Early assessment of the likely cost-effectiveness of a new technology: a Markov model with probabilistic sensitivity analysis of computer-assisted total knee replacement

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared computer-assisted total knee replacement (TKR) versus conventional TKR. Computer-assisted TKR used computer-assisted surgery (CAS) systems.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
As this was a modelling study, the characteristics and exclusion or inclusion criteria of the target population were not reported.

Setting
As this was a modelling study, the setting was not explicitly stated. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from sources published between 1989 and 2004. The cost data were derived from sources published in 2004 and were reported for the price year 2003.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies, supplemented with some authors’ assumptions.

Modelling
A Markov model was used to estimate and compare the cost-effectiveness of computer-assisted TKR with that of conventional TKR. To represent the natural history of disease and the possible outcomes of the surgery, the Markov model involved nine health states:

- TKR operation for knee problem (state just after primary TKR),
- normal health after primary TKR (no complication after the primary TKR operation),
- TKR with minor complications (less serious complications, e.g. knee pain),
TKR with serious complications (serious complications, e.g. loosening, instability, and fracture),
simple revision (i.e. complications needing to be treated by simple revision operation),
complex revision (i.e. complications needing to be treated by complex revision)
other treatments (i.e. complications needing to be treated by other methods, not revision),
normal health after TKR revision, and
death (i.e. the patient dies because of TKR-related treatments or from other causes).

A patient entered the model in the health state "TKR operation for knee problem" and all patients incurred a probability of death in all health states apart from the initial one. Each cycle of the model was 1 month in length and transition probabilities were expressed as 1-month probabilities. The time horizon was 10 years.

The model assumed that the principal effect of CAS was to reduce the transition probabilities to the state "TKR with serious complications". The model also assumed that the transition probabilities would remain constant over the 10 years.

**Outcomes assessed in the review**
The following transition probabilities for conventional TKR were used as input parameters in the model:

- the probability of moving from TKR to normal health after primary TKR, to TKR with minor complications, and to TKR with serious complications;
- the probability of moving from serious complications to minor complications, to simple revision, to other treatments, and to complex revision;
- the probability of moving from minor complications to serious complications, to normal health after primary TKR, to simple revision, and to other treatments;
- the probability of remaining in a minor complication state or in normal health after primary TKR;
- the probability of moving from normal health after primary TKR to minor complications or to serious complications;
- the probability of moving from complex revision to serious complications or to normal health after TKR revision;
- the probability of moving from simple revision to serious complications, to minor complications, to other treatments, and to normal health after TKR revision;
- the probability of moving from other treatments to serious complications, to minor complications, to simple revision, and to normal health after primary TKR;
- the probability of moving from normal health after TKR revision to complex revision or to simple revision;
- the probability of remaining in normal health after TKR revision state;
- the probability of death due to TKR after primary TKR;
- the probability of death due to revision after TKR revision; and
- the probability of death due to all reasons.

The percentage of complications due to misalignment was also assessed.
Study designs and other criteria for inclusion in the review
Systematic reviews, randomised clinical trials and follow-up studies were included in the review. The authors only included articles written in English and containing the keyword TKR. No further inclusion or exclusion criteria were reported.

Sources searched to identify primary studies
The authors searched MEDLINE, HEED, the UK Department of Health Database, the US Department of Health and Human Services Database, the Cost-Effectiveness Analysis Registry Database, and relevant National Joint Replacement Registry Databases in Sweden, Australia and Canada for primary studies. In addition, the references of identified articles were checked.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
The validity of the primary studies does not appear to have been assessed.

Number of primary studies included
Overall, the authors used 40 primary studies as sources of effectiveness evidence.

Methods of combining primary studies
The authors used narrative methods to combine the results from individual studies.

Investigation of differences between primary studies
The authors used two-step calculations to adjust for differences in follow-up periods between the primary studies. The calculations were reported clearly. In addition, estimates of effectiveness from different primary studies were weighted by the equivalent sample size to adjust for differences in sample sizes.

Results of the review
The probability of moving from TKR to normal health after primary TKR was 0.94220, to TKR with minor complications 0.04285, and to TKR with serious complications 0.01495.

The probability of moving from serious complications to minor complications was 0.01385, to simple revision 0.00523, to other treatments 0.95236, and to complex revision 0.02469.

The probability of moving from minor complications to serious complications was 0.00921, to normal health after primary TKR 0.94236, to simple revision 0.00250, and to other treatments 0.01701.

The probability of remaining in a minor complication state was 0.02505 and in a normal health after primary TKR 0.97307.

The probability of moving from normal health after primary TKR to minor complication was 0.01385 and to serious complications 0.00921.

The probability of moving from complex revision to serious complications was 0.02545 or to normal health after TKR revision 0.96963.

The probability of moving from simple revision to serious complications was 0.01590, to minor complications 0.00816,
to other treatments 0.01701, or to normal health after TKR revision 0.95400.

The probability of moving from other treatments to serious complications was 0.00921, to minor complications 0.01385, to simple revision 0.00250, or to normal health after primary TKR 0.97057.

The probability of moving from normal health after TKR revision to complex revision was 0.02003, or to simple revision 0.01038.

The probability of remaining in normal health after TKR revision was 0.96468.

The probability of death due TKR after primary TKR was 0.00046.

The probability of death due to revision after TKR revision was 0.00151.

The probability of death due to all reasons was 0.00341.

The percentage of complications due to misalignment was 70.4%.

Methods used to derive estimates of effectiveness
The authors made an assumption to support their analysis.

Estimates of effectiveness and key assumptions
The authors assumed that CAS could reduce the serious misalignment complications by 34%.

Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs). Given the limited availability of optimal utility values in the literature, the authors used utility values from various sources including values from the Knee Society Scores and the Pain-Walking-Function-Activity Scale of the University of California at Los Angeles. There was also an absence of data on utility values for the health states "TKR operation for knee problem" and "other treatments". Thus, the authors assigned a value estimated as the mean of the utility values assigned to the states "normal health after primary TKR" and "TKR with minor complications", based on the assumption that the utility values of the missing health states would be lower than that of "normal health after primary TKR" and higher than that of "TKR with minor complications". As the time-horizon of the model was 10 years, the benefits (QALYs) were appropriately discounted at a rate of 3.5%.

Direct costs
The direct costs included in the analysis were for the operation, examinations, drugs, tests, consumables, staff time and salaries, ward costs and overheads. The authors assumed that there were no costs for the states "normal health after primary TKR", "normal health after TKR revision", "TKR with minor complications", "TKR with serious complications" and "death". Given the fact that other treatments referred to the management of injections, the cost of other treatments equaled the cost of controlling infections of the bones or joints. To account for the costs of the computer-assisted TKR, the extra cost per use of CAS were included in the analysis. This cost included the costs of the CAS system, warranty and disposables, and the extra length of surgery (including personnel costs). All costs were added to the cost of the conventional procedure.

The costs and the quantities were only reported for conventional TKR. All costs were derived from official public sources (NHS Reference Costs) and were reported for the price year 2003. The life-time of CAS equipment was assumed to be 5 years. As the time horizon of the model was 10 years, the costs were appropriately discounted at a rate of 3.5%.

Statistical analysis of costs
The authors used the Dirichlet distribution to derive a logical multi-Markov state probabilistic transition matrix from the initial point estimates. A count for each Markov state was estimated by the transition probabilities (total counts = 1,000). Random number and gamma distribution formulae were used to produce a one-parameter (standard) gamma distribution for each cell of the transition matrix. Using the variance of CAS effect, as derived from published clinical trials, the authors generated a random "effect of CAS" based on lognormal function. In addition, means and ranges of costs derived from NHS Reference Costs were used to estimate variance for the gamma distribution. However, it was reported that no variance was available for the extra costs of CAS. A beta function (with the mean equal to the point estimate and a high variance to reflect the uncertainty) was used to generate a random utility for each Markov state.

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
UK pounds sterling (GBP).

**Sensitivity analysis**
A one-way sensitivity analysis was conducted in order to investigate the robustness of the results to variations in the input parameters. The parameters investigated in the sensitivity analyses were "effect of CAS", utility values and the additional cost of CAS. It was reported that the solver function in the MS Excel software program was used to estimate the threshold values above and below which the baseline results varied. The authors also conducted a probabilistic sensitivity analysis, by running 10,000 120-cycle cohort simulations trials, randomly sampling from the distributions of transition probabilities, cost and utilities. The results were presented using cost-effectiveness plane and cost-effectiveness acceptability curves. An analysis of covariance was used to investigate the proportion of the total model sum of squares that was explained by each individual input parameter. Incremental costs and incremental QALYs were analysed separately as dependent variables.

**Estimated benefits used in the economic analysis**
Discounted benefits of the cohort simulations were reported.

During the 1st year, conventional TKR resulted in 816.8 QALYs and computer-assisted TKR in 818.4 QALYS.

During the 2nd year, conventional TKR resulted in 1,526.1 QALYs and computer-assisted TKR in 1,529.2 QALYs.

During the 3rd year, conventional TKR resulted in 2,179.9 QALYs and computer-assisted TKR in 2,184.6 QALYs.

During the 4th year, conventional TKR resulted in 2,782.5 QALYs and computer-assisted TKR in 2,788.7 QALYs.

During the 5th year, conventional TKR resulted in 3,338.0 QALYs and computer-assisted TKR in 3,345.6 QALYs.

During the 6th year, conventional TKR resulted in 3,849.9 QALYs and computer-assisted TKR in 3,859 QALYs.

During the 7th year, conventional TKR resulted in 4,321.7 QALYs and computer-assisted TKR in 4,332.2 QALYs.

During the 8th year, conventional TKR resulted in 4,756.5 QALYs and computer-assisted TKR in 4,768.5 QALYs.

During the 9th year, conventional TKR resulted in 5,157.2 QALYs and computer-assisted TKR in 5,170.5 QALYs.

During the 10th year, conventional TKR resulted in 5,526.4 QALYs and computer-assisted TKR in 5,541.2 QALYs.

**Cost results**
Discounted costs of the cohort simulations were reported. The costs were reported for each year (from year 1 to year...
10).

For the 1st year, the cost was 5,518,752 for conventional TKR and 5,650,576.8 for computer-assisted TKR.

For the 2nd year, the cost was 5,836,511.1 for conventional TKR and 5,866,250.4 for computer-assisted TKR.

For the 3rd year, the cost was 6,136,301.6 for conventional TKR and 6,070,344.1 for computer-assisted TKR.

For the 4th year, the cost was 6,418,816.0 for conventional TKR and 6,263,371.1 for computer-assisted TKR.

For the 5th year, the cost was 6,684,766.2 for conventional TKR and 6,445,331.3 for computer-assisted TKR.

For the 6th year, the cost was 6,934,874.0 for conventional TKR and 6,617,044.0 for computer-assisted TKR.

For the 7th year, the cost was 7,169,864.0 for conventional TKR and 6,778,802.4 for computer-assisted TKR.

For the 8th year, the cost was 7,390,457.3 for conventional TKR and 6,931,038.6 for computer-assisted TKR.

For the 9th year, the cost was 7,597,365.8 for conventional TKR and 7,074,185.0 for computer-assisted TKR.

For the 10th year, the cost was 7,791,288.9 for conventional TKR and 7,208,671.4 for computer-assisted TKR.

**Synthesis of costs and benefits**

An incremental cost-effectiveness analysis was performed. For the 1st year, computer-assisted TKR when compared with conventional TKR resulted in an incremental cost per QALY of 82,567.1. For the 2nd year, it resulted in an incremental cost of 9,472.6. For the following years until year 10, computer-assisted TKR proved to be the dominant strategy in comparison with conventional TKR. The analysis demonstrated that after 10 years, computer-assisted TKR reduced the cost per patient by approximately 7.5% (-583) and increased QALYs by 0.3% (0.0148). The probabilistic analysis demonstrated similar results for incremental costs (-637) and QALYs (0.0164).

The one-way sensitivity analysis demonstrated that the threshold value (above which CAS was the dominant strategy) was 10.3% (34% at baseline) for CAS effect in diminishing the transition probability to the state "TKR with serious complications". The results were sensitive to utility values assigned to "normal health after primary TKR"; the threshold value was 0.58 (0.78 at baseline analysis).

The cost-effectiveness plane demonstrated that all but 147 of the 10,000 trials were below the x-axis, and that computer-assisted TKR was the dominant strategy in 7,589 of the 10,000 trials.

The cost-effectiveness acceptability curves demonstrated that at a willingness-to-pay of 30,000 per QALY, there is 92% probability that computer-assisted TKR is cost-effective.

The analysis of variance demonstrated that the most important parameters to the total model sum of squares for incremental costs were the "effect of CAS" (57.76%), the transition probability from "normal health after primary TKR" to "serious complications" (23.19%), and the cost of "other treatments" (11.97%). On the other hand, the most influential parameter on incremental QALYs was the utility assigned to the health state "normal health after TKR revision" (33.74%).

**Authors’ conclusions**

In the long term, computer-assisted total knee replacement (TKR) is a cost-saving technology in comparison with conventional TKR and may offer small additional quality-adjusted life-years (QALYs).

**CRD COMMENTARY - Selection of comparators**

The selection of the comparators was explicitly justified. Conventional TKR seems to have represented standard
practice in the authors' setting. You should decide if this represents a widely used technology in your own setting.

**Validity of estimate of measure of effectiveness**
The authors described a systematic identification, selection and synthesis of evidence to form an estimate of effectiveness. The estimates of effectiveness were arrived at by the use of a narrative synthesis. In addition, the authors adopted a weighting scheme to reflect differences in sample size. The impact of differences between the primary studies was taken into account when estimating effectiveness.

**Validity of estimate of measure of benefit**
The measure of benefit was the health utility (QALYs) and utility values were derived from the literature. This measure enables broad comparisons with other technologies.

**Validity of estimate of costs**
The analysis of the costs was performed from the perspective of the NHS paying for the intervention. It appears that all the relevant categories of costs have been included in the analysis. Several health states were assumed to incur zero costs. However, it is not known how far this assumption has affected the authors' conclusions. The costs and the quantities were not reported separately for all cost categories, which will not enable the analysis to be easily reworked for other settings. However, the authors carried out extensive statistical and sensitivity analyses to investigate the robustness of the results to changes in the base-case estimates. Discounting and the price year were appropriately reported.

**Other issues**
The authors did not compare their findings with those of published studies, although this was because of a lack of published studies looking at the long-term effects of the technologies compared. The issue of generalisability of the results was directly addressed. The authors do not appear to have presented their results selectively. The study enrolled patients who underwent computer-assisted or conventional TKR, and this was reflected in the authors' conclusions.

The authors reported a number of limitations to their study. First, data on utility derived from the literature were poor and a rather large variance for each utility was assumed in the probabilistic analysis. This might have led to an overestimation of the uncertainty related to utility. Second, when accounting for mortality, the authors accounted for mortality due to primary TKR, revision TKR and of all causes. Therefore, double-counting was conducted since 'all causes' enclose the other two mortality causes.

**Implications of the study**
The authors did not make explicit recommendations for changes in policy or practice. However, they suggested that the "effect of CAS" on the rate of revisions requires long-term clinical evidence, and recommended that future research should focus on the derivation of more robust utility estimates.

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**Bibliographic details**