PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Robotic Arthroplasty Clinical and cost Effectiveness Randomised controlled trial (RACER-knee): a study protocol
AUTHORS	Griffin, James; Davis, ET; Parsons, Helen; Gemperle Mannion, Elke; Khatri, Chetan; Ellard, David; Blyth, MJ; Clement, Nicholas; Deehan, David; Flynn, Nicholas; Fox, Josephine; Grant, Nicholas; Haddad, Fares; Hutchinson, Charles; Mason, James; Mohindru, Bishal; Scott, Chloe; Smith, Toby; Skinner, John; Toms, Andrew; Rees, Sophie; Underwood, Martin; Metcalfe, Andrew

VERSION 1 – REVIEW

REVIEWER	Leo Nherera Smith and Nephew plc, Health Economics and Market Access
REVIEW RETURNED	26-Oct-2022

GENERAL COMMENTS	It is a well written protocol, made minor suggestions which can be addressed otherwise accept this protocol. The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Charles Okafor Griffith University School of Medicine, Centre for Applied Health Economics
REVIEW RETURNED	19-Dec-2022

GENERAL COMMENTS	This is an important paper and I have been looking forward to this kind of study. I look forward to the outcome of this important study that hopes to address salient questions. More evidence is needed to determine whether Robotic-assisted TKA should become the standard of care for knee arthroplasty in the future - this study hopes to provide more evidence. There has been a significant growth in the use of robotic assistance especially in the United States due to its capacity to increase accuracy and precision in implantation, reducing the chances of mal-positioning and hence risk of revision. Although, robotic-assisted surgery is associated with an increase in the cost of knee arthroplasty. Lack of cost-effectiveness evidence has been a barrier to the increased adoption of this technology globally due to the limited and unclear evidence on its benefits. The RCT and within-trial cost-effectiveness analysis this study proposes will indeed provide evidence to support decision making. The protocol was well written. Below I have some recommendations that could improve the outcome of this study. Major Study design

1. I would suggest the inclusion of other interventions as comparators to provide robust evidence. Consider the inclusion of patient specific instrumentation (PIS) system, sensor systems, accelerometers, and other navigation systems as comparators. I am not sure if these were intended to be captured under the conventional TKA arm. Also, it would also be good to define the surgical technique(s) briefly and clearly in the conventional arm to provide a better grasp of the "conventional" TKA because treatment strategies have evolved recently and differ across settings.

2. I am not sure if the authors intend to measure risk of revision or revision rate. This is important because revision rate is a principal outcome measure of TKA. At minimum, consider early revision rate as a primary or secondary outcome measure. Reoperation was reported as a secondary outcome measure but not all reoperations are revisions.

3. Power and sample size: Please provide information on the basis surrounding the standard deviation assumption. Was it based on a recent population-based study in the United Kingdom?

My recommendations

This is an important paper and I have been looking forward to this kind of study. I look forward to the outcome of this important study that hopes to address salient questions. More evidence is needed to determine whether Robotic-assisted TKA should become the standard of care for knee arthroplasty in the future - this study hopes to provide more evidence. There has been a significant growth in the use of robotic assistance especially in the United States due to its capacity to increase accuracy and precision in implantation, reducing the chances of mal-positioning and hence risk of revision. Although, robotic-assisted surgery is associated with an increase in the cost of knee arthroplasty. Lack of cost-effectiveness evidence has been a barrier to the increased adoption of this technology globally due to the limited and unclear evidence on its benefits. The RCT and within-trial cost-effectiveness analysis this study proposes will indeed provide evidence to support decision making. The protocol was well written. Below I have some recommendations that could improve the outcome of this study.

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VERSION 1 – AUTHOR RESPONSE

Reviewer 1's comments

This is an important protocol which describes the RACER study which assesses the clinical and cost-effectiveness of robotic-assisted TKR compared to TKR using conventional instruments. The protocol is well written and very clear. The involvement of patients in developing this protocol to validate their methodology is a powerful addition.

Many thanks to the reviewer for these supportive words.

I have minor suggestions below

Abstract

• I suggest the authors mention the type of economic evaluation in the abstract

• We have added that both within-trial and modelling approaches to the cost-effectives analysis will be included.

Introduction

• Page 6 of 28 under Introduction, Line 48 reduction in LOS, future revisions or large differences in utility suggest adding "in favour of robotic-assisted surgery", to show this ought to be in favour of the robotic approach to show the benefit

• Thank you for this helpful clarification, we have added the text as suggested on page 4 of the revised manuscript.

• Page 7 of 28 under Introduction, Line 54, can give examples of clinical outcomes that showed improvement?

Thank you, we have added some relevant examples and improved the wording of the sentence.
Methods

• Statistical analysis plan page 16 of 28, line 18, word order, it should be "primary component involved" as in line 41

• Agreed, thank you for identifying this. We have corrected the text.

• Page 5 of 28 under Article Summary should specify that the modelling approach is only used when the within trial analysis does not show
convergence or dominance as explained on Page 17 of 28 Line 34-35

• Agreed, thank you again for identifying this. We have added some more clarification to the article summary as suggested.

Reviewer 2's comments

This is an important paper and I have been looking forward to this kind of study. I look forward to the outcome of this important study that hopes to address salient questions. More evidence is needed to determine whether Robotic-assisted TKA should become the standard of care for knee arthroplasty in the future - this study hopes to provide more evidence. There has been a significant growth in the use of robotic assistance especially in the United States due to its capacity to increase accuracy and precision in implantation, reducing the chances of mal-positioning and hence risk of revision. Although, robotic-assisted surgery is associated with an increase in the cost of knee arthroplasty. Lack of cost-effectiveness evidence has been a barrier to the increased adoption of this technology globally due to the limited and unclear evidence on its benefits. The RCT and within-trial cost-effectiveness analysis this study proposes will indeed provide evidence to support decision making. The protocol was well written.

Many thanks for this thoughtful response, we are hoping the present study can provide some of the key missing answers to important research questions currently open in the field.

Below I have some recommendations that could improve the outcome of this study.
Major
Study design
1.   I would suggest the inclusion of other interventions as comparators to provide robust evidence. Consider the inclusion of patient specific instrumentation (PIS) system, sensor systems, accelerometers, and other navigation systems as comparators. I am not sure if these were intended to be captured under the conventional TKA arm. Also, it would also be good to define the surgical technique(s) briefly and clearly in the conventional arm to provide a better grasp of the "conventional" TKA because treatment strategies have evolved recently and differ across settings.
Thank you for this, it is an important point to clarify. The comparator for this trial will be conventional instruments without patient specific instruments or computer navigation, as we believe these represent different research questions. We have clarified this in the text. We are not planning for kinematic alignment or any other emerging alignment strategy. In this trial, planning is performed to mechanical alignment, but surgeons are allowed to make adjustments in either arm as they determine appropriate according to their normal clinical practice. This represents a pragmatic trial framework but with a consistent approach to pre-operative planning.

2.   I am not sure if the authors intend to measure risk of revision or revision rate. This is important because revision rate is a principal outcome measure of TKA. At minimum, consider early revision rate as a primary or secondary outcome measure. Reoperation was reported as a secondary outcome measure but not all reoperations are revisions.
Thank you, this is a good point. We will categorise re-operations into revision procedures (using standard definitions) and other re-operations. We will present these alongside the other secondary outcomes. Full analysis details will be presented in the separate Statistical Analysis Plan as the appropriate analysis will be dependent on the number of events observed. We expect that these events will be rare within 24 months, so will be likely initially be presented as incidence in each group and analysed using Fisher's Exact test.

3.   Power and sample size: Please provide information on the basis surrounding the standard deviation assumption. Was it based on a recent population-based study in the United Kingdom?
The choice of standard deviation was based on available data from the two most recent relevant studies in the literature (references 54 and 55), one of which was conducted in the UK. We have amended the text to make this clear. Another reference from a study on the validity and reliability of the FJS in the TKA setting is provided for the reader (reference 33).

VERSION 2 – REVIEW

REVIEWER	Leo Nherera Smith and Nephew plc, Health Economics and Market Access
REVIEW RETURNED	02-Feb-2023

GENERAL COMMENTS	Great work, just need to provide a reference for NICE guidance line The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Charles Okafor Griffith University School of Medicine, Centre for Applied Health Economics
REVIEW RETURNED	10-Feb-2023

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.