

**Study Title:** **Explanatory comparative study of conventional Total Knee Arthroplasty versus Robotic assisted Bi-UniCompartmental Knee Arthroplasty**

**Study Acronym:** TRUCK Trial  
(Total vs Robotic bi-UniCompartmental Knee Trial)

**Study Website:** <https://w3.abdn.ac.uk/hsru/truck/>

**Ethics Reference:** 14\WS\0134

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**Commercial partner:** MAKO Surgical Corp (Florida, USA)

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Table 2: Study stages with Go / No-Go decisions and Milestones

Table 3: Study Timeline (Gantt Chart)

## 1. Amendment History

Amendment No.	Protocol Version No.	Date	Author(s) of changes	Details of Changes made
1. Minor	3.0	18/11/14	Iain Anthony and Mark Blyth	<p>Points of clarification requested by Trial Steering Committee:</p> <ul style="list-style-type: none"> <li>• Additional information to clarify inclusion/exclusion criteria</li> <li>• Move 3 month post-op long leg x-ray to 1 year time point</li> <li>• Add clarification statement regarding mechanical axis targets from surgery</li> <li>• Clarify version of AKSS score being used</li> <li>• Correct omission of FJS score in text.</li> </ul> <p>Ack by REC 22.12.15 Ack by R&amp;D 05.01.15</p>
2. Substantial	3.2	05/12/16	Matthew Banger Mark Blyth	<p>Additional routes to approach patients added</p> <p>Approved by REC -07.12.16 Not approved by R&amp;D- <b>to be include in next sub amendment and approved by MHRA prior to R&amp;D approval</b></p>
3. Substantial	4.0	11.10.17	Matthew Banger  Iona Donnelly  Mark Blyth	<ol style="list-style-type: none"> <li>1. Addition of human performance laboratory analysis at 2 year follow-up</li> <li>2. Update of 12.3.2. Reporting of SAEs, SADEs, UADEs to the sponsor</li> <li>3. Update of patient recruitment target and recruitment phase extension. Sections 19,</li> </ol>

				<p>21 and 23. Flowchart and Gantt Chart updated.</p> <p>4. Inclusion of participant and nurse questionnaires at 2 or 5 year follow up</p> <p>5. Inclusion of newsletter at 4 and 7 years follow up to maintain participant engagement</p> <p>Submitted to REC Submitted, <b>with previous amendment</b> to MHRA</p>
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Approvals for Amendment number 3 (Substantial) were approved as follows:

1. REC – Approved by West of Scotland REC 4 on 14 MAR 2018
2. MHRA – Approved by MHRA on 03 APR 2018
3. Sponsor – Approved by NHS Greater Glasgow & Clyde on 14 APR 2018

Rationale for sample size amendment

On re-visiting the power calculation, it appears that the original calculation had included a conservative LTFU rate of ~23%. At the time of compiling the Study Recovery Plan (March 2017) the study statistician looked at the available data we had obtained. Our actual LTFU was 8%. Re-doing the power calculation based on a realistic LTFU of 10% meant that we could reduce the target number to 80 whilst still retaining 90% power for the primary outcome measure to ensure that the most robust and complete dataset possible is obtained to reliably answer the research question, and detect a clinically significant difference between the 2 treatment arms. The Study Recovery Plan was approved by NIHR EME on 03 MAY 2017.

## 2. Synopsis

<b>Study Title</b>	Explanatory comparative study of conventional Total Knee Arthroplasty versus Robotic assisted Bi-UniCompartmental Knee Arthroplasty
<b>Type of study</b>	<i>Pre- CE marking / extension of current CE marking</i>
<b>Trial Design</b>	Randomised Controlled Trial
<b>Trial Participants</b>	Patients with osteoarthritis of the knee affecting both the medial and lateral compartments
<b>Planned Sample Size</b>	80
<b>Follow-up duration</b>	10 years
<b>Planned Trial Period</b>	15 years
<b>Primary Objective</b>	To carry out an explanatory randomised controlled trial to compare a novel robotic assisted surgical technique (Bi-Unicompartmental Knee Arthroplasty) against a standard surgical technique (Total Knee Arthroplasty) in patients with osteoarthritis of both the medial and lateral compartments of the knee.
<b>Secondary Objectives</b>	<ol style="list-style-type: none"> <li>1. To provide evidence of early phase efficacy and safety for Robotic Assisted Bi-Unicompartmental Knee replacement.</li> <li>2. To determine the biomechanical mechanism through which patients derive benefit from Robotic Assisted Bi-Unicompartmental Knee replacement.</li> </ol>
<b>Primary Endpoint</b>	Percentage of patients with a bi-phasic (normal) moment curve during gait (level walking)
<b>Secondary Endpoints</b>	<ul style="list-style-type: none"> <li>• Percentage of patients with a bi-phasic (normal) moment curve during gait (level walking) at two years</li> <li>• Biomechanical performance–Gait during stair climb/descent and lunge, functional activity assessment (using electrogoniometers).</li> <li>• Activity – Overall daily activity levels, maximum sport/physical activity, functional activity test times (stair climb, timed up and go)</li> <li>• Impairment - Range of motion, proprioception, quadriceps strength (short term outcome) and progression of OA in contralateral knee (long term outcome).</li> <li>• Clinical Outcomes – Clinical knee scores (Oxford Knee Score, New American Knee Society Score and Forgotten Joint Score), pain, analgesic use, complications, implant fixation and satisfaction.</li> <li>• Safety profile (Determined by revision rate, adverse events, robotic system errors and accuracy of implantation)</li> <li>• Accuracy of surgical implantation (determined by post-op CT analysis)</li> </ul>
<b>Device Name</b>	MAKO Restoris MCK
<b>Manufacturer Name</b>	MAKO Surgical Corp (Florida, USA)
<b>Principle intended use</b>	Unicompartmental Knee Replacement (CE Marked)
<b>Study use</b>	Bi-Unicompartmental Knee Replacement (not currently CE marked for this indication)

### 3. Abbreviations

ACL	Anterior Cruciate Ligament
AKSS	American Knee Society Score
Bi-UCKA	Bi-UniCompartmental Knee Arthroplasty
FJS	Forgotten Joint Score
CRF	Case Report Form
OA	Osteoarthritis
OKS	Oxford Knee Score
PCL	Posterior Cruciate Ligament
RIO	Robotic arm Interactive Orthopaedic
TKA	Total Knee Arthroplasty
UKA	Uni-Compartmental Knee Arthroplasty
VAS	Visual Analogue Scale

#### 4. Background: Existing research and Rational

Osteoarthritis (OA) is the most common form of joint disease. It causes pain and stiffness and affects at least 8 million people in the UK imposing a considerable economic and personal burden. The knee is one of the most common sites affected by OA. Felson et al surveyed 1,800 subjects aged 63-94 and reported radiographic evidence of knee OA in 27% of subjects under the age of 70 and 44% over the age of 80, indicating a high prevalence of this disease in the knee joint (1).

The knee can be divided into three anatomical compartments; medial, lateral and patello-femoral (figure 1). OA can develop in any one of three compartments in isolation, or, more commonly in two or more compartments. Knee Replacement, or Arthroplasty, is the current surgical treatment of choice for end stage OA of the knee. In England and Wales 76,870 Knee Replacements were carried out in 2010 which represents an increase of 30% since 2005 (2). There were a further 6884 Knee



Figure 1 Compartments of the knee

Replacements carried out in Scotland(3). In the UK and worldwide there are 3 main forms of Primary Knee Arthroplasty utilised; Total Knee Arthroplasty (91%), Medial or Lateral Unicompartmental Knee Arthroplasty (8%) and Patello-femoral Arthroplasty (1%) (2). Total Knee Arthroplasty (TKA) is the most commonly used Arthroplasty for end stage OA and is necessary for patients with OA of all three compartments of the knee. However, it is also frequently used in patients with less extensive Bi or UniCompartmental disease.

TKA is highly successful in reducing knee pain and revision rates for TKR are relatively low at just under 3%, 5 years after surgery (3). Despite this there remains a significant number of individuals who are either dissatisfied with their outcome or who continue to suffer chronic pain associated with their knee joint. Estimates of the number of dissatisfied patients range from 9-19% (4-8), while chronic pain occurs in 13-30% of patients (9-10). Revision surgery is generally only carried out where the knee joint is either infected or the implant has loosened, as few patients with chronic post-operative knee pain are offered revision surgery, revision as an endpoint is a poor indicator of successful surgery. There are many potential reasons for the high rate of dissatisfaction in this patient group including poor replication of normal knee kinematics by current TKA prosthesis.

Knee kinematics in TKA patients have been consistently shown to be worse than aged matched controls (11-13). Poor knee kinematics are likely to be perceptible by patients and therefore influence satisfaction with surgery and ability to confidently undertake activities. High demand activities are likely to be severely limited by the poor kinematics offered by TKA designs and this is reflected in patient satisfaction surveys. Mohamed et al report 20% dissatisfaction with results of TKA surgery for improving ability to participate in recreational activity (14).

In TKA surgery the anterior cruciate ligament is removed, although the posterior cruciate ligament is sometimes retained depending on surgeon preference, prosthesis type and individual patient factors. The primary function of the anterior cruciate ligament is to resist anterior displacement of the tibia on the femur when the knee is flexed and control the screw-home mechanism of the tibia in terminal extension of the knee. The main function of the posterior cruciate ligament is to allow femoral rollback in flexion and resist posterior translation of the tibia relative to the femur. The PCL also acts as a secondary restraint of external rotation of the tibia with increasing knee flexion. Removal of the ACL and PCL inevitably impacts on patients gait patterns and knee kinematics.

Unicompartmental Knee Arthroplasty (UKA) is currently used as an alternative to TKA when only one side of the knee joint is diseased; usually the medial side. In contrast to TKA, UKA involves a minimally invasive surgical approach removing only the damaged areas of the joint.

UKA involves smaller surgical incisions, less bleeding, quicker recovery, and less bone loss than TKA. Crucially, in UKA surgery neither the prosthesis nor the surgery interferes with existing knee ligaments and damage to the quadriceps tendon and muscle is usually avoided. This results in quicker post-operative recovery, lower pain, better post-operative knee kinematics (which are closer to normal than that achieved with TKA), greater knee stability and better stair-climbing ability than TKA (15-16).

Proprioception (awareness of the position of the joint) is important for balance when standing or moving and is also essential for many everyday tasks such as driving. Loss of proprioception occurs during progression of OA, but is improved in the majority of patients after UKA. Issac et al have demonstrated 60% reduction in postural sway (a marker of proprioception) after UKA compared to just 7% improvement after TKA (17). Proprioception has three components 1- static awareness of joint position, 2- awareness/detection of movement, and 3- a closed loop efferent activity which starts reflex responses and regulates muscles. A key component of this system is the mechanoreceptors found in the fibers of the ACL. These receptors (along with the mechanoreceptors located in the PCL, the collateral ligaments and capsular fibers), play an important role in the complicated neural network of proprioception. Loss of knee proprioception occurs in patients with ACL injuries/deficiencies and after TKA surgery, in both cases damage or loss of the ACL mechanoreceptors are key contributors. Loss of proprioception leads to a feeling of instability and giving way even though the knee itself does not actually sublux on clinical examination. The ability to preserve proprioception or even improve it after knee arthroplasty is vital for improving outcome of knee Arthroplasty as lack of proprioception leads to altered gait and therefore non-physiological joint loading.

In a comparative gait analysis between UKA and TKA, Chassin et al have demonstrated that a greater percentage of UKA patients (70%) maintained a normal biphasic flexion/extension moment pattern about the knee when compared with similar groups of TKA patients (23%) (18-19). Other studies have found similar low proportions of patients achieving biphasic gait after TKA; Simon et al report just 20% with PCL retaining TKA and Wilson et al 25% with PCL sacrificing TKA (20-21). Gait has two phases swing (when the foot is no longer in contact with the ground) and stance (when parts of the foot are in contact with the ground). Stance phase represents 60% of the gait cycle, with normal gait requiring stability throughout the 4 phases of stance: heel strike, foot flat, heel off and toe off. Knee moment is a measure of the turning effect produced by a force about the knee axis. A bi-phasic 'normal' gait pattern occurs when the moment curve oscillates between extension and flexion during the stance phase of gait (Figure 2). Abnormal sagittal moment patterns that are not bi-phasic are described as being either, a quadriceps avoidance patterns – "stiff leg gait" - (where an extension moment is present throughout stance phase of gait), or quadriceps over use pattern (where a flexion moment is present throughout stance phase of gait). The net effect of a persistent flexion moment is to limit knee extension, which in turn causes mechanical overload of the joint during gait (walking). Development of an abnormal gait pattern following TKA may therefore have important additional consequences over time. Gait patterns are predictive of component migration and prosthetic loosening (22). Furthermore, following unilateral TKA, osteoarthritis is exacerbated in joints in the non-operated limb and this deterioration may be accelerated by biomechanical factors such as aberrant joint loading in the operated limb. Additionally, excessive pre-operative knee flexion moments are predictive of anterior knee pain post-surgery, further underlining the importance of achieving correct post-operative gait in order to produce a post-operative knee with 'normal' feel and function (23).

Although UKA offers potential functional advantages over TKA, one of the greatest challenges to both uptake of UKA by surgeons and the ultimate success of the surgery has been the technically demanding nature of the surgery. Ideal placement of the joint



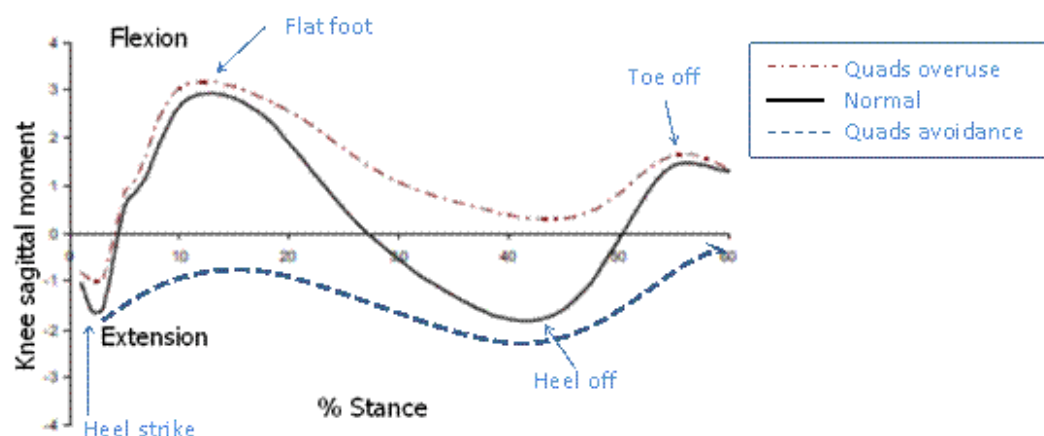


Figure 2 Graph representing the biphasic knee moment pattern in the sagittal plane (solid black line), knee flexor moment pattern (dashed red line), knee extensor moment pattern (dashed blue line)

prosthesis and optimal soft tissue balancing can be difficult to reproduce accurately by hand and eye with only mechanical guides for assistance, prosthesis placement is further complicated by variable patient joint anatomy and ligament laxity. Poor prosthesis alignment has been associated with early failure of UKA and is likely to contribute to the higher revision rate observed with UKA in comparison to TKA (1.4% vs 4.6% at 3 years) (24).

In recent years advances in Orthopaedic surgery have been afforded by the introduction of surgical navigation systems which aid the surgeon in achieving accurate and repeatable implantation of devices. Most navigation systems utilise a passive optical tracking system. An infrared-emitting camera is used to monitor the position of tracking rods inserted into the patient's femur and tibia to facilitate tracking of bone position and hence the knee joint, the system also tracks surgical instruments being used.

In UKA surgery accuracy has been further advanced by the introduction of Robotic Assistive technology. There are now a limited number of Robotic systems available to facilitate UKA surgery. These are based around the principal of surgical navigation but with a robotic arm or tool used to accurately resect the necessary bone, providing accurate, reproducible implant positioning. Currently the system with the greatest market share is the MAKO Robotic arm Interactive Orthopaedic (RIO) System, which has been in use since 2006.

A pre-operative CT scan is used by the RIO system to build a 3D model of the patient's knee. This is then used by the surgeon to plan implant positioning prior to surgery with a high degree of accuracy. The system calculates which areas of bone need to be removed in order to allow correct fit of the implant.

Traditionally surgeons would use jigs and saw blades to resect bone for this type of surgery resulting in inaccurate cuts and heat generated bone necrosis. The RIO system uses a high speed, water cooled milling burr attached to a haptic robotic arm to remove bone with sub-millimetric accuracy, removing the minimum amount of bone required. The surgeon manipulates the arm guided by on screen CAD images of the patient's joint and haptic feedback from the robotic system (Figure 3). Milling outside of the pre-planned zones is prevented by the robotic arm.

The potential advantages of the system are:

1. *Minimal bone removal with the burr able to cut exact 3D dimensional shapes providing a perfect fit with implants*
2. *Accuracy of implant positioning is significantly improved over that achieved with conventional instruments (fig 3)*
3. *Post-operative knee alignment is improved*
4. *Decrease in immediate post-operative pain*
5. *Improved post-operative knee kinematics*

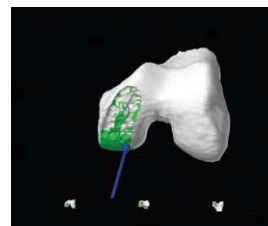


Figure 3 RIO Screen shot - 3D model with bone still to be resected coded Green

The MAKO RIO system has been in use at Glasgow Royal Infirmary since 2009 and has been evaluated by the Orthopaedic Research Unit at Glasgow Royal Infirmary and the University of Strathclyde Bioengineering Unit as part of a randomised controlled trial comparing robotic assisted and traditional, medial UKA surgery (n=150).

Our early data from this study show increased accuracy of implant placement. The robotic system implanting all knees evaluated to date (100%) within 3 degrees of target for tibial flexion/extension, compared to just 38% with manual instrumentation. At 3 months post-operatively there is a 10 point difference in American Knee Society Score. However, the most impressive difference relates to post-operative pain, with those receiving robotic assisted surgery consistently reporting 50% lower pain scores from day 1 post-op to 3 months post-op (further time points are not yet available).

Currently the MAKO RIO system is used for either medial or lateral UKA, yet the system has the facility to implant both medial and lateral UKA at the same time in the same knee – Bi-UniCompartmental Knee Arthroplasty (Bi-UCKA). Bi-UCKA surgery offers the functional and kinematic benefits of UKA for a proportion of the patients with arthritis affecting the medial and lateral sides of the joint who would normally be faced with the limitations of TKA.

A number of studies of varying sizes have published outcomes from Bi-UCKA carried out without the aid of robotic assistance [18-23]. Data from these studies highlights good clinical outcome measures with good pain relief (25-28). In addition, Banks et al have shown that Bi-UCKA produces knee kinematics approaching that achieved with UKA and better than the kinematics anticipated from TKA (29). Although good functional outcome has been achieved with non-Robotic assisted Bi-UCKA, implant survivorship for Bi-UCKA does appear to be poorer than TKA. Parratte et al report 78% survivorship at 17years (n=100), Confaloneri et al 100% at 4 years (n=22), Goodfellow et al 88.5% at 6 years (n=114) and Stewart et al 73% at 10 years (n=156) (26-28, 30). This compares to averages from the National Joint Registry (England & Wales) of 98% for TKA, 91% for UKA and 90% for Patellofemoral Joint Replacement at 5 years post-op (2). It is interesting to note that the relatively small study by Confaloneri et al which utilised surgical navigation (though without robotic guidance) has achieved very promising early survivorship (25-26). Surgical variation and inaccuracy leads to mal-aligned components and potentially early loosening and wear of joint replacements. Given that these are the major causes of failure in UKA, it is reasonable to think the best implant survivorship for both UKA and Bi-UKA will be achieved using robotic assistive technology. A number of surgeons in the US have begun to utilise robotic assisted surgery to perform Bi-UCKA. Stefan Kreuzer and Azim Karim (Memorial Bone and Joint Clinic, Houston, TX) have undertaken 10 surgeries with mean post-op American Knee Society – Knee Score of 76/100 (mean follow-up 11 months range 2-20 months) [pers. comm.]. Mean Knee injury and Osteoarthritis Outcome Scores (KOOS) for the group are promising and better than that reported for TKR (KOOS symptom 85, Pain 88, Function in daily living 86 and Participation in sports 59) (31).

We conservatively estimate that 10-20% of the ~76,000 patients, who currently receive TKA, could be suitable for Bi-UCKA; at least equal to the proportion of patients who are offered UKA surgery in the UK. Other groups have suggested even higher levels, 36-48%, of patients may be suitable for a compartmental approach to replacement surgery (32-33).

In order for patients to be suitable for and benefit from Bi-UCCA surgery they need to have intact Cruciate Ligaments; Douglas et al 2010 demonstrated that 78% of TKA patients have an intact ACL (34). Our own internal audit has revealed very similar rates in our cohort. Exclusions to Bi-UCCA surgery include: absence of cruciate ligaments, flexion contracture  $>10^{\circ}$ , deformities with bone and soft tissue changes that make a compartmental approach to surgery unsuitable. Bi-UCCA could offer significant functional benefits for between 9,000 and 18,000 people in the UK every year who currently receiving TKA for OA of the knee. As Bi-UCCA is tissue preserving it can retain the normal biomechanical function of the knee to a much greater extent and hence may, if carried out accurately using robotic assistance, lead to a better functional and kinematic outcome than is currently achieved with TKA. Figure 4 demonstrates the differences in bone removal between Bi-UCCA and TKA. Bi-UCCA surgery may also offer a valuable precursor to TKA surgery particularly for younger patients who are likely to outlive their joint replacement and require revision surgery at a later time point. Conversion from Bi-UCCA to TKA in these patients may delay or prevent the need for costly and complex revision TKA surgery.



Figure 4 UKA, TKA and Bi-UCCA radiographs highlighting the difference in bone resection required.

We hypothesise that robotic assisted Bi-UCCA surgery undertaken in appropriately selected patients can offer improved knee kinematics and proprioception in comparison to that afforded by TKA. Furthermore we hypothesise that accurate positioning of implants by robotic assistive technology will improve implant survivorship in Bi-UCCA to the levels achieved with TKA and UKA.

We propose to undertake a randomised controlled trial to compare TKA and robotic assisted Bi-UCCA. We will use a battery of impairment and functional tests to explore the mechanisms underpinning any functional improvements that are observed.

## 5. Risks and Benefits

The risks associated with Bi-UCCA surgery are similar to other forms Arthroplasty surgery (TKA and UKA), for example Venous Thrombo Embolic events, infection, chronic pain and/or stiffness and nerve damage. The only additional risk that we perceive for patients enrolling in the study are: 1) additional radiation exposure for both groups as a result of non-standard CT scans, and 2) an increased duration of surgery time for the Bi-UCCA group. We use a minimal dose CT scan in order to reduce patient exposure to radiation. On average we anticipate that each Bi-UCCA surgery will take 20-30 minutes longer to complete. Data from Kreuzer et al (Perscomm) indicates this estimate to be accurate.

The benefits of Bi-UCCA surgery are likely to be better knee kinematics with improved proprioception which will result in better knee function, reduced strain on the contralateral knee, more natural feeling knee and greater patient satisfaction than might be achieved with TKA. As Bi-UCCA surgery is bone sparing, conversion to a standard primary TKA will be feasible should the implants wear over time, thus making Bi-UCCA an ideal option for the increasing number of young patients under 55 who are undergoing TKA surgery.

## 6. Research Objectives

### Hypothesis:

The use of robotic assistive technology in Bi-UniCompartmental Knee Arthroplasty is a safe and clinically effective surgical alternative to Total Knee Arthroplasty that offers improved kinematic, clinical and functional outcome for patients with OA of the medial and lateral compartments of the knee.

### Aims:

1. To carry out an explanatory randomised controlled trial to compare a novel robotic assisted surgical technique (Bi-UniCompartmental Knee Arthroplasty) against a standard surgical technique (Total Knee Arthroplasty) in patients with osteoarthritis of both the medial and lateral compartments of the knee.
2. To provide evidence of early phase efficacy and safety for Robotic Assisted Bi-UniCompartmental Knee replacement.
3. To determine the biomechanical mechanism through which patients derive benefit from Robotic Assisted Bi-UniCompartmental Knee replacement.

### Research Questions:

1. What are the biomechanical kinematic benefits of Robotic Bi-UCKA surgery compared to TKA?
2. Are improved knee kinematics and proprioception associated with better clinical and functional outcomes after surgery?
3. Is the revision rate after Robotic Assisted Bi-UCKA surgery comparable with TKA surgery?
4. Does Robotic Assistance facilitate accurate implantation and alignment of all 4 components of a Bi-UCKA?

## 7. Research design

The study will be a prospective randomised double blinded controlled study comparing two surgical techniques. Patients randomised to Group 1 of the study (controls) will receive a standard TKA. Patients randomised to group 2 will receive Bi-UKA surgery carried out with the aid of Robotic Assistive Technology.

The study will be blinded, meaning that researchers undertaking post-operative patient assessments will not be informed which intervention patients have been randomised to receive. Surgeons involved in the study will be aware of which arm of the study patients have been randomised to. However, all post-operative data relating to the study will be collected by independent research nurses and no post-operative data will be collected by the operating surgeons. Patients will not be directly informed which arm of the study they have been randomised to.

Randomisation will be carried out after informed consent has been obtained and prior to the day of surgery. This duty will be carried out by research nurses and not by the investigators. A web-based interface will be used to access a dedicated randomisation programme created by the NIHR registered Clinical Trials Unit at the University of Aberdeen's Centre for Healthcare

Randomised Trials (CHaRT) which is supporting the trial. Randomisation for the study will be stratified by surgeon.

Pre-operative and post-operative data collection will be carried out by research nurses at the time points specified in this protocol. Data will be collected on paper Case Report Forms (CRF) and this will be transcribed into a secure database. We have successfully used similar methodology for several other randomised controlled trials.

## 8. Study population

### Inclusion criteria:

- Patients with medial and lateral compartment osteoarthritis of the knee with intact cruciate ligaments
- Patients over the age of 18 (no upper restriction)
- Patients of any BMI
- Patients willing and able to give informed consent

### Exclusion criteria:

- Patients with osteoarthritis limited to one compartment of the knee
- Patients with rheumatoid Arthritis
- Patients with medial or lateral subluxation of the tibia on the femur
- Patients with a varus or valgus deformity greater than 15°
- Patients with a flexion contracture greater than 10°
- Patients with rupture of either the ACL or PCL
- Active or recent local infection
- Patello-femoral OA greater than Kellgren and Lawrence grade III
- Patients who have had previous surgery to the knee which may impact on the outcome of TKA or Bi-Unicompartmental Knee Arthroplasty
- Patients who are currently awaiting bi-lateral knee replacement surgery
- Patients with significant disease in other joints which might impact on their gait
- Patients unable to give informed consent

## 9. Planned interventions

Patients will be randomised to one of two interventions.

**Group 1- Standard TKA (Control):** Patients receiving TKA will be have a fixed bearing, cruciate sacrificing posterior stabilised Zimmer NexGen LPS TKA. These will be implanted using traditional surgical techniques and without the aid or robotics of navigation. This is the current standard of care treatment at the investigative centre and the routine method of TKA implantation in the majority of centres in the UK currently.

Mechanical axis targets for limb alignment for this group will be zero degrees.

**Group 2- Robotic assisted Bi-UKA (Experimental):** Patients randomising to Bi-UCKA will receive two unicondylar fixed bearing MAKO Restoris MCK implants, one implanted on the medial side of the knee and the other on the lateral side. These implants will be inserted with the aid of robotic assistance using the MAKO RIO Robotic System. A midline incision with medial and lateral quadriceps sparing parapatellar approaches will be used.

There are no fixed mechanical axis targets for the Bi-UCKA group. Instead the surgeon will aim to restore the constitutional angle of the joint.

All other pre and peri-operative factors will be equal for both groups. All patients will receive a spinal anaesthetic combined with peripheral nerve block and prophylactic antibiotics. Above knee tourniquets will be used routinely. Post-operative rehabilitation will consist of daily physiotherapy for the duration of the patients stay in hospital. After discharge a routine physiotherapy class will be offered for 7-14 days after surgery. Additional physiotherapy will only be offered to those patients who fail to achieve standard rehabilitation milestones and in particular those with restricted range of motion. The need for additional physiotherapy will be determined by a blinded practitioner.

### **9.1. Study devices**

- MAKO Restoris Multi Compartmental Knee (MCK) System (MAKO Surgical Corp., Fort Lauderdale, Florida, USA). THE MCK system offers a choice of tibial components onlay or inlay. For the purposes of this study only the tibia onlay system will be used. All components are currently CE marked for use in Medial Unicompartmental or Lateral Unicompartmental Knee replacement, but not both medial and lateral combined in a single joint.
- Zimmer NexGen Legacy Posterior Stabilised (LPS) fixed bearing knee (Zimmer Inc., Warsaw, Indiana, USA). All components are CE marked for the appropriate indications for use in this study.

## **10. Outcome measures**

### **Primary Outcome Measure:**

- Percentage of patients with a bi-phasic (normal) moment curve during gait (level walking) at one year – see section 8 for definition of bi-phasic gait.

### **Secondary Outcome Measures:**

- Percentage of patients with a bi-phasic (normal) moment curve during gait (level walking) at two years
- Biomechanical performance–Gait during stair climb/descent and lunge, functional activity assessment (using electrogoniometers).
- Activity – Overall daily activity levels, maximum sport/physical activity, functional activity test times (stair climb, timed up and go)
- Impairment - Range of motion, proprioception, quadriceps strength (short term outcome) and progression of OA in contralateral knee (long term outcome).
- Clinical Outcomes – Clinical knee scores (Oxford Knee Score and New American Knee Society Score, Forgotten Joint Score), pain, analgesic use, complications, implant fixation and satisfaction.
- Safety profile (Determined by revision rate, adverse events, robotic system errors and accuracy of implantation)
- Accuracy of surgical implantation (determined by post-op CT analysis)

## **11. Assessment and follow up**

Patients will be assessed pre-operatively and then post-operatively in clinic at 3 months, 1 year, 2 years, 5 years and 10 years. Patients will also complete personal diaries over the first 6 weeks post-op, these will record pain (VAS), function and analgesic use daily for the first 2 weeks and

weekly thereafter. Table 1 defines the follow up regime for both study groups. At 3 months post-operatively all patients will have a full leg CT scan of the operated limb. At 1 year post-operatively, in addition to clinical assessments, all patients will undergo full gait analysis, functional knee assessment, knee proprioception testing and participate in 5 day activity monitoring.

**Table 1:**

Assessment	Time point	Pre-Op	0-6 weeks	3 Month	1 Year	2 year	5 Year	10 Year
<b>Clinical</b>								
Oxford Knee Score		X		X	X	X	X	X
New American Knee Society Score (2012 version)		X		X	X	X	X	X
Forgotten Joint Score				X	X	X	X	X
EQ-5D		X			X	X	X	X
Pain (VAS)		X		X	X	X	X	X
X-ray (AP and lateral knee)		X		X	X	X	X	X
X-ray (long leg standing)		X			X			
CT scan (Knee)		X		X				
Satisfaction		X		X	X	X	X	X
Patient diary – Pain, function, Analgesic use			X	X	X			
Complications		X		X	X	X	X	X
Assessment of contralateral knee		X			X	X	X	X
<b>Function and Activity</b>								
Gait Analysis		X			X	X		
Functional knee assessment		X			X	X		
UCLA Activity Score		X		X	X	X	X	X
Active Pal Activity monitoring		X			X	X		
Stair climb test		X		X	X	X		
Timed Up and Go Test		X		X	X	X		
<b>Impairment</b>								
Proprioception		X			X	X		
Range of motion		X		X	X	X	X	X
Quadriceps strength testing		X			X	X		
Stiffness (VAS)		X		X	X	X		
Patient Questionnaire						X	or X*	

\*Participants will be invited to complete a questionnaire at 2 or 5 years (if completed at 2 years, not necessary to complete again, but if not done at 2 years, this can be completed at 5 years) to capture participant's impressions on the surgery they thought they had received, and this will allow us to investigate the effect of patient bias on the results.

In addition to these research clinic visits, we will compile a newsletter which will be sent out to participants when all recruited participants have reached 4 and 9 years post-op. Due to the length of time between research visits, this will serve to maintain participant engagement

#### **Gait analysis, functional knee assessment and dynamic proprioception:**

Biomechanical Gait and Stair analysis will be carried out using our 12 camera VICON Nexus system in the Bioengineering Unit (University of Strathclyde). Gait will be recorded during flat walking, stair ascent/descent and lunge movements allowing comparison between the two

surgical treatment options. We will also make comparisons with existing data from age matched controls. We have collected aged match data from 84 control subjects and therefore do not need to recruit any further control subjects. The following Kinetic parameters will be defined by this analysis: number of subjects with bi-phasic sagittal moment pattern at the treated knee, maximum flexion and extension moments for both limbs (Nm), and maximum adduction and abduction moments (Nm).

The primary outcome measure for the study will be proportion of patients in each group with a bi-phasic sagittal knee moment pattern during gait. We will define a Biphasic gait as one in which a significant knee flexion and extension moment are generated during stance phase of gait. Our system reports Flexion moments with a positive value and Extension moments with a negative value. In order for a patient to be classified as having "Bi-phasic Gait", the patient must produce a moment pattern with both flexion (positive) and extension (negative) values – this can be assessed by looking at the maximum and minimum moment values and verifying that the maximum value has a positive value and minimum a negative value. Patterns that have either all positive or all negative max and min values will be defined as non-Bi-Phasic. Hence the decision as to whether a bi-phasic gait in stance exists will be produce without subjective inference from the researchers carrying out the test.

Functional knee kinematic data will be derived from analysis of patients undertaking 13 tasks that are common in everyday living: Level walking, ascent of a 5 degree slope, descent of a 5 degree slope, ascent of a 20 step flight of stairs, descent of a 20 step flight of stairs, descent from standing into a low chair, ascent from a low chair to standing, descent from standing into a standard chair, ascent from a standard chair to standing, , getting down to a squatting position, getting up from a squatting position a deep lunge with the left leg and a deep lunge with the right leg. Electrogoniometers will be used to record knee joint angles continuously during these activities.

In order to assess dynamic proprioception we will record patients' ability to maintain a static position during one legged stance; measuring sway area during a 30 second period. This will be carried out for both the operated and non-operated limb, pre and post-operatively.

### Activity monitoring:

We will use ActivPAL activity monitoring system over a 5 day period to record patients activity. Software algorithms are used to classify an individual's free-living activity into periods spent sitting, standing and walking. This information can be used to estimate daily energy expenditure and changes in the activity profile. Patients will undergo this assessment pre-operatively and at 1 and 2 years post-operatively.

### CT scan protocol:

Imaging of three regions is required; hip, knee and ankle as detailed below.

	Hip	Knee	Ankle
kV	100	100	100
mAs	80	100	45
Scan length	~ 50 mm	~200mm	~ 50 mm
Collimation	4 mm	1 mm	4 mm
FOV	Includes femoral head	Must include 100mm above and below the joint-line between the femur and the tibia	Must include the talus and distal tibia

### CT analysis:

Pre-operative CT scans will be used to plan robotic surgery and measure pre-operative joint alignment. Post-operative CT scans will be used to:

1. Validate the intra operative implant alignment values recorded by the Robotic System.
2. Describe the differences in absolute implant positioning in order to characterise the differences between the two surgical philosophies being employed.



3. Compare the degree of variation from the planned position of implants and the actual position of implants between the two groups.
4. Determine if the femoral and tibial components are correctly aligned with respect to each other, checking for example for possible mismatch of rotation between the components. 2D and 3D models of the replaced knee will be generated from CT data, these will be used to determine the following variables for each patient:

**Mechanical Axis Alignment of the knee joint** - Measured through the centre of the hip (centre of the spherical femoral head), centre of the knee (centre of the tibial plateau) and centre of the ankle (centre of the talus).

**Varus / Valgus Alignment (Alignment in coronal plane)** - Femoral Coronal Angle measured as the angle between: The femoral mechanical axis (centre of the hip and the centre of the knee) and the medial/lateral axis of the condylar implant.

Tibial Coronal Angle measured as the angle between: The tibial mechanical axis (centre of the knee and the centre of the ankle) and the medial/lateral axis of the tibial implant.

**Slope Alignment (Alignment in sagittal plane)** - Tibial Slope measured as the angle between: Tibial implant / bone interface and the tibial mechanical axis.

Femoral Flexion measured as the angle between: Femoral mechanical axis and Femoral implant peg axis.

**Rotation Alignment (axial plane)** - Femoral Rotation measured as the posterior condylar angle, angle between: the surgical transepicondylar axis (TEA), connected the centre of the sulcus of the medial epicondyle and the most prominent point of the lateral epicondyle and the posterior condylar axis of the implant.

Tibial rotation measured as the angle between: the perpendicular line to the tangent of the posterior rim of the tibial plateaus and the tangent to the AP axis of the tibial implant.

### 11.1. Assessment of efficacy/effectiveness

This is an explanatory randomised controlled trial and as such as concerned with demonstrating efficacy rather than generalisable effectiveness.

Efficacy will be determined in a number ways. Kinematic measures as outlined above will determine if the novel Robotic Assisted Bi-UKA surgery can produce measurable improvements in knee kinematics and kinetics which result in more normal gait pattern than is typically achieved with traditional TKA surgery. This will be determined at 1 year post-operatively using full gait analysis and functional electrogoniometry. Improved gait is likely to be associated with improved clinical outcome scores, reduced pain, higher activity levels, lower physical impairment and greater implant longevity.

#### Improved function and activity will be measured using:

- Stair Climb Test
- Timed Up and Go Test • UCLA Activity Score

#### Improved clinical outcome will be measured using:

- Mechanical alignment of the knee
- Oxford Knee Score, New American Knee Society Score, Forgotten Joint Score
- Analgesic use, Pain Score
- Satisfaction

#### Decreased patient impairment will be measured using:

- Knee joint proprioception
- Active and passive Range of Motion
- Isometric Quadriceps strength
- Progression of OA in the contralateral knee will be measured using Kellgren and Lawrence grading of knee X-rays

**Surgical accuracy will be measured using:**

- CT analysis of accuracy of implant positioning in the sagittal, coronal, axial planes.

We have used the CT and gait analysis methodology described here in several recent studies and therefore the methodology for each has been established and validated. We have a number of manuscripts that have been or are due to be published that report data from UKA or TKA cohorts using these methodologies.

**11.2. Assessment of safety**

Patient safety will be assessed by comparing complications of surgery / adverse events related to surgery (infection, DVT, PE, delayed discharge from hospital, manipulation under anaesthetic, re-operation and implant survivorship). Safety of the RIO Robotic device will be assessed by recording system errors and malfunctions, as well as by assessing accuracy of implantation.

**12. Safety****12.1. Definitions****12.1.1. Adverse Events (AE) An****AE or adverse event is:**

Any untoward medical occurrence in a patient or other clinical investigation participant taking part in a trial of a medical device, which does not necessarily have to have a causal relationship with the device under investigation.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not considered related to the device.

**12.1.2. Adverse Device Effect (ADE)**

All untoward and unintended responses to a the medical device.

The phrase "responses to a medical device" means that a causal relationship between the device under investigation and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualifies as a device effect.

This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

**12.1.3. Serious Adverse Event (SAE)**

SAE is an adverse event that

- Led to death
- Led to fetal distress, fetal death or congenital abnormality or birth defect.
- Led to serious deterioration in the health of the subject that

- Resulted in a life-threatening illness or injury

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the

event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Resulted in a permanent impairment of a body structure or a body function
- Required in-patient hospitalisation or prolongation of existing hospitalisation
- Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function
- Other important medical events\*

\*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

#### **12.1.4. Serious Adverse Device Effect (SADE)**

A serious adverse device effect (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics a characteristics of a serious adverse event.

A SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

All cases judged by either the reporting medically qualified professional or the sponsor.

#### **12.1.5. Unanticipated Serious Adverse Device Effect (USADE)**

Any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of the subject.

#### **12.1.6 Device deficiency**

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

## 12.2. Reporting and Documentation

### 12.2.1. Reporting and Documentation of Adverse Events and Adverse Device Effects

Adverse Events and Adverse Device Effects will be documented on Adverse Event Report Forms for the duration of the investigation. Furthermore the outcome of such complications will be documented and any changes in outcome updated during the course of the study. Each adverse event and adverse device effect must be assessed for seriousness, causality and expectedness. All AEs will be reported to the Chief Investigator.

### 12.2.2. Reporting of SAEs, SADEs, USADEs to the sponsor

The following events should be reported to the sponsor

- any SAE,
- any Investigational Medical Device Deficiency that might have led to a SAE if
  - a) suitable action had not been taken or
  - b) intervention had not been made or
  - c) if circumstances had been less fortunate
- new findings/updates in relation to already reported events

All SAE/SADE/USADEs must be reported to the PV office within 24 hours of the investigator becoming aware of the event; regardless of relationship to the device. The PV office should remain blinded to the participants allocation and therefore causality unless there is a clinical need to unblind for patient safety. The chief investigator should assess all the causality and expectedness of all SAEs occurring within the study using the information below and their clinical judgement

SAEs are reported using the Serious Adverse Event Report Form for a Non-CE-marked Medical Device. Device deficiencies should be reported using the Device Deficiency Report

#### Definitions of related and unanticipated events:

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unanticipated" – that is, the type of event is not listed in the protocol as an expected occurrence.

#### Anticipated adverse events that can occur with any orthopaedic surgery include:

Re-admission, implant failure, implant removal or revision, periprosthetic fracture, infection (superficial or deep), wound washout for infection, deep vein thrombosis, pulmonary embolism, stroke, neurovascular complications, post-operative confusion, pain, decreased range of motion and swelling of the leg. **Anticipated adverse events that may occur due to the use of the trial device or trial specific procedures include:** Damage to lateral ligaments, damage to the patellar tendon, damage to the anterior cruciate ligament, and early loosening of the device components (within 2 years of surgery).

Events will be followed up until resolution, any appropriate further information will be sent by the research team in a timely manner.

The Sponsor acting on behalf of the manufacturer has a legal obligation to report all events that need to be reported to the MHRA immediately (without any unjustifiable delay) after a link is established between the event and the device, within the following time periods:

- SAEs that indicate the death of a participant, an imminent risk of death, serious injury, or serious illness that requires prompt remedial action for other participants, users or other persons, or a new finding relating to a previously reported SAE of this seriousness must be reported to the MHRA no more than 2 calendar days following awareness of the event by the sponsor
- Other reportable events not described above or follow up information relating to those events must be reported to the MHRA within 7 days of the sponsor becoming aware of the event
- USADES will be submitted to the REC within 15 days of the PV office becoming aware of the event.

### **12.2.3. Reporting of SAEs, SADEs, UADEs to the manufacturer**

#### **Device deficiencies**

The PV office will report any device deficiencies to the manufacturer following unblinding of the participants allocation.

Device deficiencies due to the MAKO Restoris MCK will be reported to the manufacturer; MAKO Surgical Corp following unblinding.

Device deficiencies due to the comparator Zimmer NexGen LPS TKA will be reported to the Incident Reporting and Investigation Centre (IRIC – part of NHS National Services Scotland) via the following means. <http://www.hfs.scot.nhs.uk/online-services/incident-reporting-and-investigation-centre-iric/how-to-report-an-adverse-incident/>

**Unblinded members of staff should ensure that they do not allow blinded members of the trial team, the sponsor, data managers and trial statisticians to access unblinded SAEs**

### **12.3. Annual Report**

In addition to the above reporting the Chief Investigator will submit once a year, for the duration of the trial, or on request a progress/safety report to the REC and NHS GG&C R&D.

### **13. Discontinuation or withdrawal of participants from the study**

Each participant has the right to withdraw study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation

- Significant non-compliance with treatment regimen or study requirements
- Consent withdrawn
- Lost to follow up

The reason for withdrawal will be recorded in the CRF.

#### **Withdrawal of patients at the time of surgery:**

Any patient found to have grade 4 (Kellgren and Lawrence) changes on the lateral facet at the time of surgery, that was not evident pre-operatively) will be withdrawn from the Trial and will be given a Total Knee Arthroplasty outwith the Trial. The patient will be withdrawn even if they have been randomised to receive a Total Knee Arthroplasty within the study. The justification for the latter scenario is to ensure that both Trial groups remain balanced in terms of patient pathology and extent of disease.

Bi-UCCA surgery aims to treat patients with disease in both the medial and lateral compartments of the knee. Any patient who is found to have only minimal disease in one of the compartments at the time of surgery which was thought to be more severe pre-operatively, will remain within the study. The rationale for this is that the standard of care treatment for unilateral osteoarthritis of the knee in the majority of centres in the UK is a Total Knee Arthroplasty and therefore as Bi-UCCA is an alternative to a Total Knee Arthroplasty it is acceptable to use this in these cases.

#### **Revision of primary arthroplasty:**

Patients who have their primary arthroplasty (Bi-UCCA or TKA) revised will continue to be followed up at scheduled study time points. Information regarding the type of revision surgery will be recorded in the CRF. Data from any patients who are revised will not be included in the overall study analysis after the point of revision. However, data will continue to be collected in order that an assessment of the morbidity associated with revision arthroplasty can be made.

#### **14. Definition of End of Trial**

The trial will end on the date that the final follow-up visit for the last patient occurs.

#### **15. Sample size**

The primary outcome measure is proportion of patients in each arm with a bi-phasic (normal) gait. 23% of TKA patients have a bi-phasic gait after surgery compared to 70% of UKA patients. Bi-UCCA surgery is unlikely to achieve quite the same level as UKA, nevertheless it is anticipated that a substantial proportion of this effect should be achievable. We therefore believe that 60% of Bi-UCCA patients might have a normal bi-phasic gait after surgery. To detect a difference of this size with a power of 90% at a 5% level of significance using a chi-squared test we would need to study 36 patients per group (calculated using 'sampsi' in Stata 11.2 without continuity correction). We will allow an additional 10% for loss to follow up at 1 year and will therefore study 40 patients per group (80 in total) recruited over 41 months. All patients will be recruited at Glasgow Royal Infirmary and will be operated on by one of three surgeons and randomisation will be stratified by surgeon. It is expected that each surgeon will conduct roughly similar numbers of operations, in both randomised groups. We will adjust for any clustering generated within surgeon by fitting surgeon as a random effect, and would expect to recover and possibly have a net increase in power by adjusting for pre-specified baseline covariates that would be strongly associated with 1 year outcome.

## **16. Statistical analysis**

All statistical analyses will be governed by a comprehensive Statistical Analysis Plan, which will be agreed by the research group and approved by the independent Data Monitoring Committee. The primary outcome (at 1 year) will be analysed according to the intention to treat principle, and will use a mixed effects logistic regression model, with surgeon fitted as a random effect. We will also consider a per protocol analysis, including those who received the surgery as intended. We would adjust this primary analysis for baseline gait i.e. the primary outcome measured at baseline. At present there are no subgroup analyses proposed for the primary outcome.

Analysis of secondary outcomes will be similar to that for the primary outcome, except using generalised linear models appropriate to the distribution of the specific outcome (e.g. linear or logistic). At present there are no count data (e.g. Poisson or negative binomial regression) or time to event outcomes (e.g. Cox proportional hazards regression) being considered. For the secondary outcomes that have serial measures post randomisation (e.g. 3m, 1 y, 2y, 5y, 10y) we will use repeated measures models to explore any possible time development of a treatment effect we identify.

As indicated above, we will explore the robustness of any findings we report to patterns of missing data, most prominently using multiple imputation models exploring missing data mechanisms assumed to be generated under a 'missing at random' assumption. There will be no formal adjustment for multiple comparisons given the explanatory rather than confirmatory nature of this study.

The independent Data Monitoring Committee will not conduct any formal interim analyses of the efficacy outcomes – their role will be primarily concerning safety.

## **17. Ethical arrangements**

### **17.1. Declaration of Helsinki**

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

### **17.2. ICH Guidelines for Good Clinical Practice**

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

### **17.3. Ethical Approval**

Ethical approval to carry out the study will be obtained from the West of Scotland Research Ethics Committee prior to initiation of the study. The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to West of Scotland Research Ethics Committee (REC), regulatory authorities (MHRA), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

### **17.4. Patient Information and Consent**

Prior to any treatment patients are reviewed from a common surgical waiting list. Patient information sheets will be posted along with a clinical appointment letter for surgical review. Patients will be contacted by phone by a member of the study team (Research nurse) on behalf of the consultant to provide a detailed explanation of the study and asked if they are interested

in trial participation. On confirmation of interest in participation, the patient will be recruited from the common surgical list and noted as a potential TRUCK trial participant. Patients will be assessed at the clinical appointment by the surgeons, and if meet the study inclusion/exclusion criteria the patient will be invited to take part in the study and to confirm this by signing a consent form before surgery. All patients will have an opportunity to discuss the study with the Chief Investigator or a co-investigator before written consent is sought. Those not meeting the study inclusion/exclusion criteria will drop out of the recruitment cohort and proceed through the normal surgical process.

### 17.5. Patient Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act 1998 which requires data to be anonymised as soon as it is practical to do so.

### 18. Data handling and record keeping

The participants will be identified by a study specific participants number and/or code in any study database. The name and any other identifying detail will NOT be included in any study data electronic file. Data will be collected on paper based CRF's at the time of clinic visits or surgery. Data will then be entered into a secure online study database provided by CHaRT (Centre for Healthcare Randomised Trials, University of Aberdeen). Paper based CRF's will be stored on site at Glasgow Royal Infirmary under locked conditions for the duration of the trial, these will be considered source documents for this study.

### Direct access to source data and documents

Direct access will be granted to authorised representatives from the sponsor, host institutions and the regulatory authorities to permit trial-related monitoring, audits and inspections.

### 19. Finance and Insurance

The study will be funded by the Medical Research Council (MRC) Efficacy and Mechanism Evaluation (EME) programme, with support from MAKO surgical corp (Florida, USA). (Note HEI values are 80% FEC). Funds will be requested from EME on a quarterly basis over the duration of the study and administered by NHS GGC. NHS GGC will put in place sub-contract agreements with University of Strathclyde and University of Aberdeen for distribution of appropriate funds (detailed below) to each institute for the duration of the study. All values below are given in pound sterling.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
NHSGGC	97,905	37,459	49,616	48,267	40,091	28,523	28,809
STRATHCLYDE	34,878	34,878	34,878	34,879	800	1,440	0
ABERDEEN	70,573	31,070	63,107	0	0	0	0
Patient/Steering group travel	3,200	3,200	3,200	3,200	600	0	0
	206,556	106,607	150,801	86,346	41,491	29,963	28,809



	Year 8	Year 9	Year 10	Year 11	Year 12	Year 13	Year 14	Year 15	TOTAL
NHSGGC	11,946	6,308	3,457	3,492	8,527	9,695	5,619	0	379,715
STRATHCLYDE	0	0	0	0	2,240	0	0	0	143,993
ABERDEEN	0	0	0	0	0	0	0	0	164,750
Patient/Steering group travel	500	0	0	0	6 0 0	0	0	0	14,500
	12,446	6,308	3,457	3,492	11,367	9,695	5,619	0	<b>702,958</b>

In addition to the funds detailed above to be requested from MRC EME Programme, additional support will be provided by MAKO Surgical Corp to NHS GGC as detailed below:

- Loan of a MAKO RIO system for the duration of the recruitment/surgery phase of the study (2 years) - £236,000.
- Implants – 1 set for each Bi-UCCA patient supplied free of charge and the second set supplied at the same cost as a single TKR implant (~£1,300) - ~£52,000.
- Training for surgeons and technicians - £25,000.
- RIO system support for 2 years - £120,000

Total MAKO Surgical Corp contribution in kind £433,000

### **Insurance:**

NHS bodies are legally liable for the negligent acts and omissions of their employees. If a study participant is harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

### **20. Research governance**

NHS Greater Glasgow and Clyde will act as Sponsors of this study.

A trial steering committee (TSC), including an independent chair and at least two other independent members, will be set up prior to initiation of the study. Reports from the TSC will be supplied to both the sponsor and the funding body. We will invite two lay members onto the committee. A separate Data Monitoring Committee (DMC) will also be set up, consisting of a minimum of 2 appropriate clinicians and 1 statistician. The DMC will meet every 6 months for the first 3 years of the study. Thereafter, as the study moves into the long term follow-up phase with infrequent study visits, the DMC will decide how often they will be required to meet in order to appropriately carry out their role.

## **21. Project timetable: Stages, Go/No-Go Decision Points and Milestones**

We have assumed that contracts will be agreed and signed between NHS GGC and DoH by June 2013. We will allow 6 months prior to study initiation in order to obtain appropriate approvals, recruit staff and set up the study. Recruitment will begin in Dec 2013 and will last for 41 months.

Patient follow-up will last 10 years from the time of surgery, meaning that the final patient assessment will be at the end of July 2028. It is vital that patients are followed up for a minimum of 10 years in order to establish long term performance of this novel surgical method. Although we will follow up patients for a 10 year period, the primary knee kinematic data and early surgical outcome data will be collected 1 year after surgery has been completed on each patient. 1 year data collection will be completed by the end of July 2019. We will therefore analyse our 1 year data during August - September 2019 and will aim to have the first sets of publications arising from the study submitted by winter 2019. Subsequent publications will be produced end of 2020 (2 year data), 2023 (5 year data) and 2028 (10 year data).

Critical stages (with Go/No-Go decision points) and Milestones are given in table 2 below. Table 3 contains a gantt chart with key study timelines. . A study recovery plan was submitted to the funder to permit the extension of recruitment from a period of 24 months to 41 months. This was granted and the resulting study timeline updates are reflected in Table 3.

## **22. Expertise**

Our multi-disciplinary team includes surgical researchers from the Orthopaedic Research Unit at Glasgow Royal Infirmary, Bio-Engineers from Strathclyde University (Glasgow) and statistical and trial methodological support from the Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen.

The 3 members of our surgical team have extensive experience using the MAKO RIO system and have just completed recruitment in the first randomised controlled trial in the world to use the system. Our research team also have experience using the competitor Stanmore Sculptor system and BlueBelt NAVIO (the two competing systems in the market place) and we believe we are the only surgical team to have such experience. Our unique expertise with this type of technology places us in an optimal position to carry out a trial of this nature. In the last few years our Research Team has undertaken 8 randomised controlled trials and numerous non-randomised studies, securing ~£4M of funding in the last 3 years. While we have been relatively successful in securing funding for projects, the long term nature of most Orthopaedic studies has resulted in a lag time to publication. 2013 will mark a milestone for our Unit with significant numbers of studies reaching publishable follow-up time points and we anticipate that the Unit will generate 25+ publications in 2013.

The Research Unit at Glasgow Royal Infirmary has been set up and structured around a full time Senior Clinical Research Manager with support from dedicated research nurses and administrative support staff. The professional setup within our Unit has allowed us to run multiple complex studies.

Professor Philip Rowe will lead the team at Bio-Engineering Unit at the University of Strathclyde which is Scottish Centre of excellence in Rehabilitation Research. Professor Rowe has expertise in functional gait analysis. He also leads the University's Centre for Robotic Surgery and will provide input on the Robotic system, the biomechanical, function and activity outcome measures.

Professor John Norrie will lead the input from the NIHR registered CTU in Aberdeen University – the Centre for Healthcare Randomised Trials (CHaRT), in the Health Services Research Unit. Professor Norrie is an experienced trialist and statistician, with a particular interest in the design, conduct, analysis and reporting of non-drug complex interventions, including orthopaedic surgical trials. Professor John Norrie has left his post at CHaRT and has been replaced by Prof Graeme

MacLennan who worked with Prof Norrie for many years at CHaRT and was involved in many of the trials in collaboration with Prof Norrie.

### **23. Publication policy**

Data generated by the study will be presented at national and international meetings by the investigators at the following time points: 1, 2, 5 and 10 years after the final patient recruited to the study has received their surgery. Data will also be published in peer reviewed journals at the same time points.

#### **Authorship:**

The investigator who provides the majority contribution towards drafting any paper will be named as first author on the paper. For clinical papers the Chief Investigator will be named as senior author and for Bio-mechanical papers, Prof Philip Rowe will be named as senior author. Any paper submitted to a journal for publication will be given to MAKO Surgical Corp at least 60 days in advance to review and comment. Submissions for conference abstracts will be given at least 30 days in advance.

All reasonable efforts will be made to respond to and accommodate comments by MAKO Surgical Corp, without compromising the Investigators duty to publish accurate and complete data.

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## 25. Flow Diagram

