Study Title: Community based Rehabilitation after Knee Arthroplasty (CORKA). A prospective individually randomised two arm randomised controlled trial.

Short Title: CORKA Study

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

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1. SYNOPSIS

MAIN STUDY		
Study Title	Community based Rehabilitation after Knee Arthroplasty (CORKA). A prospective individually randomised single blinded two arm randomised controlled trial.	
Short title	CORKA Study	
Study Design	A pragmatic prospective individually randomised single blinded two arm randomised controlled trial.	
Study Participants	Patients undergoing total knee replacement (KR) assessed at risk of poor outcome	
Study Treatments	Participants will be randomized to receive either: 'Community-based rehabilitation or 'Standard rehabilitation'	
Planned Sample Size	600	
Planned Study Period	51 months (Patients will be followed up for a period of 12 months)	
	Objectives	**Endpoints**
Primary	To determine if a multi-component rehabilitation programme improves the outcome of patients who undergo a KR.	• 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 versus standard care rehabilitation.	• 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 – the Timed Up and Go, 3 metre walk and a step climb 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.

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 COAST 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 • Pilot

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
Health Economics: **Cost utility analysis**	• Collect health utility data to calculate Quality Adjusted Life Years (QALYs) • We will conduct a cost utility analysis from both NHS and a societal perspective.	• EQ-5D • Cost data from participant completed diary

2. ABBREVIATIONS

CCTR	Critical Care, Trauma and Rehabilitation Trials Group (part of OCTRU)
CI	Chief Investigator
COAST	Clinical Outcomes in Arthroplasty Surgery Trial
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
QALY	Quality Adjusted Life Years

3. BACKGROUND AND RATIONALE

3i 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 is currently in existence.

Generally, patients who are 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 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 have developed an intervention that uses both qualified physiotherapists and rehabilitation assistants. 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 have two phases; in the first phase a study prognostic screening algorithm 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 NIHR funded COAST study which contains pre-operative and 6 month outcome data on patients which seeks to predict outcome following arthroplasty. The screening tool will

then be used to identify individuals for the CORKA main RCT and to assess the inclusion threshold for those patients likely to benefit from a multi-component rehabilitation programme.

3 ii 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.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Our objectives within this study are to design a screening tool to identify patients at risk of poor outcome and to evaluate the impact of a bespoke rehabilitation intervention versus usual care.

We will analyse data from the COAST study (outcomes in arthroplasty) to develop an algorithm to be used at the pre-operative assessment to identify patients likely to be at risk of poor outcome after knee replacement.

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

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 and serious adverse events associated with the treatment programme

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 patients about their visits to their GP, district nurse, physiotherapy, occupational therapy, any hospital visits and medication and equipment 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 and quality of life of this new rehabilitation protocol versus standard care of out-patient based post-operative physiotherapy.	1. The primary outcome will be the Late Life Function and Disability Instrument (LLFDI) score; a validated questionnaire previously used in rehabilitation trials of community dwelling elders. 2. It will be used at baseline 6 and 12 months post randomisation.
Secondary Objectives • To assess the safety and serious adverse events associated with the treatment programme. • To assess the acceptability and adherence to the treatment programme for patients and therapists through both a RCT and a nested qualitative study. • To assess the cost effectiveness of the different treatment strategies.	At Baseline, at 6 and 12 months post randomisation Questionnaires: 1. Oxford Knee Score 2. Quality of Life subscale of the Knee Osteoarthritis Outcome Score (KOOS) 3. Physical Activity Scale for the Elderly (PASE) questionnaire. 4. Health economics using EQ-5D Diary: 5. Diary: On discharge the participant will be given a diary for daily/regular completion, recording: o Daily pain using VAS for first 6 weeks, then once a month until 1 year o Exercises undertaken o Medication taken o Use of healthcare services and personnel Adverse events throughout study

Tertiary Objectives

Develop a screening algorithm for use in the main RCT • Central study team to develop • To be piloted in one site	• Identify factors associated with poor outcome after knee arthroplasty • Develop screening algorithm to identify those at high risk of poor outcome following knee arthroplasty • Carry out literature review • Gather expert opinion • Modeling of existing data set • Examine COAST study data
Develop a targeted rehabilitation programme for use in the main RCT • Central study team to develop • To be piloted in one site	• Develop a targeted rehabilitation programme suitable for delivery in participants own home • Using lit review, consensus/ expert peer review
Main study: Qualitative study (Selected sites/selected participants only)	• Experiences and views of participants • Explore experiences and views of participants about their treatment interventions • Participant interviews using phenomenological analysis approach
Main study: Health economic cost utility analysis	• Collect health utility data to calculate QALYs • We will conduct a cost utility analysis from both NHS and a societal perspective. • EQ-5D • Cost data from participant completed diary

5. STUDY DESIGN

CORKA is a prospective individually randomised controlled trial with blinded outcome assessment at baseline, 6 and 12 months. 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 current standard care. The study will take place in a minimum of five NHS hospitals across the UK. The study includes a qualitative and health economic analysis.

Prior to the RCT two activities will take place:

1) A multidisciplinary home-based rehabilitation exercise intervention will be developed which will be used in the main study as the intervention.
2) A screening algorithm will be developed to identify those at higher risk of poor outcome

During the trial people undergoing knee replacement will be screened for suitability during their admission for surgery and will be approached to consider the study post-operatively. Once informed consent is gained participants will be enrolled in the trial, baseline data will be collected and randomisation will take place using either the telephone or website option provided by the Oxford Clinical Trials Research Unit (OCTRU) randomisation service. Participants will be allocated to receive one of two rehabilitation options, either 'Standard rehabilitation' or 'Community-based rehabilitation programme'. Participants and those delivering rehabilitation will be aware of the treatment allocation due to the nature of the intervention.

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 frames, 6 and 12 months after randomisation. 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.

A subsection (approximately n=15) of trial participants and physiotherapists, occupational therapists and rehabilitation assistants providing the treatment (approximately 10) will undergo one interview to obtain in-depth views about the intervention and how it is delivered.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

People scheduled to undergo KR who are assessed 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

6.2. Inclusion Criteria

Participants will be given a brief assessment to determine any absolute contraindications to exercise and the optimal exercise intensity for each participant.

- 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 intensive rehabilitation programme if randomised to the intervention arm

6.3. Exclusion Criteria

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

- Severe cardiovascular or pulmonary disease (New York Heart Association III-IV)
- Severe dementia, assessed using local hospital dementia screening tool.
- Rheumatoid arthritis
- Further lower limb arthroplasty surgery planned within 12 months

7. STUDY PROCEDURES

7.1. Site Recruitment

A minimum of 5 NHS hospitals who carry out elective KR will participate to recruit 600 participants. Each site will recruit for 15 months depending on set up time frame, with a target recruitment of approximately 10 patients per month, per site.

The leading site is Oxford University Hospital NHS Trust.

7.2. Participant Recruitment

People who are scheduled to receive a KR will 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. Those who are willing to participate will be checked for eligibility and given the opportunity to ask questions and appropriate informed consent will be gained. Baseline outcome data will be collected 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 per-operative complications or failed to meet expected in-patient mobility milestones. If eligible, participants will have their consent confirmed and will be randomisation will take place using either the telephone or website option provided by the OCTRU randomisation service. Participants will be allocated to receive one of two rehabilitation options, either 'Standard Rehabilitation or 'Home-based exercise programme'. Participants and those delivering the rehabilitation are aware of the treatment allocation due to the nature of the intervention.

7.3. 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 allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. 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.

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.

7.4. Screening and Eligibility Assessment

Patient 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 within 4 weeks after randomisation.
- Screening/informed consent/baseline data collection/randomisation takes place before patient's discharge from hospital

7.5. 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 OCTRU. The service may be accessed by both telephone (during office hours 8am to 5pm), or via a secure randomisation website (24 hours/ 7 days a week).

Where research staff are not available at a weekend, randomisation will occur on the first working day after the patient's discharge.

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.

7.6. Baseline Assessments

Baseline data will be collected on paper questionnaire and the majority is patient-reported:

1. Demographics (name, age, surgery, ASA rating) including contact details

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 total 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 aA 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, lesuire 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 a descriptive system of 5 dimensions, mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
   measure of health status. In addition to an EQ visual analogue scale (VAS). 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 Timed Up and Go, Figure of 8 walk test and a step climb test. [Steffan 2002, Hess 2010]

9. On discharge the participant will be given a diary for daily/regular completion, recording:
    - Daily pain using a visual analogue scale for 6 weeks
    - Exercises undertaken completed for 6 weeks daily and weekly thereafter
    - Medication taken
    - Use of healthcare services and personnel
    - Adverse events

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

7.7. Subsequent Visits

Follow up data will be collected on paper questionnaire and the majority is patient-reported.

The study has two follow up timeframes, at 6 and 12 months post-surgery. Follow up takes place at the participants own home (those allocated to home-based exercise intervention), or the hospital out-patients department (those allocated to standard rehabilitation). Local site staff will organise the follow up and liaise directly with the participant to organise the home-based follow up or standard rehabilitation follow up. The following will be collected at the two follow up time points.

1. Complications: any apparent KR related complications since discharge
2. Late Life Function and Disability Instrument.
3. Oxford Knee Score
4. KOOS -quality subscale.
5. Physical Activity Scale for the Elderly (PASE) questionnaire.
6. EQ-5D-5L
7. Functional Co-morbidities Index
8. Timed functional tests – TUG, Figure of 8 walk and step test.

7.8. Qualitative interviews

In addition to the main study, a qualitative study will take place in selected sites for a small number of participants. There will be a separate consent process for the qualitative interviews. This nested study aims to find out what makes the proposed intervention acceptable and patients willing to participate and adhere to the treatment programme.

We will conduct a number of interviews in the pilot phase to gain feedback on a range of issues. These interviews will inform the refinement and delivery of the main treatment interventions. We will also use qualitative approaches later in the research programme to inform the results of the main trial.

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 which includes; female and male participants, those with differing levels of function and disability selected using their LLFDI score and patients of varying activity levels.
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 patient, from previous experience this is most likely to be at patient'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
check their transcript, 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.

7.1. Health economics

A health economic cost utility analysis will take place. We will collect data to calculate QALYs using the EQ-5D and the cost data from the participant-completed diary. Cost utility will be evaluated from both NHS and societal perspectives. The health economic evaluation will determine whether a home-based multidisciplinary rehabilitation package compared to usual care represents good value for money in patients undergoing total knee replacement (KR) for chronic arthropathy is planned as part of the trial design.

The economic evaluation will be a cost-effectiveness analysis (specifically a cost-utility analysis) from a societal perspective and quality-adjusted life years (QALYs) will be used as the main health outcome measure. NHS health care resource use data will be collected through a participant diary at baseline, 6 months and 12 months follow-up. These will include GP visits, related-hospitalisations, outpatient visits, district and practice nurse visits, physiotherapy visits and any occupational therapy visits. A microcosting method will be used to calculate costs of the home-based rehabilitation intervention. We will also collect patient incurred costs including visits to private practitioners, complementary therapists, and equipment purchased to provide the appropriate environment for home exercise and everyday tasks. We will also ask about any unpaid informal care provided by relatives and / or friends. Unit cost data will be taken from national sources such as the NHS reference costs, and PSSRU costs of health and social care [Herdman 2011, Lothgren 2000].
A maximum of one-year follow-up data will be available for the economic evaluation. However, it is likely that the course of costs and benefits for the target population will extend beyond that period. Therefore, the one-year results will be extrapolated to an additional 5 years using parametric methods or a decision analytic model.

7.2. Discontinuation/Withdrawal of Participants from Study

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

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation, e.g. attending additional outpatient physiotherapy appointments.

7.3. 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 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.

7.4. Definition of End of Study

The end of study is the date of the last 12 month follow up of the last participant randomised, if follow up is possible.

8. INTERVENTIONS

8.1. 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 package incorporates an exercise programme with progressive resistance and mobility exercises and integrated adherence strategies in its provision. The largest component will be an exercise programme to be delivered in the patients' 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 following 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. The use of rehabilitation assistants to supervise and facilitate exercise under the guidance of qualified staff will be piloted to test the skills required to implement an exercise based programme that is affordable.

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 community-based rehabilitation programme. It will commence delivery within 4weeks of TKR 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.

8.2. Standard rehabilitation

Standard rehabilitation as offered to KR patients locally. This is likely to include:

- Written advice on exercises to do at home, given on discharge from hospital
- Up to 6 sessions of traditional out-patient physiotherapy (over 10 weeks), as required
- Delivered by qualified Physiotherapist
- Home requirements assessed by Occupational Therapist is barriers to discharge or identified problems

8.3. Staff training: rehabilitation programme

Only staff trained in the CORKA home-based exercise programme may deliver the study intervention.

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. 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 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 will travel to deliver the training) in accordance with the requirements of the CORKA study. The CORKA site training log will be signed off by the trainer and/or the local PI. A copy will be sent to the co-ordinating office in Oxford, the original filed in the ISF at the site.

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.

9. SAFETY REPORTING

9.1. Definition of 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.

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.

9.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

10. STATISTICS AND ANALYSIS

10.1. Proposed sample size

The total sample size required for this study is 632 (i.e. 316 per group). 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 0.25, which is a value that we expect to be clinically important and realistic in rehabilitation trials. Assuming SMD of 0.275 or 3 points in the LLFDI we would need a total sample size of 568, needing to recruit 632 at 90% power and 5% level of significant (2-sided) and loss to follow up rate is 10%.

We have also assessed the impact of mean treatment difference if there was any clustering effect of therapists in the study. From previous studies we conducted, we anticipate that the intracluster class correlation is likely to be between 0.01 and 0.04. The mean difference in LLDFI between the two groups will become 3 points and 5 points, respectively.

10.2. 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. Primary outcome will be analysed using a linear mixed effects method with repeated measures, on outcome measurements at 4 and 12 months, adjusting for baseline score and stratification/minimisation 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 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 more detailed account of the proposed statistical analysis will be prepared before the trial recruitment starts.

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations. All data and documentation will be stored in accordance with regulatory requirements and acces to the data will be restricted to authorised trial personnel. Oxford Clinical Trials Research Unit will securely hold the database.

11.2. 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 frames (6 and 12 months), will be via a home visit or an out-patient clinic visit onto paper questionnaire/CRF. These will be sent by a member of the local research team to the central trial office in Oxford by post, using a Freepost account.

The data will be entered into a study-dedicated database provided by the Oxford Clinical Trials Research Unit, a UKCRN Registered Clinical Trials Unit. OpenClinica software is used and this is the world's leading clinical trial software used for clinical data management. 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.

12. QUALITY ASSURANCE PROCEDURES

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

13. ORGANISATION

13.1. Project timetable and milestones

The aim is to randomise 600 patients to the trial over a period of 15 months. Approximately each of the 5 main recruitment clusters hospitals included in the trial will carry out 300 elective knee arthroplasty operations each year. A conservative estimate of the proportion of patients who would be considered at risk of poor outcome is 50%. We anticipate that a total of 10 per month per site - ~ 40% of eligible patients would need to be recruited to achieve the estimated sample size. Previous knee replacement trials have had a consent rate of 59% of eligible patients (Minns Lowe 2012) .

13.2. Trial Steering Committee (TSC)

The TSC provides overall supervision of the trial on behalf of the funder. Its terms of reference will be agreed with the HTA and published on the trail website. Meetings of the TSC will take place at least once a year during the recruitment period.

13.3. 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/the CCTR Trials Group. This group will oversee the day-to-day running of the trial and will meet regularly. The responsibilities of the group include:

1. Recruitment of participating sites
2. Distribution of appropriate CRFs/Questionnaires and other trial documents to sites
3. Receiving study data and data management
4. Organisation of the follow up questionnaires
5. Data entry and cleaning
6. Data analysis
7. Organising and servicing the DMC and TSC meetings

13.4. 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 co-ordinating 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 running a programme
7. Ensure timely delivery of the Rehabilitation Programme
8. Identify Physiotherapists to act as blinded assessors for 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

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. 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).

14.2. 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.

14.3. 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. The CCTR Trials Group reports to the Trial Steering Committee which is responsible to the Research Sponsor (University of Oxford). At each participating centre, local Principal Investigators will report to the Trial Management Group via the project funded staff based in the CCTR Trials Group.

14.4. Approvals

14.4.1. 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 xxxxxxxxxxxxxxxxxxx REC.

14.4.2. 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.

14.5. 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.

14.6. 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.

14.7. 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. Patients will be paid their travel costs at National Guidance rates. They will not receive any other payments or any other benefits.

14.8. Project Funding

The CORKA Study funding has been awarded by the National Institute for Health Research (NIHR), Health Technology Assessment (HTA) Programme.

14.9. 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/about us

14.10. 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.

15. 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 TSC for review before release.

We will provide all participants with a summary of the trial outcome.

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

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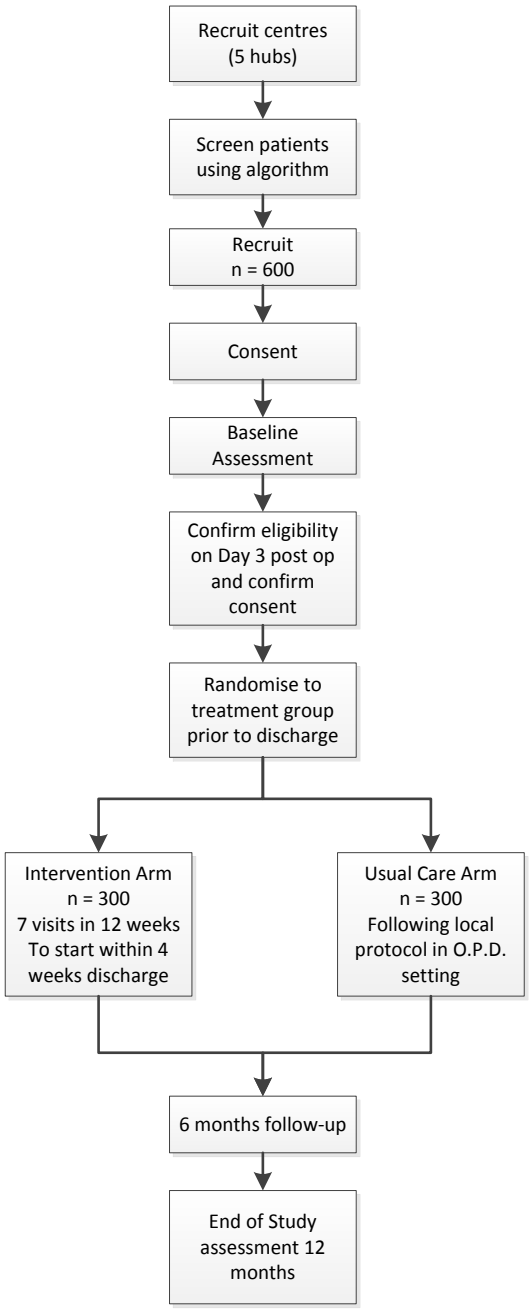
APPENDIX A: STUDY FLOW CHART



APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Time point	Surgery	Enrolment	Baseline	Allocation	Post-surgery			
					Weeks 0-2	Weeks 3-6	6 Months	12 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 – standard rehabilitation					X			
ASSESSMENTS								
• Demographics • Medical History • EQ-5D Pre-surgery recall			X					
• LLFDI score			X				X	X
• Oxford Knee Score			X				X	X
• Quality of subscale of the Knee Osteoarthritis Outcome Score (KOOS)			X				X	X
• Physical Activity Scale for the Elderly (PASE) questionnaire.			X				X	X
• Health economics using EQ-5D			X				X	X
• Timed Up and Go walk test			X				X	X
• Step climb test			X				X	X
Participant Diary: completed daily /as required at home for 6 weeks. Then weekly recording: • Daily pain using VAS • Exercises undertaken • Medication taken • Use of healthcare services and personnel								

Project Milestones & Timescale

Project Activity	<0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Recruit Research Staff	X																	
Ethics Appraisal		X																
Update systematic review	X	X																
Refine content training package programme	X	X																
Pilot Study		X	X															
Develop educational support materials			X															
Recruit & prepare centres			X	X														
Pilot study evaluation				X														
Site set-up/approvals			X	X														
Train intervention providers				X														
Main trial																		
Recruitment period					X	X	X	X	X	X								
Review recruitment rates ? add sites							X											

Intervention treatment delivery						X	X	X	X	X	X							
6 weeks follow-up							X	X	X	X	X	X	X					
6 month follow up																		
12-month follow-up										X	X	X	X	X	X			
Qualitative Trial																		
Interviews patients & therapists			X									X	X	X	X			
Thematic Analysis												X	X	X	X			
Data analysis								X	X						X	X	X	X
Economic appraisal															X	X	X	X
DMEC meeting			X			X			X			X		X			X	

APPENDIX C: AMENDMENT HISTORY

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