Study Title: A Randomised controlled trial of different knee prosthesis (KAT)

Internal Reference Number / Short title: KAT

Ethics Ref: MREC/98/0/100

IRAS Project ID: 80217

Date and Version No: 1st April 2016, Version 8

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Sponsor:	**University of Oxford**
Funder:	**National Institute for Health Research (NIHR) Health Technology Assessment Programme**
Chief Investigator Signature:	

David Murray has received consultancy fees and royalties from Zimmer Biomet. Helen Dakin has received a consultancy fee from Pfizer to undertake a systematic review in rheumatoid arthritis.

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SUMMARY

AIMS

This study addresses questions about four developments in knee replacement surgery:

- Is a metal backing plate for the tibial component of the total knee replacement better than a single high density polyethylene component?
- Is it better to resurface the patella as part of a knee replacement or not?
- Does a polyethylene moving component (bearing) between the tibia and femur have a better outcome than standard designs without a moving bearing?
- Is it better to replace a single component of the knee or to replace the whole knee joint?

The assessment of outcome for each of the comparisons is based on:

- Patient-assessed function and health status
- Reoperation rates
- The 'worth' of any additional cost to the NHS

BRIEF OUTLINE OF THE STUDY

Surgeon participants

Surgeons may opt to take part in any (or all) of the comparisons for which they have no clear preference for one of the options.

Patient eligibility

Any patient who requires a knee replacement, and who the surgeon feels would be eligible for the trial.

Information and randomisation

Individual patients will be entered into no more than two possible permutations of the study. Prior to admission to hospital, patients will be sent information about the study, inviting them to take part, and describing the possible options for their operation. If they agree to take part, they will be randomised around the time they are admitted to hospital for their operation. Randomisation will be carried out by the central Trial Office.

Data collection

During their hospital admission, standard information will be collected on the patient's operation and recovery, including short-term complications and data relating to their hospital stay.

Three months and annually after their operation, patients will be sent postal questionnaires asking about their general health, their knee function, and their use of the health service, including any re-admissions and revision surgery. Follow-up will continue for up to twenty

years after their operation, to ensure that the long-term performance of the knee operation is properly assessed.

Practical arrangements in clinical centres

The trial is designed to limit the extra work for collaborating surgeons to tasks which only they can do. They will take the lead in the study locally, but resources will be available to provide support. The clinical co-ordinating centres are in Oxford (Nuffield Orthopaedics Centre) and Dundee (Department of Orthopaedics and Trauma Surgery). Full-time co-ordinating nurses will be based in Dundee and Oxford to provide support for nurses in collaborating centres. The Trial Office within the Health Services Research Unit in Aberdeen will carry out telephone randomisation, patient postal follow-up, data management, processing and analysis.

Authorship

Publications generated from the study will be attributed to the KAT Trial Group, which will consist of all those who have wholeheartedly contributed to the trial.

FIGURE: SUMMARY OF PATIENT PROGRESS IN THE STUDY

Stages in the study	**Actions required by:**		
	Surgeon	**Study Nurse**	**Aberdeen Trial Office**
Patient deemed eligible ↓	Eligibility determined by surgeon		
Patient sent information ↓		Study nurse and Trial office liaise to send information to patient	
Patient agrees to take part, completes initial questionnaire ↓		Nurse consents patient, collects patient information	
Randomisation ↓		Nurse phones Trial Office	Randomisation by Trial Office
Operation and postoperative hospital stay ↓	Minimal operative details collected by surgeon.	Postoperative information collected by nurse	
Follow-up at 3 months ↓			Postal follow-up by Trial Office
Follow-up at 1 year ↓			Postal follow-up by Trial Office
Follow-up annually			Postal follow-up by Trial Office

CONTENTS

Appendices

This protocol describes a major UK-wide randomised trial to measure the clinical and cost effectiveness of different types of knee replacement. The trial is designed to be as simple as possible for participants and collaborating orthopaedic surgeons. Funds have been provided by the NHS R&D Health Technology Assessment Programme and include resources for both local co-ordination in trial centres and long-term follow-up.

1. OUTLINE OF THE TRIAL

The trial is evaluating four aspects of knee replacements:

A. Metal backing of the tibial component compared with a single high density polyethylene component.

B. Patellar resurfacing compared with no resurfacing.

C. A polyethylene mobile bearing component between the tibia and femur compared with a fixed bearing arthroplasty.

D. Uni-compartmental arthroplasty compared with total knee replacement.

Individual patients can participate in a maximum of two comparisons and then only if the surgeon responsible for care is substantially uncertain about these particular aspects.

2. SURGEON ELIGIBILITY

Any consultant orthopaedic surgeon may take part provided he or she:

a. undertakes knee replacements routinely.

b. is prepared to allow the choice between the specific options in at least one of the four comparisons to be decided by random allocation. (This recognises that surgeons will vary in the comparisons for which they will accept random allocation; during the trial collaborating surgeons will choose which (or all) of the four comparisons they will recruit to - see below.)

3. PATIENT ELIGIBILITY

A patient under the care of a collaborating surgeon will be eligible if:

a. a decision has been made to have primary knee replacement surgery.

b. the surgeon has no clear preference for a specific option in at least one of the comparisons. (A patient is therefore not eligible for a trial comparison if the surgeon considers that a particular type of operation is clearly indicated; an example is those patients requiring a highly constrained knee replacement to replace function of the collateral ligaments.)

It is recognised that eligibility will depend on patients' differing functional requirements which are influenced by their age. Although there will not be formal age differentiation in the trial as some people are chronologically older than their function and vice versa, the results of fixed bearing knees in terms of patient satisfaction and longevity of implant (Knutson, 1992) would strongly support the view that until better established the mobile bearing arthroplasty should be reserved for younger patients. It is amongst these patients that the undoubtedly higher technical demands of the operation which increase the risk can be matched by aspirations to increased benefit. It is therefore expected that surgeons will be more prepared to randomise younger patients to this comparison.

4. TRIAL RECRUITMENT

Potential participants will be sent information about the trial comparisons in which the surgeon responsible for care has agreed to participate. When a formal approach is made to the patient this will be to take part in one or two of comparisons, but not more than two. Exact arrangements for recruitment will depend on local admission procedures but will be based on the following:

Fully informing potential participants about the trial

Information about the trial will be given in two stages. A letter of invitation together with information about the parts of the trial in which the surgeon has agreed to participate will be sent to potential participants at home (Appendices 1 and 2). Information will also be sent to their general practitioners in case they are consulted (Appendix 3). More detailed information concentrating on the options for which the patient is eligible will be given to potential participants during discussion with a surgeon or research nurse at a pre-assessment clinic or when admitted before surgery.

Consent to participate in the trial

All eligible patients who agree to participate will sign a trial consent form (Appendix 4). On this, they will confirm that they have been given the information they require and that the study has been explained to them. They will also confirm that they understand that they will be sent a questionnaire from the Trial Office each year.

Formal trial entry and random allocation

Participants will be formally entered into the trial by telephoning an automated service within the Trials Office in Aberdeen. At this phone call, basic descriptive information is given first (hospital; surgeon; patient's name; sex and date of birth) followed by information on the American Knee Society Grade (unilateral, bilateral, generalised arthritis) and the comparison(s) (i.e. A, B, C, or D - see Sections 1 and 5) to which the participant will be recruited. Once these details have all been supplied, the random allocation will be given in return. The allocation will be stratified by the surgeon, with minimisation according to the patient's age, sex, American Knee Society Grade, and whether or not in another randomised comparison. After this phone call the participant is considered irrevocably in the trial for the purposes of the research, irrespective of what happens subsequently. Recruitment will be on the day before surgery (or sooner) to allow theatre staff to prepare appropriate equipment and prostheses. Patients in the fourth comparison (uni-compartmental compared with total) will not be eligible for any of the other comparisons. Each patient can only be entered into the trial once. In the event of a patient being admitted for bilateral knee replacements, the knee indicated by the patient to be the most painful is the knee that should be considered for randomisation.

5. THE FOUR COMPARISONS BEING MADE

The trial comparisons are outlined in Section 1.

In comparison A, the prosthesis used would be the same in every aspect of design other than the tibial component which would be metal backed or not depending on the trial allocation. This option is generally available amongst systems of knee replacement.

Comparison B is straightforward clinically in that surgeons can opt to replace the patella or not irrespective of the design of the prosthesis used.

In respect of comparison C, there may be more variation in the choice between fixed bearing and mobile bearing prostheses. Essentially, the surgeon will choose the metal backed cruciate retaining or substituting design that he or she uses routinely. This will be compared with a mobile bearing design, which preferably but not essentially should be similar in design and make to the surgeon's usual choice of fixed bearing prosthesis.

Comparison D is somewhat different to the other three comparisons. In this, surgeons will use their normal fixed bearing knee or their normal uni-compartmental knee.

6. CLINICAL MANAGEMENT IN THE TRIAL

The surgeon performing the operation will be expected to follow the trial allocation. However, if in the opinion of the surgeon, a clear indication arises for a different operative approach, this should be used and the reason specified.

All other factors will be kept similar if possible, and the surgeon will therefore usually use one manufacturer's range of total knee replacement (see section 5 above).

All other aspects of care, such as deep vein thrombosis prophylaxis, antibiotic prophylaxis, post-operative length of stay and post-operative rehabilitation, are left to the discretion of the surgeon responsible for care.

7. OUTCOME ASSESSMENT

Participation does not require any special tests or extra hospital visits (over and above standard care).

Most data describing outcomes will be collected directly from participants through postal questionnaires. The same questionnaire will be completed at three months and then annually (Appendix 5). It will include:

- the Oxford Knee Score (a twelve-item instrument measuring patients' perceptions of pain and function).
- the SF-12 (an abbreviated form of the SF-36, explaining more than 90% of the variance of the SF36).
- the EQ-5D (to derive quality-adjusted life years, QALYs).
- questions about any further hospital admissions and surgery.

Clinical data will be collected in a standardised way from casenotes to describe operative complications, and any further surgery, especially for revision.

Participants in England and Wales will be flagged at the Office for National Statistics for notification of death registration (and possible later tracing if contact has been lost during follow-up). Participants in Scotland will be followed up through the NHS Central Register (including notification of death registration)(for consent form and participant letters see appendix 4).

Follow-up is planned for twenty completed years.

8. FLEXIBILITY OF THE DESIGN TO SUIT ALL COLLABORATING SURGEONS

Individual patients can be recruited to either one or two of the comparisons. The study design is therefore a partial factorial randomised controlled trial.

Individual surgeons will choose to which of the comparisons they will recruit patients. It is unlikely that any surgeon will recruit to all four comparisons. The local trial will therefore be limited to those comparisons that a collaborating surgeon has decided to contribute to. The trial will be described to colleagues and potential participants in these terms.

A good example of the whole process may be: -

Mr Jones agrees to collaborate in the trial but only feels happy using total condylar knee replacements. He prefers cruciate substituting designs but is ambivalent about metal backing and is uncertain about patellar replacement. He therefore contracts to follow the trial allocation for metal or non-metal backing prosthesis plus or minus a patella i.e. two randomised comparisons. Information given to Mr Jones' patients will be related to these two comparisons only. Mr Jones will decide whether a particular patient is eligible for one, the other, or both these comparisons, and will then seek informed consent accordingly.

9. ARRANGEMENTS IN CLINICAL CENTRES

The role of collaborating surgeons

The trial is designed to limit the extra work for collaborating surgeons to tasks which only they can do. Study nurses will facilitate the trial locally (see below), and the central organisation will take responsibility for data management and patient follow-up.

Collaborating surgeons will:

a. establish the trial locally (for example by getting agreement from clinical colleagues, facilitating local research ethics committee approval, identifying and appointing a local study nurse, liaising with the local R&D manager, and ensuring that all clinical staff involved in the care of patients having knee replacement surgery are informed about the trial).
b. take responsibility for clinical aspects of the trial locally.
c. notify the Trial Office of any unexpected clinical event which might be related to trial participation.
d. provide support and supervision for all aspects of the work of the local study nurse.
e. represent the centre at KAT collaborators meetings.

The role of study nurses

Each clinical centre will have a part-time study nurse, physiotherapist or other equivalent form of staff, whose number of sessions of employment will depend on the number of patients being recruited in a centre. Their responsibilities will be to:

a. keep local staff informed about the trial and its progress.
b. keep regular contact with the local surgeon(s).
c. maintain regular contact with one of the co-ordinating nurses (see below).
d. identify all those having knee replacement surgery in advance of their admission, and keep a log of whether or not they were recruited to the trial (with reasons for non-participation).
e. arrange for the initial letter of invitation and information leaflet to be sent to potential participants and to their GPs.
f. assist the surgeon (for example at a pre-assessment clinic) to give additional information and seek consent to trial entry.
g. ensure that arrangements are in place for formal trial entry and random allocation, once a participant is admitted for surgery.
h. arrange for the GP to be informed about recruitment.
i. ensure that the initial data form describing the index hospital admission is completed promptly and sent to the Trial Office.
j. collect data describing complications and subsequent admissions to hospital.
k. facilitate later follow-up, by for example helping with local tracing.
l. assist in the conduct of satellite studies, if applicable.
m. provide support for participants in other ways if there are difficulties.
n. represent the centre at study nurse meetings.

10. CLINICAL CO-ORDINATION

The clinical co-ordinating centres are in Dundee (Department of Orthopaedics and Trauma Surgery) and Oxford (Nuffield Orthopaedics Centre). At the start of the trial, representatives from these centres will visit all surgeons expressing an interest in collaborating, aiming to get a commitment from collaborating surgeons to recruit to specified comparisons.

Full-time co-ordinating nurses will be based in Dundee and Oxford. They will:

a. support the study nurses in collaborating centres.

b. at the start, help to appoint and train study nurses.
c. act as a first point of enquiry about any clinical aspect of the trial.
d. help the Trial Office to ensure complete data collection (through study nurses) during the initial hospital stay, and following any later hospital admission.
e. act as an intermediary between the Trial Office in Aberdeen and study nurses, and have weekly contact with the Trial Office.
f. help the Trial Office in connection with any difficulties with later patient follow-up.
g. act as local study nurses in Dundee and Oxford.

11. DATA CO-ORDINATION

Telephone randomisation and data collection, processing and analysis will be the responsibility of the Trial Office within the Health Services Research Unit in Aberdeen. Staff there will:

a. facilitate the sending of information to patients and GPs from study nurses.
b. provide an automated telephone randomisation service for formal trial entry.
c. monitor collection of in-hospital data and process them, and seek missing or uncertain data.
d. post our personalised follow-up forms to all participants (at three months and then annually), maximising response by reminders and phone calls, and process returned forms.
e. ensure the confidentiality and security of all trial forms and data.
f. conduct extensive data checking and cleaning.
g. perform interim and main analyses.

12. STATISTICAL AND ECONOMIC CONSIDERATIONS

Sample sizes sought in the four randomised comparisons

The sample sizes sought for the four comparisons have been based on a number of considerations. They have drawn on the relationship between changes in the OKS and other well known outcome instruments, and what previous research has suggested is plausible. They have also taken account of clinical issues, such as the size of differences that seem likely judged on current experience, the possibility of adverse effects, and cost differences.

The table describes the statistical power to detect differences of 1.5, 3.0 and 4.5 in the mean OKS for three sample sizes (700, 350, and 175 in each group), firstly with an alpha error of

2P<0.01 and secondly for an alpha error of 2P<0.05. These calculations assume a standard deviation for the OKS of 10 points.

Table 3 Statistical power to identify differences of 1.5, 3.0 and 4.5 in mean OKS for three sample sizes, at two levels of statistical significance.

Mean difference in OKS		1.5		3.0		4.5	
		2P<0.01	2P<0.05	2P<0.01	2P<0.05	2P<0.01	2P<0.05
Number in	700	60	80	>99	>99	>99	>99
each randomised	350	<50	50	91	97	99	>99
group	175	<50	<50	60	80	94	98

Although the OKS is the principal outcome, possible differential effects on revision rates have also been considered where appropriate. Although these are presented here as simple rate differences, these analyses will in fact be able to identify smaller differences with the same statistical power as that indicated. There are two reasons. First, these analyses will be based on the time to revision using prosthesis 'survival curves' rather than a simple dichotomous variable. Second, survival curves will also be generated for a composite outcome which includes patients whose knee prostheses are judged (by falling below a predefined threshold on the Oxford score) to have failed, in addition to those who actually had revision (thus increasing the number of 'events', and hence statistical power).

(i) Metal backing of tibial component

The concern in this comparison is that loosening of non-metal backed tibial components may lead to severe symptoms in the long-term. The aim therefore is for a sample size which is large enough to identify a difference equivalent to a typical category change in the American Knee Society Score (that is, a difference of about 3.0 in the OKS). This will require a minimum of 175 per group to have reasonable power (80%) with an alpha error of 2P<0.05 (see Table). A comparison with 235 in each group, for example, would have 90% power to identify this difference.

(ii) Patellar resurfacing

Based on preliminary results of follow-up of a small randomised trial - currently unpublished - comparing patellar resurfacing with no resurfacing, the effect of resurfacing, if it exists, is likely to be relatively small and near a difference in the mean OKS of 1.5. The

table shows that a trial with 700 in each group would have 80% power to identify this difference (2P<0.05) A trial of this size (about 1500 people) would also have reasonable power to identify differences in revision rates over prolonged follow-up - more than 90% power to detect a halving from 10% to 5%, for example.

(iii) Uni-compartmental arthroplasty

A non-randomised comparison of two cohorts characterised by management with either a uni-compartmental prosthesis or total knee replacement showed a difference in the mean OKS scores of 3.4, whereas follow-up of similar but smaller randomised cohorts suggested a smaller difference of 1.6, albeit with a wide confidence interval. The aim is therefore for a trial with at least 175 participants in each group, so that there is a good chance of identifying a difference in the mean OKS of 3.0. There may be higher revision rates after uni-compartmental arthroplasty. A trial of this size would have 90% power to identify an increase from 5% to 15% in this respect.

(iv) Mobile versus fixed bearing arthroplasty

The substantially greater costs of mobile bearing prostheses can only be justified if there are clear benefits. The aim is to identify benefits equivalent to an increase in the OKS of 3.0 or greater. A trial with 350 in each group (see Table) has over 90% power to identify this at the 1% level of significance and 97% power to show a significant difference at the 5% level. There are concerns about possible short-term failures, such as dislocation or related mechanical problems, associated with the mobile bearing arthroplasty. If 1% such complications are expected in the fixed bearing group, a trial with 350 in each group has about 90% power to identify an increase to 5%.

Other details of the analysis plan

All analyses will be based on 'intention to treat' and no participant with data will be excluded. The principal comparisons will be between:

a. all those allocated a metal backed tibial component compared with all those allocated a single component.
b. all those allocated patellar resurfacing compared with all those allocated no resurfacing.
c. all those allocated mobile bearing compared with all those allocated fixed bearing.

d. all those allocated uni-compartmental arthroplasty compared with all those allocated total knee replacement.

These main analyses will measure the 'main effects' of the alternative approaches. The partial factorial design will, however, provide an opportunity to assess whether there is any interaction between patellar resurfacing and the other comparisons (that is, whether a combination has any greater or lesser effect than would be expected from the main effects).

Differences between the groups in revision rates might bias comparisons of the Oxford scores. For this reason these analyses will be run in two ways: firstly on the actual scores at a particular time, irrespective of further surgery (aiming to compare the clinical policies actually used, including repeat surgery); and second, after imputing a score for those who had revision surgery (aiming to compare the initial surgery used in the trial). Although patient survival will be a measure of outcome and described in trial reports, most analyses will be based on the assumption that the alternative prostheses do not have differential effects on mortality. Analyses of the Oxford score will principally be based on survivors but possible effects of excluding those who died will be explored using imputed scores based on the data available. In respect of the revision analyses, participants will be assumed to be at risk only when alive, using a multi-decrement life table approach. It is difficult to predict the proportion of participants who will die or be lost to follow-up, but allowance has been made by aiming to recruit at least 1500, 750 and 400 as applicable.

Additional analyses, stratified by surgeon, will explore any effects of make of prosthesis, surgical experience ('the learning curve') and rehabilitation policy.

Timing and frequency of analyses and reporting

Three principal analyses are planned - at six years, twelve years and then at twenty completed years.

By six years, participants will have had a median of four years follow-up (assuming it takes six months to initiate the trial, two years to recruit all patients, and six months to complete and report analyses). By this stage, data on early complications, which are likely to be mainly medical, will be available. There will be some early failures, for example due to

infection. Outright device failure will be uncommon, but differences in functional scoring could be apparent.

By twelve years, follow-up will have been for a median of ten years. A substantially larger number of device failures and subsequent revisions will have occurred by then.

Twenty completed years of follow-up will provide long term data on the clinical and cost-effectiveness of the various design options, on which strong recommendations for knee replacement practice can be based.

Confidential interim analyses will be performed at other times as requested by the Data Monitoring Committee, which is expected to meet at least annually (see below).

Economic evaluation

The type of economic analysis performed for each comparison will depend on the findings. If there are no differences in outcome for a particular comparison, cost minimisation analysis will be used. If differences emerge, cost-effectiveness analyses from a societal perspective will be performed. The primary measure of effectiveness will be pain and function as assessed by the Oxford Knee Score. Information on utilities will also be available for analysis because trial patients will also complete EQ-5D for which population-weighted values are available.

Costs of alternative forms of knee-replacement surgery may be considered as either short term or long term. In the short term, differences in costs of alternatives will arise from differences in surgical procedure, technology, forms of care during hospital stay, length of hospital stay and short-term complications (wound infection, deep vein thrombosis, pulmonary embolism). In the long term, major differences in costs of the surgical alternatives will arise in relation to differences in longer term outcomes, particularly recurrence of pain and physical dysfunction requiring further primary, community and hospital care, and, in some cases, need to revise surgery.

Three data gathering components will be used to address these major sources of variation in costs (i) early (ii) medium to long term and (iii) modelling.

(i) Early data collection

Cost generating events in the short term will be recorded by means of a patient-specific checklist administered by research nurses at the participating hospitals, using theatre records and hospital notes. This will cover time in theatre and on ward, surgical procedure(s), diagnostic and investigative procedures and tests, and duration and intensity of rehabilitation.

(ii) Medium to long-term data collection

Following initial hospitalisation, information on health care resources used will be recorded using questions integrated into the main follow-up questionnaire administered to all patients annually. This will estimate annual numbers of knee-related primary care consultations, out-patient visits, and use of other health care services. Full information on all subsequent in-patient admissions for investigative procedures or revision surgery will be recorded using the research nurse system described elsewhere in this protocol.

(iii) Modelling

Primary economic analysis will use the resource volumes and rates of revision surgery recorded during the follow-up period. However, in order to extend the economic analysis beyond the follow-up period, some modelling will be performed, using trial data on observed revision rates, resource use and risk factors to set parameter values. Uncertainty surrounding the model results will be formally reported.

Unit costs for all cost generating resource events recorded above will be obtained from participating centres and from national data sets.

13. TRIAL COMMITTEES

The Steering Committee

The trial was overseen by a Steering Committee made up of the principal grant holders, David Murray (Oxford), Ray Fitzpatrick (Oxford) and Adrian Grant (Aberdeen), together with Richard Morris (London), Alasdair Gray (Oxford), Nick Fiddian (Bournemouth), Rami Abboud (Dundee), Marion Campbell (Aberdeen) and a representative from each participating centre. Meetings were chaired by David Murray. The Steering Committee took responsibility for any major decisions, such as the need to close recruitment early to one or more parts of the study or to change the protocol for any reason. The Steering Committee met until the end of recruitment.

The Project Management Group

The trial is co-ordinated by its Project Management Group. This consists of the principal grant holders, David Murray (Oxford), Ray Fitzpatrick (Oxford) and Adrian Grant (Aberdeen, until February 2013), together with Richard Morris (London) Alasdair Gray (Oxford), Nick Fiddian (Bournemouth, until May 2013), Rami Abboud (Dundee), Marion Campbell (Aberdeen) and those employed to work on the trial in the co-ordinating centres. Observers may be invited to attend at the discretion of the Project Management Group. This group will meet at four monthly intervals initially with the meetings being chaired by David Murray. During the extended follow-up phase the Group will meet annually.

The Data Monitoring Committee

A data monitoring committee were established, independent of the trial organisers. The committee consisted of three members (one of whom acted as chairman): an orthopaedic surgeon who is not involved in the trial; a clinician with experience of trials; and a statistician with experience of monitoring accumulating trial data.

During the period of recruitment to the trial, interim analyses were supplied, in strict confidence, to the data monitoring committee, together with any other analyses that the committee requested. This could include analyses of data from other comparable trials. In the light of these interim analyses, the data monitoring committee would advise the Steering Committee if, in its view, one or more of the randomised comparisons in the trial had provided both (a) proof beyond reasonable doubt that for all or some types of patients one particular type of prosthesis was clearly indicated or contraindicated[1], and (b) evidence that might reasonably be expected to influence materially the care of people who require knee replacement by clinicians who knew the results of this and comparable trials. The Steering Committee could then decide whether or not to modify intake to the trial or to report results early. The steering committee, project management group, clinical collaborators, and trial staff (except those who supply the confidential analyses) remained ignorant of the interim results considered by the committee.

Note:

[1] Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least three standard deviations in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criteria were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed (Peto R et al *Br J Cancer* 1976; **34:** 584-612).

The frequency of interim analyses depended on the judgement of the chairman of the committee, in consultation with the Steering Committee. The Data Monitoring Committee met for the last time in March 2005

14. FINANCE

The trial is supported by a grant from the Health Technology Assessment Programme of the NHS Executive Research and Development Programme with supplementary funding from the major manufacturers of knee prostheses in the UK.

The extended follow-up study is funded solely by a grant from the National Institute of Health Research (NIHR) Health Technology Assessment Programme.

15. SATELLITE STUDIES

The funds provided by the NHS R&D HTA Programme are to conduct the main trial as described in this protocol. Nevertheless, it is recognised that the value of the KAT trial will be enhanced by smaller ancillary studies of specific aspects. Plans for such studies should, however, be discussed and agreed in advance with the Project Management Group.

16. PUBLICATION

The success of the trial depends entirely on the wholehearted collaboration of a large number of doctors and nurses. 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 trial's publication policy is described in detail in Appendix 7. The results of the trial will be reported first to trial collaborators. The main report will be drafted by the Trial Management Group, and the final version will be agreed by the Steering Committee before submission for publication, on behalf of the Collaboration.

To safeguard the integrity of the main trial, reports of any satellite studies will not be submitted for publication without prior discussion with the Project Management Group.

Once the main report has been published, a lay summary will be sent to participants who have indicated they would like to receive one.

17 ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

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

Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

Approvals

The protocol, informed consent form and participant information sheet has previously been submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

For the extended follow-up study, the Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

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. For the extended follow-up study, annual progress reports to REC are not required. An End of Study notification and final report will also be submitted to the same parties.

Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. 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.

18 INSURANCE

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

19 ARCHIVING

The sponsor is responsible for ensuring that trial data is archived appropriately. Essential data shall be retained for a period of at least five years following close of study and will be stored within the University of Aberdeen's archiving facility.

20 AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	Version 4	Approved 26/10/2001	Prof David Rowley Prof David Murray Prof Adrian Grant	Minor changes to clarify specific aspects of the trial. For example: • Only patients having primary knee replacement surgery are eligible • Clarified the choice of knee for those having a bilateral operation • Marion Campbell replaces Sue Ross on the PMG and Steering Committee • Clarified that

				study nurses in some centres were supported by knee prostheses manufacturers Changes to the appendices include: Appendix 1 The initial letter sent to patients is signed by the study nurse on behalf of the Consultant Appendix 2 Patient Information Leaflet developed into illustrated leaflets with separate leaflets for each comparisons Appendix 3 Inclusion of GP letter informing them that their patient is taking part in the study Appendix 5 Inclusion of participant letters to accompany the postal questionnaires

				Appendix 6 Inclusion of the In Hospital Care CRFs Appendix 8 Inclusion of Dummy Tables
2	Version 5	Approved 11/05/2006	Prof David Rowley Prof David Murray Prof Adrian Grant	Appendix 4 Inclusion of an additional Consent Form to reconsent Scottish participants for death notification flagging
3	Version 6	Approved 6/04/2009	Prof David Murray Prof Adrian Grant	• Prof David Murray replaced Prof David Rowley as the KAT Chief Investigator • Nick Fiddian (Bournemouth) and Rami Abboud (Dundee) joined the Steering Committee and the PMG
4	Version 7	Approved 3/05/2011	Prof David Murray Prof Adrian Grant	Extended follow-up of the KAT participants to 15 completed years
5	Version 8		Prof David Murray	1. Change of sponsorship from

				the NIHR HTA to University of Oxford 2. Extended follow-up of the KAT participants to 20 completed years 3. Request to waive the submission of annual progress reports to REC