# Cost of Revision Total Knee Replacement: A Protocol For Systematic Review And Meta Analysis

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**Protocol**

**Keywords:** Revision total knee replacement, cost, economic burden, knee, arthroplasty

**Posted Date:** May 8th, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-26924/v1



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**Version of Record:** A version of this preprint was published at PharmacoEconomics - Open on November 25th, 2020. See the published version at https://doi.org/10.1007/s41669-020-00242-7.

# Abstract

Background A major limitation of Total Knee Replacement (TKR) as to other joint replacements is the risk is revision. Revision TKR is associated with high risk and economic burden to patients, healthcare provider and the society. It will be worthwhile to analyze how close or far the economic burden of revision TKR vary across countries or already existing studies. It is important to compare the studies characteristics and identify factors that are determinants of cost and outcome variability in the management in order to inform decisions for future revision TKR. This study aim to review the literature on the cost of revision TKR to assess cost variation across countries and studies; estimate a pooled cost estimate; identify factors that contribute the high cost and provide recommendation for cost minimization; identify limitation and gaps in cost burden assessment of existing studies and provide recommendations for future research.

Methods We will search MEDLINE (OvidSp), Embase, Cochrane Library, EconLit, Google Scholar and Scopus to identify relevant studies. We will use an advanced search approach to search for relevant studies. EndNote library will be used to manage searched studies. Selection will done in two phase: screening and eligibility. Selection, data extraction assessment of risk of bias will be done in duplicates after which the data will be analysed descriptively and a meta-analysis performed.

Discussion This protocol provides a proposed stepwise plan in conducting a systematic review and meta-analyses of cost of revision total knee replacement. Findings from this systematic review will provide information about factors associated with high costs of revision TKR, proffer recommendations to minimize cost and inform where future knee arthroplasty management decisions and future research should focus.

**Systematic Review Registration:** PROSPERO CRD42020171988


# Background

One major limitation of Total Knee Replacement (TKR) as to other joint replacements is the risk is revision. Revision TKR is the repetition of TKR procedure due to surgical failure of primary TKR (1). In this case, part or all the original prosthesis is removed and replaced. The major cause of revision TKR include but not limited to the following: Infection, aseptic loosening, instability, stiff knee, periprosthetic fracture, patellar clunk, quadriceps disruption, failed unicondylar knee and metallosis (2). The incidence and causes of revision TKR continue to change with time. During the early experience with hinge and condylar knees, revisions were mostly due to knee instability, sepsis or prosthetic loosening (3). About three decades ago, major revisions were due to patellofemoral complications (4). Two decades ago, polyethylene wear was a primary cause of revision (5). A more recent review has shown that the current primary causes of revisions are Infection and prosthetic loosening (3). A recent review showed that 46% of revision cases were in the early stage (within 2 years after primary TKR) while 54% of revision cases was performed after 2 years of the primary TKR (6). Major causes of revision in the early phase were instability, infection and stiffness while major causes of revision in the late phase were infection and instability (6). Recent epidemiology and review study showed that the rate of revision TKR ranges from 2.1–9.7% (2, 7) across countries and studies in the world.

Revision TKR is associated with high risk and economic burden for patients with end-stage OA (8). The quality of life and survival rate of revision TKR has been recurrently found to be less than primary TKR (9–11).

Interestingly, the cost of revision TKR is higher than the primary TKR (12, 13). Studies have also shown that revision due to infection cost more than any other cause of revision like aseptic loosening (8, 13). Patients and insurance organization are faced with the challenge of paying for a huge unforeseen revision after the primary surgery. Due to the high economic burden especially in infection-based revision, some insurance schemes do not cover for the full cost of revision (8, 12) which leaves a huge burden on the patients or healthcare provider. Although, reports have shown a reduction in the revision rate over the years (14, 15) and the effectiveness of performed revisions (2, 16) the ultimate goal is to achieve a zero revision rate after primary TKR.

Several studies have evaluated the economic burden of revision TKR. Oduwole et al. in 2010 studied the cost in revision TKR with the aim to compare the cost difference between aseptic and septic cases of revision and identify sources to prevent an increase in revision costs (8). Kallala et al. in 2015 compared revision TKR due to infection and other causes like pain, aseptic loosening, instability and fracture from the healthcare provider perspective (13). Herbert et al. in 1996 also compared the cost of revision due to infection and the cost due to primary TKR and non-infected cause of revision from the healthcare provider perspective (12). The economic burden of revision TKR varies from country to country and from one healthcare centre to the other. It will be worthwhile to analyze how close or far the economic burden of revision TKR vary across countries or already existing studies. It is important to compare the studies characteristics and identify factors that are determinants of cost and outcome variability in the management in order to inform decisions for future revision TKR. The International Society for Pharmacoeconomics and Outcome Research (ISPOR) Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline (17) provided a guide for economic evaluations. It is important to access the methodologies and interpret how the existing studies conform to established standards, hence the need for a systematic review of the cost of revision TKR.

In this study, we propose to review the literature on the cost of revision TKR. The problem-intervention-comparator-outcome (PICO) was used to formulate the research questions. The study intends to address the following questions:

1.
What is the cost of revision TKR for different study settings and methods?
2.
What is the pooled cost estimate from existing studies?
3.
How was the cost evaluation of the different studies conducted?
4.
Which factors contribute significantly to the cost?
5.
What are the implications and prognoses of revision TKR?
6.
What are the limitations and gaps in existing studies?

# Methods

### Protocol and registration

The design of this systematic review is in accordance with the recommendation in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement (18). Details of the PRISMA-P checklist are provided (see Additional file 1). The protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO), CRD42020171988.

To aid the development of this protocol, we did a preliminary assessment of literature using PubMed and Google Scholar to identify interventions and methods for measurement. This helped us to define our inclusion and exclusion criteria in the search.

### Eligibility criteria

Studies to be included in this review must meet the following criteria:

1. Original economic evaluation of data on revision knee replacement
2. Studies must present cost data. Either direct cost, indirect cost or both
3. Cost from societal, patient, payer or health care provider perspective
4. Full-text articles and Abstracts.
5. Studies presented the English language

Studies to be excluded in this review include:

1. Opinion papers, conference proceedings, qualitative report
2. Cost not specific for revision procedure
3. Cost on TKA alone without revision cost
4. Cost on readmission without revision

### Information sources

Databases to be employed was determined based on expert librarians recommendations (19) and after assessment of the health economic core library recommendation by the U.S. National Library of Medicine (20). We will search MEDLINE (OvidSp), Embase, Cochrane Library, EconLit, Google Scholar and Scopus to identify relevant studies.

### Search strategy

We will use an advanced search approach to search for relevant studies. Using MEDLINE (OvidSp), we will create concept clusters. Each concept cluster will be created by combining a comprehensive set of possible search terms. The search terms will be created by combining related relevant Medical Subject Headings (MeSH) or combining relevant text words (title, abstract and key words). The MeSH and text words (search terms) will be combined to form a union (concept cluster). For example if A, B and C represent related MeSH and key words, the union is formed as “A or B or C”. Several relevant concept clusters will be created. The

concept clusters will be combined to form an intersection cluster. For example if X, Y and Z are clusters, they will be combined as “X and Y and Z”. The results will then be reviewed by looking at the MeSH subject headings and sub-headings, titles and abstract to check if there are terms that could improve our search. For instance, we searched for “revision knee replacement” which present results with all headings and sub-headings. We then searched alternative key words like “knee”, “knee reoperation”, “knee replacement”, “revision arthroplasty” appearing in the title, abstract, or key words. This search strategy was developed by the research team. Details of the MEDLINE search are shown in Table 1. The MEDLINE search strategy will be adapted for search in other databases. Auto-alert system will be set up to provide literature update while the data extraction and analyses are on-going.

Table 1: Search Strategy for MEDLINE (OvidSp)

| | |
|---|---|
| 1 | Prosthesis failure/ or Prosthesis-Related Infections/ or Knee Prosthesis/ or Knee Joint/ or Arthroplasty, Replacement, Knee/ or Reoperation/ |
| 2 | Aseptic loosening/ or instability/ or stiff knee/ or periprosthetic fracture/ or patellar clunk/ or quadriceps disruption/ or failed unicondylar knee/ or metallosis/ |
| 3 | (Knee revision or revision knee replacement or revision knee arthroplasty).ti,ab,kw,tw. |
| 4 | Knee reoperation.ti,ab,kw,tw. |
| 5 | 1 or 2 or 3 or 4 |
| 6 | Economic burden/ or cost-of-illness/ or cost/ |
| 7 | Cost effectiveness analysis/ or cost-benefit analysis/ or health care costs/ or "cost of illness"/ or "costs and cost analysis"/ |
| 8 | (Burden or economic burden or cost or cost analysis).ti,ab,kw,tw. |
| 9 | 6 or 7 or 8 |
| 10 | 5 and 9 |
| 11 | Limit 10 to English language |
| 12 | Limit 11 to Humans |

ti = title; ab = abstract; kw = key word; tw = text word

## Study records

*Data Management*

Result of the search from different databases will be exported into a single EndNote library. Six groups will be first created to contain searches from the different databases. The EndNote will be used to de-duplicate the studies. After de-duplication, we will initiate an auto-search for full-text of the articles. A union group will be created to contain all the articles. From this union group, we will create different subgroups to represent

exclusion criteria. Excluded studies will be exported to different exclusion folders based on criteria for exclusion. A study that does not meet inclusion criteria for multiple reasons will be exported to relevant exclusion folder in the order of priority:“revision knee replacement”, “cost analysis”, “economic evaluation”, “originality”, “clarity”, “scope”, and “language”.

## Selection process

Selection will be independently done by two reviewers against the eligibility criteria. A third reviewer will have an overview of the selection by the first two reviewers and resolve any selection disagreement among the first two reviewers. The selection will be done in phases. We will first screen titles and abstract of full length or abstract of original research articles that involve the cost of revision knee replacement. Next we will assess full-text of potential articles for eligibility like clarity, the perspective of cost used in the study whether societal, patient or payer or health provider. We will also check for the components of the direct and or indirect cost used. Relevant studies which will be excluded in the cost analysis will be listed in a table “characteristics of excluded studies”. This will help us to categorize and summarize the studies that meet the inclusion criteria and provide reasons why some relevant studies were excluded. We will assess titles, abstracts, and full-text articles. In the eligibility phase, we will use abstract of journals where there is no institutional access to full-text and if an application for subscription will take more than one month to complete. See Table 2 for more details on the selection process.

Table 2: Items on article screening form

| | |
|---|---|
| Phase 1 screening | |
| | Research article (yes / no) |
| | Original research article (yes / no) |
| | Health economic evaluation (yes / no) |
| | Evaluation on revision knee replacement (yes/ no) |
| | Evaluation involves cost (yes/ no) |
| | Other reasons for exclusion (yes / no).<br>Provide reasons if yes |
| | All phase 1 screening criteria met (yes / no) |
| Phase 2 screening (if all phase 1 screening criteria are met) | |
| | Costing method clear (yes / no) |
| | Cost perspective (societal, patient/payer/health provider) |
| | Components of the direct cost (Intervention/Laboratory test/service cost).<br>Others (specify) |
| | Components of indirect cost (productivity loss/ lost productive years/transportation/unemployment) |
| | Include article in final data extraction (yes / no) |
| | Any additional detail about the article |

### Data collection process

We will pilot an electronic data extraction form. Two reviewers will independently extract and manage the data from the included studies. Disagreement with the extraction results from the two reviewers that cannot be resolved by them will be resolved by the third reviewer. The data will be selected based on the ISPOR CHEERS guideline (17). The Larg and Moss guideline for cost-of-illness will also be used in our data collection (21). The Campbell and Cochrane Economics Methods Group guideline will also be employed in our data extraction process (22).

### Data items, outcome and prioritization

Data will be extracted based on the following:

1. Publication: title, authors, year and setting or country the study was conducted.

2. Study design: cross-sectional, longitudinal, observational, cohort etc.; aim of the study, sample size, gender, comorbidities (see Table 3 for details).
3. Cost measure: Our primary cost measure will be direct cost and indirect cost like productivity loss, cost of reduced work efficiency or workdays lost. Secondary outcomes include cost difference between primary TKR and revision TKR, number of revisions, and incidence estimates.

Table 3: Items on data collection form for included studies

| | |
|---|---|
| 1 | Author |
| 2 | Year of publication |
| 3 | Year of study |
| 4 | Research title and study objectives |
| 5 | Cause of revision |
| 7 | Comparator (s) |
| 8 | Study setting |
| 9 | Sample size |
| 10 | Patients' characteristics (age, sex, gender etc.) |
| 11 | Study perspective |
| 12 | Time horizon |
| 13 | Discounting and price year and currency |
| 14 | Type of economic evaluation |
| 15 | Study design: observational study, cross-sectional, longitudinal etc. |
| 16 | Cost components: (direct or indirect). |
| 17 | Sub-components of the cost (medications, laboratory, devices, surgical, productivity loss, transportation, service cost etc.) |
| 18 | Cost estimation approach: Bottom-up or Top-down |
| 19 | Total cost |
| 20 | Comorbidity |
| 21 | Study assumptions |
| 22 | Sensitivity analysis |
| 23 | Conflict of interest |
| 24 | Funding declaration |
| 25 | Any other relevant details |

### Risk of bias and transparency in the studies

The Consensus Health Economic Criteria (CHEC) checklist designed for conducting systematic reviews which are based on economic evaluation will be used in this study (23). This checklist has 19-point reporting standards for economic model characteristics (population, time horizon, perspective, discount rate etc.), identification and valuation of costs and outcomes, discussion section, conclusions as well as funding and conflicts of interest. We will also use the Larg and Moss guideline to check for bias in the studies (21). To further evaluate the selected studies for “transparency” of cost estimates, we will use the criteria developed by Fukuda and Immanaka to classify the studies into transparency level. The classification will depend on the extent and clarity to which the cost components are reported, and the quantity and unit price of the resources reported (24). The CHEC list will be completed in duplicate by two members of the review team. Any difference will be resolved either with the third author or by review of other related referenced articles. Details on the risk of bias are shown in additional files (Additional file 2) and (Additional file 3).

### Data synthesis

After extracting relevant data from selected studies, data synthesis and analysis will be done in two phases. First, we will perform a narrative synthesis and summary of answers to our research questions. A descriptive overview and characteristics of the studies will be presented. The selected studies will be further classified according to the risk of bias and transparency of their results. Studies whose cost data will be synthesized must pass (low or moderate score) the measurement criteria in the CHEC risk of bias checklist and Larg & Moss checklist. The studies must also have at least a fair level of transparency. The result will be presented in a tabular format and narrative summary. Descriptive statistical analyses will also be performed based on information extracted.

A meta-analysis will be performed to obtain the pooled cost estimate from the individual studies similar characteristics. Forest plot will be used to visualize the extent of heterogeneity among studies. The forest plot will show the individual study proportion with Clopper-Pearson confidence intervals (CIs) and the overall (combined) Dersimonian-Liard pooled estimate. To quantify the effect of heterogeneity, a measure of the degree of inconsistency ($I^2$) which represents the extent to which the studies are inconsistent will be done. It describes the percentage of total variation across studies that are due to heterogeneity rather than chance. The $I^2$ is calculated as $I^2 = 100\% \times (Q - df)/Q$ where $Q$ is Cochran's heterogeneity statistic and df the degrees of freedom. Negative values of $I^2$ will be represented as zero so that $I^2$ lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and large values will imply high heterogeneity (25). Since heterogeneity is expected in the cost estimates between the studies, we will adopt the random effect model. The analysis will be performed using StatsDirect (version 3) statistical software.

## Discussion

This protocol provides a proposed stepwise plan in conducting a systematic review and meta-analyses of cost of revision total knee replacement. The research questions which will be answered in the result section will be discussed in this section. The review will provide a pooled estimate of the cost. It will also provide information about study characteristics and factors associated with high costs of revision TKR and recommendations to minimize cost. Findings from this systematic review will help identify gaps and limitations in the studies and proffer recommendations for future studies on the burden of revision knee arthroplasty. Furthermore, this study will inform where future knee arthroplasty management decisions and future research should focus.

# Abbreviations

TKR
Total Knee Replacement
PROSPERO
International Prospective Register of Systematic Reviews
PRISMA-P
Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
MeSH
Medical Subject Headings
ISPOR
International Society for Pharmacoeconomics and Outcome Research
CHEERS
Health Economic Evaluation Reporting Standards
CHEC
Consensus Health Economic Criteria

# Declarations

### Ethical approval and consent to participate

Not applicable

### Consent for Publication

Not applicable

### Availability of data and materials

Data sharing is not applicable in this article as no datasets were generated or analysed during the current study

### Competing interest

The authors declare that they have no competing interests

### Funding

The authors received no funding for this research

### Authors' Contributions

CO, JB and CV were responsible for conceptualization. CO and SN developed the study design, inclusion and exclusion. CO, CV, JB and SN contributed to the synthesis and data analyses methods. CO wrote the first draft of the protocol. JB, SN and CV made corrections. All authors reviewed the final manuscript.

### Acknowledgement

Not applicable

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