**Study Title:** Optimum radiographic assessment of the medial and lateral tibiofemoral compartments within the arthritic knee

**Ethics Ref:** South Central – Oxford B REC (15/SC/0476)

**Date and Version No:** Version 1.1


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| **Sponsor:** | Oxford University Hospitals NHS Trust |
| **Funder:** | Departmental Funding, Oxford Orthopaedic Engineering Centre |
| **Chief Investigator Signature:** | Thomas Hamilton |


One or more of the investigators has received support from a commercial partner related to unicompartmental knee replacement. This funding is not related to this study.

**Confidentiality Statement**

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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## 1. SYNOPSIS

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| **Study Title** | Optimum radiographic assessment of the medial and lateral tibiofemoral compartments within the arthritic knee |
| **Short title** | Optimum radiographic assessment of the knee |
| **Study Design** | Clinical Investigation |
| **Study Participants** | Patients aged over 50 years with knee osteoarthritis, any grade, affecting the tibiofemoral joint. |
| **Planned Sample Size** | 225 |
| **Planned Study Period** | August 2015 to January 2017 (18 months) |
| | **Objectives** |
| **Primary** | To assess the accuracy of different xray views of measuring joint space width within each compartment within the knee. |
| **Secondary** | To define the sensitivity and specificity of four different xray views at predicting bone on bone arthritis and joint space narrowing within each of the knee compartments and suitability for unicompartmental knee replacement.<br>To define the sensitivity and specificity of MRI at predicting suitability for unicompartmental knee replacement.<br>To assess the sensitivity and specificity of different xray techniques at inferring the status of soft tissue structures (anterior cruciate ligament and medial collateral ligament) within the arthritic knee.<br>To develop a decision aid to help clinicians decide between likelihood of a patient being a candidate for unicompartmental knee replacement based on pre-operative xray and MRI findings. |

## 2. ABBREVIATIONS

| | |
|---|---|
| CI | Chief Investigator |
| CRF | Case Report Form |
| CTRG | Clinical Trials & Research Governance, University of Oxford |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| MRI | Magnetic Resonance Imaging |
| ICF | Informed Consent Form |
| NHS | National Health Service |
| NRES | National Research Ethics Service |
| OA | Osteoarthritis |
| PI | Principal Investigator |
| PIL | Participant/ Patient Information Leaflet |
| R&D | NHS Trust R&D Department |
| REC | Research Ethics Committee |
| SOP | Standard Operating Procedure |
| TKR | Total Knee Replacement |
| UKR | Unicompartmental Knee Replacement |

## 3. BACKGROUND AND RATIONALE

Xrays are the most frequently used imaging test when evaluating the knee for joint replacement. They are non-invasive, safe and cost effective. They allow assessment of: progression of disease, appropriateness for joint replacement (in particular UKR) as well as likely prognosis following replacement. Despite a multitude of standardised views there is a lack of consensus regarding the optimum views to evaluate joint space narrowing within each compartment (lateral, medial and patellofemoral).

The optimum imaging protocol is one that is acceptable to patients, involves the fewest xrays to obtain the most clinically relevant information and one that utilises the least resources in terms of staff and equipment. Currently standard assessment involves: standing anteroposterior, lateral and skyline views. In addition in patients being considered for joint replacement valgus/varsus stress xrays are used to evaluate the lateral compartment (as well as medial collateral ligament) and medial compartment respectively to assess the status of the cartilage. In patients with loss of cartilage on one side, typically medial, but preserved cartilage on the other a UKR, as opposed to TKR, may be indicated.

Currently there is a lack of consensus amongst orthopaedic surgeons in the UK as to the best way to image the knee joint to establish degree and pattern of arthritis [1, 2]. For a long time it has been known that weight bearing views are a better method at establishing the true joint space compared to non-weight bearing views width due to the increased forces across the joint [3-5]. In addition it is known that full extension views, despite being the most commonly used view, may also underestimate joint space

narrowing as in full extension the femur and tibia articulate across an area of the joint that is not typically not involved during activity, and hence can have relatively well preserved cartilage, giving a false impression of the joints disease state[6]. These findings have been adopted, and continue to be adopted, into routine clinical practice and there continues to be an increase in the proportion of surgeons performing standing and semi-flexed views [2]. However the best method of evaluating the disease state in each compartment has yet to be defined.

When deciding between UKR and TKR the detection of the degree and pattern of arthritis is of critical importance. UKR are known to perform poorly in partial thickness disease and require full thickness cartilage in the retained tibiofemoral compartment[7, 8]. To establish whether a patient meets the indications for UKR xrays are used with stress views being the gold standard, as well as the standard assessment that the studies of long term outcomes on UKR are based. Gibson and Goodfellow, who were first to describe stress xrays in the workup of a patient for UKR, reported that those patients with a joint space width of more than 5mm in the lateral compartment had intact lateral cartilage during surgery making them appropriate for UKR [9]. More recently Waldstein *et al.* reported that patients with a lateral joint space width of more than 4mm may be appropriate for UKR however overall they noted poor correlation between joint space width measured on valgus stress views and intra-operative Outerbridge grade[10].

In addition to the low quantity of evidence regarding the relationship between stress views and intra-operative status of the joint the feasibility of performing stress xrays also limits their use. Stress xrays are resource dependent, can be uncomfortable for patients and require an additional practitioner. As such they are often not performed with many clinicians adopting alternative xray views, MRI or direct observation via arthroscopy [11]. It has been proposed that standing views with the knee in 15 degrees then 45 degrees flexion may load the medial and lateral compartments respectively and that these views may be an alternative to stress views without the requirement for an additional practitioner. However the outcomes based on these forms of assessment, and the relationship between the joint space width measured using these contemporary techniques has not been reported. An alternative would include a stress device that allows a stress xray to be performed without the requirement of the clinician.

This study will evaluate the status of knee cartilage in 225 patients with varying degrees, and patterns, of knee OA using standing extension anteroposterior, 15 degrees flexion posteroanterior, 45 degrees flexion posteroanterior and valgus and varus stress views as well as MRI. These results will be compared to the gold standard imaging technique of stress views as well as to direct measurements of retrieved tissue in those patients who undergo knee replacement surgery. The sensitivity and specificity of each of the imaging techniques at predicting suitability for UKR will be calculated, the optimum imaging views proposed, and ultimately the results of this study will be used to develop a decision aid, based on optimum views, to help clinicians decide between likelihood of a patient being a candidate for UKR based on pre-operative xray and MRI findings.

## 4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

| Objectives | Outcome Measures |
|---|---|
| **Primary Objective**<br><br>• To assess the accuracy of different xray views of measuring joint space width within each compartment within the knee. | Joint space width in the medial and lateral tibiofemoral compartments of the knee measured in mm. |
| **Secondary Objectives**<br><br>• To define the sensitivity and specificity of four different xray views at predicting bone on bone arthritis and joint space narrowing within each of the knee compartments and suitability for UKR.<br>• To define the sensitivity and specificity of MRI at predicting suitability for UKR.<br>• To assess the sensitivity and specificity of different xray techniques at inferring the status of soft tissue structures (anterior cruciate ligament and medial collateral ligament) within the arthritic knee. | A joint space width of 0mm will be classified as bone on bone arthritis, >0mm to <5mm will be classified as joint space narrowing and >= 5mm will be classified as full thickness cartilage. The sensitivity and specificity of each technique, at detecting each disease state in each compartment, compared to the gold standard of stress views will be recorded.<br><br>The sensitivity and specificity of MRI, compared to the gold standard of stress views, at predicting the status of each compartment will be recorded.<br><br>In patients proceeding to joint replacement as part of their standard clinical pathway the sensitivity and specificity of different xray techniques at inferring the status of soft tissue structures (anterior cruciate ligament and medial collateral ligament) within the arthritic knee will be compared to operative findings. |
| **Tertiary Objectives**<br><br>• To develop a decision aid to help clinicians decide between likelihood of a patient being a candidate for UKR based on pre-operative xray and MRI findings. | The findings from this study will be used to develop a decision aid. The sensitivity and specificity of this decision aid will be calculated in the cohort of patients undergoing surgery using intra-operative audit findings as the gold standard. |

## 5. STUDY DESIGN

The study is a clinical investigation to determine the optimum xray technique for each compartment of the knee in patients aged over 50 years with knee arthritis.

All patients attending knee clinic will be informed about the study in advance. Those patients who meet the inclusion criteria will be referred to the research team in clinic. Screening would be performed in clinic and in those patients that do not have exclusion criteria further information about the study will be given and if the patients agree to participation valid informed consent will be taken. Screening and consent would take around 10 minutes. Two additional xray views will be taken alongside routine clinical views and would be expected to take a maximum of 10 additional minutes. An MRI scan would also be arranged, and this would take place at a separate time arranged at the patients convenience and would take around 30 minutes. No further research appointments would be performed. In patients who, as part of their clinical care, undergo knee replacement the excised joint surfaces, which are normally disposed of, would be retained and the degree and pattern of articular cartilage wear would be quantitatively evaluated before disposal. In addition an audit of the intra-operative findings would be performed.

Evaluation for inclusion and exclusion criteria would be via pre-tested standardised pro forma. A pain visual analogue scale would be used to assess for the presence and degree of pain during stress views. Xray images would be measured using custom measuring software (Matlab, Massachusetts , USA), MRI images would be measured using a segmentation method that has previously been described (Solidworks, Massachusetts , USA). Intra-operative audit of joint surfaces and soft tissue structures would be recorded on a standardised, pre-tested pro forma. Retrieved intra-operative samples of the joint surface would be scored using a validated technique, digitally photographed and surface geometry measured using a 3D laser scanner.

A flow chart of the study can be seen in Appendix A.

## 6. PARTICIPANT IDENTIFICATION

### 6.1. Study Participants

Patients aged over 50 years referred to knee clinic with radiographic evidence of knee osteoarthritis, any grade, affecting the tibiofemoral joint

### 6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 50 years or above.
- Knee osteoarthritis any grade, affecting the tibiofemoraljoint
- In the Investigator’s opinion, is able and willing to comply with all trial requirements.
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial.

### 6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Previous joint replacement on ipsilateral knee
- Previous anterior cruciate ligament reconstruction or injury
- Previous high tibial osteotomy
- Previous intraarticular
- fracture
- History of Inflammatory arthritis
- Unable to stand with assistance for two minutes

## 7. STUDY PROCEDURES

- Screening and consent (performed at clinic appointment) - 10 minutes
- Standard Clinical Xrays
    - Standing anteroposterior view
    - Lateral view
    - Patelofemoral view
    - Valgus stress view (clinician performed or using validated device)
    - Varus stress view (clinician performed or using validated device)
- Research xrays (performed at the same time as routine clinical xrays) – 10 minutes
    - Standing posteroanterior (PA) view 15 degrees flexion
    - Standing posteroanterior (PA) view 45 degrees flexion
- MRI (performed during a separate appointment at the patients convenience) – 30 minutes
- Measuring of routinely retrieved joint surface cartilage (performed in research laboratory)

### 7.1. Recruitment

All patients attending knee clinic will be provided with an information leaflet via the post 2 weeks before their appointment about the study. Patients will be identified as eligible by the clinical team and will be referred to the research team who will be based in clinic. The research team will screen patients using a standardised, pre-tested, pro forma. Further information about the trial will be provided. Patients who meet inclusion, but not exclusion criteria, and who are willing to participate in the study will be consented for the study.

### 7.2. Informed Consent

Consent will be performed by a member of the research team who is suitably qualified and experienced, and has been authorised to do so by the Chief Investigator.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate

in the study. The patient must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. The written Informed Consent will then be dated and signature of the person who presented and obtained the Informed Consent. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site. One copy will be filed in the patient's medical notes.

### 7.3. Screening and Eligibility Assessment

Screening will be performed via pre-tested, standardised, pro forma by a member of the research team. A maximum period of 2 months will be permitted between screening and MRI. Analysis of excised joint surfaces in those patients who undergo knee replacement as part of their clinical management will only be considered valid if the replacement is performed within 6 months of screening.

### 7.4. Baseline Assessments

At baseline a patient name, gender and date of birth will be recorded, together with hospital and NHS number will be recorded on the patient data sheet which will be linked to the CRF by way of a study number.

Research xray views will also be performed during the baseline assessment. In addition to routine clinical xrays: standing anteroposterior, lateral, skyline views and valgus/varus stress xrays two research xray views will be performed.

These two views are with the patient standing, hands resting on a frame for stability. The xrays are taken in the postero-anterior direction. The first of these standing views is taken with the knees flexed to 15 degrees, the second with the knees flexed to 45 degrees.

### 7.5. Subsequent Visits

One further appointment would be required for this study. This appointment would be for MRI of the knee. The appointment would be performed at the patient's convenience and would take 30 minutes in total. No further appointments would be required for the patient as part of this research project.

### 7.6. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the 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:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Withdrawal of Consent

In the event of patient withdrawal from the study analysis of data obtained prior to withdrawl will be analysed as part of the study.

Withdrawn participants will not be replaced.

The reason for withdrawal will be recorded in the CRF.

### 7.7. Definition of End of Study

The end of study is 6 months following recruitment of the last patient.

## 8. INTERVENTIONS

In addition to the standard clinical imaging protocol described above trial participants will undergo:

- 15 degrees flexion postero-anterior view
- 45 degrees flexion postero-anterior view
- MRI knee without contrast

In those patients undergoing surgery as part of their routine clinical management:

- Intra-operative audit of joint surface and status of ligaments within the knee
- Assessment of retrieved samples of joint surface that would otherwise be disposed of

## 9. SAFETY REPORTING

The study is low risk however in the event of an adverse event (AE) or serious adverse event (SAE) occurring to a participant this would be reported to the REC and R&D.

## 10. STATISTICS AND ANALYSIS

### 10.1. Description of Statistical Methods

Joint space width of each of the compartments will be measured on each routine and research xray views taken using a standardised technique using custom software (Matlab, Massachusetts, USA).To compare the accuracy and agreement of different radiological views at measuring joint space width statistical methods for assessing agreement between two methods of clinical measurement as described by Bland and Altman will be used with stress views defined as the gold standard for comparison [12, 13].

For the secondary outcomes each of the compartments on each of the xray views will be classified as demonstrating bone on bone arthritis, full thickness cartilage or narrowing of joint space width. The sensitivity and specificity of each of the views at predicting each of these disease states will be compared with stress views which will be defined as the gold standard. The sensitivity and specificity of each of the views at predicting suitability for UKR will be calculated based on pre-defined indications of UKR.

The sensitivity and specificity of MRI at predicting suitability for UKR, based on pre-defined xray derived indications as the gold standard will be calculated.

The sensitivity and specificity of different xray techniques at inferring the status of soft tissue structures (anterior cruciate ligament and medial collateral ligament) within the arthritic knee will be evaluated against both MRI and intra-operative findings.

A decision aid will be developed based on the findings of this research and the sensitivity and specificity of this decision aid at predicting suitability for UKR will be calculated. Further work will then be performed to validate this scoring system.

### 10.2. The Number of Participants

From two previous studies evaluating the utility of PA views in 15 degrees flexion compared with AP standing for long term evaluation of progression of knee arthritis the difference in mean joint space width measured on Lyon Schuss and AP standing views is between 0.63mm with a population standard deviation of 1.1. This gives an effect size of 0.57. At a power of 0.8 and significance level of 0.05 using the Altman nomogram the required sample size would be 100 patients. From audit it has been identified that 50% of patient from clinic will be treated with surgery. In addition to allow for errors in xray alignment making interpretation not valid an additional 25 patients will be added giving a sample size of 225 patients.

### 10.3. Analysis of Outcome Measures/Endpoints

Each image will be measured independently and statistical analysis will be performed blinded to the treatment outcome. Should a patient withdraw consent prior to termination of the study data that has been collected will only be used for analysis where, for each endpoint, a complete set of data is present.

## 11. DATA MANAGEMENT

### 11.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

### 11.2. Data Recording and Record Keeping

A password protected database containing patient identifiable information solely for identifying patients who have subsequently had surgery and for collecting the results of intraoperative findings will be kept on a secure university computer. This database will be securely destroyed six months following the end of the study. No other patient identifiable information will be kept.

Xrays and MRI images will be measured in duplicate using pre tested software (Matlab, Massachusetts, USA) with the evaluator blinded to other images in that patients series as well as the final treatment outcome.

The majority of data will be generated electronically and it will be stored and backed up securely within the research institute. Where data is required to be transcribed from a paper pro forma this information will be checked by an independent member of the research team. Data will be analysed using Stata version 13 (Texas, USA).

Data will be retained for 10 years in line with our organisations policy.

## 12. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

## 13. ETHICAL AND REGULATORY CONSIDERATIONS

### 13.1. Declaration of Helsinki

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

### 13.2. 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.

### 13.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), 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.

### 13.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

### 13.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. A password protected database containing patient identifiable information solely for identifying patients who have subsequently had surgery and for collecting the results of intraoperative findings will be kept on a secure university computer. This database will be securely destroyed six months following the end of the study. No other patient identifiable information will be kept. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. Patient identifiable information held on the secure database will be linked to the CRF and other study records by way of study number.

### 13.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

## 14. FINANCE AND INSURANCE

### 14.1. Funding

Insurance Mr Hamilton is funded for this work through and NIHR grant. Mr Pandit, Dr Mellon and Professor Murray are funded independently. Additional funding for this study is provided by departmental research funding to our research group.

### 14.2.

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical research study 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 Oxford University NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

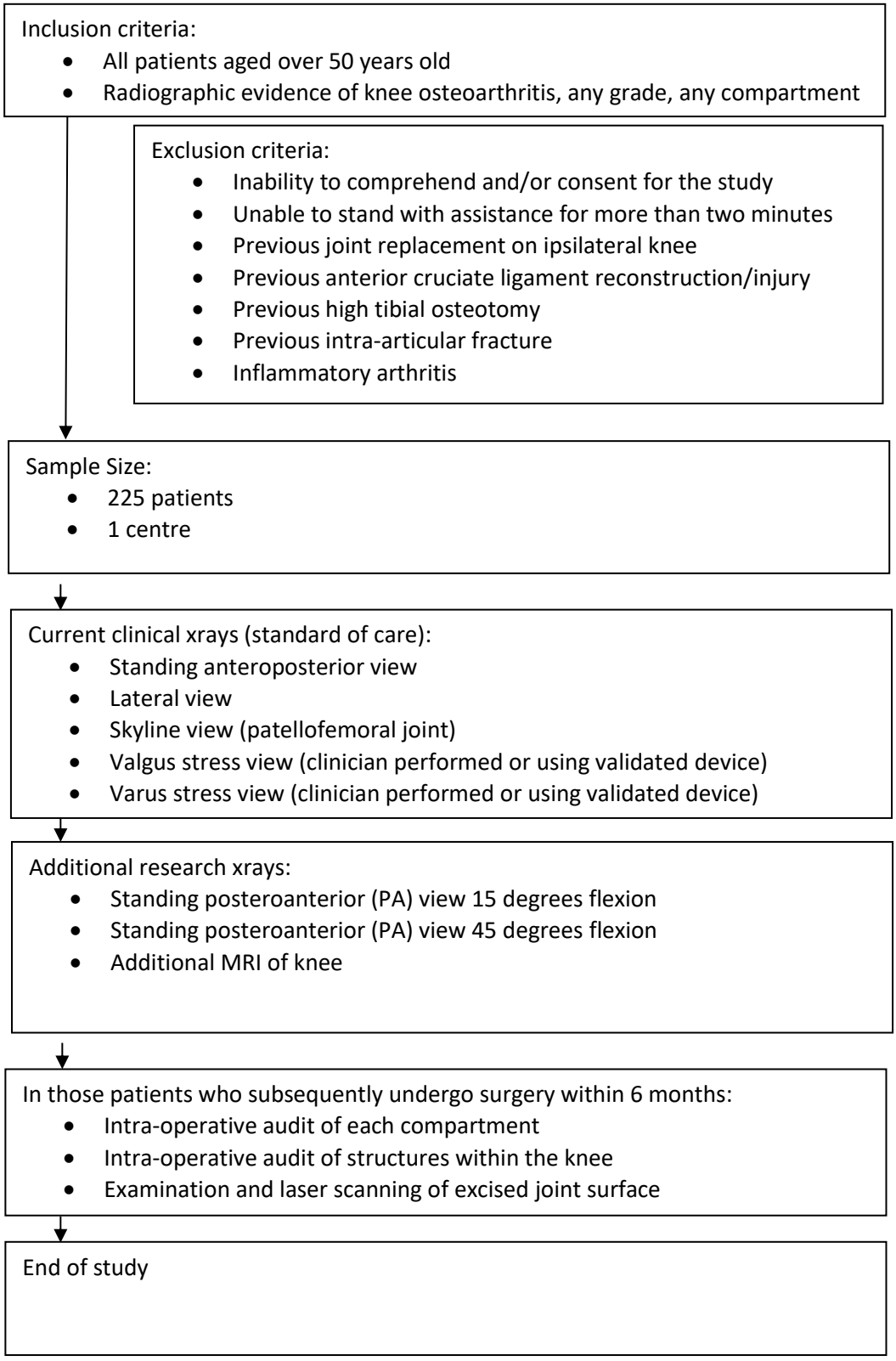
## 15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

## 16. REFERENCES


1. Vince, A.S., A.K. Singhania, and M.M. Glasgow, *What knee X-rays do we need? A survey of orthopaedic surgeons in the United Kingdom.* Knee, 2000. **7**(2): p. 101-104.
2. Bhatnagar, S., et al., *Evidence-based practice in the utilization of knee radiographs--a survey of all members of the British Orthopaedic Association.* Int Orthop, 2006. **30**(5): p. 409-11.
3. Thomas, R.H., et al., *Compartmental evaluation of osteoarthritis of the knee. A comparative study of available diagnostic modalities.* Radiology, 1975. **116**(3): p. 585-94.
4. Leach, R.E., T. Gregg, and F.J. Siber, *Weight-bearing radiography in osteoarthritis of the knee.* Radiology, 1970. **97**(2): p. 265-8.
5. Ahlback, S., *Osteoarthrosis of the knee. A radiographic investigation.* Acta Radiol Diagn (Stockh), 1968: p. Suppl 277:7-72.
6. Buckland-Wright, C., *Which radiographic techniques should we use for research and clinical practice?* Best Pract Res Clin Rheumatol, 2006. **20**(1): p. 39-55.
7. Pandit, H., et al., *Unicompartmental knee replacement for patients with partial thickness cartilage loss in the affected compartment.* Knee, 2011. **18**(3): p. 168-71.
8. Pandit, H., et al., *Unnecessary contraindications for mobile-bearing unicompartmental knee replacement.* J Bone Joint Surg Br, 2011. **93**(5): p. 622-8.
9. Gibson, P.H. and J.W. Goodfellow, *Stress radiography in degenerative arthritis of the knee.* J Bone Joint Surg Br, 1986. **68**(4): p. 608-9.
10. Waldstein, W., et al., *The value of valgus stress radiographs in the workup for medial unicompartmental arthritis.* Clin Orthop Relat Res, 2013. **471**(12): p. 3998-4003.
11. Eriksson, K., et al., *Stress radiography for osteoarthritis of the knee: a new technique.* Knee Surg Sports Traumatol Arthrosc, 2010. **18**(10): p. 1356-9.
12. Bland, J.M. and D.G. Altman, *Measuring agreement in method comparison studies.* Stat Methods Med Res, 1999. **8**(2): p. 135-60.
13. Bland, J.M. and D.G. Altman, *Statistical methods for assessing agreement between two methods of clinical measurement.* Lancet, 1986. **1**(8476): p. 307-10.

## 17. APPENDIX A: STUDY FLOW CHART



## 18. APPENDIX C: AMENDMENT HISTORY

| Amendment No. | Protocol Version No. | Date issued | Author(s) of changes | Details of Changes made |
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