☐ Moderately	☐ Severely	☐ Totally
Q3 How troubled are you with lack of confidence in your knee?	☐ Not at all	☐ Mildly	☐ Moderately	☐ Severely	☐ Totally
Q4 In general, how much difficulty do you have with your knee?	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

MACQUARIE University
SYDNEY·AUSTRALIA

PARTICIPANT ID: | | | | |

Questionnaire 2 – WOMAC

Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle **one number** for each activity

Pain	1. Walking	0 1 2 3 4
	2. Stair Climbing	0 1 2 3 4
	3. Nocturnal	0 1 2 3 4
	4. Rest	0 1 2 3 4
	5. Weight bearing	0 1 2 3 4
Stiffness	1. Morning stiffness	0 1 2 3 4
	2. Stiffness occurring later in the day	0 1 2 3 4
Physical Function	1. Descending stairs	0 1 2 3 4
	2. Ascending stairs	0 1 2 3 4
	3. Rising from sitting	0 1 2 3 4
	4. Standing	0 1 2 3 4
	5. Bending to floor	0 1 2 3 4
	6. Walking on flat surface	0 1 2 3 4
	7. Getting in / out of car	0 1 2 3 4
	8. Going shopping	0 1 2 3 4
	9. Putting on socks	0 1 2 3 4
	10. Lying in bed	0 1 2 3 4
	11. Taking off socks	0 1 2 3 4
	12. Rising from bed	0 1 2 3 4
	13. Getting in/out of bath	0 1 2 3 4
	14. Sitting	0 1 2 3 4
	15. Getting on/off toilet	0 1 2 3 4
	16. Heavy domestic duties	0 1 2 3 4
	17. Light domestic duties	0 1 2 3 4

Total Score: _____ / 96 = _____%

Comments / Interpretation (to be completed by therapist only):

HTO/DFO Questionnaire Updated 06/05/2021

MACQUARIE University
SYDNEY·AUSTRALIA

PARTICIPANT ID: | | | | |

Questionnaire 3 – Short-form 36 (1/4)

SF-36 Questionnaire

This questionnaire asks for your views about your health. For ALL questions, please tick, cross or colour the circle that most closely matches your response. There are no right or wrong answers. Please answer ALL questions.

1. In general, would you say your health is:	Poor ◯	Fair ◯	Good ◯	Very good ◯	Excellent ◯
2. Compared to one year ago, how would you rate your health general in now?	Much worse now than one year ago ◯	Somewhat worse than one year ago ◯	About the same as one year ago ◯	Somewhat better than one year ago ◯	Much better than one year ago ◯

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	No, not limited at all	Yes, limited a little	Yes, limited a lot
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	◯	◯	◯
b. Moderate activities, such as moving a table pushing a vacuum cleaner, bowling, or playing	◯	◯	◯
c. Lifting or carrying groceries	◯	◯	◯
d. Climbing <u>several</u> flights of stairs	◯	◯	◯
e. Climbing <u>one</u> flight of stairs	◯	◯	◯
f. Bending, kneeling or stooping	◯	◯	◯
g. Walking more than a mile	◯	◯	◯
h. Walking several blocks	◯	◯	◯
i. Walking one block	◯	◯	◯
j. Bathing or dressing yourself	◯	◯	◯

MACQUARIE University
SYDNEY·AUSTRALIA

PARTICIPANT ID: | | | | |

Questionnaire 3 – Short-form 36 (2/4)

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other daily activities as a result of your physical health?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Cut down on the amount of time you spent on work or other activities	○	○	○	○	○
b. Accomplished less than you would like	○	○	○	○	○
c. Were limited in the kind of work or other activities	○	○	○	○	○
d. Had difficulty performing the work or other activities (e.g. it took extra effort)	○	○	○	○	○

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Cut down on the amount of time you spent on work or other activities	○	○	○	○	○
b. Accomplished less than you would like	○	○	○	○	○
c. Did work or other activities less carefully than usual	○	○	○	○	○

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	All of the time

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe

MACQUARIE University
SYDNEY·AUSTRALIA

PARTICIPANT ID: | | | | |

Questionnaire 3 – Short-form 36 (3/4)

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	A liitle bit	Moderately	Quite a bit	Extremely
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...					
	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. did you feel full of life?	○	○	○	○	○
b. have you been very nervous?	○	○	○	○	○
c. have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○
d. have you felt calm and peaceful?	○	○	○	○	○
e. did you have a lot of energy?	○	○	○	○	○
f. have you felt downhearted and depressed?	○	○	○	○	○
g. did you feel worn out?	○	○	○	○	○
h. have you been happy?	○	○	○	○	○
i. did you feel tired?	○	○	○	○	○
10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	None of the time	A little of the time	Some of the time	Most of the time	All of the time
11. How TRUE or FALSE is each of the following statements for you?					
	Defintely false	Mostly false	Don't know	Mostly true	Definitely true
a. I seem to get sick a little easier than other people	○	○	○	○	○

HTO/DFO Questionnaire Updated 06/05/2021

MACQUARIE University
SYDNEY·AUSTRALIA

PARTICIPANT ID: | | | | |

Questionnaire 3 – Short-form 36 (4/4)

b. I am as healthy as anybody I know	○	○	○	○	○
c. I expect my health to get worse	○	○	○	○	○
d. My health is excellent	○	○	○	○	○

MACQUARIE University
SYDNEY·AUSTRALIA

PARTICIPANT ID:

THANK YOU FOR YOUR PATIENCE COMPLETING THESE SURVEYS

Please check and ensure all details on the first page are correct.

If you feel that any of these questions have caused distress, please make an appointment to see your GP.

If you have any questions or queries, do not hesitate to ask or contact us.

HTO/DFO Questionnaire Updated 06/05/2021