

## REVIEW ARTICLE

# A systematic review of the cost-effectiveness of rFVIIa and APCC in the treatment of minor/moderate bleeding episodes for haemophilia patients with inhibitors

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**Summary.** The clinical, humanistic and economic consequences associated with haemophilia and inhibitors are considerable. Primary treatment for mild-to-moderate bleeding disorders in such patients is recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (APCC). The aims of this study were to identify, review and evaluate the quality of the published literature on the relative cost-effectiveness of rFVIIa and APCC in treating haemophilia patients with inhibitors. The review concentrates on model type, design and assumptions, and results. The results of this study suggest that rFVIIa may be the cost-effective alternative to treatment with APCC. In seven out of the nine studies, rFVIIa had the lower average treatment cost. The difference in average treatment cost to resolve a bleed, between rFVIIa and APCC in these seven studies, ranged from \$3000 to \$17 000. The adapted modelling framework is similar in all the economic

models reviewed, suggesting clinical acceptability of the approach used. The estimates of efficacy varied between the models, especially for APCC. The efficacy for APCC derived from retrospective studies was lower than reported in the literature. Sensitivity analysis was undertaken in the majority of the economic analyses and the results were found to be robust to realistic parameter variations. Only one of the studies was a cost-utility study, showing the lack of measuring health status within this area. This systematic review showed that models based on different sources of data produced fairly similar robust results despite differences in the estimates of efficacy, average dosage required, and unit costs. However, ideally there should be a systematic approach to identifying the relevant data.

**Keywords:** APCC, cost-effectiveness, cost-utility, haemophilia, rFVIIa, systematic review

## Introduction

The management of bleeding episodes for haemophilia A or B patients with inhibitors to factor VIII/IX is primarily undertaken by the administration of either recombinant factor VIIa (rFVIIa, Novo Seven®; Novo Nordisk, Bagsvaerd, Denmark) or plasma-derived activated prothrombin complex concentrate (APCC) with FVIII inhibitor-bypassing activity (FEIBA®; Baxter, Vienna, Austria).

Economic evaluation is increasingly being used to inform the decisions of various healthcare authorities/payers regarding the need to allocate finite resources between numerous competing interventions and healthcare programmes [1].

Improvements in treatment protocols have, in the main, shifted the management of patients from the hospital setting to the home. The true cost of treating a bleeding episode should take into account the total direct cost needed to achieve bleed resolution, and not just the cost per dose of treatment. In addition to the drug cost, the efficacy of the agent, the dose regimen, the time to achieve bleed resolution, and the need to retreat a patient following a re-bleed need to be considered.

The efficacy of rFVIIa and APCC has been reported in numerous studies, and over the last few years, cost-effectiveness analyses have been

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undertaken on the cost-effectiveness of using these treatments in haemophilia patients with inhibitors. Cost-effectiveness analysis is a systematic approach of comparing two or more alternative treatments by analysing the costs and consequences of each, with the consequences or clinical outcomes being measured in the same units (e.g. cases prevented, symptom-free days or life-years gained). Cost-utility analysis is a specific type of cost-effectiveness analysis in which the clinical outcomes are measured as quality-adjusted life-years (QALYs). QALYs incorporate an estimate of the utility or quality of life of the life-year gained, where a score of 1 represents perfect health and 0 represents death.

The objectives of this article were to identify, review and evaluate the quality of the published literature on the cost-effectiveness of rFVIIa and APCC in treating on-demand bleeding episodes for haemophilia patients with inhibitors. The quality appraisal of the published economic models was conducted by an experienced health economist and concentrated on the model type, the model design, model assumptions, results and conclusions.

## Methods

The authors conducted a systematic literature review of the health economics of treating on-demand bleeding episodes with rFVIIa and APCC in haemophilia A and B patients with inhibitors.

### Search strategy

We conducted a systematic literature review using MEDLINE (from 1990 to April 2008), EMBASE (from 1990 to April 2008) and the Cochrane Library (Issue 1, 2008), which includes NHS EED and HTA databases. In addition, we carried out both general Internet searches and targeted searches of a number of specialist haematological websites. These included the World Federation of Haemophilia, the European Haematology Association, the American Society of Hematology, the British Society for Haematology, and the International Society on Thrombosis and Haemostasis. Reference lists of key reviews were hand-searched for further relevant studies.

Searches of electronic databases used a combination of terms relating to haemophilia A and B, inhibitors, health economics and interventions of interest. The health economics keywords included 'cost', 'cost-effectiveness', 'cost-utility', 'cost-benefit', 'cost analysis', 'economic', 'pharmacoeconomic', 'economic model', 'modelling', 'decision model' and 'QALY' (full search strategies are listed in the

Appendix). The search was limited to a time period covering 1990 to April 2008 and there was no language restriction.

### Selection of eligible studies

After removing duplicates, titles of all studies were screened and any irrelevant studies were removed. Abstracts of the remaining studies were independently screened by two experienced reviewers and any irrelevant studies were removed. The same reviewers also examined full text of the selected articles to finalize their selection of studies. At each of the screening stages, the reviewers selected eligible studies based on the patient population, the comparator interventions (rFVIIa and APCC) and the economic model type (Table 1). Any differences between the reviewers were resolved by consensus. Both published abstracts and unpublished conference abstracts were included in the review.

### Quantity of available evidence

The systematic search yielded 80 hits in MEDLINE, 210 in EMBASE and 21 in Cochrane Library. Of these 311, 85 were identified as duplicates and removed. An additional 155 studies were excluded at title screening. Six studies were added following completion of hand searches, resulting in a total of 77 studies for which abstracts were reviewed. Of these 77, 60 were excluded after review of abstracts and five were excluded after review of the full text article, resulting in 12 eligible studies for inclusion in the review (Fig. 1).

### Data extraction and quality assessment

The data from included studies were extracted independently by two reviewers using a predefined data extraction form. The form included a number of domains, including general descriptive information regarding the study; the adopted study methods and settings including the type of economic model and time horizon, the country and cost year; where the

**Table 1.** Study inclusion criteria.

| Criteria     | Definition                                      |
|--------------|---|
| Population   | Patients with haemophilia A or B and inhibitors |
| Intervention | rFVIIa and APCC                                 |
| Study type   | Cost-effectiveness or cost-utility studies      |

rFVIIa, recombinant factor VIIa; APCC, activated prothrombin complex concentrate.

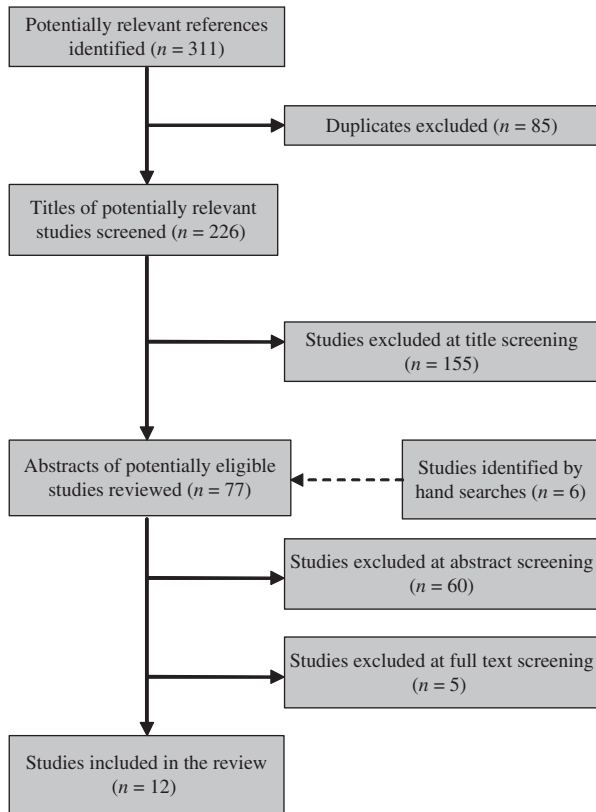


Fig. 1. Study selection flow chart.

data source for the model was derived (from literature, expert opinion and/or bespoke study); and the results and key findings including sensitivity analysis (Table 2). The quality appraisal was performed by an experienced health economist.

The intention was to assess the quality of the economic studies by using a general checklist of basic criteria such as the ‘Drummond checklist’ (Table 3), which had been specifically developed to critically appraise economic models and is one of the quality

Table 2. Data extraction domains.

| Field               | Description  |
|---------------------|--|
| General information | Authors, title, publication details, Study’s ID, Reviewer’s ID   |
| Methods/setting     | Comparisons, study objectives, type of analysis/model structure, outcome measures, perspective, time horizon, discount rates, country, cost year |
| Data sources        | Data sources for efficacy, quality of life/utilities, costs  |
| Key findings        | Model base-case results, details of sensitivity analysis and results   |
| Quality appraisal   | Drummond’s checklist + bespoke analysis  |

Table 3. Drummond checklist for critical appraisal of economic literature.

| Assessment attribute   |
|--|
| 1. Was there a well-defined question?  |
| 2. Was there a comprehensive description of the competing alternatives?                                |
| 3. Was there evidence that the effectiveness had been established?                                     |
| 4. Were the relevant costs and consequences identified?  |
| 5. Were costs and consequences measured accurately in appropriate units?                               |
| 6. Were costs and consequences valued credibly?  |
| 7. Were costs and consequences adjusted for differential timing?                                       |
| 8. Was an incremental analysis of costs and consequences of alternatives performed?                    |
| 9. Was allowance made for uncertainties in the estimates of costs and consequences?                    |
| 10. Did the presentation and discussion of the study results include all issues of concern to readers? |

assessment tools recommended by the National Institute for health and Clinical Excellence (NICE) in critically appraising economic literature [2,3].

However, after initial perusal through the articles, it became apparent that all of the models had taken roughly the same approach; therefore, the majority of the questions in Drummond’s checklist would be answered similarly. All of the economic analysis had a well-defined question, had a comprehensive description of the competing strategies, had done some form of sensitivity analysis and had valid conclusions based on the model results. The crucial questions that remained were those relating to the costs and outcomes and whether these were measured accurately (questions 3–6 in Table 3). It became apparent that the crucial parameters that determined the results of each model were:

- 1 The efficacy (probability to resolve the bleed);
- 2 The average dosage or dosing schedule of each medication needed to achieve bleed resolution and
- 3 The unit cost of each agent.

Therefore, the quality assessment for the cost-effectiveness models concentrated on these three key parameters and how the values were derived.

## Search results

### Description and assessment of studies

A total of 12 studies were identified that met the inclusion criteria of comparative economic analysis of APCC vs. rFVIIa (Table 4). These included four conference abstracts from which only minimal information regarding the study could be ascertained. One study was a cost-utility analysis [4], one study was a lifetime analysis [5], while the other 10

**Table 4.** Economic analyses summary table.

| Study                                     | Country       | Comparisons  | Methods and perspective  | Data source   |
|---|---------------|--|--|---|
| Ekert <i>et al.</i> [4]                   | Australia     | rFVIIa vs. usual care with plasma-derived agents. Six months with plasma-derived agents, 12 months with rFVIIa                       | Cost utility analysis. Longitudinal study before and after introduction of rFVIIa in three 6-month phases. Australian government perspective | Prospective study using patient/family interviews and patient diaries               |
| Knight <i>et al.</i> [5]                  | UK            | Three on-demand protocols:<br>i) APCC/APCC/rFVIIa<br>ii) APCC/rFVIIa/rFVIIa<br>iii) rFVIIa only                                      | Cost-minimization. Lifetime costs, direct medical costs, UK NHS perspective  | Literature  |
| Joshi <i>et al.</i> [12]                  | US            | Three on-demand strategies for home treatment:<br>i) APCC/APCC/rFVIIa<br>ii) APCC/rFVIIa/rFVIIa<br>iii) rFVIIa only                  | Cost per resolved bleed. Direct medical costs, adapted Knight 2003 to US payer perspective   | Literature  |
| Odeyemi and Guest [13]                    | Home – UK     | rFVIIa vs. APCC to manage mild-to-moderate bleeds at home  | Cost per resolved bleed. UK NHS perspective  | Literature, clinical opinion  |
| Odeyemi and Guest [14]                    | Hospital – UK | rFVIIa vs. APCC to manage mild-to-moderate bleeds at a haemophilia treatment center  | Cost per resolved bleed. UK NHS perspective  | Literature, clinical opinion  |
| Huth-Kuehne <i>et al.</i> [15] (abstract) | Germany       | Three on-demand protocols:<br>i) APCC/APCC/rFVIIa<br>ii) APCC/rFVIIa/rFVIIa<br>iii) rFVIIa only                                      | Cost per resolved bleed. Direct medical costs, adapted Knight 2003 to German perspective   | Literature  |
| Chung <i>et al.</i> [18] (abstract)       | US            | rFVIIa vs. APCC for first-line treatment to manage mild-to-moderate bleeds   | Cost per resolved bleed  | Literature  |
| Carlsson <i>et al.</i> [19] (abstract)    | US/Sweden     | rFVIIa vs. APCC  | Cost per resolved bleed from US and Swedish perspective  | Literature (FENOC study [20])   |
| Dundar <i>et al.</i> [24]                 | Turkey        | Four on-demand strategies rFVIIa, APCC, APCC, APCC APCC, rFVIIa, rFVIIa, rFVIIa HDFVIII, PCC, APCC, rFVIIa PCC, HDFVII, APCC, rFVIIa | Cost per resolved bleed. Direct medical costs from the perspective of the Turkish Reimbursement Institutions                                 | Prospective/retrospective study of 105 bleeds from 24 patients and clinical opinion |
| Ozelo <i>et al.</i> [23]                  | Brazil        | Two on-demand strategies rFVIIa, APCC vs. APCC, rFVIIa   | Cost per resolved bleed. Direct medical costs from the perspective of the Brazilian National Health Service                                  | Prospective/retrospective study of 103 bleeds from 25 patients                      |
| Yoo <i>et al.</i> [25] (Abstract)         | South Korea   | rFVIIa vs. APCC for first-line treatment to manage mild-to-moderate bleeds   | Cost per resolved bleed. Korean reimbursement institutions perspective   | Prospective/retrospective study of 56 bleeding episodes                             |
| Putnam <i>et al.</i> [27]                 | US            | APCC vs. rFVIIa for first-line treatment   | Cost per resolved bleed. US drug cost perspective  | Clinical opinion  |

studies were decision models that evaluated the average treatment cost using APCC or rFVIIa in resolving a mild-to-moderate bleed. The 12 cost-effectiveness analyses had a consistent theme, which was a decision analysis where a mild-to-moderate bleeding episode could be treated with either an APCC-based regimen or an rFVIIa-based regimen. The cost-effectiveness models could be categorized into four separate approaches: cost-utility models, cost-effectiveness models based on

published evidence, cost-effectiveness models based on observational data and cost-effectiveness models based on expert opinion.

#### *Cost-utility study*

The study by Ekert *et al.* [4] in 2001 was the only cost-utility based study identified. This study, based in Australia, is the only one to include an incremental cost per QALY comparing rFVIIa with other agents.

The objective of this study was to determine the cost-effectiveness of providing on-demand rFVIIa therapy compared with 'usual care' [4]. 'Usual care' included treatment with APCC, PCC, porcine FVIII (pFVIII) or plasma-derived FVIII. The study, which included six patients aged between 0 and 18 years with haemophilia and long-standing inhibitors, was conducted in three phases. Phase 1 was a retrospective analysis of treatment with 'usual care' for 6 months preceding switching to rFVIIa; Phase 2 was a retrospective analysis of on-demand treatment with rFVIIa for 6 months and Phase 3 was a patient diary-based prospective analysis of treatment with rFVIIa for 6 months. The patient-reported quality-of-life (QoL) was assessed by the Australian Authorized Adaptation of the Child Health Questionnaire-Child Form (CHQ-CF80) and Australian CHQ-Parent Form (CHQ-PF50). At the end of the study, three health-state scenarios were presented to the patients, which were derived from the key outcomes reported in both the questionnaires and the patients' diaries. Respondents were blinded as to the study phase represented by the scenario and were asked to complete the EuroQol questionnaire. Utility values were derived using the EuroQol multi-attribute utility valuation instrument [6]. Medication costs and costs of other healthcare services were based on the usage of healthcare resources derived from the patient records at the treating centres, with the quantity of factor adjusted to allow for the heavier body mass of the patients in Phase 3.

Efficacy, in terms of the percentage of bleeds resolved, is not reported. However, the study does report the difference in healthcare resources and key clinical outcomes between the treatment phases. When compared with the prior treatments with plasma-derived products, the introduction of rFVIIa resulted in a 63–92% reduction in the number of re-treatments, duration of painful episodes, delay up to initiation of treatment, days when crutches or wheelchair were required, emergency room visits and lost carer time. The utility value derived for the first 6-month phase ('usual care') was -0.11. The average utility value derived for the two rFVIIa treatment phases was 0.47, 0.46 for phase 2 and 0.48 for phase 3. This resulted in an overall incremental utility improvement associated with rFVIIa of 0.58. The rFVIIa dose administered was 90 µg kg<sup>-1</sup> repeated every 2 h in Phase 2 and Phase 3. However, for Phase 1, 'usual care', the dosage of the agents is not reported.

The unit cost of rFVIIa was AUS \$0.875 per microgram with the unit cost of APCC, PCC, pFVIII and plasma-derived FVIII being AUS \$2.50 per IU,

AUS \$1.10 per IU, AUS \$2.62 per IU, and AUS \$0.95 per IU, respectively. For APCC, guidelines recommend 50–100 IU kg<sup>-1</sup> every 6–12 h, depending on bleed type and severity [7]. Assuming the average APCC dosage is 75 IU kg<sup>-1</sup> per infusion, then the cost of an APCC infusion is over twice the cost of a 90 µg kg<sup>-1</sup> injection of rFVIIa. The average drug cost per patient for patients receiving rFVIIa in Phase 2 and Phase 3 was AUS \$16 000 more than their 'usual care'. As the cost of APCC treatment appears much higher than rFVIIa, it must be assumed that the 'usual care' consisted of a high proportion of treatment with the less expensive PCC and plasma-derived FVIII.

The total average treatment cost, including healthcare resources, for the two rFVIIa phases was AUS \$219 214 (approximately €136 000) which was AUS \$29 901 higher than the cost associated with 'usual care' in Phase 1. The incremental cost per QALY ratio was AUS \$51 533 (or €31 000), which the authors indicate is less than the incremental cost per QALY ratio calculated for hospital dialysis (AUS \$57 053) in Australia.

Although the study was small in size with only six patients, the authors do point out that this represents almost one quarter of the 26 paediatric haemophilia patients with inhibitors in Australia at the time of the study. Treatment prior to the introduction of rFVIIa was considered ineffective in four out of the six patients, which resulted in patients having a preference for pain relief rather than replacement therapy. This appears to have led to the large 30-h difference between the delay in treatment between Phase 1, and Phase 2 and 3. The authors conclude that as a result of the treatment delay, there was an increase in the number of bleeds caused by persistent joint damage and associated muscle weakness. It is known that the delay in receiving treatment for the bleed has a significant effect on the amount of factor needed and the time taken to resolve the bleed [8].

An Italian prospective prevalence-based multi-centre study by Gringeri *et al.* reported a mean utility value of 0.66 [standard deviation (SD) 0.25], measured using the EuroQol questionnaire, for 52 patients with moderate-severe haemophilia A or B and inhibitors [9]. Although this value of 0.66 is higher than the values of 0.47 from Ekert *et al.* [4], the SD is large and shows the spread of quality of life scores because of differing disease severity caused by joint damage and the span of years with the disease. With a utility score of 0 representing death and 1 representing perfect health, the values derived from this study show the effect that haemophilia with inhibitors has on the quality of life of the affected

individuals. The utility values elicited in this study could be used to reflect the health state of patients enduring a bleed before resolution and could be incorporated into a cost-utility analysis comparing APCC with rFVIIa. Cost-utility analysis is seen as the ‘gold standard’ in health economic modelling and is preferred by reimbursement authorities such as NICE [10] and the Scottish Medicines Consortium [11].

### Cost-effectiveness models based on published evidence

There were seven published economic studies (including three conference abstracts) that used published sources on effectiveness and/or dosing regimens to derive the efficacy and dosing schedule estimates for APCC and rFVIIa. It should be noted that the Odeyemi and Guest publications solicited data from 22 consultant haematologists on resource use and treatment patterns for bleeds that were not resolved with the first-line treatment. However, initial success rates were based on published literature. The model structure of all of these economic models was similar in that they were all comparing the cost to resolve a mild-to-moderate bleed using a decision-tree framework. The models had up to three stages in which to treat and resolve the bleed using either APCC or rFVIIa. At each stage, the treatment could change and/or the treatment setting (i.e. home, day case admission and inpatient admission) could change.

Figure 2 reflects the underlying structure to each of these models. Once initial treatment with either rFVIIa or APCC is initiated, it is either successful (bleed is controlled) or non-successful (bleed is not controlled). When the bleed is not controlled, the patient receives second-line treatment, which may be the same as the initial treatment or a switch to the other therapy. If the second-line treatment is unsuccessful, the patient receives third-line treatment, which usually entails switching to another therapy.

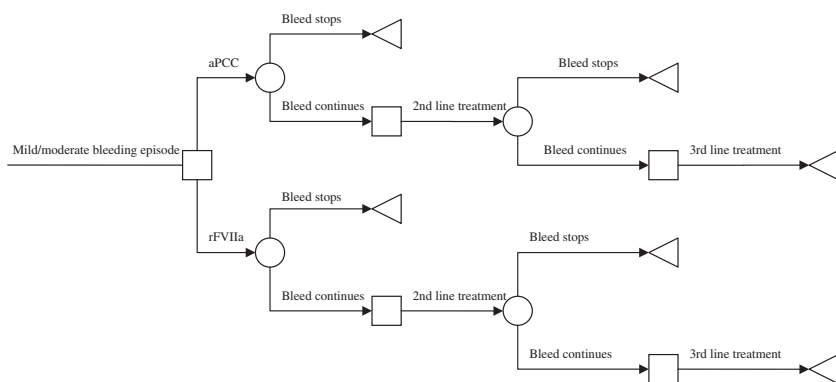


Fig. 2. Simple model schematic.

It is assumed that third-line treatment is successful. Some models included a probability of a re-bleed once the initial bleed had been resolved where the patient would be re-treated with the last therapy that was successful in controlling the initial bleed. The treatment costs and resource costs, including any hospitalization costs to evaluate which of the therapies costs lower in resolving an average bleed, are then summed up for both APCC and rFVIIa. It should be noted that the model by Knight *et al.* [5] was a lifetime model that incorporated annual bleed rates, while the remaining models were based on resolving a single bleeding episode.

Table 5 shows the assumptions for both APCC and rFVIIa regarding efficacy (bleed resolution), average dosage to achieve bleed resolution and the unit cost of each agent used in each model together with the model results.

### Efficacy assumptions

Five of the studies that use published sources to derive efficacy rates, Knight *et al.* [5], Joshi *et al.* [12], two studies by Odeyemi and Guest [13,14], and Huth-Kuehne *et al.* [15], all use similar efficacy rates for first-line treatment with APCC and rFVIIa. With the exception of estimates used by Huth-Kuehne *et al.* [15], the estimates for efficacy rates come from the same two clinical studies (Hilgartner *et al.* [16] and Key *et al.* [17] for APCC and rFVIIa, respectively). The study by Huth-Kuehne [15], which is only published as a conference abstract and as such could be deemed as of less quality, assumes efficacy rates for APCC and rFVIIa of 76.5% and 90.9%, respectively, but no reference to the data source is given.

The study by Hilgartner *et al.* [16], which is the source of efficacy rates for APCC in most of the models reviewed, was an open-label study designed to evaluate the efficacy and safety of APCC for the treatment of bleeding episodes in haemophilia A

Table 5. Summary of key assumptions and results from models based on published literature.

| Study   | Efficacy assumption  |  | Average dose to achieve bleed resolution   |   |                        | Cost assumption (per unit) |   | Results |
|---|--|--|--|---|------------------------|----------------------------|---|---------|
|   | APCC   | rFVIIa   | APCC   | rFVIIa  | APCC                   | rFVIIa                     |   |         |
| Knight <i>et al.</i> [5] (UK)                       | Home: 79%<br>Hospital: 88%   | Home: 92%<br>Hospital: 92%   | First- and second-line:<br>180 UI kg <sup>-1</sup><br>(2.4 × 75 UI kg <sup>-1</sup> )<br>Third-line: n/a | First- and second-line:<br>207 µg kg <sup>-1</sup><br>(2.3 × 90 µg kg <sup>-1</sup> )<br>Third-line: 414 µg kg <sup>-1</sup><br>(4.6 × 90 µg kg <sup>-1</sup> ) | £0.57                  | £0.52                      | Lifetime cost: Regimen of rFVIIa only = £2 047 344<br>Regimen of APCC/APCC/rFVIIa = £2 225 755  |         |
| Joshi <i>et al.</i> [12] (US)                       | 78%  | 92%  | First- and second-line:<br>180 UI kg <sup>-1</sup><br>(2.4 × 75 UI kg <sup>-1</sup> )<br>Third-line: n/a | First- and second-line:<br>207 µg kg <sup>-1</sup><br>(3 × 90 µg kg <sup>-1</sup> )<br>Third-line: 414 µg kg <sup>-1</sup><br>(4.6 × 90 µg kg <sup>-1</sup> )   | \$1.68                 | \$1.54                     | Cost per resolved bleed: Regimen of rFVIIa only = \$28 076<br>APCC-based regimens = \$31–32 000 |         |
| Odeyemi and Guest [13] (Home – UK)                  | Home: 79%<br>Hospital: dependent on type of admission                                | Home: 92%<br>Hospital: dependent on type of admission                                      | First-line: 225 UI kg <sup>-1</sup><br>Subsequent line: dependent on type of admission                   | First-line: 207 µg kg <sup>-1</sup><br>Subsequent line: dependent on type of admission  | £573 no units provided | £683 no units provided     | Cost per resolved bleed: rFVIIa: £12 944<br>APCC: £14 645                                       |         |
| Odeyemi and Guest [14] (Hospital – UK)              | First-line: 79%<br>Second-line: 62%<br>third-line: 80%                               | First-line: 92%<br>Second-line: 100%   | First-line: 225 UI kg <sup>-1</sup><br>Subsequent line: dependent on treatment stage                     | First-line: 207 µg kg <sup>-1</sup><br>Second-line: 567 µg kg <sup>-1</sup>   | £573 no units provided | £683 no units provided     | Cost per resolved bleed: rFVIIa: £11 794<br>APCC: £20 467                                       |         |
| Huth-Kuehne <i>et al.</i> [15] (abstract – Germany) | First-line: 76.5%  | First-line: 90.9%  | First- and second-line:<br>180 UI kg <sup>-1</sup><br>Third-line: n/a                                    | First- and second-line:<br>207 µg kg <sup>-1</sup><br>Third-line: 414 µg kg <sup>-1</sup>   | €1.21                  | €0.73                      | Cost per resolved bleed: Regimen of rFVIIa only: €14 328<br>APCC-based regimens = €22–23 500    |         |
| Chung <i>et al.</i> [18] (abstract – US)            | First infusion: 53%<br>Second infusion: 13%<br>Third infusion: 13%<br>Based on FENOC | First infusion: 25.6%<br>Second infusion: 21.2%<br>Third infusion: 40.5%<br>Based on FENOC | 75 UI kg <sup>-1</sup> per infusion  | 90 µg kg <sup>-1</sup> per infusion + maintenance dose of 90 µg kg <sup>-1</sup>  | Not stated             | Not stated                 | Cost per resolved bleed: rFVIIa: \$35 091<br>APCC: \$19 274                                     |         |
| Carlsson <i>et al.</i> [19] (abstract – US/Sweden)  |  |  | Not stated   | Not stated  | Not stated             | Not stated                 | Results state APCC was the dominant strategy because of lower cost and higher efficacy          |         |

patients with inhibitors. The percentage of bleeds controlled with APCC was 78% (although stated 79% in abstract). The study by Key *et al.* [17], which is the source of efficacy rates for rFVIIa in most models, is an open-label study designed to evaluate treatment of mild-to-moderate bleeds at home using up to three doses of  $90 \mu\text{g kg}^{-1}$  rFVIIa in haemophilia A or B patients with inhibitors. The reported bleed control rate with rFVIIa was 92%.

The study by Chung *et al.* [18] assumes an efficacy rate with APCC of 79%, presumably taken from Hilgartner *et al.* [16], and an efficacy rate of 87.3% for rFVIIa (source not stated). Carlsson *et al.* [19] failed to report any efficacy assumptions but are reportedly based on the findings from the FENOC study [19,20]. Again both these studies are only reported as conference abstracts and as such could be treated as being of less quality than the peer-reviewed published articles.

Sensitivity analysis on the efficacy values was reported in detail in all four articles (excluding abstracts) that use published sources to derive efficacy rates [5,12–14]. Knight *et al.* [5] reported that the efficacy of rFVIIa would have to fall to below 84% or the efficacy of APCC would have to increase to over 88% to change the result from rFVIIa based treatment protocols having the lowest treatment cost. Analysis undertaken by Odeyemi and Guest [13,14] on home treatment of mild-to-moderate bleeds showed that the results were sensitive to the efficacy assumptions, especially regarding rFVIIa. For the treatment costs to be equivalent, the efficacy of APCC would have to increase to 90% from 79%, but the efficacy of rFVIIa need only to fall to 90% from 92%. However, analysis by Odeyemi and Guest [13,14] for the treatment costs of mild-to-moderate bleeds using rFVIIa and APCC within a comprehensive care centre showed that efficacy rates of rFVIIa and APCC were not sensitive to the results. The most comprehensive sensitivity analysis was undertaken by Joshi *et al.* [12] who carried out both a probabilistic sensitivity analysis and one-way or univariate analysis. The univariate analysis showed that the efficacy of rFVIIa would have to be as low as 82% for the overall cost of treatment to be the same between an rFVIIa strategy and the APCC-containing strategies.

#### *Dosing assumptions*

Five of the economic models [5,12–15] interpret the rFVIIa dosage to be 2.3 doses of  $90 \mu\text{g kg}^{-1}$  rFVIIa to attain a 92% bleed control rate, as reported by Key *et al.* [17]. Chung *et al.* [18] incorporated a

maintenance dose of  $90 \mu\text{g kg}^{-1}$  rFVIIa for all bleeds that are controlled. However, studies by Santagostino *et al.* [21] and Key and Laurian [22] support the views that additional injections may not be necessary to maintain haemostasis after a successful response in home treatment with rFVIIa.

Odeyemi and Guest [13,14] interpret the dose of APCC needed to attain a 79% bleed control rate to be a full three doses of  $75 \text{ IU kg}^{-1}$ . Knight *et al.* [5], and also Joshi *et al.* [12] and Huth-Kuehne *et al.* [15], which are based on the assumptions in Knight *et al.* [5], assume a dose of  $180 \text{ IU kg}^{-1}$  (equivalent to  $2.4 \times 75 \text{ IU kg}^{-1}$ ) needed to attain a 79% bleed control rate. Knight *et al.* [5] showed that reducing the average number of APCC infusions by 9% from  $2.4$  to  $2.2 \times 75 \text{ IU kg}^{-1}$  would result in both the on-demand protocols being equivalent. The sensitivity analysis undertaken by Odeyemi and Guest [13,14] shows how the results vary in terms of robustness. The results from the analysis undertaken in the comprehensive care centre is very robust and sensitivity analysis showed that the dosage level of APCC could not be reduced sufficiently to alter the result of rFVIIa having the lowest overall treatment cost. Also, for this result to change, an average of five doses of  $90 \mu\text{g kg}^{-1}$  rFVIIa would have to be administered to control 92% of bleeds. The results of the economic analysis by Odeyemi and Guest [13,14] comparing home treatment of bleeds is less robust. If the number of doses of  $90 \mu\text{g kg}^{-1}$  rFVIIa were to increase to 2.8 or the number of APCC doses decrease to  $2.5 \times 75 \text{ IU kg}^{-1}$  then the overall treatment cost for both treatments would be similar. Joshi *et al.* [12] reported that if either the average dose of rFVIIa were to increase by 20% to  $2.8 \times 90 \mu\text{g kg}^{-1}$  or the average dose of APCC were to decrease by 20% to  $1.9 \times 75 \text{ IU kg}^{-1}$  then this would be sufficient to change the result.

The model by Chung *et al.* [18] confirms a similar interpretation of the Hilgartner *et al.* [16] clinical data by assuming that 52% of bleeds are controlled with one infusion; however, this model also assumes that the remaining 26% of bleeds that are controlled are equally divided between the second and third infusion. Chung *et al.* [18] also includes the percentage of bleeds resolved by 1, 2, or 3 injections of rFVIIa as 25.6%, 21.2% and 40.5%, respectively. Although the source of the rFVIIa data is unknown, the equivalent values calculated from Key *et al.* [17] were 27%, 22.4%, 42.7% for the percentage of bleeds resolved by 1, 2, or 3 injections of rFVIIa, respectively, which equates to an average of 2.2 injections.

### Unit cost of each agent

For all of the models based on published data (Table 5), where the unit cost of each agent was stated, the cost of rFVIIa was generally lower (between 9% and 40%) than the cost of APCC. However, the average cost per dose of APCC and rFVIIa administered is similar because of the dosing regimens of the two agents.

The exceptions to this were the two Odeyemi and Guest [13,14] models, which only provided the total acquisition cost for each treatment, with rFVIIa being more expensive. Without the cost per unit, it is difficult to ascertain what the average cost per dose of APCC and rFVIIa administered is. Sensitivity analysis on the unit cost of each agent was reported by Knight *et al.* [5], Joshi *et al.* [12] and in the analysis within the comprehensive care centre by Odeyemi and Guest [13,14]. Altering the unit cost of a product has the same effect on cost as increasing the dose. Thus the results of the sensitivity analysis reported in the dosing assumptions section are equally as applicable here.

### Cost-effectiveness models based on observational data

There were three articles identified that used retrospective and/or prospective studies either in isolation or with the published literature, to estimate the efficacy and effective dosage for APCC and rFVIIa (Table 6) [23–25]. Although the key parameters of

efficacy, dosing assumptions and unit cost rFVIIa and APCC have been addressed, each of these studies has been appraised separately.

A Brazilian study by Ozelo *et al.* was a mixture of a retrospective and prospective analysis of patient records from four treatment centres, validated by an expert panel of Brazilian haematologists, to ascertain efficacy and dosage estimates [23]. Bleeds were defined as mild if signs and symptoms of haemorrhage were evident but did not prevent the patient from performing normal activities and moderate if it did prevent the patient from undertaking normal activities. Severe bleeds were excluded. Effectiveness was defined clinically based on pain relief, reduction in swelling, improvement of joint mobility, or cessation of bleeding occurring within 48 h of treatment initiation. A prospective analysis had to be conducted as a result of lack of patient bleeds treated with rFVIIa because of the current prescription guideline in Brazil regarding rFVIIa provided as a first-line treatment. A total of 103 bleeds in 25 patients were treated with either APCC (67) or rFVIIa (36), and bleed severity was similar in both groups. The effectiveness of rFVIIa (100% for new bleeds and 100% for bleeds treated in 12 h and 100% for re-bleeds) was higher than that of APCC (corresponding values: 56.7%, 63.6% and 40.0%, respectively). The mean time to achieve bleed resolution was also significantly less for rFVIIa (4.4 h) compared with APCC (62.6 h). An average of 1.6 doses and 2.3 doses of 92 µg kg<sup>-1</sup> of rFVIIa was used for mild and moderate bleeds, respectively. For

**Table 6.** Summary of key assumptions and results from models based on observational studies and/or clinical opinion.

| Study   | Efficacy assumption   |   | Average dose to achieve bleed resolution                                 |   | Cost assumption (per unit) |            | Results  |
|---|---|---|--|---|----------------------------|------------|--|
|   | APCC  | rFVIIa  | APCC   | rFVIIa  | APCC                       | rFVIIa     |  |
| Dundar <i>et al.</i> [24] (Turkey)              | Study result: 66.7%<br>Model used: 79%                      | Study result: 89.3%<br>Model used: 89.3%                    | 168.8 UI kg <sup>-1</sup><br>mean total dose                             | 204 µg kg <sup>-1</sup><br>mean total dose  | \$1.02                     | \$0.83     | Cost per resolved bleed:<br>rFVIIa: \$9113<br>APCC: \$12 542   |
| Ozelo <i>et al.</i> [23] (Brazil)               | Study result: 56.7%<br>Model used: 56.7%                    | Study result: 100%<br>Model used: 100%                      | 260.2 UI kg <sup>-1</sup><br>mean total dose                             | 189.9 µg kg <sup>-1</sup><br>mean total dose  | \$0.61                     | \$0.692    | Cost per resolved bleed:<br>rFVIIa: \$7790<br>APCC: \$13 500   |
| Yoo <i>et al.</i> [25] (abstract – South Korea) | First-line: 64%<br>No further data                          | First-line: 87.1%<br>No further data                        | Not stated   | Not stated  | Not stated                 | Not stated | Cost per resolved bleed:<br>rFVIIa: \$12 311<br>APCC: \$18 085 |
| Putnam <i>et al.</i> [27] (US)                  | First-line: 75%<br>Hospital: dependent on type of admission | First-line: 90%<br>Hospital: dependent on type of admission | First-line: 75 UI kg <sup>-1</sup><br>Continued: 120 UI kg <sup>-1</sup> | First-line: 270 µg kg <sup>-1</sup><br>(3 × 90 µg kg <sup>-1</sup> )<br>Continued: 270 µg kg <sup>-1</sup><br>(3 × 90 µg kg <sup>-1</sup> ) | \$1.30                     | \$1.40     | Cost per resolved bleed:<br>rFVIIa: \$33 400<br>APCC: \$21 000 |

APCC, averages of 3.6 doses of 58 IU kg<sup>-1</sup> and 3.9 doses of 75 IU kg<sup>-1</sup> were required for mild and moderate bleeds, respectively.

A decision tree similar to Fig. 2 was constructed using the aforementioned efficacy and average dosage data to reflect Brazilian clinical practice. The results of the model showed that the mean total direct medical costs per bleed were around \$6000 lower using rFVIIa as the first line treatment compared with APCC. The authors acknowledge that the average extended time to initiate APCC treatment may have affected the effectiveness values for APCC. However, comparing bleeds initiated ≤12 h from onset still showed rFVIIa to be superior. The effectiveness rate for APCC of 56.7% is lower than that reported in the published literature (approximately 79% [16,26]). However, this difference does not appear to be as a result of a lower dose rate, as an average of 3.6 doses of 58 IU kg<sup>-1</sup> and 3.9 doses of 75 IU kg<sup>-1</sup> for mild and moderate bleeds, respectively is within the recommended dose for APCC (50–100 IU kg<sup>-1</sup>) [7]. The unit cost of rFVIIa is 13% higher than that of APCC; however, because of lower dosages, the average cost of each agent used to treat a bleeding episode in the model is less for rFVIIa. This, together with the assumed superior efficacy and fewer second-line costs, results in rFVIIa being the cost-effective treatment option. Sensitivity analysis showed that even increasing the baseline efficacy assumption of APCC to 80%, the efficacy of rFVIIa would have to decrease below 66% before the total treatment cost of both products became equivalent. Extensive sensitivity analysis of other parameters confirmed that the results were robust and not subject to substantial variation in parameter values.

A study by Dundar *et al.* evaluated the economic impact of four different treatment regimens (high-dose factor VIII or IX, PCC, APCC and rFVIIa) for mild-to-moderate bleeds in patients with haemophilia and inhibitors [24]. They constructed a decision-analysis model, similar to Fig. 2, using data derived both from the published literature and from their own retrospective analysis of 105 bleeds in 24 patients over a 6-year period at three haemophilia care centres in Turkey. The analysis of the patient records showed that patients treated with APCC had a bleed resolution rate of 66.7% after being treated with an average of 4.8 doses (mean dose per episode 166.8 IU kg<sup>-1</sup>) and patient treated with rFVIIa had a bleed resolution rate of 89.3% after being treated with an average of 3.6 doses (mean dose per episode 204 µg kg<sup>-1</sup>). The time to bleed resolution was shorter for rFVIIa (17.3 h) compared with APCC (43.6 h). The treat-

ment was considered effective if pain or swelling were absent within 24 h. The 89.3% bleed effectiveness rate for rFVIIa was supported by both the literature review and by expert opinion and so adopted as the default value for the model. However, the expert opinion felt that the APCC rate from the study was low and thus, for the model, a bleed effectiveness rate of 79% reported by Hilgartner *et al.* [16] was used. The results of the model showed that the mean direct health care costs were around US \$3400 lower per bleeding episode treated with rFVIIa compared with APCC therapy.

The average total dose of rFVIIa administered (204 µg kg<sup>-1</sup>) to achieve an 89.3% bleed resolution rate is similar to the average total dose reported in the clinical study by Key *et al.* [17]. The average total dose of APCC administered (166.8 IU kg<sup>-1</sup>) is lower than doses used in any of the other models reviewed, which may have affected the 66.7% bleed resolution rate. The baseline unit cost of APCC was 23% higher than that of rFVIIa, so the average cost of each agent to treat a bleed was nearly identical at around \$170 per dose. However, as rFVIIa has the assumed superior efficacy to APCC, and hence a smaller number of patients requiring a second-line treatment and associated costs, rFVIIa is the cost-effective option. Sensitivity analysis showed that when comparing rFVIIa treatment to APCC only, treatment with rFVIIa was always the cost-effective option and was robust to major variation in the baseline assumptions to efficacy and unit cost.

Yoo *et al.* [25] also developed an economic model using a specific observational study to populate the parameters. This was a Korean study that was based on a prospective and retrospective study of 56 bleeding episodes resolved within 24 h of initiating treatment. As this is an abstract, little information is available. However, first-line effectiveness of rFVIIa was reported as 87.1% with a mean time to bleed resolution of 6.6 h compared with 64% effectiveness for APCC with mean time to bleed resolution of 25.2 h. The average total medical cost per bleeding episode was reported as US \$18 085 for APCC compared with US \$12 311 for rFVIIa. The conclusion from this study was that rFVIIa is associated with greater effectiveness and lower total medical costs.

The main message from these models relates to the assumptions related to clinical efficacy. The efficacy of APCC reported in the observational trials that are used as the sources of data is consistently lower, while the efficacy rates for rFVIIa from the observational studies are consistently close to the value of 92% reported by Key *et al.* [17]. Sensitivity analysis

has shown these results to be robust to increasing the efficacy of APCC to levels reported in the literature.

The dosing schedules of rFVIIa in both the Ozelo *et al.* [23] and Dundar *et al.* [24] are similar at a mean total dose of 190 and 204  $\mu\text{g kg}^{-1}$  respectively. However, the mean total dose of APCC administered varied considerably between the studies, with 170 IU  $\text{kg}^{-1}$  reported by Dundar *et al.* [24] and 260 IU  $\text{kg}^{-1}$  by Ozelo *et al.* [25]. This variation in the mean administered dosage of APCC probably reflects different country clinical practice; however, it is surprising that a higher efficacy rate was reported for the lower mean administered dose (Table 6).

The unit cost of APCC in Turkey is reportedly approximately 23% higher than that of rFVIIa [24]. However, in the study by Ozelo *et al.*, rFVIIa was reported as costing 13% higher than APCC. This difference in unit cost could be because of regional differences in price setting by the pharmaceutical companies. The sensitivity analysis explored the importance of the unit cost of each agent, and found that the baseline results were robust.

### Cost-effectiveness models based on expert opinion

A cost-minimization model developed by Putnam *et al.* was based on data derived from a panel of 11 US-based haemophilia experts who were presented with a clinical scenario of treating a 10-year-old boy with severe haemophilia A and inhibitors who developed a shoulder haemarthrosis [27].

#### *Efficacy assumptions*

The two choices for initiating first-line therapy at home were APCC or rFVIIa, and the clinicians had to provide estimates of efficacy at two time points, within 8–12 h (Time 1) and at 24 h (Time 2). The efficacy rates at Time 1 were estimated as 90% for rFVIIa, based on a dosage of  $3 \times 90 \mu\text{g kg}^{-1}$  and 75% for APCC based on a dosage of 75 IU  $\text{kg}^{-1}$ .

#### *Dosing assumptions*

The dosing assumptions suggested by the clinical opinion suggest that only one dose of APCC (75 IU  $\text{kg}^{-1}$ ) is needed to resolve 75% of bleeds while three doses of rFVIIa ( $3 \times 90 \mu\text{g kg}^{-1}$ ) are needed to achieve a 90% bleed resolution rate. Although the authors compare their efficacy assumptions to the published literature, they fail to account for the differences in the dosing level of APCC needed to achieve a 75% bleed resolution rate [16].

#### *Unit cost of each agent*

The unit cost of rFVIIa is 8% higher than the unit cost of APCC and this, coupled with the average dose administered of each agent, produces an average cost of a bleed treated with rFVIIa being four times more expensive than a bleed treated with APCC.

The results of the model showed that the average cost to achieve bleed resolution was US \$12 400 lower for treatment initiated with APCC compared with initial treatment with rFVIIa. Despite the superior efficacy, the dosing assumptions regarding the amount of each factor needed to achieve their respective bleed resolution rates coupled with the higher unit cost of rFVIIa results in APCC being the preferred treatment option. A published response to the Putnam [27] model (Seremetis *et al.* [28]) had two main criticisms: the unit cost of APCC was apparently 15.4% lower in the model than the actual price, and, more importantly, there was a discrepancy regarding the total dose of rFVIIa needed to resolve a bleed. In order to ascertain the required dose of rFVIIa, the clinical panel was asked to estimate the dose of rFVIIa in two separate ways; this produced conflicting results. First, the expert panel estimated an initial total dose of 270  $\mu\text{g kg}^{-1}$  rFVIIa in the first 8–12 h at which point the bleed was reassessed.

The expert panel then chose to give an additional total dose of 270  $\mu\text{g kg}^{-1}$  of rFVIIa in the next 12–16 h even though the bleed was predicted to be clinically improved. Thus a total dose of 540  $\mu\text{g kg}^{-1}$  of rFVIIa was used as the baseline assumption. However, when the panelists were asked separately to estimate the total dose of rFVIIa required to resolve the bleed, the consensus was that 360  $\mu\text{g kg}^{-1}$  would be sufficient. Using the higher estimated dose of rFVIIa needed to resolve the bleed inflated the treatment cost of rFVIIa. With these issues addressed, Seremetis *et al.* [28] concluded that the costs of APCC and rFVIIa needed to resolve the bleed were comparable.

### Conclusions/recommendations

This systematic review identified 12 cost-effectiveness analyses comparing rFVIIa and APCC in the treatment of mild-to-moderate bleeding episodes in haemophilia patients with inhibitors. The study by Ekert *et al.* [4] that introduced rFVIIa treatment and compared it with the patients' usual treatment, including APCC, for on-demand bleeding episodes showed that rFVIIa was the cost-effective alternative. This study remains the only cost-utility analysis

within this area and highlights the need for more such studies.

The other 11 cost-effectiveness analyses adopted a similar model framework as depicted in Fig. 2, which because of its wide exposure to clinical opinion must be considered a suitable modelling structure. The Knight *et al.* [5] analysis was over the patient's lifetime, while the other studies estimated the average cost of treating a single bleed episode with either APCC or rFVIIa.

Figure 3 shows the results for the nine analyses that reported the average cost per resolved bleed. All the costs have been converted to US dollars assuming US \$1.0 equates to €1.46 and £1.96. Figure 3 excludes the lifetime analysis by Knight *et al.* [5] showing rFVIIa as the preferred treatment option and excludes the abstract by Carlsson *et al.* [19] that failed to report any data although stated that APCC had lower costs and higher efficacy. The average cost to resolve a bleed is lower using rFVIIa than APCC in seven out of the nine economic analyses presented in Fig. 3. The average amount that rFVIIa is lower than APCC ranges between \$3000 and \$17 000 per resolved bleed. The two studies that reported APCC as having the lower mean cost to resolve a bleed both have quality issues. The Chung *et al.* [18] abstract disregarded any second-line treatment from the analysis and did not report the unit costs of the agents. By not considering the treatment costs associated with second-line and subsequent therapy, the resulting average cost of treatment would be biased against the treatment with the higher efficacy, namely rFVIIa. The quality issues relating to the Putnam *et al.* [27] study have already been discussed in detail, and with those issues addressed, the cost per resolved bleed was similar for both APCC and rFVIIa.

All of the models that are based on published evidence assume a higher efficacy rate for rFVIIa than for APCC, and all of these models assume a dosing regimen of  $3 \times 90 \mu\text{g kg}^{-1}$  for rFVIIa and up to  $3 \times 75 \text{ IU kg}^{-1}$  for APCC. For the four fully published models, the data sources of Hiltgartner *et al.* [16] and Key *et al.* [17] are used for the efficacy assumptions of APCC and rFVIIa, respectively. However, it is the interpretation of the average number of doses needed for both rFVIIa and APCC to achieve these efficacy rates that varies across the studies. Currently, there are only two head-to-head trials comparing APCC with rFVIIa [20,29]. The FENOC study compares  $75 \text{ IU kg}^{-1}$  of APCC with  $2 \times 90 \mu\text{g kg}^{-1}$  of rFVIIa and the conclusion was that at no time point statistically significant equivalence between the two treatments could be shown. The study by Young *et al.* [29] is a three-armed trial comparing  $1 \times 270 \mu\text{g kg}^{-1}$  of rFVIIa vs.  $3 \times 90 \mu\text{g kg}^{-1}$  of rFVIIa vs.  $1 \times 75 \text{ IU kg}^{-1}$  of APCC. Young *et al.* [29] reported efficacy rates, measured as percentage of subjects not requiring rescue medication after 9 h, of around 91% for the two rFVIIa treatment regimens and only 63.5% for APCC. It should be noted that clinical opinion has been employed by certain models to ascertain parameter values. Although clinical opinion can be open to bias the need to seek clinical opinion is there because of the lack of head-to-head trials and systematic review of the efficacy data. A published abstract detailing a meta-analysis undertaken on the efficacy of APCC and rFVIIa demonstrated that medication type together with the dosage had a statistically significant effect on efficacy [29]. The results of the derived model estimated that 75%, 94% and 98% of bleeds would be treated effectively with rFVIIa after 12, 24,

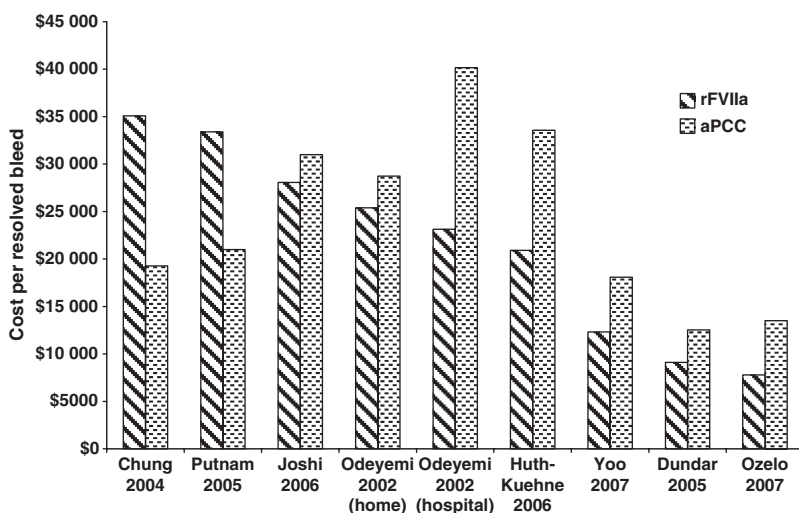


Fig. 3. Comparison of the mean cost per resolved bleed.

and 36 h respectively. In contrast, for APCC the model estimated that 39%, 63% and 78% of bleeds would be treated effectively at the equivalent time points. The findings from this study appear to support the efficacy estimates for both rFVIIa and APCC used in the published economic models derived from the literature and incorporate the plausible range of efficacy values investigated within the sensitivity analysis.

The three economic models based on retrospective analysis are set in Turkey, Brazil and South Korea [23–25]. The common theme throughout these studies is the low efficacy rate reported for APCC both in comparison to rFVIIa and to the efficacy rates of APCC reported in the literature. The mean total dose of APCC administered in the Ozelo *et al.* [23] retrospective study is excessive when compared with the amount assumed by the models based on the published literature, and produced the lowest APCC bleed control rate of 56.7%. While retrospective studies are, by their nature, not controlled and therefore open to bias, it can be argued that the actual clinical setting in these studies better reflects reality compared with the sterile setting in a clinical trial. The recent reported efficacy estimates from the meta-analysis model for APCC at 12 and 24 h after treatment initiation appear to support a lower estimate of APCC efficacy compared with the published literature. The results from these studies and the extensive sensitivity analysis undertaken support the rFVIIa assumptions regarding the economic models built using published literature, but may cast doubt on the reported high efficacy rates for APCC.

With eight out of the 11 studies resulting in rFVIIa being the preferred treatment option, the current weight of economic opinion would suggest that rFVIIa is cost-effective when compared with APCC in the treatment of mild-to-moderate bleeds for haemophilia patients with inhibitors. This systematic review has shown that models that although have a similar framework are based on different sources of data have produced fairly similar robust results despite differences in the estimates of efficacy, average dosage required to treat a bleed, and unit cost of the haemostatic agents. However, attaining appropriate estimate for the key parameters is paramount, and ideally there should be a systematic approach to identifying the relevant data. The lack of data from relevant randomized head-to-head trials is a contributing factor to the variation in efficacy rates and average dosages assumed for each comparator. This is partly because of the difference in administration between rFVIIa, which is given intravenously as a bolus injection, and APCC, which is given intravenously by infusion, making patient blinding to

treatment in a clinical trial setting difficult. However, using an indirect comparison method, as undertaken by Treur *et al.*, to help synthesize the evidence and elicit appropriate parameter estimates may be a way forward [30].

One of the main factors that is difficult to quantify within the economic analyses reviewed here is the speed of bleed resolution. The time taken to stop a bleeding episode is very important to the patient as it reduces the time a patient is in pain, the amount of haemostatic agent required, the potential long-term damage to the joint, and the subsequent cost of undergoing a joint arthroplasty [31]. The current labelled dosing for rFVIIa of 90  $\mu\text{g kg}^{-1}$  every 2–3 h or a single dose of 270  $\mu\text{g kg}^{-1}$  compared with APCC labelling of 75 IU  $\text{kg}^{-1}$  every 8–12 h shows that three doses of rFVIIa of 90  $\mu\text{g kg}^{-1}$  or one dose of rFVIIa of 270  $\mu\text{g kg}^{-1}$  would take only 6–9 h to resolve a bleed compared with 16–36 h for two or three doses of APCC. Although some of these models alluded to the time taken to resolve a bleed it is difficult to quantify in economic terms as a cost or an outcome such as health-related quality of life. Ekert *et al.* [4] attempted to reflect the difference between the two treatments in terms of duration of pain, number of re-treatments and other resource use using quality of life measures and ultimately producing QALYs. Future economic models would ideally incorporate quality of life data to produce cost-utility analysis, which is seen as the ‘gold standard’ of health economic modelling.

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## Appendix

### Search strategies

MEDLINE (via PubMed)

Search undertaken in April 2008

- #1 (hemophilia OR “hemophilia A” OR “hemophilia B” OR hemophil\*) AND (inhibitors OR inhibit\* OR anti-inhibit\* OR antibod\*) NOT (acquired [Title])
- #2 apcc\*
- #3 APCC
- #4 “activated prothrombin complex concentrate”
- #5 FEIBA
- #6 Autoplex
- #7 “recombinant factor VIIa”
- #8 rFVIIa
- #9 NovoSeven
- #10 bypass\*
- #10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
- #11 cost
- #12 cost\*
- #13 cost-analysis
- #14 cost analysis
- #15 cost-effectiveness

- #16 cost effectiveness
- #17 \*economic\*
- #18 pharmacoeconomic
- #19 pharmaco-economic
- #20 cost-utility
- #21 cost utility
- #22 cost-benefit
- #23 cost benefit
- #24 economic-model
- #25 QALY[Title/Abstract]
- #26 modelling
- #27 “decision model”
- #28 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
- #29 #1 AND #10 AND #28, Limits: Publication date from 1990 to 2008

EMBASE (via Dialog)

Search undertaken in April 2008

File 73:EMBASE 1974–2008/April

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Set Items Description

S1 4413 (HEMOPHIL? OR HEMOPHILIA!) AND (INHIBIT? OR ANTI()INHIBIT? OR ANTIBOD?)

S2 4091 S1 NOT ACQUIRED/TI

S3 760 S2 AND (APCC? OR ACTIVATED()PROTHROMBIN()COMPLEX OR FEIBA OR AUTO- PLEX OR RECOMBINANT()FACTOR()VIIA OR RFVIIA OR NOVOSEVEN OR RECOMBINANT() BLOOD() CLOTTING()FACTOR()7A OR BYPASS?)

S4 190 S3 AND (COST OR COSTS OR COSTED OR COSTING OR COST! OR ECONOMIC? OR ECONOMICS! OR PHARMACOECONOMIC? OR PHARMACOECONOMICS! OR QALY/TI,AB OR MODELLING OR MODELING OR DECISION()MODEL? OR MODEL!)

S5 185 S4/1990:2007

The Cochrane Library (including NHS EED and HTA databases)

Search undertaken in April 2007

#1 hemophilia AND inhibitors