Study Title: **CO**mmunity based **R**ehabilitation after **K**nee **A**rthroplasty (CORKA). A Prospective two arm individually randomised controlled trial.

Short Title: CORKA Study

HTA Ref: 12/196/08

ISRCTN 13517704

Ethics Ref: 15/SC/0019

Date and Version No: V6.0_03Oct2017

Chief Investigator: **Dr Karen Barker**, Clinical Director and Head of Physiotherapy, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust.
Telephone: 01865 738080 Email: karen.barker@ouh.nhs.uk

Investigators:
Professor David Beard, Professor of Musculoskeletal Sciences[1]
Dr Gary Collins, Senior Medical Statistician[1]
Professor Avril Drummond, Professor of Healthcare Research[2]
Professor Sallie Lamb, Kadoorie Professor of Trauma Rehabilitation[1]
Professor Andrew Price, Professor of Orthopaedic Surgery[1]
Dr Helen Campbell, Senior Health Economist[1]
Dr Francine Toye, Qualitative Research Lead [3]
Professor Martin Underwood, Professor of Primary Care Research[4]
Dr Ly-Mee Yu , Senior Trials Statistician[1]

1 University of Oxford 2 University of Nottingham 3 Oxford University Hospitals NHS Trust 4 University of Warwick

Sponsor: University of Oxford

Funder: NIHR Health Technology Assessment Programme

Chief Investigator Signature:

Dr Karen Barker

Date: 03Aug2015

There is no conflict of interest to declare.

TABLE OF CONTENTS

1. ABBREVIATIONS 7
2. BACKGROUND AND RATIONALE 8
2.1. Introduction 8
2.2. Current Practice 11
3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS 11
3.1. Development Phase 11
3.2. Main Study Phase 12
4. STUDY DESIGN 14
4.1. RCT Study 14
4.2. Qualitative study 14
4.3. Economic analysis 15
5. PARTICIPANT IDENTIFICATION 15
5.1 Study Participants 15
5.1.1 RCT Trial 15
5.2 Inclusion Criteria 15
5.3 Exclusion Criteria 15
6. STUDY PROCEDURES 16
6.1 Site Recruitment 16
6.2 Participant Recruitment 16
6.3 Informed Consent 16
6.4 Confirmation of Eligibility and Randomisation 17
6.5 Randomisation, blinding and code-breaking 18
6.6 Baseline Assessments - Pre Surgery 18
6.7 Subsequent Visits 20
6.8 Qualitative interviews 21
6.9 Health economics 22
6.10 Discontinuation/Withdrawal of Participants from Study 23
6.11 Reporting a death 23
6.12 Discontinuation/Withdrawal of a site 24
6.13 Definition of End of Study 24
7 INTERVENTIONS 24
7.1 Rehabilitation Programme 24

7.2 Usual Care 25
7.3 Staff training: rehabilitation programme 26
8 SAFETY REPORTING 27
8.1 Definitions 27
8.1.1 Serious Adverse Events 27
8.1.2 Foreseeable Adverse Events 27
8.1.3 Other Foreseeable Adverse Events 28
8.2 Reporting Procedures for Serious Adverse Events 28
9 STATISTICS AND ANALYSIS 29
9.1 Proposed sample size 29
9.2 Data Analysis 29
10 DATA MANAGEMENT 30
10.1 Access to Data 30
10.2 Data Recording and Record Keeping 30
11 QUALITY ASSURANCE PROCEDURES 31
12 ORGANISATION 31
12.1 Project timetable and milestones 31
12.2 Trial Committees 31
12.2.1 Trial Steering Committee (TSC) 31
12.2.2 Trial Management Group (TMG) 31
12.2.3 Data Monitoring and Safety Committee (DMSC) 32
12.3 Local Co-ordination 32
13 ETHICAL AND REGULATORY CONSIDERATIONS 33
13.1 Declaration of Helsinki 33
13.2 Guidelines for Good Clinical Practice 33
13.3 Research Governance 33
13.4 Approvals 33
13.4.1 Ethics approval 33
13.4.2 Local approvals 34
13.5 Reporting 34
13.6 Participant Confidentiality 34
13.7 Expenses and Benefits 35
13.8 Project Funding 35
13.9 Participating sites funding 35

13.10 Insurance 35
14 PUBLICATION POLICY 36
15 REFERENCES 37
APPENDIX A: STUDY FLOW CHART 42
APPENDIX B: SCHEDULE OF STUDY PROCEDURES 43
APPENDIX C: PROJECT MILESTONES AND TIMESCALE 44
APPENDIX D: CORKA SUB STUDY 45
APPENDIX E: AMENDMENTS 47

SYNOPSIS

PRE-RCT DEVELOPMENT		
Screening Algorithm	• Identify factors associated with poor outcome after knee replacement • Develop screening algorithm to identify those at high risk of poor outcome following knee replacement	• Carry out literature review • Gather expert opinion • Examine KAT study data
Rehabilitation intervention	• Develop a targeted rehabilitation programme suitable for delivery in participants own home	• Carry out literature review • Identify likely programme elements. • Review with clinicians and expert workshops • Expert patient review

MAIN STUDY - RCT		
Study Title	**CO**mmunity based **R**ehabilitation after **K**nee **A**rthroplasty (CORKA)	
Short title	CORKA Study	
Study Design	A pragmatic prospective individually randomised single blinded two arm randomised controlled trial	
Study Participants	Patients undergoing knee replacement (KR) assessed at risk of poor outcome	
Study Treatments	Participants will be randomized to receive either: 'Community-based rehabilitation' or 'Usual Care'	
Planned Sample Size	620 participants	
Planned Study Period	Project 65 months	
	Objectives	**Endpoints**
Primary	To determine if a multi-component rehabilitation programme improves the outcome of patients who undergo a KR.	At 12 months post-surgery: • Late Life Function and Disability Instrument (LLFDI) score.
Secondary	To assess the impact of a multi-component rehabilitation programme on physical function and quality of life and cost effectiveness analysis versus usual care rehabilitation.	At 6 and 24 months post-surgery: • LLFDI At 6, 12 and 24 months post-surgery:

		• Measurement of disease specific function by the Oxford Knee Score • Measurement of quality of life by the subscale of the Knee Osteoarthritis Outcome Score (KOOS) • Measurement of physical activity by the Physical Activity Scale for the Elderly (PASE) questionnaire • Measurement of physical function by the physical performance tasks – 30 sec chair stand test, figure of 8 walking test, single leg stance test • Measurement of pain using the visual analogue score (VAS) • Measurement of health economics using the EQ5D-5L and a patient diary • Cost utility analysis from both the NHS and a societal perspective.

STUDIES EMBEDDED IN THE RCT		
Qualitative study: **Experiences and views of participants** (Selected sites/selected participants only)	• Explore experiences and views of participants about their treatment interventions	• Participant interviews using phenomenological analysis approach
Study Participants	• Approx. 15 participants and 15 staff members will be interviewed to share their experiences.	

CORKA is defined as a Clinical Research Study.

1. ABBREVIATIONS

AE	Adverse Event
CCTR	Critical Care, Trauma and Rehabilitation Trials Group (part of OCTRU)
CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ISF	Investigator Site File
KR	Knee Replacement
NHS	National Health Service
NRES	National Research Ethics Service
OCTRU	Oxford Clinical Trials Research Unit
PI	Principal Investigator
PIL	Patient Information Leaflet
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
KAT	Knee Arthroplasty Trial
QALY	Quality Adjusted Life Years

2. BACKGROUND AND RATIONALE

2.1. Introduction

The existing literature demonstrates that predicting who will do well after knee replacement is a complex construct and not a simplistic linear relationship between factors such as age or pre-surgical function. A number of studies have investigated the influence of preoperative predictors on postoperative outcome of knee replacement. However, no screening algorithm that can accurately identify and predict who is at a risk of poor postoperative outcome associated with rehabilitation is currently in existence. Generally, patients who have a higher level of pre-operative status (i.e. better preoperatively) tend to have a better postoperative outcome [Jones 2003, Fortin 1999, Hawker 2013, Judge 1012]. The influence of co-morbidities on postoperative outcome is inconclusive, with a number of studies demonstrating the association of co-morbidities with the worse postoperative outcome [Hawker 2013, Clement 2013, Jones 2001] and others not observing such an association [Fortin 1999, Fitzgerald 2004]. This could be due to the differences in the classification of co-morbidities as well as the definition of poor outcome used in these studies. Further research is required to examine the influence of specific co-morbidities on the outcome of KR in more detail.

Osteoarthritis is the commonest cause of disability in older people [Martin 1988] with painful knee osteoarthritis affecting 10% of people over 55 in the UK [Peat 2001]. The number of knee replacements taking place in the UK is continuing to rise; over 84,000 knee replacements took place in the UK during 2011 which is an increase of over 3% from 2010. Age should not be a barrier to having a good outcome from knee replacement, with reports of successful outcome in patients aged over 80 years [Clement 2011].

Furthermore, it is known that outcome following knee replacement is multi-faceted; around 15% of patients do not report a good outcome from their knee replacement and have continuing pain and mobility problems which limit or prevent them from being able to do the activities they would like to be able to do after their surgery [Jones 2007]. It is thought that factors such as the amount of pain and limitation of balance and muscle strength may contribute to poorer outcome [Westby 2008] and it is believed that the development of effective rehabilitation interventions may contribute to optimising post-operative return to functional activities.

Rehabilitation Approaches

In 2007 a systematic review evaluating the effectiveness of exercise supported the use of functional physiotherapy exercise interventions following discharge to obtain short term benefit following elective primary KA [Minns Lowe 2007]. A 0.33 (0.08 to 0.58) small to moderate standardised effect size , in favour of functional exercise, was seen for function at 3-4 months post operatively. Small to moderate weighted mean differences of 2.91 (0.65 to 5.17) for range of joint motion and 1.66 (-0.97 to 4.29) for quality of life were seen, in favour of functional exercise, at 3-4 months post operatively. Post-treatment benefits faded and were not carried through to 1 year. The review revealed the complexity involved in deciding the best rehabilitation after knee replacement. Notably there are also a growing number of studies that have chosen to apply an intervention at a later point in the rehabilitation pathway (often between 6 weeks to 6 months). Delayed intervention avoids the period of early pain, effusion and early limitations in motion associated with the early postoperative stage [Piva 2010, Moffett 2004]. The lack of knowledge regarding current physiotherapy practice has been recognised internationally [Naylor 2006]. An Australian survey of physiotherapy practice [Naylor 2006] and an observation cohort study of USA rehabilitation services [DeJong 2009] have recently been published and have begun to address this knowledge gap. However, there are no published randomised controlled trials of occupational therapy after knee replacement and other published studies have serious methodological limitations, or it is difficult to extrapolate the contribution of occupational therapy from the overall rehabilitation package. From anecdotal sources the current amount of physiotherapy in the UK appears to range from no routinely organised physiotherapy following discharge to interventions of up to 12 sessions of outpatient physiotherapy. Typically, primary care trusts seem willing to fund an average of 4-6 sessions. Concern has been raised that many exercise programmes lack adequate intensity to lead to optimal recovery [Westby 2008]. Internationally, where much greater doses of physiotherapy are often provided, research indicates that 12-18 hours of physiotherapy [Moffett 2004] or a mean of 17 visits [Petterson 2009] may be needed to produce benefit. These levels of care may be well beyond those provided in the UK and, in the current economic climate, may be more than the NHS can afford given the numbers of KAs undertaken each year. Supervised progressive self-management programmes would seem to be a possible way to increase the intensity of rehabilitation within current available resources.

Currently it is normal practice for patients to receive a short course (between 4 -6 sessions) of post-operative physiotherapy after their surgery. This is usually delivered in a physiotherapy out-patient clinic setting. Previous research has shown that this short course of physiotherapy is not needed by all patients to help them recover after their operation [Rajan 2004]. Given the increasing number of knee replacements, the relative limited physiotherapy resource available and the increasing age and frailty of

patients receiving joint replacements, it is important that we concentrate our rehabilitation resources on those patients who need most help to avoid a poor outcome.

In this trial we are testing a pragmatic intervention. The optimal approach from the evidence to date includes a structured rehabilitation programme that incorporates muscle strengthening exercises, including resistive muscle strengthening exercises which are regularly progressed, exercises to improve balance and exercises which facilitate improvement or maintenance of daily activities such as housework, personal care activities of daily living plus endurance exercises to improve baseline levels of physical activity, as overall health permits. It is imperative that exercise and functional rehabilitation is linked to demonstrable increases in activity output and participation levels.

Many of the trial participants would also benefit from environmental modifications, aids and appliances where impairments cannot be overcome or as part of the therapeutic programme to increase their functional performance. Our approach is to include exercises which address more than one aim, which are carried out as patient's performance allows and which are progressed. Patient specific goals regarding physical and functional activity will also be included and progressed.

Cognisant of the need to develop an intervention that can translate into normal clinical practice within the funding envelope of the Clinical Commissioning Groups, we will develop an intervention that is staffed by both qualified physiotherapists and rehabilitation assistants. Assistants are routinely used in the rehabilitation of patients following orthopaedic surgery. We will test the safety and efficacy of this model of delivery.

This pragmatic study will therefore assess in those scheduled for KR and prospectively identified as individuals who based on the CORKA study tool are expected to have a poor outcome, if a multi-component rehabilitation programme delivered in patient homes can improve their outcome compared to those receiving the standard out-patient physiotherapy course.

The study will design a prognostic screening algorithm which will be developed based on an analysis of factors associated with poor outcome. The analysis will be undertaken on an existing NHS patient dataset from a pre-operative assessment clinic which has data on patients and data from the KAT study which contains pre-operative, 3 month, 1 year and 2 year outcome data on patients after knee replacement. The screening tool will then be used to identify individuals for the CORKA RCT and to assess the inclusion threshold for those patients likely to benefit from a multi-component rehabilitation programme. The randomised controlled trial will compare the community based rehabilitation programme against usual care. In addition to a qualitative analysis exploring the thoughts of both patients and clinicians on the use

of the community based rehabilitation programme. Finally an economic analysis will take place. This will compare the cost-effectiveness of the intervention and usual care.

2.2. Current Practice

All patients who have a KR receive some post-operative physiotherapy. The amount of physiotherapy given is dependent upon the patient's response to the operation, their existing co-morbidities and local practices. This study will not change current practice as all those who undergo a KR will start the standard hospital specific physiotherapy programme immediately after their operation. Those who have consented and been enrolled in the trial will be randomised to either a community-based exercise intervention or standard rehabilitation at hospital discharge. Standard rehabilitation is currently written advice and a home exercise programme on discharge from hospital and up to 6 sessions of traditional out-patient physiotherapy.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1. Development Phase

The objectives for the development phase are to design a screening tool to identify patients at risk of poor outcome and to develop a bespoke rehabilitation intervention to be used in the main trial.

We will analyse data from existing NHS datasets and also data from the KAT study to develop an algorithm to be used at pre-operative assessment to identify patients likely to be at risk of poor outcome after knee replacement.

We will also develop a rehabilitation intervention that can be delivered in patients' own homes by rehabilitation assistants supervised by qualified therapists.

We will conduct an internal pilot by using the intervention in one site to review for feasibility. During this internal pilot phase we will recruit patients until we have a minimum of 5 in each arm. This evaluation of the first 5 patients in each arm of the trial will evaluate:

1. The clarity of the trial materials and information provided to participants and therapists e.g.; exercise instructions, home diaries, and treatment manuals.

2. Whether the outcome measure package is feasible and acceptable to patients and assessors e.g.; are measurement procedures practical, are measures relevant to patients.

3. The acceptability of the interventions to participants.

4. The practicality of delivering the interventions for therapists e.g.; any issues around session timing and progression in treatment.

5. To provide information on the number of participants eligible and willing to be randomised.

From the internal pilot we will invite up to six participants to take part in interviews where they will be asked for feedback about their participation. We will also interview therapists undertaking the interventions to provide feedback.

On completion of the treatment of those patients in the internal pilot we will assess if any modifications are needed.

Develop a screening algorithm for use in the main RCT • Central study team to develop	• Identify factors associated with poor outcome after knee replacement • Develop screening algorithm to identify those at risk of poor outcome following knee replacement • Carry out literature review • Gather expert opinion • Examine KAT study data
Develop a targeted rehabilitation programme for use in the main RCT • Central study team to develop	• Develop a targeted rehabilitation programme suitable for delivery in participants own home • Using literature review, consensus/ expert peer review

3.2. Main Study Phase

In this phase of the study we will compare the clinical outcomes of this new rehabilitation protocol vs. usual care of out-patient based post-operative physiotherapy.

We will assess the safety associated with both the treatment programmes by collecting adverse events.

We will assess the acceptability and adherence to the treatment programmes for patients and therapists using a RCT with a nested qualitative study.

We will assess the cost effectiveness of the different treatment strategies. We will use a number of established outcome measures to assess whether this new intervention improves patient's functional abilities, quality of life and their taking part in social activities. Additionally, we will use information from diaries kept by all patients about their visits to their GP, district nurse, physiotherapy, occupational

therapy, any hospital visits and medication and equipment throughout the trial to perform an economic analysis about the costs and benefits of the new intervention compared to usual care.

Objectives	**Outcome Measures/Endpoints**
Primary Objective To compare the patient reported functional outcome of this new rehabilitation protocol versus usual care of out-patient based post-operative physiotherapy.	**Primary outcome**: Late Life Function and Disability Instrument (LLFDI) score; a validated questionnaire previously used in rehabilitation trials of community dwelling elders. Primary endpoint:12 months post-surgery
Secondary Objectives • To assess the impact of a multi-component rehabilitation programme on physical function and quality of life and cost effectiveness versus usual care rehabilitation • To assess the safety associated with both the treatment programmes by collecting adverse events	**Secondary outcomes:** 1. LLFDI also used at baseline and 6 months post-surgery At Baseline, 6 and 12 and 24 months post randomisation: 2. Questionnaires: i. Oxford Knee Score ii. Quality of Life subscale of the Knee Osteoarthritis Outcome Score (KOOS) iii. Physical Activity Scale for the Elderly (PASE) questionnaire. iv. Health economics using EQ-5D 3. Diary: on discharge the participant will be given a diary for daily/regular completion, recording: a. Exercises undertaken b. Medication taken c. Use of healthcare services and personnel 4. Adverse events throughout study
• Health economic cost utility analysis	5. Collect health utility data to calculate QALYs EQ-5D Cost data from participant completed diary

4. STUDY DESIGN

CORKA is a prospective individually randomised controlled trial with blinded outcome assessment for the clinical outcomes at baseline, 6, 12 and 24 months (See Appendix D for the addition of 24 Months' time point) (Primary Outcome) It aims to determine if a multi-component rehabilitation programme provided to patients who have a knee replacement and are deemed at risk of poor outcome by the CORKA screening algorithm, is better than usual care. The study will take place in a minimum of ten NHS hospitals across the UK. It will also include a qualitative and health economic analysis.

4.1. RCT Study

During the trial people undergoing knee replacement will be screened for suitability during their pre-operative assessment clinic. Once informed consent is gained participants will be enrolled in the trial and baseline data will be collected. After surgery participants eligibility will be confirmed and randomisation will take place using the website provided by the Oxford Clinical Trials Research Unit (OCTRU) randomisation service. Participants will be allocated to receive one of two rehabilitation options, either 'Usual care' or 'Community-based rehabilitation programme'. Participants and those delivering rehabilitation will be aware of the treatment allocation due to the nature of the intervention.
As some participants may live quite a distance from the participating site or traffic can be denser in some areas, a 45 minute travel inclusion zone can be used when screening patients for therapists travelling to treat participants.

Participants will remain in the study until data related to their 12 month follow up has been collected. The study has two follow up time points, 6 and 12 months after randomisation. Those participants that reach the 24 month time point whilst the study is still active will be sent the same questionnaire they completed at 6 and 12 months. (See Appendix D) Follow up will take place in the participants home or in the out-patient department. The Physiotherapists carrying out follow up will remain blind to the participants' allocation.

4.2. Qualitative study

As part of the main study a nested qualitative study will take place. A subgroup (approximately n=15) of trial participants who have undertaken the community based rehabilitation programme and a subgroup (approximately n=15) of clinical staff including physiotherapists, occupational therapists and rehabilitation

assistants who have provided the treatment, will undergo one-one interviews to obtain in-depth views about the intervention and how it is delivered.

4.3. Economic analysis

Once all participants have completed their 12 month follow up appointment. An economic analysis comparing the community based rehabilitation programme and usual care will take place.

5. PARTICIPANT IDENTIFICATION

5.1 Study Participants

5.1.1 RCT Trial

The RCT will take place in a minimum of 6 UK hospitals. People scheduled to undergo KR who are assessed as at risk of a poor outcome will be screened to see if they are suitable to take part in this trial using key milestones of the in-patient integrated care pathway

5.2 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study
- Male or Female, aged 55 years or above
- Primary unilateral KR as a scheduled procedure
- Deemed by study screening tool developed to be at risk of poor outcome
- Happy to allow physiotherapy teams to attend their home to deliver the Community based rehabilitation programme if randomised to the intervention arm.

5.3 Exclusion Criteria

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

- Any absolute contraindications to exercise
- Severe cardiovascular or pulmonary disease (New York Heart Association III-IV)
- Severe dementia, assessed using the hospital dementia screening tool
- Rheumatoid arthritis
- Further lower limb arthroplasty surgery planned within 12 months.
- Serious perioperative complications

6. STUDY PROCEDURES

6.1 Site Recruitment

A minimum of 6 NHS hospitals that carry out elective KR will participate to recruit 620 participants. Each site will recruit for a maximum of 15 months depending on set up time frame, with a target recruitment of up to 5 participants per month, per site once all sites are active. The leading site is Oxford University Hospital NHS Trust.

6.2 Participant Recruitment

People who are scheduled to receive a KR will be invited to take part in the trial either by being sent the Participant Invitation letter before they attend their Pre-operative assessment clinic appointment or once they have been be assessed for likelihood of poor outcome using the screening tool developed as part of this study. This will be administered in the pre-operative assessment clinic and the data will be screened for study suitability by a member of the local team. Patients identified by the screening tool as potentially suitable for inclusion will be given information about the study and invited to discuss the study with a member of the research team. The information will include a reply slip which potential participants can return to the research team. Those who are willing to participate can be visited at home, or can visit their local research facility. They will be checked for eligibility and given the opportunity to ask questions and appropriate informed consent will be gained, in addition to baseline outcome data being collected. This will take place no more than 4 weeks prior to the date of surgery. However, the final decision about inclusion and recruitment to the trial will be made at Day 3 post operatively, when patients may be excluded if they have had serious peri-operative complications. If eligible, participants will have their consent confirmed and randomisation will take place using the RRAMP website provided by the OCTRU randomisation service. Participants will be allocated to receive one of two rehabilitation options, either 'Usual Care' or 'Home-based exercise programme'. Participants and those delivering the rehabilitation are aware of the treatment allocation due to the nature of the intervention.

6.3 Informed Consent

Informed consent will be carried out before any study-related procedures take place. The informed consent process will be carried out by the Principal Investigator (or a qualified health care professional

with delegated authority), we anticipate in most sites this will be a research nurse/physiotherapist who will be a part of the Local Clinical Research Network.

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

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 given up to 4 weeks 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. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant, and one copy will be sent to the study office. The original signed form will be retained at the study site in the Investigator Site File and a copy placed in the medical notes along with a copy of the Participant Information Sheet.

The qualitative interviews will take place in selected sites in a small sample of participants. The qualitative work has a separate information sheet and consent form. A copy of the signed Informed Consent will be given to the participant, and one copy will be sent to the study office. The original signed form will be retained at the study site.

6.4 Confirmation of Eligibility and Randomisation

Patients will be screened and the inclusion/exclusion criteria checked after KR surgery. Following these checks they can be considered for the study as long as the following criteria have been fulfilled:

- KR procedure has been undertaken
- No immediate severe operative/post-operative complications
- The centre is able to provide treatment for both interventions within 4 weeks after randomisation

- Screening/informed consent/baseline data collection has taken place prior to surgery
- Randomisation may take place on the first working day after the patient's discharge.

6.5 Randomisation, blinding and code-breaking

The majority of participants will be randomised during their inpatient admission following their KR. Participants will be randomly allocated to one of two rehabilitation regimes via the randomisation service provided by the Oxford Clinical Trials Research Unit (OCTRU). The service may be accessed by a secure randomisation website (24 hours/7 days a week).

Where research staff are not available at a weekend, randomisation may take place on the first working day after the patient's discharge. The Participants will be telephoned once randomised to be informed which group they have been allocated to.

Randomisation uses permuted blocks of random and undisclosed sizes stratified by site.

Both participants and those delivering the intervention will be aware of allocation due to the nature of the rehabilitation delivered. Clinical outcome assessors will be blinded to allocation where possible.

Code-breaking facility is not required for this study as participants and those delivering the intervention are aware of the allocation.

6.6 Baseline Assessments - Pre Surgery

Baseline data will be collected on paper questionnaire and the majority is patient-reported, the baseline assessment should last approx. 1 hour. . Baseline assessments can be carried out either at the participant's home or in the Hospital. Wherever the baseline assessment takes place the 6 and 12 month follow up must also be carried out here. See Appendix B for allowable timeframes:

1. Demographics (name, age, surgery, ASA rating) including contact details and review of medical notes

2. Late Life Function and Disability Instrument [Primary outcome]. A 16-item disability component and a 32-item function component. This is an outcome instrument developed specifically for community-dwelling older adults, which assesses and responds to meaningful change in two distinct outcomes: function-a person's ability to do discrete actions or activities, and disability- a person's performance of socially defined life tasks. [Jette 2002, Haley 2002]

3. Oxford Knee Score. A disease specific measure to assess function and to allow comparison with data from large epidemiological cohort studies. It is a 12 item patient reported outcome measure, designed to measure pain and function after knee replacement surgery. [Murray 2007].

4. KOOS – Quality of Life subscale. Specific instrument for knee osteoarthritis, which can also be analysed to calculate a WOMAC Index. It is a self-reported questionnaire consisting of 5 subscales: pain, other symptoms, function in daily living (ADL), function in sport and recreation (sport/rec) and knee related quality of life (QOL). The quality subscale of KOOS, consists of four self-reported questions. [Roos 2003]

5. Physical Activity Scale for the Elderly (PASE) questionnaire. A self-reported scale designed to measure physical activity level of those aged 65 years and older. It consists of three subscales, leisure time activity, household activity and work related activity. This is a short, self-administered questionnaire to assess activity in the past week [Washburn 1993].

6. Health economics using EQ-5D-5L. A self-reported outcome measure consisting of 5 dimensions, mobility, self-care, usual activity, pain and discomfort and anxiety and depression. Each dimension has 5 categories of response. It is designed to provide a generic measure of health status, for clinical and/or economic evaluation [Euroqol 1990].

7. Functional Co-morbidities Index. Will be completed as other diseases are likely to be present in this older population which might affect physical outcomes [Katz 1996].

8. Physical Measures. Measures of outcome include measures of balance, mobility and physical activity, all areas affected by knee arthroplasty. Each test is reliable and valid, has been used with older, community dwelling adults and has been shown to be responsive in previous rehabilitation studies. Physical function will be measured by a physical performance tasks – the, Figure of 8 walk test, 30 Second Chair Stand Test and single leg stance. [Jones 1999, Springer 2007, Hess 2010]

    a. Figure of 8 walk test, participants are asked to walk in a figure of 8 around 2 cones, this is timed, the number of steps taken is counted, in addition to accuracy (if a participant stays with in boundary of the test) being recorded

b. 30 Second Chair Stand Test - The participant starts sitting on a chair which has a seat high of 17 inches, the participant is asked to complete as many full stands in 30 seconds, the participants' sits in between each stand. The number of full stands a person can complete is recorded.

c. Single leg stance - The participant is asked to stand and lift one leg without using any other support, they will be timed standing on one leg. The participant will be stood with a chair in front of them should they require support

9. Health Resource Diary. On discharge the participant will be given a diary for daily/regular completion, recording:
   - Exercises undertaken and will be completed for 6 weeks daily and weekly thereafter
   - Medication taken
   - Use of healthcare services and personnel
   - Falls
   - Adverse events

To ensure that the Health Resource Diaries are completed by the participants, a reminder letter or email (determined by the participant) can be sent out 3 months after randomisation by the study team.

The participants GP will be informed of their participation in the CORKA study.

Programme Allocation:

The participants will be randomly allocated by a computer generated system to either Arm A or Arm B.

Arm A: Rehabilitation Group –Participants will be seen at home 7 times. Please refer to 7.1 for more detail.

Arm B – Usual Care – Participants will attend out-patient physiotherapy according to centre's usual practice; these will include a minimum of 1 treatment session. Please refer to 7.1 for more detail.

6.7 Subsequent Visits

The study has three follow up time points, at 6, 12 and 24 (See Appendix D for the addition of 24 Months' time point) month's post-randomisation. Follow up can take place at the participants own home or at the hospital, depending on where the baseline took place, is where the follow up should be completed. Local site staff will organise the follow up and liaise directly with the participant to

organise the home-based follow up. Once confirmed an appointment reminder letter or email can be sent out to the participants with the appropriate questionnaire, this helps with the timings at the actual visit if the questionnaire has already been completed beforehand. The following will be collected at the two follow up time points.

1. Complications/adverse events: including any apparent KR related complications since discharge
2. Falls, including time to first fall
3. Late Life Function and Disability Instrument.
4. KOOS quality subscale.
5. Oxford Knee Score
6. Physical Activity Scale for the Elderly (PASE) questionnaire.
7. EQ-5D-5L
8. Timed functional tests – 30 sec Chair Stand Test, Figure of 8 Walk Test and Single Leg Stance.
9. Diary collection/issue of new diary.

6.8 Qualitative interviews

In addition to the main study, a qualitative study will take place in selected sites for a small number of participants (approximately 15 participants, in addition to approximately 15 members of staff). There will be a separate consent process for the sub study before the qualitative interviews are carried out. This nested study aims to find out what makes the proposed intervention acceptable and patients willing to participate and adhere to the treatment programme. Recruitment will take place throughout the study to ensure a spread of participants that is representative of the recruited population. Some of the interviews will be completed during the internal pilot phase.

Design: Qualitative study using Smith's experiential approach of interpretative phenomenological analysis (IPA) [Smith 2008].

Sample: Purposive sampling will be used to achieve a sample of participants which includes; female and male participants, those with differing levels of function and disability selected using their baseline LLFDI score and patients of varying activity levels. In addition a sample of clinical staff who have delivered the intervention from differing professional backgrounds, physiotherapists, occupational therapist and rehabilitation assistants.

Methods: Data collection. Trial participants will be invited to participate in in-depth semi-structured interviews following the intervention. Interviews will be held at a convenient time and location for

each participant, from previous experience this is most likely to be at participant's homes. Interviews will be digitally recorded and fully transcribed. Field notes and memos will be recorded using a digital notepad. Participants will be offered the opportunity to view a summary of their results, providing an opportunity for them to remove anything with which they do not feel comfortable (member checking).

Data Analysis: Audio recordings will be transcribed and coded. NVIVO software will be used to assist in managing the data and presenting the findings to co-applicants during data analysis.

6.9 Health economics

A health economic evaluation is planned as part of the trial to determine whether a home-based multidisciplinary rehabilitation package represents good value for money when compared to usual care in patients undergoing knee replacement for chronic arthropathy.

The economic evaluation will take the form of a cost-utility analysis from a societal perspective and quality-adjusted life years (QALYs) will be used as the main health outcome measure. A micro-costing approach will be used to calculate costs of the home-based rehabilitation intervention and data will be collected from each trial patient on NHS and social care contacts out to 12 months through use of a participant diary. Contacts recorded will include GP visits, related-hospitalisations, outpatient visits, district and practice nurse visits, physiotherapy visits and any occupational therapy visits. Unit costs to value these contacts will be taken from national sources such as the NHS reference costs, and the PSSRU unit costs of health and social care publication.[Department of Health 2012-13, Curtis L 2013) We will also collect information on costs incurred by patients themselves including visits to private practitioners, complementary therapists, and equipment purchased to provide the appropriate environment for home exercise and everyday tasks (previous studies have shown that following arthroplasty patients consult private practitioners including complimentary therapists). We will also ask patients to record any unpaid informal care provided to them by relatives and / or friends.

Assessments of the health-related quality of life (HRQoL) of participants in each arm of the trial will be conducted using the EQ-5D-5L instrument at baseline, 6, 12 and 24 months.(Brooks 1996) The UK value set to derive utilities from the EQ-5D-5L is currently under development but it is expected that will become available before data analysis begins. Utility values derived from the EQ-5D-5L data will be combined with patient survival data and used to estimate QALYs for each patient to 12 months.

Mean (standard deviation) costs and QALYs per patient will be estimated for each arm of the trial. The difference (95% confidence interval) in mean costs and QALYs between trial arms will be estimated and if necessary an incremental cost-effectiveness ratio (ICER) calculated to determine the additional cost of generating one additional QALY. Results will be presented separately for a NHS, patient and societal (including informal care) perspective as recommended by current guidance. Cost-effectiveness acceptability curves will be used to determine the probability that the home rehabilitation programme is cost-effective at different values of society's willingness to pay for a QALY.

A maximum of one-year follow-up data will be available for the economic evaluation however it is possible that the intervention may impact on costs and benefits beyond this period. Sensitivity analysis will be used to explore the impact on results of various assumptions around the continuation of any treatment effects observed beyond 12 months.

6.10 Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study intervention at any time. The attending investigator may also request the participant is withdrawn from receiving the study intervention. Where possible the participant will continue to be followed up. The PI (or delegated individual) will record any reason for withdrawal on the study CRF and the participant will be asked if the study team may use the data collected to the point of withdrawal and/or contact them for collection of patient-reported follow up data.

An intention-to-treat analysis will be carried out therefore all participants remain in the study irrespective of whether they receive or continue with their allocated treatment (unless the participant themselves withdraws consent).

6.11 Reporting a death

The PI or their delegated individual should contact the central coordinating team in Oxford to report the death of a participant. This notification ensures no participant is contacted for further follow up or result reporting.

See also Safety Reporting section in this protocol to evaluate whether the death should be reported as a study Serious Adverse Event.

6.12 Discontinuation/Withdrawal of a site

Recruitment and screening data will be monitored by the trial team. This will also be reviewed by the Trial Management Group, the Trial Steering Committee and the Data Monitoring and Safety Committee. Where necessary, after appropriate support, if a site has persistent low recruitment or is unable to facilitate the timely delivery of the intervention, a site may be required to close and resources used to establish another site.

6.13 Definition of End of Study

The end of study is the date of the last 12 month follow up of the last study participant. The study has received an extension request from the HTA for the project to end in December 2019

7 INTERVENTIONS

7.1 Rehabilitation Programme

This trial will test physiotherapy and occupational therapy in a multi-component package of rehabilitation delivered by a generic rehabilitation therapist. The Occupational therapy element will focus on assessment and adaptations to patients' homes to enable a safe environment for home exercise and everyday functional tasks. Physiotherapy will include a home based intervention with an emphasis on a functional, activity based rehabilitation programme. We will test if the intervention can be delivered by generic rehabilitation therapists, rather than uni-professionally.

The intervention is a multi-component rehabilitation programme designed to improve both the function of 'at risk' patients, but also their participation in activities. The largest component will be an exercise programme to be delivered in the participants' own homes in order to make it accessible to those without good social support or those with physical or mental frailty. Attention will also be paid to pain management, confidence building, appropriate provision of aids and appliances and suitability of the lay out of the home environment. The exercise component will include assessment of current functional level and gait re-education, progression/removal of walking aids, plus the exercises to promote balance, strengthening and range of motion. Repetition rate, frequency and progression of exercises will be based upon a treatment algorithm. The intervention protocol involves instruction by a qualified therapist, followed by supervised practice by a rehabilitation assistant and additional unsupervised practice by the participants. The qualified therapist will re-visit half way through the

programme to ensure correct progression of the exercise package has occurred and will provide supervision to the rehabilitation assistant throughout. Clear algorithms and decision rules will be linked to assessment results to determine the starting point of each participant on the package and their rate of progression.

Task training will be included: sit to stand, activities in standing, steps or stairs as appropriate, getting in/out of a car. Participants will be asked to practice exercises at home and will be assisted in this by a number of strategies using techniques to maximise compliance in older people such as patterning and copying, calendar and reminder systems. Strategies will also be employed within the programme to address motivation to engage with the treatment programme.

We plan to include the use of rehabilitation assistants to assist with the delivery of the intervention, an approach that has been successful in other community based therapy trials. In order to make the intervention affordable to the NHS, the trial will use a combination of qualified physiotherapists, occupational therapists and rehabilitation assistants to deliver the intervention.

Attention will be paid to the interface with other members of the primary care health team such as district nursing, health visiting and community social services, to ensure appropriate awareness and reinforcement of the rehabilitation strategy and programme. The programme will focus on both improving functional outcome but also participation levels.

Collaborating sites will provide the CORKA home-based rehabilitation programme. It will commence delivery within 4 weeks of KR surgery. [A window of 2-8 weeks for starting the intervention will be allowed before a protocol deviation is considered to have occurred.]

The home-based rehabilitation programme will include:

- Up to 7 visits to participants own home over 12 weeks
- Delivered by Rehabilitation Assistants
- Supervised by Physiotherapists
- Home requirements assessed by Occupational Therapist

7.2 Usual Care

Usual care as offered to KR patients locally. This is likely to include:

- Written advice on exercises to do at home, given on discharge from hospital
- Between 1-6 sessions of traditional out-patient physiotherapy, as required
- Delivered by qualified Physiotherapist
- Home requirements assessed by Occupational Therapist, identification of barriers to discharge.

It is recognised that usual care can vary geographically (Artz 2012). This may include the number of sessions of physiotherapy given post-discharge. In order to standardise the usual care arm, without changing it significantly, there will be a minimum and maximum number of session that will be included in usual care. Participants will be expected to attend at least one session of outpatient physiotherapy.

7.3 Staff training: rehabilitation programme

Only staff trained in the CORKA home-based exercise programme may deliver the study intervention and the PI at each site will identify local staff to undertake the relevant training.

Physiotherapist training

The study will provide training to the local Physiotherapists and Occupational Therapists who are overseeing the delivery of the home-based exercise intervention by a Senior Physiotherapist from The Nuffield Orthopaedic Centre. Training will be recorded on the CORKA training logs and signed off by either the trainer and/or the local PI. A copy will be sent to the local site for updating the Delegation Log, and for filing in the ISF.

Rehabilitation Assistant training

Rehabilitation Assistants will be trained in delivery of the intervention by the local Physiotherapist (or by a member of the central study team in Oxford who will travel to deliver the training) in accordance with the requirements of the CORKA study. Training will be competency based and tailored to the need of the individual, assessed by the framework developed for the role. The CORKA site training log will be signed off by the trainer and/or the local PI. A copy will be sent to the coordinating office in Oxford, the original filed in the ISF at the site. The Delegation Log must be updated accordingly.

Assessor Training

The study will also provide training to the local assessors. Training will include both the protocol for the self-reported questionnaires and the physical outcomes. The CORKA site training log will be signed

off by the trainer and/or the local PI. A copy will be sent to the coordinating office in Oxford, the original filed in the ISF at the site. The Delegation Log must be updated accordingly.

The study office will maintain a record of all Physiotherapists, Occupational Therapists and Rehabilitation Assistants trained in intervention delivery which will be made available as required for any monitoring purposes.

The PI at each site will record the delegated responsibilities of trained staff on the CORKA Delegation Log. New staff should be trained and added to the log, as required, as the study progresses. The Delegation Log is part of the Investigator Site File (ISF).

8 SAFETY REPORTING

8.1 Definitions

8.1.1 Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which there 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.

8.1.2 Foreseeable Adverse Events

Fall risk is an important issue, these patients are at higher risk for falls, whether the home exercise group is at higher risk is debatable but needs consideration and so will be carefully monitored. The following data will be collected and recorded on the Participant Diary:

- A fall in the home: during active delivery of the home-based rehabilitation programme that does not meet the criteria in 8.1.1.
- A fall in the home: at any time outside of the delivery of the home-based rehabilitation programme
- A fall in the garden at home
- A fall at any other location/outside of the home environment

Falls which are assessed as being **related** to the study intervention and are categorised as serious according to 8.1.1, will also be recorded and reported to the trial office using an SAE form as per section 8.2.

8.1.3 Other Foreseeable Adverse Events

Some AEs will be expected as part of the surgery received rather than inclusion in the CORKA study/receiving rehabilitation. These will be collected as part of standard data collection on the study questionnaires/CRFs but are not classified as reportable SAEs:

- Infection of KR
- Fracture
- Venous thromboembolism/Pulmonary embolism

8.2 Reporting Procedures for Serious Adverse Events

Serious adverse events (SAEs) which are considered to be related to the study must be reported on an SAE form and sent to the trial office within 24 hours of the local research team becoming aware of the event. The trials office will process and review reported SAEs according to OCTRU SOPs and safety reporting for non CTIMPS. All SAEs will be reviewed by an independent assessor and where opinion differs to that of the local PI, the trials office will facilitate discussion. Both final opinions will be recorded. All SAE forms must eventually be signed off by the PI; the local PI should be informed at the earliest possible opportunity.

<u>Collaborating sites – PI assessment of an event prior to reporting</u>

The PI must assess causality of any suspected SAEs before the event is reported to the study coordinating office in Oxford. The SAE Form must be completed as fully as possible, and faxed or emailed to trial office in Oxford. Full contact details are provided on the SAE Form.

Reporting SAEs to REC

The trials office will be responsible for reporting all study SAEs occurring to a participant to the REC that gave a favourable opinion of the study where, if the event is confirmed as 'serious' 'related' and 'unexpected'. The information provided to the REC will be unblinded and will be reported within 15 days of the trial office being made aware.

9 STATISTICS AND ANALYSIS

9.1 Proposed sample size

There is currently little information from the existing literature about the likely treatment difference in LLFDI component scores for this type of study. Therefore, our sample size calculation is based on a moderately small standardised effect size of 0.275, which is a value that we expect to be clinically important and realistic in rehabilitation trials. Therefore, 620 participants (310 per arm) are required to detect a standardised effect size of 0.275 with 90% power, 5% (2-sided) significance and allowing 10% loss to follow-up. This standardised effect size is equivalent to detecting a 3 points difference on the LLFDI between treatment arms assuming a standard deviation of 10.91. The 15 Participants that were randomised during the Internal Pilot study will be used in the final analysis by incorporating them into the original planned sample size of 620.

9.2 Data Analysis

The principal comparisons will be performed on an intention-to-treat basis. The results from the trial will be presented as comparative summary statistics (i.e. difference means) with 95% confidence intervals. The primary outcome will be analysed using a linear mixed effects method with repeated measures, on outcome measurements at 6 and 12 months, adjusting for baseline score and stratification/ variables. An interaction between time and randomised group will be fitted to allow estimation of treatment effect at each time point. We will formally assess the distribution of the change from baseline for evidence of departure from normality. If necessary, data will either be transformed or analysed using a non-parametric equivalent. Similar approaches will be carried out for other continuous outcomes.

The nature and mechanism for the missing outcomes will be investigated, though mixed effects models implicitly account for data following a missing at random mechanism. Sensitivity analyses will be carried out to examine the robustness of the results with different assumptions about departures from randomisation policies, and handling of missing data.

A statistical analysis plan containing a more detailed account of the proposed statistical analysis will be drafted early in the trial and finalised prior to the primary analysis data lock. Any changes at this time will be incorporated into the final SAP and signed off as per current OCTRU SOPs. Any changes/deviations from the original SAP will be described and justified in protocol and/or in the final report, as appropriate.

10 DATA MANAGEMENT

10.1 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. All data and documentation will be stored in accordance with regulatory requirements and access to the data will be restricted to authorised trial personnel. Oxford Clinical Trials Research Unit will securely hold the database.

10.2 Data Recording and Record Keeping

Data will be collected from participants and the research team onto paper questionnaires/CRFs. Data collected for the two study follow up time points (6 and 12 months), will be via a home visit or an out-patient clinic visit onto paper questionnaire/CRF. Data for the 24 month time point will be sent out to the participants via post (See Appendix D). The originals will be sent by a member of the local research team to the study coordinating office in Oxford by post, using a Freepost account, keeping a copy at site.

Upon receipt of questionnaires/CRFs, appropriate data quality and validation checks will be carried out and the data entered into a study-dedicated database which is developed and maintained by the Oxford Clinical Trials Research Unit, a UKCRN Registered Clinical Trials Unit. OpenClinica software will be used. To identify manual entry errors a 10% double entry check will be carried out at regular intervals during the data collection phase of the study.

Trial documentation must be retained for 5 years after completion of study-related activities. Collaborating sites are delegated the responsibility of archiving local essential documents (including the

Investigator Site File) in an appropriate secure environment. The study office will archive the central Trial Master File and associated documents according to University of Oxford policy and this may include the use of an external professional archiving site.

All data will be processed according to the Data Protection Act 1998, and all documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent form, the participant will be referred to by the study participant number/code, not by name.

11 QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures. A Monitoring Plan will be developed according to OCTRU's SOPS which involves a risk assessment. The monitoring activities are based on the outcome of the risk assessment and may involve central monitoring and site monitoring.

12 ORGANISATION

12.1 Project timetable and milestones

The aim is to randomise 620 patients to the trial over a period of 15 months. We will assess the number of participants that each site can randomise and predict the number of participants expected at each site accordingly. Previous knee replacement trials have had a consent rate of 59% of eligible patients (Minns Lowe 2012).

12.2 Trial Committees

12.2.1 Trial Steering Committee (TSC)

The TSC, which includes independent members provides overall supervision of the trial on behalf of the funder. Its terms of reference will be agreed with the HTA and will be drawn up in a TSC charter which will outline its roles and responsibilities. Meetings of the TSC will take place at least once a year during the recruitment period.

12.2.2 Trial Management Group (TMG)

The TMG is made up of the Investigators listed on the front of this protocol, and staff working on the project within OCTRU/ CCTR Trials Group. This group will oversee the day-to-day running of the trial and will meet regularly throughout the lifetime of the study.

12.2.3 Data Monitoring and Safety Committee (DMSC)

The DMSC is a group of independent experts external to the trial who assess the progress, conduct, participant safety and, if required critical endpoints of a clinical trial.

The study DMSC will adopt a DAMOCLES charter which defines its terms of reference and operation in relation to oversight of the trial. They will not be asked to perform any formal interim analyses of effectiveness. They will, however, see copies of data accrued to date, or summaries of that data by treatment group and they will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. They may advise the chair of the Trial Steering Committee at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. DMSC meetings will be held at least annually during the recruitment phase of the study.

12.3 Local Co-ordination

Each participating site will identify a local Physiotherapy Principal Investigator and local nurse/physiotherapist co-ordinator (as necessary). The responsibility of local coordinators will be to:

1. Be familiar with the trial
2. Liaise with the CORKA coordinating team in Oxford
3. Disseminate CORKA protocol and information to staff involved in the trial locally
4. Ensure mechanisms are in place to facilitate the recruitment of eligible patients, monitor recruitment locally and identify barriers to recruitment and work towards solving them
5. Ensure Rehabilitation Assistants are recruited to ensure coverage for the intervention period of the study
6. Ensure all staff delivering the intervention have received CORKA training prior to running a programme
7. Ensure timely delivery of the Rehabilitation Programme
8. Identify Physiotherapists to act as blinded assessors of clinical outcomes at the 6 and 12 month follow ups
9. Ensure timely follow up of participants
10. Work with local Research and Development staff to facilitate approvals
11. Ensure questionnaires and recruitment documents are easily accessible and available, and that they are fully completed and returned to the study office in Oxford
12. Deal promptly with missing data queries and return these to the study office
13. Notify the study office of serious adverse events within the timeframe specified in the protocol
14. Facilitate other aspects of local collaboration as appropriate

15. Make all data available for verification, audit and inspection purposes as necessary
16. Ensure participant confidentiality is respected by all persons at all times

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Declaration of Helsinki

The investigators will ensure that this study is conducted in accordance with the principles of the current revision of the Declaration of Helsinki (last amended October 2008).

13.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice and with the applicable requirements as stated in the Research Governance Framework for Health and Social Care (2nd Edition 2005). Local investigators must ensure the study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3 Research Governance

The sponsor of the trial is the University of Oxford and the University's Clinical Trials & Research Office (CTRG) will oversee the roles and responsibilities delegated to them as research sponsor. The trial will be run on a day-to-day basis by the Critical Care, Trauma and Rehabilitation (CCTR) Trials Group, a group within the Oxford Clinical Trials Research Unit, an UKCRC Registered Clinical Trials Unit.

13.4 Approvals

13.4.1 Ethics approval

The trial can only start after approval from one of the Health Research Authority Ethics Committee and local 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 Chief Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

The REC has the purpose to look after the rights, well-being and dignity of patients. The REC reference number is given on the front page of this protocol. The NHS REC that reviewed this study was the Oxford B REC.

13.4.2 Local approvals

The study office will assist collaborating sites with the necessary approvals to allow the study to take place within their Trust. Typically this involves the submission of a Site Specific Information electronic form via the on-line Integrated Research Application System, and a signed contract between the Sponsor and the local site's Research and Development Office. Once these approvals are in place the study office will inform the local Principal Investigator of the date the study can open to recruitment at their site.

13.5 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. In addition, the funder requires regular Progress Reports throughout the study period.

13.6 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.

Personal data and sensitive information required for the study will be collected directly from trial participants and hospital notes. All personal information received in paper format for the trial will be held securely and treated as strictly confidential. All staff involved in the study share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be entered and stored on a password protected access

restricted secure server at the University of Oxford under the provisions of the Data Protection Act and/or applicable laws and regulations.

13.7 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. In such cases patients will be paid their travel costs based on the University of Oxford's expenses policy. They will not receive any other payments or any other benefits.

13.8 Project Funding

The CORKA Study funding has been awarded by the National Institute for Health Research (NIHR), Health Technology Assessment (HTA) Programme (project number 12/196/08).
Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health.

13.9 Participating sites funding

The CORKA Study is a UK CRN portfolio study and as such collaborating sites may have access to resources within the Local Clinical Research Network (LCRN) in England. The lead network for CORKA is the Thames Valley & South Midlands LCRN, the UK CRN website details key local contacts within the LCRN, see http://www.crn.nihr.ac.uk/aboutus
Funding is available for Rehabilitation Assistants delivering the intervention for the period of intervention delivery. In addition, a fee will be payable to collaborating sites for successful follow up data collection at 6 and 12 months.

13.10 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). NHS indemnity operates in respect of the clinical treatment which is provided.

14 PUBLICATION POLICY

Data from this study should not be presented in public or submitted for publication without requesting consent from the Trial Steering Committee.

Authors will acknowledge that the study was funded by the NIHR HTA. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

The Chief Investigator will co-ordinate dissemination of data from this study. All publications using data from this study to undertake original analyses will be submitted to the DSMC, TMG and TSC for review before release. The final study report will be available on the HTA website.

We will provide all participants with a summary of the trial outcome. All participants will be given a choice whether they would like to receive the summary via the study website, if they do not have access to a computer they will be able to receive the summary by post.

In addition to the NIHR monograph report, the results will be published in peer-reviewed medical literature.

15 REFERENCES

Artz N, Dixon , Wylde V, Beswick A, Blom A, Gooberman-Hill R. Physiotherapy provision following discharge after total hip and total knee replacement: A survey of current practice at high-volume NHS hospitals in England and Wales. Musculoskeletal Care 2012: 11(1): 31-38

Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. Journal of Rheumatology 1988 15: 1833-40.

Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53-72

Clement ND, MacDonald D, Howie CR, Biant LC. The outcome of primary total hip and knee arthroplasty in patients aged 80 years or more. JBJS Br 2011; 93,9: 1265-70.

Clement N, Jenkins P, McDonald D, Nie Y, Patton J, Breusch S, et al. Socioeconomic status affects the Oxford knee score and Short-Form 12 score following total knee replacement. Bone & Joint Journal. 2013;95(1):52-8.

Curtis L. Unit Costs of Health and Social Care 2013. Canterbury. Personal and Social Services Research Unit University of Kent 2013

DeJong, G., Tian, W., Smout, R., Horn, S., Putman, K ., Smith, P., Gassaway, J., DaVanzo, J. (2009) Use of rehabilitation and other health care services by patients with joint replacement after discharge from skilled nursing and inpatient rehabilitation facilities. Archives of Physical Medicine and Rehabilitation, 90(8):1297-1305.

Department of Health. NHS National Schedule of Reference Costs 2012-13. Available from: https://www.gov.uk/government/publications/nhs-reference- costs-2012-to-2013.

EuroQol Group EuroQol – a new facility for the measurement of health-related quality of life. Health Policy,1990; 16, 199-208.

Fitzgerald JD, Orav EJ, Lee TH, Marcantonio ER, Poss R, Goldman L, et al. Patient quality of life during the 12 months following joint replacement surgery. Arthritis Care & Research. 2004;51(1):100-9.

Fortin PR, Clarke AE, Joseph L, Liang MH, Tanzer M, Ferland D, et al. Outcomes of total hip and knee replacement: preoperative functional status predicts outcomes at six months after surgery. Arthritis & Rheumatism. 1999;42(8):1722-8.

Haley SM, Jette AM, Coster WJ, et al. Late Life Function and Disability Instrument, II: development and evaluation of the function component. J Gerontol A Biol Sci Med Sci. 2002;57:M217–M222.

Hawker GA, Badley EM, Borkhoff CM, Croxford R, Davis AM, Dunn S et al. Which patients are most likely to benefit from total joint arthroplasty? Arthritis and Rheumatism 2013; 65: 1243-52.

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., Bonsel, G. and Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res; 20(10): 1727-1736.

Hess RJ, Brach JS, Piva SR, VanSwearingen JM. Walking skill can be assessed in older adults: Validity of the figure of 8 walk test. Phys Ther 2010 90: 89-99.

Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community residing older adults. Res Q Exerc Sport 1999 70(2): 113-9

Jones CA, Voaklander DC, Johnston DWC, Suarez-Almazor ME. The effect of age on pain, function, and quality of life after total hip and knee arthroplasty. Archives of internal medicine. 2001;161(3):454.

Jones CA, Voaklander DC, Suarez-Almazor ME. Determinants of function after total knee arthroplasty. Physical therapy. 2003;83(8):696-706.

Jones, C. A., Beaupre, L. A., Johnstone, D. W. C., Suarez-Almazor, M. E. (2007) Total joint arthroplasties: current concepts of patient outcomes after surgery. Rheumatic Disease Clinics of North America, 33:71-86.

Jette AM, Haley SM, Coster WJ, et al. Late Life Function and Disability Instrument, I: development and evaluation of the disability component. J Gerontol A Biol Sci MedSci. 2002;57:M209–M216.

Judge A, Arden NK, Cooper C, Javaid MK, Carr AJ, Field RE, et al. Predictors of outcomes of total knee replacement surgery. Rheumatology. 2012;51(10):1804-13.

Katz, JN, Chang, LC, Sangha O, Fossel, AH, Bates, DW Can comorbidity be measured by questionnaire rather than medical record review? Medical Care 1996; 34:73-84.

Lothgren, M. and N. Zethraeus. Definition, interpretation and calculation of cost-effectiveness acceptability curves. Health Economics, 2000. 9(7): 623-630.

Martin, J., Meltzer, H., Elliot, D. OPCS surveys of disability in Great Britain. Report 1. The prevalence of disability among adults. Office of Population Censuses and Surveys, Social Survey Division. London: HMSO, 1988.

Minns Lowe CJ, Barker KL, Dewey M, Sackley CM. Effectiveness of physiotherapy exercise after knee arthroplasty for osteoarthritis: systematic review and meta-analysis of randomised controlled trials. British Medical Journal 2007; 335: 812.

Minns Lowe CJ, Barker KL, Holder R, Sackley CM. Comparison of post-discharge physiotherapy versus usual care following primary total knee arthroplasty for osteoarthritis: an exploratory pilot randomized clinical trial. Clin Rehabil 2012 26:629-41.

Moffet, H., Collet, J. P., Shapiro, S. H., Paradis, G., Maquis, F., Roy, L. (2004) Effectiveness of intensive rehabilitation on functional ability and quality of life after first total knee arthroplasty: a single blind randomized controlled trial. Archives of Physical Medicine and Rehabilitation, 85:546-556

Murray DW, Fitzpatrick R, Rogers K, Pandit H, Beard DJ, Carr AJ, Dawson J. The use of the Oxford hip and knee scores. Journal of Bone Joint Surgery [Br] 2007; 89:1010-1014.

Naylor, J. M., Harmer, A. R., Fransen M, Crosbie J, Innes L. Status of physiotherapy rehabilitation after total knee replacement in Australia. Physiother Res Int. 2006; 11: 35-47.

Peat, G., McCarney, R., Croft, P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Annals of the Rheumatic Diseases 2001;60:91-7.

Petterson, S.C., Mizner, R. L., Stevens, J. E., Raisis, L., Bodenstab, A,, Newcomb, W., Snyder-Mackler, L. (2009) Improved function from progressive strengthening interventions after total knee arthroplasty: a randomised clinical trial with an imbedded prospective cohort. Arthritis and Rheumatism, 61(2):174-183.

Piva SR, Gill AB, Almeida GJ, DiGiola AM, Levison TJ, Fitzgerald GK. A balance exercise program appears to improve function for patients with total knee arthroplasty: a randomized clinical trial. Phys Ther 2010; 90: 880-94.)

Rajan RA, Pack Y, Jackson H, Gillies C, Asirvatham R. No need for outpatient physiotherapy following total knee arthroplasty: a randomized trial of 120 patients. Acta orthopaedica Scandinavica. 2004 Feb;75(1):71-3.

Roos E, Toksvig S-Larsen: Knee injury and Osteoarthritis Outcome Score (KOOS) -validation and comparison to the WOMAC in total knee replacement. Health and Quality of Life Outcomes 2003, 1.: 17

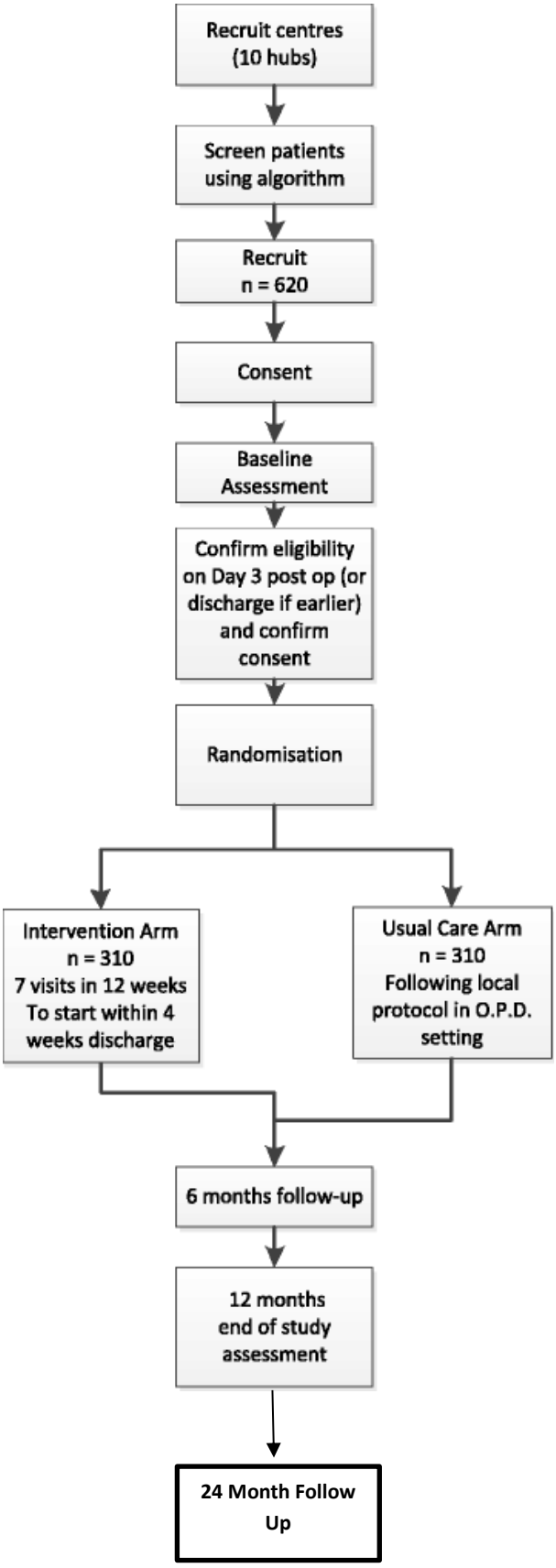
Smith JA and Osborn, M (2008) Interpretative phenomenological analysis. In JA Smith (ed) Qualitative Psychology: A Practical Guide to Methods. London: Sage. (2nd ed).

Springer BA, Marin , Cyhan T, Roberts H, Gill NW. Normative values for the unipedal stance test with eyes open and closed. J Geriatr Phys Ther 2007: 30(1): 8-15

Washburn, R, A, Smith, K, W, Jette, A, M, Janney, C, A The physical activity scale for the elderly (PASE): Development and Evaluation. Journal of Clinical Epidemiology 1993; 46:153-162.

Westby, M.D., Kennedy, D. , Jones, D., Jones, A., Doyle-Waters, M. M., Backman, C. (2008) Post-acute physiotherapy for primary total knee arthroplasty. (Protocol) Cochrane Database of Systematic Reviews, Issue 2. Art. No.:CD007099. DOI:10.1002/14651858. CD007099.

APPENDIX A: STUDY FLOW CHART



APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Time point	Enrolment/Pre Op Clinic	Baseline	Surgery	Allocation	Post-surgery				
					Weeks 0-2	Weeks 3-6	6 Months	12 Month	24 Month
KR surgery			X						
High-risk screening tool applied	X								
Eligibility screen: Inclusion/Exclusion Criteria	X								
Informed consent	X								
Baseline questionnaire		X							
RANDOMISATION				X					
Allocation A: Intervention – home-based exercise programme					X				
Allocation B: Control – Usual care					X				
ASSESSMENTS									
• Demographics • Medical History • EQ-5D Pre-surgery recall		X X X							
• LLFDI score • Oxford Knee Score • Quality of subscale of the Knee Osteoarthritis Outcome Score (KOOS) • Physical Activity Scale for the Elderly (PASE) questionnaire. • Health economics using EQ-5D • 30 sec chair stand test • Figure of 8 walk test • Single leg stance		X X X X X X X					X X X X X X	X X X X X X	X X X X X
Participant Diary: completed daily /as required at home for 6 weeks. Then weekly recording: • Exercises undertaken • Medication taken • Use of healthcare services and personnel					X	X	X	X	
Adverse events Collected throughout			X		X	X	X	X	
This table excludes the Qualitative sub study taking place in selected sites/participants									

- ±2 weeks for the 6 and 12 month time point

APPENDIX C: PROJECT MILESTONES AND TIMESCALE

Project Activity	<0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	65
Recruit Research Staff	**X**																						
Ethics Appraisal		**X**																					
Update systematic review	**X**	**X**																					
Refine content training package programme	**X**	**X**																					
Internal Pilot Stage			**X**	**X**																			
Develop educational support materials			**X**																				
Recruit & prepare centres			**X**	**X**																			
Internal Pilot study evaluation				**X**																			
Site set-up/approvals			**X**	**X**																			
Train intervention providers				**X**																			
Main trial																							
Recruitment period					**X**	**X**	**X**	**X**	**X**	**X**	X	X	X	X	X								
Review recruitment rates & add sites							**X**	X	X														
Intervention treatment delivery						**X**	**X**	**X**	**X**	**X**	**X**	X	X	X	X	X							
6 Month follow-up							**X**	**X**	**X**	**X**	**X**	**X**	**X**	X	X	X	X						
12 month follow up										X	X	X	X	X	X	X	X	X	X				
24month follow-up													**X**	**X**	**X**	X	X	X	X				
Qualitative Trial																							
Interviews patients & therapists			**X**									**X**	**X**	**X**	**X**	X							
Thematic Analysis												**X**	**X**	**X**	**X**	X							
Data analysis								**X**	**X**						**X**	**X**	**X**	**X**	**X**	**X**			
Economic appraisal															**X**	**X**	**X**	**X**	**X**	**X**			
DMEC meeting			**X**			**X**			**X**			**X**		**X**			**X**						
Progress Reports to HTA			**X**	**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**					

APPENDIX D: CORKA SUB STUDY

Background and Rationale for Amendment

The CORKA study was developed in response to a commissioned call by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme for research into a functional home based rehabilitation programme for patients who may be at risk of poor outcome after knee arthroplasty.

The CORKA study has been recruiting since March 2015, recruitment was initially supposed to end in October 2016, however due to slower recruitment than planned, an extension has been requested from the HTA to continue recruiting until December 2017.

As many of the patients that were recruited at the beginning of the trial will now be reaching 2 years post knee replacement, we would like to continue to find out how the participants are doing by capturing 2 year follow up data.

Objective

The aim of sending the questionnaires out to participants is to gain a better understanding of how the primary outcome of the study is doing at 2 years post knee arthroplasty**.**

Design

The CORKA trial is a prospective individually randomised controlled trial with blinded outcome assessment at baseline, 6 and 12 months. Participants will be randomised to one of two arms, 'home-based rehabilitation' or 'Usual Care'. Those in the usual care arm will receive a minimum of 1 and a maximum of 6 sessions of physiotherapy as delivered locally, e.g. class, one to one, etc. Those in the intervention arm will receive 7 sessions of a functional rehabilitation programme over a 12 week timescale. The intervention will be delivered using physiotherapists and physiotherapy assistants in the participants' home. Participants will be followed up at 6 months and 12 months. This amendment is in addition to the data already collected at baseline, 6 and 12 months. We would like to add another time point for data collection which will be 2 years post op.

Method, Participants, Sample size

The current questionnaire pack that is used at the 6 and 12 month follow up will be used, this includes the Late Life Function and Disability Index (LLFDI), Oxford Knee Score, EQ5D, Physical Activity Score In the Elderly (PASE) and the Knee injury and Osteoarthritis Outcome Score (KOOS) – Quality of life subscale.

Participants that have reached the 2 years post-surgery time point whilst the trial is still running will be sent the questionnaire pack in the post by the CORKA trial team. Their address will be found by using their NHS number, which is recorded on the randomisation form and their date of birth via the NHS Spine system.

This won't have any impact on the trial sites as this will all be managed from the CORKA trial office in Oxford. Sites may need to be contacted to ask for participant names if NHS numbers weren't given at randomisation.

Pre-paid envelopes will be sent with the questionnaires along with a letter explaining why they are being sent another questionnaire pack. The covering letter will state a deadline to send the questionnaire back by. This will then be followed up with a reminder letter if we do not receive the questionnaire packs after a month of being sent the questionnaire. We will send up to 2 reminder letters to participants to get as many responses as possible.

Approx. 326 participants will have reached the 2 year post surgery stage by the end of January 2019 which is when the follow up period will end for the last participant randomised.

Outcomes

This will be part of the secondary outcomes for the trial.

Statistical Analysis

The data collected from the 2 year follow up will become part of the Statistical Analysis Plan.

Informed Consent

Consent forms will be checked to ensure that participants ticked question 5 when they consented to taking part in the CORKA trial.

APPENDIX E: AMENDMENTS

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	August 2015	Nicola Kenealy	The Internal Pilot phase evaluated. 45 minute travel inclusion zone added. Qualitative Study now called interviews. Invitation letters can be sent out prior to Pre Op. Assessments can be carried out either at home or in the outpatient department. The sample size has been recalculated. KOOS has been added to the questionnaire pack.
2	3.0	November 2015	Nicola Kenealy	The sample size has been confirmed to add in the participants randomised in the internal pilot part of the trial. A reminder letter has been added to send to participants to remind them to complete their Health Resource Diaries and also when their appointment is.

3	4.0	January 2017	David Smith	Reduction of the revised sample size back to the original planned 620 participants by incorporating the 15 pilot study participants into the total rather than in addition to the 620.
13	5.0	May 2017	Nicola Kenealy	Correction of two typos changing the number from 632 to the correct number 620.
14	6.0	Oct 2017	Nicola Kenealy	Adding in a 2 year follow up time point for those participants who reach 24 months whilst the trial is still running.