Economic evaluation of major knee surgery with recombinant activated factor VII in hemophilia patients with high titer inhibitors and advanced knee arthropathy: exploratory results via literature-based modeling

Ballal R D, Botteman M F, Foley I, Stephens J M, Wilke C T, Joshi A V

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.

CRD summary
The study examined the cost-effectiveness of major knee surgery using recombinant activated factor VII versus no surgery in haemophilia patients with high titre inhibitors, mild to severe knee arthropathy, and recurring joint bleeding episodes. The study demonstrated that major knee surgery was more effective than no surgery, and that it was likely to generate cost-savings in the long term from the perspective of the US payer. Overall, the quality of the study methodology was satisfactory.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective of the study was to examine the cost-effectiveness of major knee surgery using recombinant activated factor VII (rFVIIa) versus no surgery in haemophilia patients with high titre inhibitors, mild to severe knee arthropathy, and recurring joint bleeding episodes.

Interventions
The four types of surgery considered were total knee replacement, knee arthrodesis, proximal tibial osteotomy and distal femoral osteotomy. Patients also received rFVIIa before during and after surgery. Dosing was frequent immediately after surgery (90 μg/kg every 2 hours), then transitioned to moderate (90 μg/kg every 3 hours), and turned to low dose (90 μg/kg every 4 hours) during physiotherapy. The option of surgery was compared with a conservative strategy of no surgery.

Location/setting
USA/hospital.

Methods
Analytical approach:
A decision model was developed to compare the costs and benefits of the two strategies. Specifically, the authors stated that a single-decrement life table (i.e. a special case of recursive Markov model) was used. A lifetime horizon was considered. The authors stated that a modified payer perspective was adopted in the analysis.

Effectiveness data:
Patient demographics and clinical characteristics were obtained from a systematic review of the literature. The clinical estimates were derived from a review of the literature, details of which were not reported. The key clinical estimate was the effect of major knee surgery with rFVIIa on spontaneous bleeding. Short-term data on treatment effectiveness were taken from two published studies that were combined using the weighted average. Neither study focused specifically on patients with high titre inhibitors. The short-term data were extrapolated to a long-term horizon on the basis of a key authors’ assumption that the rate of bleeding episodes remained fairly constant over time. Survival data were derived from selectively identified published sources.

Monetary benefit and utility valuations:
Utility valuations were determined through a systematic search of the literature. Little information was found for the
direct impact of knee surgery on patient quality of life. Only data on pain after major orthopaedic surgeries were found. The authors then transformed these data to obtain the utility levels required in the model, using scores from the EuroQol at 5 dimensions. The whole process was explained clearly and extensively.

Measure of benefit:
The summary benefit measure was the expected number of quality-adjusted life-years (QALYs). These were estimated using the decision model. QALYs accrued after the first year were discounted at an annual rate of 3%.

Cost data:
The health service costs included in the analysis were surgical procedures, post-surgery services such as physiotherapy, and rFVIIa (dosage depending on the type of surgery). The cost of repeat knee surgery was included on the basis of the published rate. The cost of a spontaneous bleeding episode was also included and was derived from a published study. The costs and resource use data were derived from a combination of database analysis and literature sources. For example, the inpatient costs of the surgical procedures were based on the 2004 Healthcare Cost and Utilization Project, adjusted to take into account the longer hospital stay for patients with haemophilia. The cost of rFVIIa was based on the average sales price calculated by the Centers for Medicare and Medicaid services. The price year was 2006. The costs were expressed in US dollars ($). The long-term costs were discounted at an annual rate of 3%.

Analysis of uncertainty:
Univariate sensitivity analyses were performed on key model parameters. In addition, a first-order probabilistic sensitivity analysis was conducted to assess the robustness of the model results.

Results
Over a patient's lifetime, the cumulative discounted QALYs were 7.56 without surgery and 15.17 with surgery (difference 7.61). The QALYs gained with surgery were apparent after the first year post-intervention (gain of 0.38) and increased over time (1.77 after 5 years, 3.26 after 10 years, and 4.48 after 15 years).

The total costs of surgery ranged from $735,568 with proximal tibial osteotomy to $855,282 with total knee replacement. The greatest component of total costs (about 90%) was the acquisition of rFVIIa. However, over time, the cost-savings due to reduced bleeding episodes increased.

The authors estimated that the time necessary for knee surgery to reach cost-neutrality (and thus become dominant, less costly and more effective) versus no surgery was between 7 and 10 years, depending on the surgical procedure. The time for knee surgery to be considered cost-effective versus no surgery when using a threshold of $50,000 per QALY ranged from 6 to 8 years, depending on the surgical procedure.

The sensitivity analysis showed that the model findings were sensitive to variations in the cost of a bleeding episode (the higher the cost of an episode, the sooner the cost of surgery is recovered), the bleeding rate before surgery (the higher rate, the sooner the surgery cost is recovered), and the amount of rFVIIa used during and after surgery (the lower the amount used, the sooner the surgery cost is recovered).

The probabilistic sensitivity analysis highlighted the uncertainty in the results. For example, the 90% confidence interval for the time to break-even cost for total knee replacement ranged from 1 to 28 years. In general, the probability that the cost per QALY gained across all four procedures would be less than $50,000 was ≥ 42% at 5 years and ≥ 79% at 10 years.

Authors' conclusions
The authors concluded that major knee surgery in haemophilia patients with high-titre inhibitors receiving perioperative coverage with rFVIIa was more effective than no surgery, and was likely to generate cost-savings in the long-term from the perspective of the payer in the USA.

CRD commentary
Interventions:
The rationale for the choice of the comparator was clear in that no surgery was the standard of care before the advent of
rFVIIa. These comparators are also likely to be relevant in other settings. The justification given for the selection of the four types of knee surgery appears appropriate.

**Effectiveness/benefits:**
The authors did not report the methods and conduct of the review of the literature that was undertaken to identify key clinical estimates, although it may have been systematic. The clinical estimates were taken from two published studies that estimated the reduction in bleeding episodes from patients without inhibitors, given the lack of evidence on patients with high-titre inhibitors; this was acknowledged to be a limitation of the analysis. In general, the authors described the choice of the estimates found in the literature and justified some of the assumptions made in the model. Details on the derivation of the benefit measure were extensively reported and the use of QALYs represents a strength of the analysis, although the utility weights could not be directly estimated from patients receiving knee surgeries. A key assumption of the clinical analysis was that short-term data would also stand in the long term.

**Costs:**
The categories of costs used in the analysis were consistent with the authors' stated perspective. The selection of the sources used to derive the costs and resource data was justified, the authors stating that, owing to the relatively rare frequency of the surgical procedures in this specific patient population, the actual costs could not be easily identified. Thus, the data were combined using multiple sources and mixed patient populations. Details of the cost calculations were presented in a technical appendix. Other relevant details, such as use of discounting and the price year, were reported.

**Analysis and results:**
The synthesis of the costs and benefits was presented using break-even data as the authors stated that high uncertainty was found around cost and benefit results, thus the incremental ratios would have been very unstable. However, this approach might be relevant to US decision-makers, who might be interested in the time to reach cost-neutrality. The description of the decision model and its structure was clear. The issue of the sensitivity analysis was satisfactorily addressed and its results were presented clearly.

**Concluding remarks:**
Overall, the quality of the study methodology appears to have been satisfactory, with good reporting of some clinical estimates and basic results. The authors' conclusions appear valid given the extensive use of sensitivity analysis.

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