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TOPKAT
Total Or Partial Knee Arthroplasty Trial

Total or Partial Knee Arthroplasty Trial - TOPKAT

A multi-centre randomised controlled trial comparing partial with total knee replacement

Ethics Ref: 09/H0606/88

Version 3, June 2012

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
5	2	26/01/2012	Professor David Beard	Inclusion of additional OKS questionnaire at 1 year post surgery for participants with a time between randomisation and surgery greater than 12 weeks.
4	2	09/02/2011	Professor David Beard	Revision of \primary Procedure Hospital Form and inclusion of Readmission form.
3	2	04/10/2012	Professor David Beard	Clarity given to the Inclusion and Exclusion criteria.
2	2	June 2010	Professor David Beard	Inclusion of the High Activity Arthroplasty Score (HAAS) to the secondary outcome measures.
1	1	09/06/2009	Professor David Beard	Revision of criteria on Surgeon/Site Inclusion form.

2. SYNOPSIS

Study Title	TOPKAT
Internal ref. no.	
Study Design	Randomised Controlled Trial
Study Participants	Patients with osteoarthritis of the medial knee
Number of Participants	500
Planned Study Period	January 2010 to December 2018
Primary Objective	To assess the clinical effectiveness of partial and total knee replacements.
Secondary Objectives	To assess the cost effectiveness of partial and total knee replacements.
Primary Outcome	Oxford Knee Score at 5 years post randomisation
Secondary Outcomes	American Knee Society Score, Patient Activity, Radiographic evidence, Complications, Health Economics, Patient Satisfaction, Other outcomes
Intervention (s)	Unicompartmental knee replacement or Total knee replacement

3. ABBREVIATIONS

AKKS	American Knee Society Score
ASA	American Society of Anesthesiologists
BASK	British Association for Surgery of the Knee
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
DPHPC	Department of Public Health and Primary Care
GCP	Good Clinical Practice
HAAS	High Activity Arthroplasty Score
HTO	High Tibial Osteotomy
ICF	Informed Consent Form
KAT	Knee Arthroplasty Trial
NDORMS	Nuffield Department of Orthopaedic, Rheumatology & Musculoskeletal Sciences
NRES	National Research Ethics Service
OKS	Oxford Knee Score
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
QALY	Quality Adjusted Life Year
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
TKR	Total Knee Replacement
UCLA	University of California Los Angeles
UKR	Unicompartmental Knee Replacement

4. BACKGROUND AND RATIONALE

Osteoarthritis in the knee affects different people in different ways. In the majority of patients with osteoarthritis of the knee the disease originates in the medial compartment. There are varying forms of treatment for this and these aim to relieve pain and discomfort, to reduce stiffness and to minimise further damage to the joint. Such approaches include physiotherapy, medicines and surgery to replace the diseased joint. There are different approaches to replacing this arthritic area. Some surgeons feel that it is always best to replace both the knee compartments with a Total Knee Replacement. (TKR). Others feel it is best to replace just the damaged component of the knee with a Unicompartmental Knee Replacement (UKR). There is little agreement amongst knee surgeons. The majority support TKR and the minority UKR. Fewer than 5% of knee replacements worldwide are unicompartmental, although it is thought that up to 30% of patients requiring knee replacements have only unicompartmental disease that would be suitable for a UKR (1-3).

There are arguments for both approaches. Both interventions are established and well documented procedures. Each intervention is considered standard care. There exists little evidence, however, to prove the clinical and cost effectiveness of either management option. The TKR surgeons believe that their operation is less complex than UKR and thus, in the short-term TKRs are less susceptible to early problems and failures. They also believe that in the longer term the joint disease will progress to the other, normal, compartments of the knee. It is felt that a UKR would eventually fail and require revision surgery, which involves a TKR procedure. In contrast, the UKR surgeons believe the UKR gives faster recovery, fewer complications, superior function, is more cost effective than TKR, and it is associated with long term survival of the joint. UKR supporters indicate that such success is only achievable if high quality implants and suitable techniques are used on patients with osteoarthritis of the medial knee (2-4).

Current patient management for medial osteoarthritis is based on limited evidence. There have been individual cohort studies, indirect comparisons and retrospective studies. These have usually

been undertaken to address specific aspects and many involve only short-term assessments (5-20). No large powered, multi-centre randomised controlled trial has been undertaken to directly compare the UKR and the TKR. The only other previous attempt at comparing these operations on a large scale was that from one of the arms in the Knee Arthroplasty Trial (KAT). However this arm of the study failed due to lack of equipoise and confidence towards the UKR amongst surgeons. This led to such a low patient recruitment figure that this arm of KAT was stopped. Other previous studies which show a trend towards TKR being the more effective management have displayed low level evidence, consensus and peer influence (21-24). In order to test the validity of these results, further investigation is required. Using an appropriate patient base and long term assessments, the clinical and cost effects of both treatment options can be examined.

5. OBJECTIVES

5.1 Primary Objective

The primary objective for TOPKAT will be to assess the clinical effectiveness of Total Knee Replacements compared to Unicompartmental Knee Replacements in patients with medial osteoarthritis.

5.2 Secondary Objectives

Secondary objectives revolve around the cost implications of the knee replacements for patients, surgeons and health care providers.

6. STUDY DESIGN

6.1 Summary of Study Design

The design of the study will be a single layer multi-centre prospective superiority type randomised controlled trial of unilateral knee replacement patients. The randomised controlled trial design will help reduce and prevent potential bias influencing the evaluation.

Participants will be randomised to either UKR or TKR. The trial has a combined equipoise/expertise approach. It enables surgeons who are not in equipoise to deliver only one of the two operations

while also allowing surgeons in equipoise to provide both operations. A surgeon who is in equipoise ("equipoise surgeon") and has sufficient experience to perform both TKR and UKR will deliver the allocated operation (UKR or TKR). The same surgeon will perform the operation for both arms of the study.

Not all surgeons are able to practice this equipoise. They may hold a preference for one treatment over the other, due to a lack of confidence and practice with one or another. These surgeons may also feel they are unable to perform one of the operation types, even though they believe the patient may benefit from it.

Equipoise is scientifically difficult to portray. Self declaration has been used as the main approach but in order to sufficiently secure this state the following aspects are important:

- The equipoise considered must be patient or individual based equipoise rather than an overall or general category equipoise based on operation type. The surgeon must consider their position for each individual patient. Only if they believe that either operation will be suitable for an individual patient then the patient can be recruited.
- No surgeon will ever knowingly perform what they consider a substandard surgical procedure.

In order to complete the trial by seeking to maximise surgeon participation, an "expertise" based delivery of the intervention will also occur. For this approach there must be a surgeon with expertise in TKR and a surgeon with expertise in UKR in the same centre who will act together as a "delivery unit". Patients recruited to the study who are under the care of such a surgeon ("expertise surgeon") will be randomised to one of the two groups and treated by the appropriate surgeon. This "expertise" approach allows for those UKR surgeons who work alongside TKR surgeons to team up and participate in the study. Subsequent surgery may be carried out by a surgeon different to that at the initial consultation. In such cases the patient is internally referred to the other surgeon's operating list. A study flowchart is detailed in Appendix A. No restriction is made upon the number of delivery units within a centre. A surgeon can only be in one delivery unit i.e. they are either an "equipoise surgeon" or an "expertise surgeon".

To ensure participating surgeons have appropriate expertise, a simple audit of participating surgeons' routine practice will be undertaken. UKR surgeons must have had appropriate training, been practicing the technique for at least one year and have performed the operation at least 10 times in the past year. They must also be aware of their clinical results and these must be acceptable to the study team. Implants used by UKR surgeons in the study must have good clinical results and be a commonly used knee system which does not require patella dislocation. TKR surgeons must satisfy similar criteria. They must have had many years experience with TKR and will use a conventional approach with patella dislocation. "Equipoise surgeons", who deliver both operations, are required to satisfy the criteria for both operations i.e. they will have appropriate training in both operations and have performed 10 UKR and 10 TKR procedures.

6.2 Primary and Secondary Outcome Measure

Primary Outcome Measure

TOPKAT primary outcome measure is the Oxford Knee Score. This is a patient based questionnaire and is a validated and effective measure of change over time. The score will be analysed at 5 (* and 10 year) points post randomisation.

Secondary Outcome Measures

Secondary outcome measures for TOPKAT are:

- American Knee Society Score - measures Range of Motion & Function of the knee
- UCLA Activity Score - will measure how active the patient is
- High Activity Score

*Subject to additional funding

- Xrays - will check for immediate problems, assess the outcome of surgery, complications and make long-term predictions
- EQ-5D - will provide data for the economic evaluation
- Lund Score - measures patient satisfaction
- Complications

- Length of stay
- Revision rates
- Composite failure outcome
- Other outcomes may be collected at some participating TOPKAT centres, please refer to Satellite Protocols for further information.

6.3 Health Economics

The health economic evaluation proposed will take the form of a cost-utility analysis. Health outcomes will be assessed at each trial follow-up point using the EuroQol EQ-5D questionnaire and each patient's resulting utility profile will be used to calculate the number of Quality Adjusted Life Years (QALYs) they experience over the duration of the trial.

To estimate the direct health care costs associated with both types of knee replacement, information will be collected from each patient in the trial on the resources consumed during initial surgery (including hospital inpatient stay and subsequent outpatient visits), and on any subsequent related health care use for complications and surgical revision. Data relating to direct costs patients may incur as a result of their knee condition, including rehabilitation, will be recorded. Information will be collected from patients on return to paid employment.

Within-trial cost-effectiveness analyses will be conducted at 5 years (*and at 10 years). If appropriate, results will be expressed as an incremental cost per QALY gained, with uncertainty around this ratio determined through the use of non-parametric bootstrapping and cost-effectiveness acceptability curves. Longer-term extrapolation of results will also be conducted and will use trial data, for example surgical revision rates will be projected using a simple parametric model and will be assigned appropriate event costs and utility scores.

6.4 Study Participants

6.4.1 Overall Description of Study Participants

Participants with osteoarthritis of medial compartment of the knee will be included in the study. Patients must satisfy surgeon's general requirements for a medial UKR which are listed below as

the inclusion criteria. It should also be noted that if patients meet the inclusion criteria with both their knees, only one knee can be entered into the study. TOPKAT will not examine bilateral knee replacements. Future knee replacements on the other knee will also not be considered by the study.

6.4.2 Inclusion Criteria

- Medial compartment osteoarthritis with exposed bone on both femur and tibia
- Functionally intact Anterior Cruciate Ligament (superficial damage or splitting is acceptable)
- Full thickness and good quality lateral cartilage present
- Correctable intra-articular varus deformity (suggestive of functionally intact medical cruciate ligament)
- Medically fit showing an ASA of 1 or 2

6.4.3 Exclusion Criteria

- Require revision knee replacement surgery
- Have rheumatoid arthritis or other inflammatory disorders
- Are unlikely to be able to perform required clinical assessment tasks
- Have symptomatic foot, hip or spinal pathology
- Previous knee surgery other than diagnostic arthroscopy and medial menisectomy
- Previously had septic arthritis
- Have significant damage to the patella-Femoral Joint especially on the lateral facet.

6.5 Study Procedures

500 patients will be recruited from approximately twenty centres over a period of two years. Potential patients will be identified and approached in outpatients and at pre-assessment clinics by the participating surgeon or their late stage trainee. At this stage patients will be provided with an "Invite letter" and information sheet which will explain why they have been approached and will provide further details about the study. At this stage patients will indicate if they are willing to be contacted again by the research team, using the TOPKAT Yes/No form. Those patients who indicate "Yes" will be contacted by local study staff to arrange a screening visit to assess their

eligibility for the study. If the patient is identified during an outpatient appointment the screening visit could coincide with their pre-assessment clinic appointment. The pre-assessment appointments are routinely scheduled for a short time before their scheduled operation date. If patients were identified at their pre-assessment clinic appointment, an extra visit will have to be coordinated for the screening to take place before the patient's operation date. Contact with the patient must be made at least 48 hours following introduction to the study.

Potential patients may also be identified from local databases. These patients will be sent a letter and a TOPKAT YES/NO form to return documenting if they are willing to be contacted further.

During the screening visit patients will be asked to sign a full consent form. This allows their details to be entered into the TOPKAT web based data collection system. Patient details and pre-operative assessments (OKS and AKSS) will be recorded and a study number will be allocated.

6.5.1 Randomisation Procedures

Randomisation will occur using a web based randomisation service at the Centre for Healthcare Randomised Controlled Trials (CHaRT), Health Services Research Unit, University of Aberdeen. The minimisation algorithm will incorporate gender, age and baseline OKS and "delivery unit". A delivery unit is either an "equipoise surgeon" or a pair of "expertise surgeons" with complementary expertise (i.e. one TKR and one UKR). This factor is included to ensure balance is maintained for individual equipoise surgeons and more generally by centre. Surgeons are not allowed to change practice during the course of the trial. Within a centre there may be a mixture of delivery unit types. Local recruitment officers at each site will undertake the randomisation. The randomised treatment will be recorded in the patient's hospital notes and study notes and the surgeon will be notified. If the allocated operation is not provided by the recruiting surgeon (e.g. they are an "expertise surgeon" who provide the other operation), an "internal referral" to their delivery unit colleague will be initiated. A standard letter informing the admissions department/care-pathway coordinators will be sent. Local study staff will oversee this referral. Patients' GP's will also be notified at this time.

6.5.1 Informed Consent

Full Consent will be obtained during the Screening Visit by the participating surgeon, their late stage trainee or local centre study staff. The principal investigator at this centre will have overall responsibility for consenting patients, but can delegate the task to reliable members of the study team. Such delegation will be recorded on a Task and Responsibilities log during centre initiation. Informed consent will be obtained according to GCP guidelines. Patients will be given sufficient time to accept or decline involvement. They will be free to withdraw from the study at any time without affecting their routine peri-operative care.

(Patient information sheets, consent forms, and patient letters are available in Appendix B).

6.5.2 Study Assessments

Patients will be assessed preoperatively. Operative details will be recorded. They will then be assessed clinically at 2 months, 1 and 5 years post operation. At years 1--5 patients will complete an annual postal questionnaire. Their first follow up appointment will be given to each patient on discharge from the hospital. Where there is more than 12 weeks between randomisation of patient to treatment and their operation date, an additional OKS will be administered at the clinical assessment 1 year post surgery. Additional clinical and postal questionnaire assessments are planned for year 7 and 10 subject to funding. The components of follow up are shown in the table below.

	Pre	2/12	1 yr	2 yr	3 yr	4 yr	5 yr	7 yr	10 yr
OKS (self report function)	▲	○	○	○	○	○	○	○	○
AKSS (clinical exam)	▲	▲	▲				▲		▲
UCLA (self report activity)	▲	○	○	○	○	○	○	○	○
High Activity Arthroplasty Score	▲	○	○	○	○	○	○	○	○
X-rays	▲	▲*					▲		▲
EQ5D	▲	○	○	○	○	○	○	○	○
Lund (patient satisfaction)		○	○	○	○	○	○	○	○
Complications		▲	▲	○	○	○	▲	○	▲

▲ = Clinical Assessments ○ = Postal Questionnaires *=Immediately Post Op

(Data collection forms are shown in Appendix C).

6.6 Definition of End of Study

The end of study is the date of the last clinical assessment visit of the last participant scheduled.

7. INTERVENTIONS

TOPKAT will be pragmatic in terms of implant selection. Providing the above conditions are met, surgeons will be entirely free to use an implant of their choice or will use the current implants used at their institution. Implant type used on each patient will be recorded.

7.1 Total Knee Replacement

A total knee replacement involves all surfaces of the knee being replaced. The procedure involves excising both diseased and normal femoral condyles, the tibial plateau and often the patella. This is done through a large skin incision which provides easy access to the knee joint. Each component will be replaced with an artificial implant, which may be cemented in position.

7.2 Partial Knee Replacement

A partial knee replacement or unicompartmental knee replacement involves only the diseased area of the joint being replaced. The healthy compartment of the knee is retained and artificial implants are inserted in place of the diseased area. This is done via a minimally invasive surgical procedure.

7.3 Delivery of the intervention

The randomisation procedure will identify which type of implant (TKR or UKR) will be used.

- If the patient is under the care of an “equipoise surgeon”, this surgeon will carry out the allocated operation, either UKR or TKR.
- If the patient is under the care of an “expertise surgeon”, the designated surgeon in that delivery unit with the appropriate expertise will carry out the allocated operation, either UKR or TKR. This may be the surgeon the patient is currently under the care of. Alternatively, it may require the patient to be transferred into the care of the surgeon performing the allocated operation.

8. SAFETY

8.1 Safety concerns

The TOPKAT trial involves routine knee replacement surgery for medial compartmental osteoarthritis. There are no additional risks to patients. They will undergo knee replacement as per standard management regime. The benefits will be to future patients although involvement in the trial with specific outcome measurement may be perceived as a benefit by some patients. Patients will be informed of the standard risks associated with anaesthetic and knee replacement operations. Possible (expected) complications and consequences are:

All knee replacement procedures whether primary surgery or revision procedures carry a risk of anaesthesia related problems, death, morbidity including wound infection, bleeding intra and post operatively, thrombo-embolic complications and complications secondary to existing co-morbidity e.g. ischaemic heart disease.

Specific complications following knee replacement procedures include loosening of components – Tibia/Femur/both, dislocation of knee/bearing, superficial and deep infection, unexplained knee pain, knee stiffness, haematoma, mechanical failure of replacement, periprosthetic fracture. These complications may result in the need for further surgery such as revision operations, arthroscopy, washout, manipulation under anaesthetic, debridement (open), aspiration, above knee amputation, patella resurfacing.

8.2 Definition of Serious Adverse Event

For the purpose of TOPKAT, a SAE is defined as any adverse event during the course of the study resulting from the administration of any of the research procedures required by the protocol that:

- Results in death,
- Is life-threatening,

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.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

All SAEs will be notified to the appropriate authorities (Research Ethics Committee (REC) and Sponsor) within the timelines outlined in the guidelines, as detailed in section 8.3.

8.3 Reporting Procedures for Serious Adverse Events

The reporting procedures for all study related adverse events are detailed in appendix G and are in accordance with the guidance from the National Research Ethics Service (NRES). When the web based SAE form is completed detailing any possible related and unexpected SAEs, the Chief Investigator (CI) or deputy will be notified automatically. If, in the opinion of the local surgeon and the CI, the event is confirmed as being related and unexpected (i.e. not listed in section 8.1 as a possible expected occurrence), the CI will submit a report to the main REC and the study sponsors within 15 days of the CI becoming aware of it.

8.4 Reporting of Post Surgical Complications

The annual postal self report questionnaires will ask patients if they have been admitted to hospital at any point over the last 12 months. Any readmissions will be followed up by the trial coordinator in Oxford who will contact the recruitment officers at the patient's hospital and ask them to collect further information about the readmission event. Details of any readmissions that are study related (i.e. result from administration of any of the procedures required by the trial protocol) and are expected (i.e. listed in section 8.1 as a possible expected occurrence)will be collected.

At the **routine follow up clinical visits**, patients will also be asked if they have experienced any complications related to their study knee since their last scheduled TOPKAT visit, which resulted in them visiting a Health Care Practitioner. This information will be collected.

9. STATISTICS AND ANALYSIS

9.1 Sample size

The sample size for the trial (250 in each arm, 500 overall) has been based on a number of considerations, drawing on what previous research has suggested is both plausible and the likely size of difference that is clinically significant.

(Projected recruitment targets are displayed in Appendix D).

9.1.1 Primary outcome - OKS score

The table shows the number of subjects required in each randomised group to give either 80% or 90% power to detect differences in the OKS of 2.0, 3.0, and 4.0, at either the 1% or 5% significance level and with SD of 8.0, 9.0, or 10.0.

Number in each group		Mean difference in OKS					
		2.0		3.0		4.0	
Power	SD	2p<0.01	2p<0.05	2p<0.01	2p<0.05	2p<0.01	2p<0.05
90	8.0	480	340	215	150	120	85
	9.0	600	430	270	190	150	110
	10.0	740	520	330	**235**	190	130
80	8.0	375	**250**	170	110	100	60
	9.0	470	320	210	140	120	80
	10.0	590	390	260	175	150	100

The minimal clinically significant difference of the OKS is judged to be 2.0, and the likely SD of the OKS is 8.0 (25). This suggests that a sample size of 500 patients (250 in each group) would provide 80% power to detect a difference of 2.0 at p<0.05. Since it is possible that the SD of the OKS could be higher than 8.0 (26), this size of sample would allow for the detection of a difference of 3.0 in OKS with a SD of 10.0 at p<0.05 and 90% power and also a difference of 3.0 at p<0.01 with 80% power. Indeed, almost all of the above scenarios are detectable if the difference in OKS is 3.0

rather than 2.0. This difference of 3.0 in the OKS is equivalent to a typical category change in the American Knee Society Score (27). Furthermore, a difference in the OKS of 4.0 would, with 250 patients per group allow for some subgroup analyses. As previous research (the Bristol RCT) suggests that the difference between the groups is indeed likely to be larger than 2.0 (2), a sample size of 250 in each arm would allow for some non-response (n=30) yet still detect differences. For further improvement to sample size requirements, the statistical analysis will adjust for baseline values and will account for the surgical delivery unit. This will reduce the required sample size. Any missing data would have the reverse impact.

9.1.2 Revision of the device

UKR may be associated with higher revision rates. The revision rate after TKR is approximately 5%. A sample size of 250 patients per group would give 80% power at $p<0.05$ to detect an increase to 12% (compared to just under 5%), and 90% power at $p<0.05$ to detect an increase to 14%. Analysis based on the time to revision using survival analysis will likely be more than sufficient.

9.1.3 Composite failure outcome

A composite outcome will be created which will be a combination of revision and objective assessment of 'failure' in terms of a score below a predefined threshold on the OKS. Thus, from the calculations above based on revision only, the power of the comparison will likely be sufficient.

9.2 Statistical Analysis

Principle analyses will be based on an 'intention to treat' basis where participants will be analysed according to the allocated group using all available participant data. Statistical significance will be judged at the 2-sided 5% level with corresponding 95% confidence interval presented. A short summary of the proposed analyses is given below. Further details of the planned statistical analyses are contained in the Statistical Analysis Plan, which will be finalised, prior to the unblinding of data.

Three sets of analyses are planned, based on the assumption that it takes six months to initiate the trial, and up to 18 months to recruit all patients. By two years, all patients are anticipated to have

received surgery. Analyses are planned at one year post operation (3 years into the trial), at five years post operation (7 years into the trial) and 10 years post operation (12 years into the trial).

The primary outcome OKS score will be compared at each assessment point alone (multiple linear regression analysis adjusted for minimisation factors). For the analysis planned once 5 and 10 years follow-up has matured, a complementary analysis will also compare the OKS over all assessments (the follow-up period) using a multilevel type analysis to allow for repeated measurements for participants. A stratified analysis will be performed to account for the expertise versus equipoise delivery of the treatments and the potential impact upon the comparison. Secondary analysis will explore the potential impact of missing data.

Secondary outcomes will be analysed in a similar manner adjusting for minimisation factors where appropriate within a generalised linear models framework. Confidential interim analysis will be performed as requested by the Data Monitoring Committee.

10. ETHICS

All potential participants will be provided with information about the study and given over 48hours to decide whether they would like to participate or not. Patients will be asked to sign a consent form before any study related procedures are undertaken. A copy of this consent form will be given to the patient.

10.1 Participant Confidentiality

The study 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 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.

10.2 Other Ethical Considerations

Patients who are unable to consent for themselves, and patients with cognitive or language impairment, will not be included in the study. The physical nature of some of the assessments, the long term follow up with postal questionnaires and the nature of the randomisation require patients with a full understanding of, and commitment to, what the study involves. It will be emphasised to all potential patients in the expertise allocation group that a different surgeon may perform their operation.

Surgeons must also portray a commitment to the study. Those in the device allocation group must stay in equipoise for the duration of the study. This is not an issue provided the intended individual or patient based equipoise is applied. The surgeons in Oxford, and many within the study, are proponents of UKR and there is the potential for unwitting bias. This is accounted for by;

1. Randomisation
2. Multi-centre design
3. Robust outcome measures resistant to manipulation or bias
4. Overview by an authoritative Trial Steering Committee
5. Furthermore, the surgical team in Oxford have agreed to adjust practice according to study results.

10.3 Minor Amendments

Amendments to study related documents will be assessed by the Chief Investigator to deem if they are substantial or minor. Minor amendments include:

- Administrative changes to patient letters and forms (e.g. format changes)
- Consequential amendments to forms created by approved amendments to related forms (e.g. new version of patient information sheet entered into consent form)

11. DATA HANDLING AND RECORD KEEPING

All data collected and stored as a result of the study will comply with the Data Protection Act. The participants will be identified by a study specific participants number and/or code in any database.

The name and any other identifying detail will NOT be included in any study data electronic file. Clinical assessment data (screening data excluded) and patient questionnaires will be collected centrally *(Oxford or Aberdeen)* and entered into the TOPKAT database.

Data management systems are based on a Microsoft SQL Server 2005 and are protected by both Oxford and Aberdeen University academic LAN network.

12. FINANCING AND INSURANCE

The TOPKAT study is funded by the UK NHS Health Technology Assessment Programme (Ref 08/14/08). The Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences at the University of Oxford will manage the finances and budget.

The University of Oxford sponsor the TOPKAT study. Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the University is legally liable as the Research Sponsor will be covered by the University of Oxford.

The University of Oxford have authority to audit the process of the TOPKAT study. Authorised University staff may review aspects of the trial, such as; the consenting process, data collection and storage. TOPKAT state that a period of 10 working days notice must be given before these reviews occur.

The NHS will owe a duty of care to those undergoing clinical treatment, with Trust Indemnity available through the NHS litigation Authority Scheme.

13. PUBLICATION

The success of the trial depends entirely on the wholehearted collaboration of a large number of health care workers. For this reason, chief credit for the trial will be given, not to the committees or central organisers, but to all those who have wholeheartedly collaborated in the trial. The trials' publication policy is described in Appendix F.

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the TOPKAT Project Management Group, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the TOPKAT collaborators. To safeguard the integrity of the main trial, reports of satellite studies will not be submitted for publication without prior agreement from the TOPKAT Project Management Group.

We plan to maintain interest in the study by publication of TOPKAT newsletters at three monthly intervals for collaborators and annually for participants. The newsletters will inform their audience of how the study and recruitment is progressing and any relevant interim results. TOPKAT have deemed it important to communicate with the collaborators so that common problems may be addressed and protocol adherence may be monitored.

Patients who participate in TOPKAT will also be offered a report detailing the study's findings. This will also be available on the study website.

14. ORGANISATION

(Milestones are shown on the Gantt Chart in Appendix D).

14.1 In Summary

A detailed plan and timetable of study organised is given in the Gantt chart (Appendix D). In summary, it is as follows;

April 2009 to Jan 2010: team assembly, office set up and remaining ethics approval.

January 2010 to December 2011: all sites designated active, 200 patients recruited in total and data monitoring initiated.

December 2011 to September 2013 : all patients recruited (n=500)

January 2015 to September 2018 : 5 year follow up data on all patients (n=500)

July 2018 to December 2018: Main analysis complete. Outcome and survival analysed. Paper prepared for publication.

14.2 Local organisation in centres

Their responsibility will be to:

- Establish the study locally (e.g.; help facilitate local research ethics committee approvals, liaise with the local R&D department and inform support services about the study)
- Initiate recruitment, screen potential patients and consent participants into the study
- Randomise the patients
- Conduct the follow-up clinical assessments
- Organise the internal referral for the expertise allocation group
- Or ensure the surgeons in the equipoise allocation are aware of the randomised treatment.
- Notify the study office Oxford of any unexpected clinical events which might be related to study participation
- Maintain communication with the study office in Oxford regarding allocated surgical treatment, operation dates, discharge instructions and surgery withdrawals or cancellations

14.3 Lead consultant surgeon

Each collaborating centre will identify a lead consultant surgeon who will assume responsibility for research staff and the patients involved at their centre.

14.4 Central organisation of the study

As successfully implemented in previous studies involving these grant holders, trial functions will be divided between the Oxford coordinating team and the Aberdeen data centre.

14.4.1 Study coordination in Oxford

The TOPKAT study team in Oxford is divided between the Nuffield Department of Orthopaedic, Rheumatology & Musculoskeletal Sciences (NDORMS) and the Department of Public Health and Primary Care (DPHPC). Both Departments are a part of the University of Oxford with NDORMS situated in the Nuffield Orthopaedic Centre NHS Trust.

NDORMS

The NDORMS team will be responsible for all clinical aspects of the study including: the recruitment and education of surgeons and their corresponding research team, recruitment of participants, the daily management and troubleshooting of clinical issues from staff and participants in the study.

DPHPC

The TOPKAT team in DPHPC are responsible for the design, conduct and analysis of the concurrent economic evaluation and outcome questionnaires.

14.4.2 Study coordination in Aberdeen

The Aberdeen team are based at the Centre for Health and Randomised Trials (CHaRT) within the Health Services Research Unit at the University of Aberdeen. They will be responsible for all data aspects of the trial including the design and set-up of trial databases, the randomisation system and the management of postal participant follow-up, and data management. ChaRT will also be responsible for the conduct of all trial analyses including supplying interim analyses to the Data Monitoring Committee and blinded data to the Trial Steering Committee (see14.6 and 14.7).

14.5 TOPKAT Management Group

The trial management group will oversee all aspects of the conduct and progress of the trial and ensure that the protocol is adhered to. They will meet at 6 monthly intervals to review the progress of the trial. The group consists of the grant holders, trial coordinator and representatives from both the study offices in Oxford and Aberdeen.

14.6 TOPKAT Steering Committee

The study is overseen by an independent Steering Committee. This committee will meet annually or more frequently if circumstances dictate. They will take responsibility for any major decisions, such as the need to close recruitment or more parts of the study or to change the protocol for any reason. Members of the TSC include:

- Professor Simon Donell (Chair) (Honorary Professor & Consultant Orthopaedic Surgeon, Norfolk and Norwich Hospital)

- Mr Jonathan Waite (Consultant Orthopaedic Surgeon, Warwick Hospital)
- Mr Shawn Tavares (Consultant Orthopaedic Surgeon, Royal Berkshire Hospital).
- Ms Donna Dodwell (Patient Representative)
- Professor Marion Campbell (Unit Director Health Services Research Unit, University of Aberdeen)
- Professor Ray Fitzpatrick (Professor of Public Health & Primary Care, University of Oxford)
- Dr Helen Campbell (Senior Research Officer, Health Economics Research Centre, University of Oxford)

14.7 TOPKAT Data Monitoring Committee

The Data Monitoring Committee is independent of the study organisers. During period of recruitment to the study, interim analyses will be supplied, in the strictest confidence, to the data monitoring committee, together with any other analyses that the committee may request. This may include analyses of data from other comparable trials. In light of these interim analyses, the Data Monitoring Committee will advise the Trial Steering Committee if, in its opinion, the trial has provided both:

a) Proof beyond reasonable doubt that for all or some types of participants one intervention is clearly indicated in terms of clinical and cost effectiveness

b) Evidence that might reasonably be expected to influence materially the care of the people with medial osteoarthritis by clinicians who know the results of this and comparable trials.

The Trial Steering Committee can then decide whether or not to modify intake to the trial. Unless this happens the Trial Steering Committee, Management Group, consultant surgeons and study office staff (except those who supplied the confidential analyses) will remain ignorant of the interim results.

The frequency of the interim analyses will depend on the judgement of the Chairman of the committee, in consultation with the Trial Steering Committee.

Members of the DMC include:

- Professor Gordon Murray (Professor of Medical Statistics, University of Edinburgh)
- Professor Hamish Simpson (Professor of Orthopaedics and Trauma, University of Edinburgh)
- Dr Karen Barker (Clinical Director for Musculoskeletal Services at Nuffield Orthopaedic Centre, Oxford)

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APPENDIX A: STUDY FLOW CHART

Total or Partial Knee Replacement (TOPKAT)

(based on Consort E-Flowchart)[1]