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Modelling the economic impact of recombinant activated Factor VII and activated prothrombin-complex concentrate in the treatment of a mild to moderate bleed in adults with inhibitors to clotting Factors VIII and IX at a comprehensive care centre in the UK

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Summary

To estimate the costs and consequences of using recombinant activated Factor VII (rFVIIa; NovoSeven (Novo Nordisk)), compared with activated prothrombin-complex concentrate (aPCC; FEIBA (Baxter Healthcare)), to manage a minor (i.e. mild to moderate) bleeding episode at a haemophilia treatment centre (Comprehensive Care Centre; (CCC)) in the UK among adults with high titre, high responding inhibitors (>10 BU).

This was a modelling study performed from the perspective of the UK's National Health Service (NHS).

Clinical outcomes and resource utilisation attributable to managing a minor bleed were obtained from published literature, supplemented with information about treatment patterns and associated resource utilisation derived from interviews with 22 consultant haematologists experienced in managing inhibitor patients. Using these data sources, a decision tree modelling the management of a minor bleed at a CCC was constructed. Unit resource costs at 1999/2000 prices were applied to the resource utilisation estimates in the model to calculate the expected NHS cost of managing a minor bleeding episode. Consensus on the probabilities and resource utilisation estimates in the model were reached at a meeting comprising seven of the 22 consultant haematologists.

Key words: activated prothrombin-complex, costs, Factor VII, economics, haemophilia

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The expected NHS cost of managing a minor bleeding episode among adults initially treated with rFVIIa or aPCC was estimated to be £11,794 and £20,467, respectively. Additionally, the expected time to resolving a minor bleeding episode when initially treated with rFVIIa or aPCC was estimated to be 30 hours and 58 hours, respectively.

Our model suggests that rFVIIa is a cost effective treatment compared to aPCC for the treatment of a minor bleed at a CCC, since it improves clinical outcome and reduces NHS costs. This finding warrants further investigation in a prospective, comparative, randomised controlled study.

Introduction

The development of inhibitors to coagulation Factors VIII and IX is one of the most serious complications of haemophilia treatment[1]. Most patients with high titre, high responding inhibitors cannot be treated with conventional therapies, hence bleeding episodes in these patients are usually treated first-line in the UK with activated recombinant Factor VII (rFVIIa; NovoSeven*;[2–5]) or activated prothrombin-complex concentrate (aPCC; FEIBA)[6–14].

The benefits of managing bleeding episodes in haemophilia patients in either a home or hospital setting has been studied using porcine Factor VIII[15] and rFVIIa[2,3]. Additionally, rFVIIa's efficacy has been shown to increase with shorter time between bleed onset and the start of treatment. This led to suggestions that early treatment at home may improve outcome[2,3] and reduce costs[16]. However, no comparable study has been reported for aPCC .

We have previously estimated the economic impact of rFVIIa in the home treatment of a minor bleed[17]. In this present study we evaluated the costs and consequences of rFVIIa and aPCC in the management of a minor bleeding episode at a haemophilia treatment centre (Comprehensive Care Centre; (CCC)) in the UK among adults with high titre, high responding inhibitors (>10 BU), from the perspective of the NHS.

Methodology

Clinical outcomes and resource utilisation

There are no published studies directly comparing the treatment of a minor bleed with rFVIIa and aPCC. Therefore, the efficacy and resource utilisation associated with treating inhibitor patients who develop a minor bleed with first-line rFVIIa and aPCC was derived from separate studies[5,12]. These studies were selected because the patients in both were comparable and the description of the trial protocol and results were sufficiently informative to enable us to compare the dose, dosage and efficacy of treatments.

Since none of the published studies described the treatment patterns and

* Novo Seven is a registered trademark of Novo Nordisk, Denmark.

associated resource use attributable to managing a minor bleed following first-line treatment, this was estimated by interviewing 22 consultant haematologists from across the UK who have experience of managing patients with inhibitors. Haematologists were selected on the basis of being representative of the healthcare they provided for inhibitor patients and of being geographically representative of England, Scotland, Wales and Northern Ireland. These interviews were semi-structured, qualitative and quantitative discussions that evolved with each expert interview. They included standard questions on patient management, treatment paths and resource use as well as open questions that enabled any other information to be recorded. The minutes of each meeting were sent to the haematologists for annotation and verification. Consensus on the probabilities and resource utilisation estimates were reached at an expert meeting comprising seven of the original 22 haematologists. The expert panel members were selected in accordance with set guidelines for selection of Delphi panel members[18].

Decision model

Using the decision analysis software package DATA™ 3.5 for Windows (Treeage, USA) and information obtained from the published literature and haematologists, a decision tree modelling the management of a minor bleed, was constructed (Figure 1).

The model comprises the initial and subsequent treatments for a bleed, probability of switching from one treatment to another, duration of use for each treatment and probability that each treatment will resolve a bleed. In addition, the model contains resource utilisation estimates associated with haemostatic drugs, co-medication, outpatient visits, inpatient stay, clinical tests/investigations and ambulance transport.

Unit resource costs at 1999/2000 prices[19–21] were applied to the resource utilisation estimates in the decision model to determine the expected NHS cost of initially managing a minor bleeding episode with rFVIIa and aPCC. The model also estimated the expected time to bleed resolution.

Sensitivity analyses

Sensitivity analyses tested the model's robustness by varying probabilities and resource use values in the model to determine how they affected the economic impact of rFVIIa compared with aPCC. The large values used for these analyses reflect the large range of uncertainties within the model.

Results

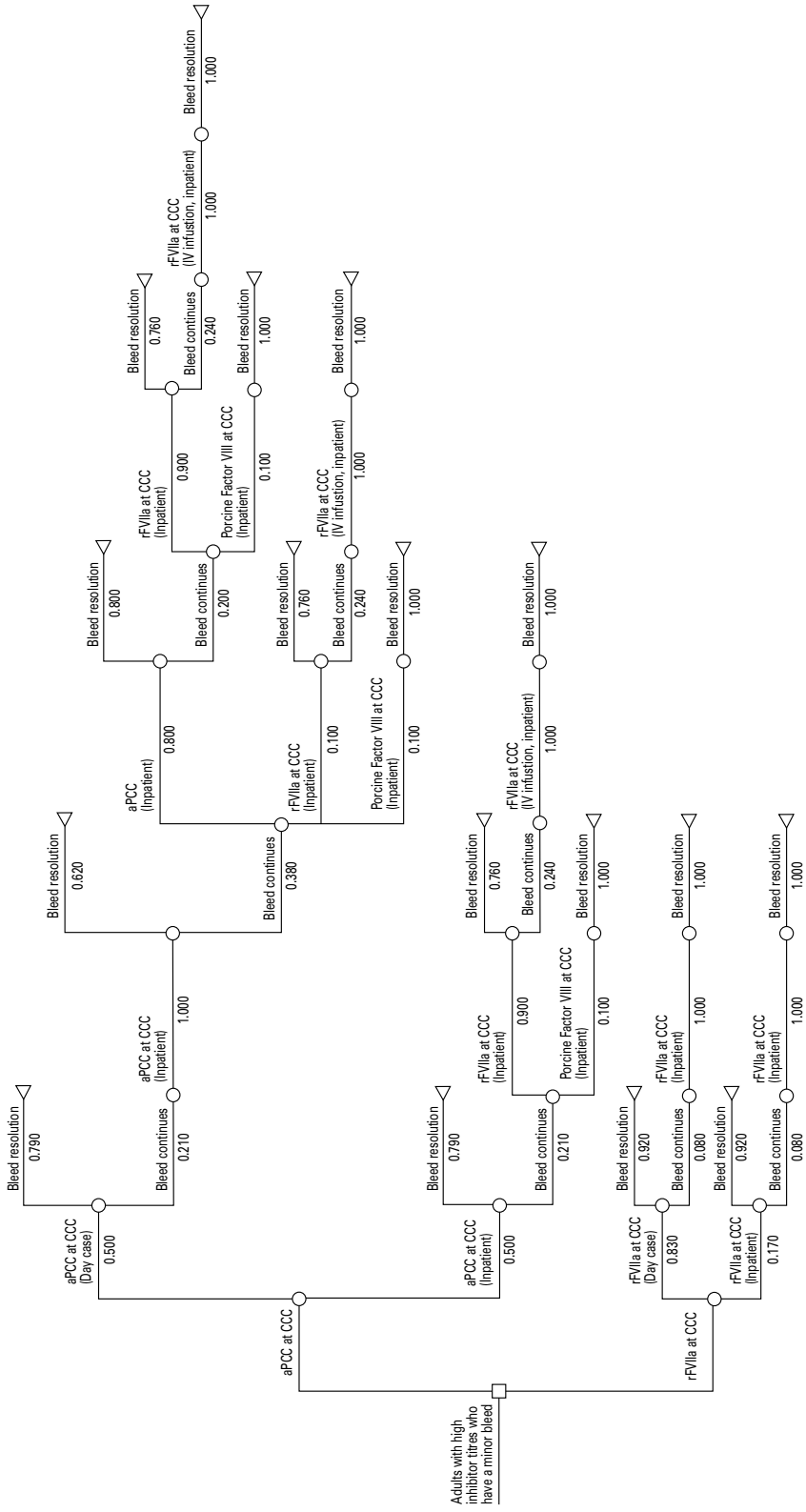
Treatment patterns for managing a minor bleed at a CCC

The decision model incorporated the following treatment patterns and associated estimates of resource utilisation.

Management with aPCC

The haematologists considered that 50% of patients treated with first-line aPCC at a CCC would be treated as a day case and

Figure 1. Decision tree modelling the management of a minor bleed among adults with high titre high responding inhibitors (>10 BU) who start treatment at a CCC with rFVIIa or aPCC. Numbers denote the probability that a patient will follow a particular path.



the other 50% as an inpatient. On the basis of published data[12], it was assumed that all patients would receive 3 aPCC doses of 75 units/kg body weight, of which 79% of bleeds would resolve without further treatment[12] and 21% would require subsequent treatment.

The haematologists considered that the day case patients with unresolved bleeds following first-line aPCC would be admitted to a CCC and receive 4.8 aPCC doses (100 units per kg body weight) over 2.4 days. They also considered that 62% of these bleeds would resolve and 38% would require further treatment of which it would be expected that:

- 80% would receive 9 doses of aPCC (100 units per kg body weight) over 3 days. Of these, 80% would resolve and 20% of bleeds would require further treatment of which:
  - 90% would be switched to rFVIIa and receive 6.3 doses of 90 μg/kg body weight over 2 days. Seventy-six percent of these bleeds would resolve and 24% would require a continuous iv infusion of rFVIIa* (20 μg/kg body weight per hour over 2.5 days) for all bleeds to resolve.
  - 10% would be switched to Porcine Factor VIII (2 doses of 100 units/kg body weight over 24 hours) after which all bleeds would resolve.
- 10% would be switched to rFVIIa and receive 6.3 doses of 90 μg/kg body weight over 2 days. Of these, 76% would resolve and 24% would require a continuous iv infusion of rFVIIa* (20 μg/kg body weight per hour over 2.5 days) for all bleeds to resolve.
- 10% would be switched to Porcine Factor VIII and receive 2 doses of 100 units/kg body weight over 24 hours, after which all bleeds would resolve.

According to the haematologists, of the 21% of inpatients with unresolved bleeds following first-line aPCC it would be expected that:

- 90% would be switched to rFVIIa and receive 6.3 doses of 90 μg/kg body weight over 2 days. Of these, 76% of bleeds would resolve and 24% would require a continuous iv infusion of rFVIIa* (20 μg/kg body weight per hour over 2.5 days) for all bleeds to resolve.
- 10% would be switched to Porcine Factor VIII and receive 2 doses of 100 units/kg body weight over 24 hours, after which all bleeds would resolve.

Management with rFVIIa

The haematologists expected that of patients treated with first-line rFVIIa at a CCC, 83% would be treated as a day case and 17% as an inpatient. On the basis of published data[5], it was assumed that all patients would receive 2.3 doses of rFVIIa at 90 μg/kg body weight over 24 hours, of which 92% of bleeds would resolve without further treatment[5] and 8% would require subsequent treatment.

The haematologists considered that all unresolved bleeds following first-line rFVIIa, irrespective of whether patients were treated as a day case or an inpatient, would receive 6.3 rFVIIa doses of 90 μg/kg

* rFVIIa is not licensed for continuous iv infusion in the UK.

body weight over 2 days as an inpatient, after which all bleeds would resolve.

Re-bleeds

The haematologists considered that a second bleed would be directly related to the initial episode if it occurred at the same site within 7 days after the initial bleed resolved. Furthermore, they considered that a re-bleed would occur in 12% of bleeding episodes. Re-bleeds would be managed using the same treatment as that which controlled the initial episode.

Other resource use

The haematologists considered that tranexamic acid (25 mg/kg body weight, 3 times daily) would be administered to 6% of bleeds treated with aPCC and 50% of bleeds treated with rFVIIa. They also considered that Fibrin Glue (1.5 ml) would be administered to 3% of bleeds regardless of whether the initial treatment was aPCC or rFVIIa.

The haematologists considered that patients would also receive the following medication for pain relief:

- Diamorphine (96 mg daily) would be prescribed to 1% of patients.
- Morphine sulphate (23 mg, twice daily) would be prescribed to 1% of patients.
- Pethidine (100 mg, 6 times daily) would be prescribed to 1% of patients.
- Dihydrocodeine (57 mg, 5 times daily) would be prescribed to 2% of patients.
- Kapake (codeine phosphate/paracetamol — 1.5 tablets, 5 times daily) would be prescribed to 2% of patients.
- Paracetamol (375 mg, 4 times daily) would be prescribed to 40% of patients.

Routine tests

The haematologists considered that adult patients attending a CCC would undergo the following tests:

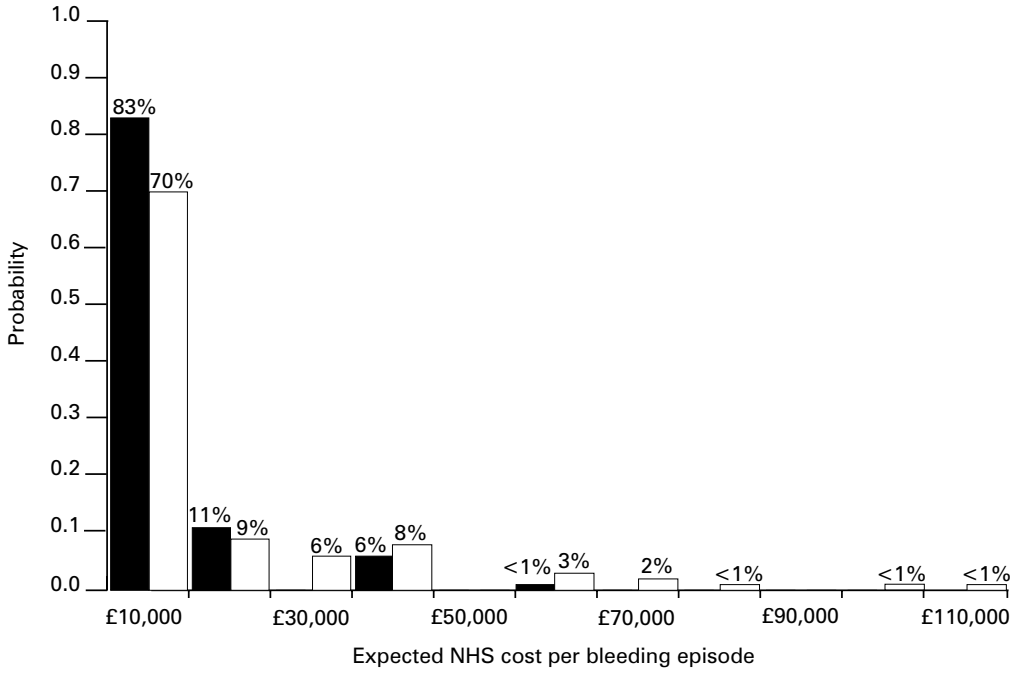
- Inhibitor (Bethesda) assay for 33% of patients at admission.
- Biochemistry tests for 20% of patients at admission.

Table 1. Expected costs of the treatment components attributable to managing adults with a minor bleeding episode, stratified by initial treatment

	Expected NHS cost (£s) per bleeding episode following initial treatment of a minor bleed at a CCC with:	
	aPCC	*rFVIIa*
aPCC	13,497 (66.0%)	–
rFVIIa	5,994 (29.0%)	11,607 (98.0%)
Porcine Factor VIII	360 (1.8%)	–
Ambulance travel	8 (<1%)	8 (<1%)
Co-medication	4 (<1%)	6 (<1%)
Inpatient stay	554 (2.7%)	119 (1.0%)
Outpatient consultations	42 (<1%)	47 (<1%)
Tests	8 (<1%)	7 (<1%)
Total	20,467	11,794

Percentage of total expected cost is in parentheses.

Figure 2. Distribution of the expected NHS cost of managing adults with a minor bleed at a CCC. ■, rFVIIa; □, aPCC.



- Factor VII plasma level assay for patients who receive a continuous iv infusion of rFVIIa and this would be repeated every 24 hours.
- Ultrasound for 5% of all patients.

Ambulance travel

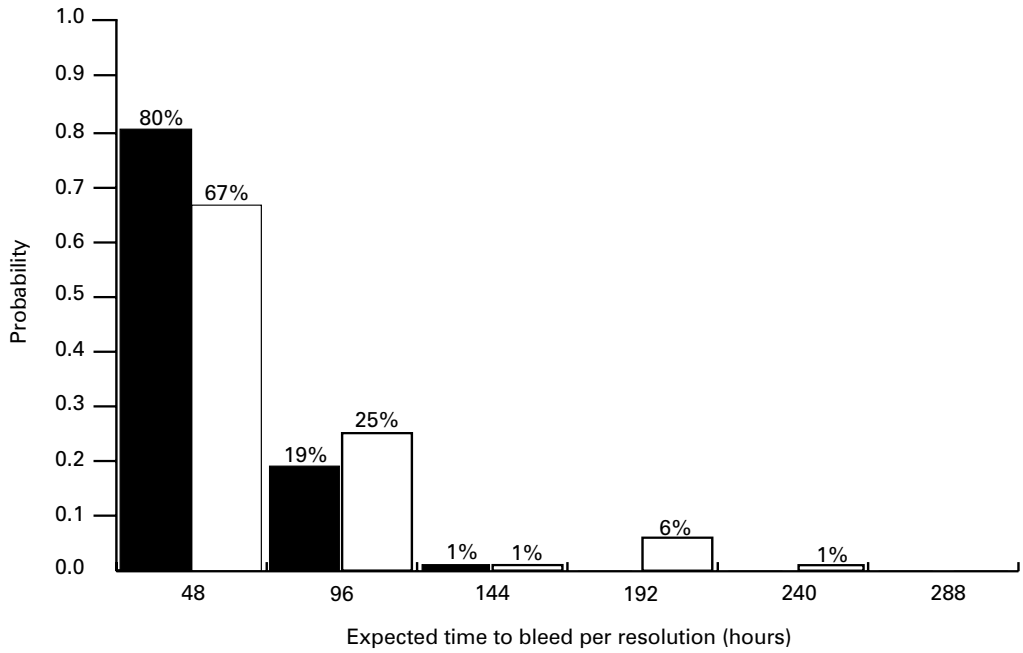
The haematologists estimated that 4% of patients would be transported to hospital by ambulance following commencement of a minor bleed irrespective of their subsequent haemostatic treatment. Once the bleed has started, patients would generally stay within the vicinity of the hospital until the bleed has resolved and would not make any further use of ambulance transportation.

Costs and consequences analyses

The expected cost of managing a minor bleeding episode following initial treatment with rFVIIa and aPCC was estimated to be £11,794 and £20,467, respectively. Table 1 illustrates that drug acquisition costs are the key cost driver associated with managing a minor bleed at a CCC. In both strategies, the cost of the haemostatic agents account for most of the expected management costs.

Figure 2 illustrates that in 83% of cases treated with rFVIIa, the expected NHS cost of managing a minor bleeding episode would be no more than £10,000 and in up to 11% of cases the expected cost would be between £10,000 and £20,000. Up to

Figure 3. Distribution of the expected time to bleed resolution in adults following initial treatment at a CCC. ■, rFVIIa; □, aPCC.



another 6% of cases would be expected to cost >£20,000. In 70% of cases treated with aPCC, the expected NHS cost of managing a minor bleeding episode would be no more than £10,000 and in up to 9% of cases the expected cost would be between £10,000 and £20,000. Up to another 21% of cases would be expected to cost >£20,000.

The expected time to resolving a minor bleed at a CCC with rFVIIa or aPCC was estimated to be 30 hours and 58 hours, respectively. Hence, the time to resolving a minor bleed would take almost twice as long using aPCC instead of rFVIIa.

Figure 3 illustrates that up to 80% of minor bleeds initially managed with rFVIIa at a CCC would be expected to resolve within 48 hours, and another 19% within 96 hours. Fewer than 1% of bleeds initially managed with rFVIIa at a CCC would be expected to require more than 96 hours to resolve. In contrast, up to 67% of minor bleeds initially managed with aPCC at a CCC would be expected to resolve within 48 hours, and another 25% within 96 hours. Up to another 8% of bleeds initially managed with aPCC at a CCC would be expected to require more than 96 hours to resolve.

These distributions were derived from random sampling of the probabilities across all the branches in our decision tree model. This provides a more realistic estimate of the distribution of costs and time that would be seen in actual clinical practice, since it takes into consideration the prevailing standard deviations around the means of all the decision nodes in the model.

Table 2. Sensitivity analyses

Parameter	*Baseline value*	*Threshold value*
Acquisition cost of rFVIIa ranges from £230 to £2,000	£683	£1,739
Acquisition cost of aPCC ranges from £190 to £1,700	£573	£205
Probability of successful treatment with first-line rFVIIa given to a day case ranges from 25% to 100%	92%	50%
Probability of successful treatment with first-line rFVIIa given to an inpatient ranges from 25% to 100%	92%	–
Probability of successful treatment with first-line aPCC given to a day case ranges from 25% to 100%	79%	–
Probability of successful treatment with first-line aPCC given to an inpatient ranges from 25% to 100%	79%	–
Time to initial bleed resolution with rFVIIa given to a day case ranges from 8 hours to 72 hours	24 hours	54 hours
Time to initial bleed resolution with rFVIIa given to an inpatient ranges from 8 hours to 72 hours	24 hours	–
Time to initial bleed resolution with aPCC given to a day case ranges from 8 hours to 72 hours	36 hours	–
Time to initial bleed resolution with aPCC given to an inpatient ranges from 8 hours to 72 hours	36 hours	–
Probability of being admitted and given rFVIIa ranges from 0% to 100%	17%	–
Probability of being admitted and given aPCC ranges from 0% to 100%	50%	–
Dose of rFVIIa given to a day case ranges from 1 to 6 doses	2.3 doses of 90 μg/kg bw	5 doses of 90 μg/kg bw
Dose of rFVIIa given to an inpatient ranges from 1 to 6 doses	2.3 doses of 90 μg/kg bw	–
Dose of aPCC given to a day case ranges from 1 to 9 doses	3 doses of 75 units/kg bw	–
Dose of aPCC given to an inpatient ranges from 1 to 9 doses	3 doses of 75 units/kg bw	–
Dosage of rFVIIa given to a day case ranges from 50 to 200 μg/kg bw	90 μg/kg bw (2.3 doses)	197 μg/kg bw (2.3 doses)
Dosage of rFVIIa given to an inpatient case ranges from 50 to 200 μg/kg bw	90 μg/kg bw (2.3 doses)	–
Dosage of rFVIIa given as a continuous iv infusion case ranges from 10 to 40 μg/kg bw	20 μg/kg bw /hour	–
Dosage of aPCC given to a day case ranges from 35 to 150 units/kg bw	75 units/kg bw (3 doses)	–
Dosage of aPCC given to an inpatient ranges from 35 to 150 units/kg bw	75 units/kg bw (3 doses)	–
Probability of a rebleed ranges from 0% to 25%	12%	–

Sensitivity analyses

Sensitivity analyses (Table 2) determined how the expected NHS cost of managing a minor bleed initially treated with aPCC or rFVIIa at a CCC would be affected by varying the various components of treatment.

Table 2 demonstrates that the economic impact of using rFVIIa compared to aPCC in the management of a minor bleeding episode among adults at a CCC is sensitive to the dose and dosage of rFVIIa administered as an iv bolus to a day case patient. The economic impact of using rFVIIa compared to aPCC is also potentially sensitive to the probability of successful treatment with first-line rFVIIa given to a day case patient. However, it is not sensitive to changes in any other parameter of treatment.

Discussion

The decision to treat inhibitor patients with either rFVIIa or aPCC at home or at a CCC is influenced by several factors including severity of bleed, site of bleed, ability of patient/carer to self-treat, history of compliance, availability of products, and the proximity of where a patient lives relative to a haemophilia treatment centre. However, irrespective of the prevailing factors influencing the choice of either location to initiate treatment, the long-term cost effectiveness of the haemostatic agent has been suggested as a necessary consideration in the management of bleeds in inhibitor patients[16,22–24].

Some studies have reported that early treatment at home with rFVIIa compared to treatment in a hospital setting improves outcome and reduces the amount of product used[2,3]. However, it has also been reported that home treatment with rFVIIa leads to a higher product usage[16], with implications for costs. However, there is no comparable study involving the use of aPCC. Moreover, in the absence of published data directly comparing rFVIIa and aPCC in the management of minor bleeds at a CCC, the expert panel endorsed the use of the study by Key *et al*[5] and Hilgartner *et al*[12] as the basis for the efficacy and associated resource utilisation pertaining to the first-line treatments used in our model. Lusher[2,3] found comparable efficacy for rFVIIa to that of Key *et al* in the treatment of minor surgical bleeds (86%) and dental bleeds (92%). In contrast, Hilgartner *et al*[12] found that a mean three doses of aPCC controlled 78% of mild to moderate bleeds after 36 hours, whereas Negrier *et al*[13] reported that 81.3% of bleeds would be controlled with less than three infusions of aPCC. However, Negrier *et al*'s study was retrospective and uncontrolled and not all the efficacy data were available so the authors assumed the efficacy of aPCC in some cases[13]. Notwithstanding this, it was the view of the haematologists who were interviewed that a mean 3 doses of aPCC would be required to control a minor bleed at a treatment centre in the UK and the impact of changing this has been subjected to sensitivity analysis.

Haemophilia's rarity, the difficulty in predicting patterns of bleeding episodes and

their outcomes, as well as the high treatment cost of managing bleeds and associated complications make planning and budgeting for haemophilia problematic[22,25]. Accordingly, our data should enable a better prediction of the distribution of costs which should aid the management of haemophilia patients with inhibitors in the UK. Against this background, we estimated that the expected cost of managing a minor bleeding episode first-line with rFVIIa at home[17] and at a CCC are comparable (£12,944 versus £11,794). However, the expected cost of managing a minor bleeding episode first-line with aPCC at a CCC is 42% higher than the cost of initiating treatment at home[17] with this agent (£20,467 versus £14,463). One of the reasons for this seems to be related to the treatment patterns. Patients whose bleed is uncontrolled with aPCC following first-line treatment at home would be expected to be treated at a CCC with comparable quantities (as first-line treatment) of aPCC and those patients whose bleed remains uncontrolled would be expected to be switched to rFVIIa[17]. However, patients treated as a day case at a CCC whose bleed is uncontrolled with first-line aPCC would be expected to be hospitalised and receive substantially higher doses of aPCC thereby increasing costs considerably, rather than being switched to rFVIIa. In contrast, the treatment pattern of a patient whose bleed is initially treated with rFVIIa at home[17] would be expected to be comparable to that of a patient whose treatment starts at a CCC.

Notwithstanding the costs of management, using first-line rFVIIa instead of aPCC either at a home[17] or hospital setting reduces the expected time to resolving a minor bleeding episode by approximately 50% (from approximately 60 hours to 30 hours). Moreover, other studies have demonstrated that prolonged bleeding often results in greater morbidity, prolonged hospitalisation, and in some cases, subsequent need for corrective surgical procedures[2,3]. Hence, the use of rFVIIa instead of aPCC to resolve a minor bleeding episode has the potential to reduce morbidity over the longer term and this would have a positive economic impact on the NHS and improve the quality of life of patients.

Clinical trials have demonstrated that rFVIIa's efficacy increases with shorter time between bleed onset and the start of treatment[2–4]; however, we were unable to find comparable data for aPCC. Therefore, the model does not consider the impact of time from onset of bleed to initial treatment at a CCC. Nevertheless, the key to successful long-term management is the early administration of a haemostatic following the onset of a bleed, thereby minimising damage to affected joints or tissues[3].

The major limitation of this study was the use of a panel of haematologists to obtain data that were unavailable in published studies. However, the analysis showed that the economic impact of rFVIIa compared to aPCC is most sensitive to parameters pertaining to treatment that were derived from published trials, and not to those pertaining to data obtained from the haematologists. There are a limited number of inhibitor patients in the UK and the unpredictable nature of bleeds has meant

that there is varied clinical experience. However, as more experience is gained about managing inhibitor patients and more robust data become available, the decision model could be updated accordingly. The model only considers direct healthcare costs and not the direct costs to patients and their families, indirect costs to society, such as loss of productivity, and intangible costs, such as changes in quality of life. Future analyses should examine the economic and quality of life implications of rFVIIa compared to aPCC in minimising damage to affected joints or tissues in the longer term.

In conclusion, the cost of managing a minor bleeding episode at a CCC with rFVIIa is 45% of the cost of initiating treatment with aPCC. Moreover, initiating first-line treatment with rFVIIa instead of aPCC is expected to resolve a minor bleeding episode in about half the time. Hence, our model suggests that rFVIIa is a cost effective treatment compared to aPCC for the treatment of a minor bleed at a CCC, since it improves clinical outcome and reduces NHS costs. This finding warrants further investigation in a prospective, comparative, randomised controlled study.

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* participated at the expert meeting.

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