Treatment for life for severe haemophilia A: a cost-utility model for prophylaxis vs. on-demand treatment

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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.

CRD summary
The study evaluated the cost-effectiveness of different life-long treatment strategies for severe haemophilia A. The authors concluded that while their model relied on as yet unconfirmed clinical assumptions, that lifetime prophylactic treatment had undoubted benefits. There is considerable uncertainty surrounding the estimates of the parameters in the model (such as the relative risk of developing inhibitors) and uncertainty was insufficiently analysed. The validity of the results is highly uncertain but the author's cautious conclusions appear reasonable.

Type of economic evaluation
Cost-utility analysis

Study objective
The study evaluated the cost-effectiveness of different life-long treatment strategies for severe haemophilia A using a decision analytic model.

Interventions
Two interventions were compared: prophylactic treatment from the first soft tissue manifestations of haemophilia after birth and before onset of joint or life-threatening bleeds; and on-demand treatment initiated at the first joint or other haemorrhage.

Location/setting
UK, USA, Sweden/Outpatient

Methods
Analytical approach:
The economic evaluation was based on a lifetime Markov model. The Markov model had three primary health states: alive (no inhibitors), alive (with inhibitors) and dead.

Patients who developed inhibitors would receive immune tolerization therapy (ITT) which may or may not succeed; where it failed patients would retain inhibitors for the rest of their life. The model followed haemophilia patients from birth until death in 100 one-year cycles. Half-cycle correction was applied to model results.

Several perspectives were analysed: UK NHS perspective, USA third party payer perspective and Swedish Dental and Pharmaceuticals benefits agency perspective.

Effectiveness data:
The key effectiveness parameter in the model was the probability of having inhibitors in cycle one of the model. The likelihood of inhibitors for each intervention was based on different studies (see Other Publications of Related Interest, Auerswald et al. 2012 and Colowick et al. 2000). The model assumed that prophylaxis patients had no need of orthopaedic surgery or treatment for intracranial haemorrhage.

Further effectiveness parameters in the model included age adjusted probability of intracranial haemorrhage derived from a French study of intracranial haemorrhage in haemophilia patients, and mortality rates for prophylactic and on-demand patients derived from UK study on haemophilia mortality. Differences in mortality between prophylactic and
on-demand patients were based on an assumption that prophylaxis reduced patient haemophilia category risk from severe to mild/moderate; this assumption was justified by an often-cited published study.

Monetary benefit and utility valuations:
Utility scores for UK and USA were derived from a published multinational study of severe haemophilia patients who had received prophylactic, on-demand, or combined therapy. Swedish utilities were derived from two published studies (one each for patients with inhibitors and without inhibitors). Utilities were modified for aging based on a commonly used published algorithm.

Measure of benefit:
The summary measure of benefit was quality-adjusted life years (QALYs). Discount rates varied by national perspective. UK NHS perspective future benefits were discounted at 1.5% annually. USA third party payer perspective and the Swedish Dental and Pharmaceuticals benefits agency perspective future benefits were discounted at 3% annually.

Cost data:
Cost categories included drug costs and surgery costs. Drug costs were based on dosages by age dependant patient body weight; dosages were derived from various published sources. Body weight was derived from 2010 Health Survey of England Trend Tables. Orthopaedic surgery costs were calculated based on an assumption of two events per lifetime based on the average cost of knee and hip surgery from a published 2005 study.

Costs were reported in the currency of their analytical perspective; UK pounds (£), United States dollars ($) or Swedish kroner (SEK). Future costs were discounted at 3.5% annually for the UK and 3% annually for USA and Sweden.

Analysis of uncertainty:
One way and probabilistic sensitivity analyses were undertaken for the UK NHS and USA third party payer perspectives. One way sensitivity analyses varied parameters between high and low values derived from the literature informing the parameters and were presented as tornado diagrams. Probabilistic sensitivity analysis was conducted for 500 iterations. Probabilistic sensitivity analysis (PSA) results were presented as cost-effectiveness acceptability curves (CEAC).

Results
UK NHS perspective analysis: prophylaxis was £280,866 less costly and produced 9.69 more QALYs than on-demand haemophilia treatment (dominant).

USA third party payer analysis: prophylaxis was $412,999 more costly and produced 6.06 more QALYs resulting in an incremental cost-effectiveness ratio (ICER) of $68,109/QALY.

Swedish perspective: prophylaxis was SEK 5,331,051 more expensive and produced 10.99 more QALYs resulting in an ICER of SEK 484,888/QALY. Prophylaxis was considered cost-effective across all perspectives.

One way sensitivity analyses identified that the most important factors in the model were the dosage of FVIII on prophylaxis followed by probability of inhibitor development on prophylaxis and on-demand, discount rate applied to QALYs and the number of bleeds per year for on-demand treatment.

ICERs ranged between -£113,651 and £288,896/QALY for UK NHS analyses and between -$374,404 and $1,717,256/QALY in the USA analyses. PSA for the UK NHS perspective showed a nearly 100% chance of cost effectiveness at a cost-effectiveness threshold of £30,000/QALY.

In the USA third party payer perspective cost-effectiveness was judged against several cost-effectiveness threshold (there was no established threshold in the USA). Probability of cost-effectiveness in the USA ranged from approximately 55% at $50,000/QALY to 75% at $150,000/QALY.

Authors’ conclusions
The authors concluded that while their model relied on as yet unconfirmed clinical assumptions, lifetime prophylactic
treatment had undoubted benefits.

**CRD commentary**

**Interventions:**
The interventions were detailed and generally well reported. The authors acknowledged that the prophylaxis intervention assumed immediate diagnosis of haemophilia after birth; this did not realistically represent haemophilia diagnosis as many children with haemophilia are born to families without a history of haemophilia and not all children with severe haemophilia have bleeding events severe enough at birth to warrant diagnostic evaluation for haemophilia. It was not clear what effect assuming later diagnosis might have on results.

**Effectiveness/benefits:**
As acknowledged by the authors, many aspects of their analysis relied on unconfirmed clinical assumptions. It appeared that appropriate sources were chosen for effectiveness data in the model but it was unclear how/why these sources were selected and what effect alternative choices might have had.

Sensitivity analyses showed that probability of inhibitor development was a key parameter in the model but the data appeared to be observational with different studies providing incidence rates; no information was provided about the characteristics of the patients analysed in the different studies.

**Costs:**
Sources for costs appeared reasonable and were reported with good detail; how costs were selected was neither reported nor justified. Costs were derived from multiple years and currencies but the method of inflation and conversion was not reported. No price year was reported.

The authors assumed that costs for orthopaedic surgery occurred only in the on-demand treatment arm. The authors acknowledged that this assumption had some disagreement in the field and that long term data to confirm the assumption were not available. There was no sensitivity analysis to test alternative assumptions and the substantial assumed cost of surgery could change conclusions. The cost of orthopaedic surgery was given as a flat cost and was assumed to occur twice in the lifetime of the patient. No timing of the occurrence or annual probability of orthopaedic surgery was reported; these may be important for the purpose of discounting costs incurred in the future.

**Analysis and results:**
As the authors acknowledged, the base case model assumed a seldom-used discount rate for the UK of 1.5% for future benefits. The standard discount rate in the UK is 3.5%; this discount rate should have been presented as a specific sensitivity analysis given the paucity of data to demonstrate large, sustained benefits from the specific prophylactic plan used in the model. A 3.5% discount rate would significantly increase the incremental cost-effectiveness ratio.

The probabilistic sensitivity analysis parameters were presented as non-transparent model code; reporting variables with variances and distribution used in PSA would be more transparent. Not all important variables were subject to uncertainty (for example, the success rate of ITT, mortality and probability of intracranial haemorrhage). The reporting was not clear on intracranial haemorrhage in the model as no costs or benefits for intracranial haemorrhage were reported.

Many sensitivity analyses reported negative ICERs, which have ambiguous interpretation. Presenting the analysis in a net benefit framework would produce more clear interpretations.

The authors conducted an appropriate and detailed discussion of results differences between their study and other authors' work and acknowledged substantial limitations in their study.

**Concluding remarks:**
There is considerable uncertainty surrounding the estimates of the parameters in the model (such as the relative risk of developing inhibitors) and uncertainty was insufficiently analysed. The validity of the results is highly uncertain but the author's cautious conclusions appear reasonable.

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