

# Long-Term Health Outcomes Comparison between Prophylaxis and On-Demand aPCC Treatment in Patients with Severe Haemophilia A with Factor VIII Inhibitors in Spain

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## INTRODUCTION

- The development of inhibitors complicates the management of hemophilia A due to the neutralizing effect of inhibitors on administered FVIII concentrates<sup>1-2</sup>.
- Current treatment in patients with high-responding/high-titer inhibitors ( $\geq 5\text{BU}$ ) or those with low-titer ( $< 5\text{BU}$ ) inhibitors refractory to replacement therapy<sup>3-5</sup> requires the administration of bypassing agents such as FEIBA, an activated prothrombin-complex concentrate (aPCC)<sup>6</sup>.
- The aPCC indications include on-demand treatment and prophylaxis of bleeds in haemophilia A patients with Factor VIII inhibitors.
- The available evidence<sup>7-12</sup> supports that the prophylactic use of aPCC, reduces the appearance of bleeding events compared with on-demand approach.
- The existing evidence is related to short-term follow-up periods. To cover longer periods modelling techniques, based on the available evidence, can be an alternative approach to estimate long-term outcomes.

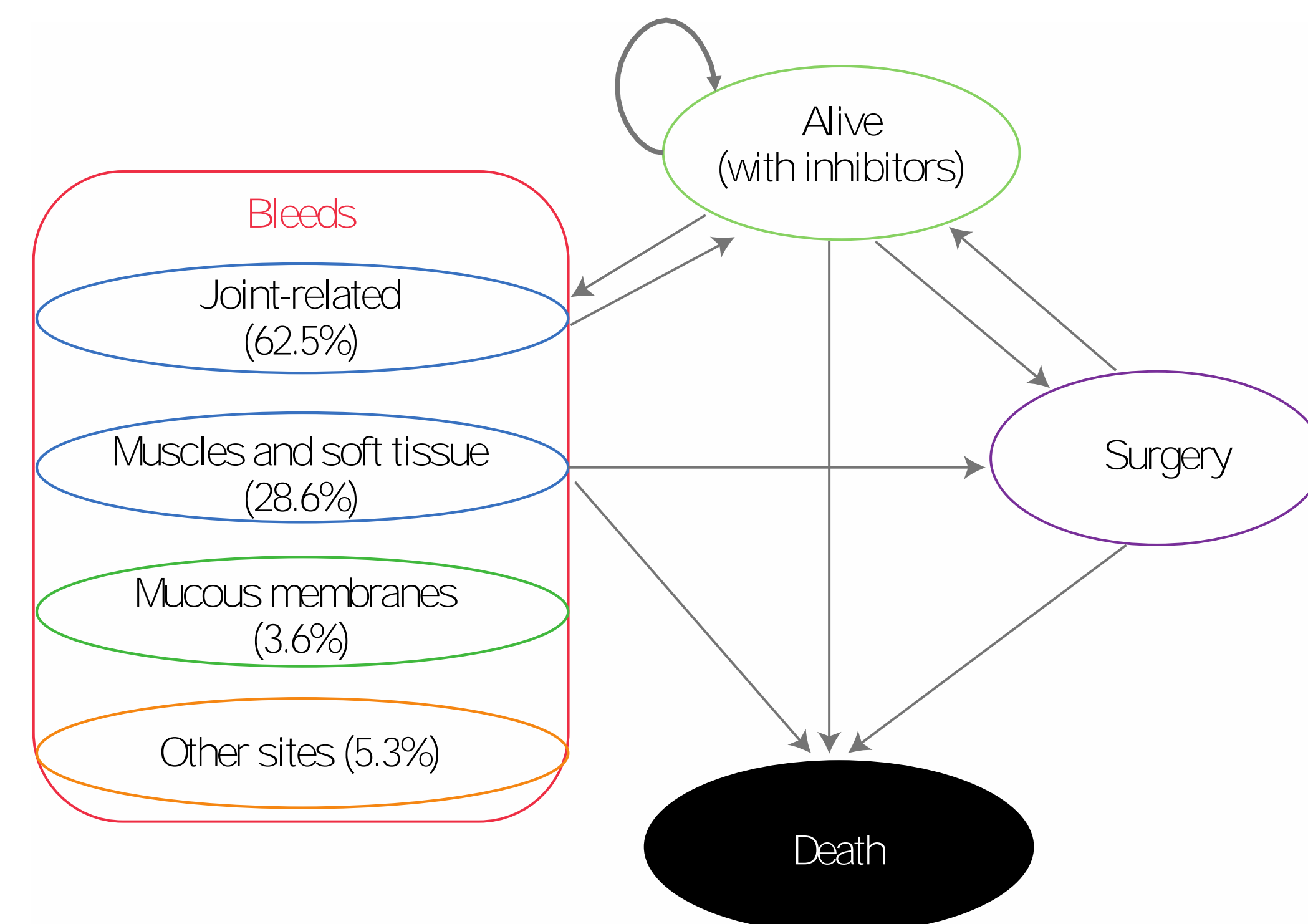
## OBJECTIVE

- To compare long-term outcomes between prophylaxis and on-demand regimens in patients with severe haemophilia A with FVIII Inhibitors treated with aPCC, through an extrapolation of the available evidence by means of modelling techniques.

## MATERIALS AND METHODS

- A Markov model was developed to estimate health outcomes over a 40-year period. Cycle length was 1 week.
- Four health-states were established: alive with the presence of inhibitors, active bleeds (4 sub-states according bleeds location), surgery and death (Figure 1). Surgery state refers to potential surgical interventions required by disease complications
- The following health outcomes were estimated: number of bleeding episodes, life years gained (LYG) and quality-adjusted life years (QALYs) for any of the treatment strategies.
- Two treatment strategies, prophylaxis vs on-demand treatment of bleeding episodes, were compared.
- The model assessed two hypothetical cohorts of 100 HA adult patients treated with one of the strategies. The cohort mean age was 23.20 years<sup>13</sup>.
- Proportions of bleeding episodes by location was obtained from literature<sup>8</sup>.

Figure 1. Markov model structure



- Based on available evidence, prophylaxis strategy was associated to 68.65% reduction of annual frequency of bleeds<sup>7-12</sup>, given an average of 8 bleeds per patient per year, of annual frequency of bleeds (25.23 per patient)<sup>14</sup>.
- Annual rate of surgery (2.3%)<sup>15</sup> was assumed independent of bleed location or treatment strategy.
- Death probability derived from mortality age-standardized rates from Spanish National Statistics Institute<sup>16</sup>. An additional risk of death was applied to the surgery state, weekly increment was estimated based on annual rate of 0.023<sup>15</sup>.
- Lineal models were applied to obtain the utility values for each health-state. The models and coefficients used were obtained from the literature<sup>17-19</sup>.
- A probabilistic sensitivity analysis (PSA) was performed with 10,000 Monte-Carlo simulations. Model parameters varied using probability distributions (normal distributions for utility coefficients and for the average reduction of bleeds, Dirichlet distributions for bleed locations).
- PSA results were estimated as the median values of the simulations, with the correspondent 95% credible interval (95%CrI), for both avoided bleeds and incremental QALYs in patients treated with prophylaxis vs on-demand.

## RESULTS

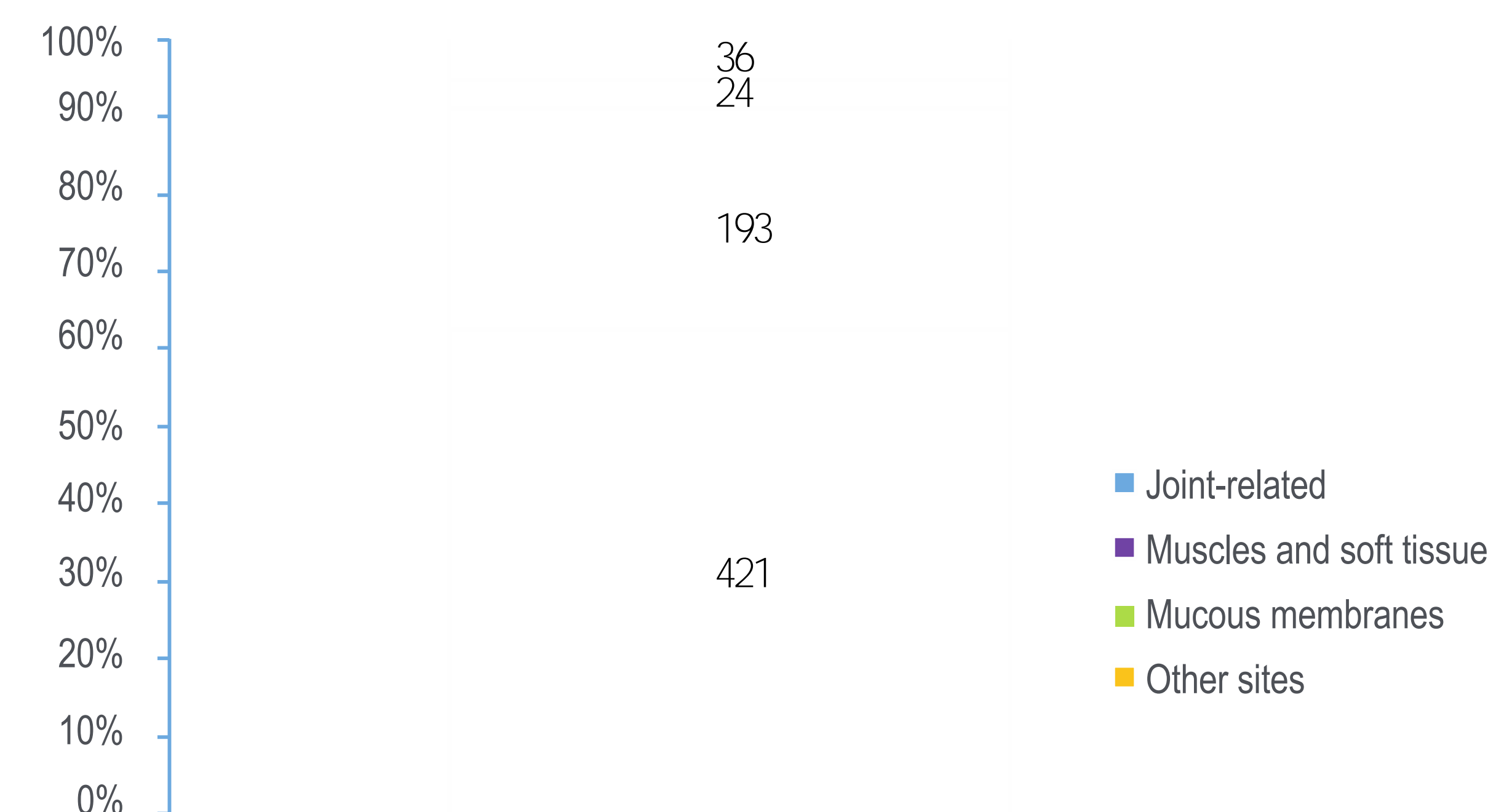
### Base case results

- The base case analysis showed that at the end of the 40 years of simulation, the obtained mean number of bleeds for a patient treated with on-demand regimen was 983.
- Prophylaxis strategy avoided a mean of 673 bleeds per patient in comparison with on-demand treatment (Table 1). From these bleeds avoided, 62.5% were located in joints, 28.6% located in the muscles or soft tissue, 3.6% in mucous membranes and 5.3% in other locations (Figure 2).

Table 1. Base case analysis results

	On-Demand	Prophylaxis	Difference (prophylaxis vs on-demand)
Bleeds	983 Bleeds	309 Bleeds	-673 Bleeds
Life years gained (LYG)	39.02 LYG	39.02 LYG	0.00 LYG
Quality-adjusted life years (QALY)	22.20 QALY	33.82 QALY	11.63 QALY

Figure 2. Location of avoided bleeds at 40 years



- The achieved survival was 39.02 LYG for both cohorts (prophylaxis and on-demand).
- The prophylaxis strategy was associated with a higher benefit in QALYs compared to on-demand (33.82 vs 22.20). Difference between both strategies was 11.63 QALYs.
- Evolution of bleeds frequency during the 40-year simulation for the cohort of patients treated on-demand is shown in Figure 3 and for the cohort of patients in prophylaxis is shown Figure 4.

Figure 3. Bleeds frequency: patients treated on-demand over time

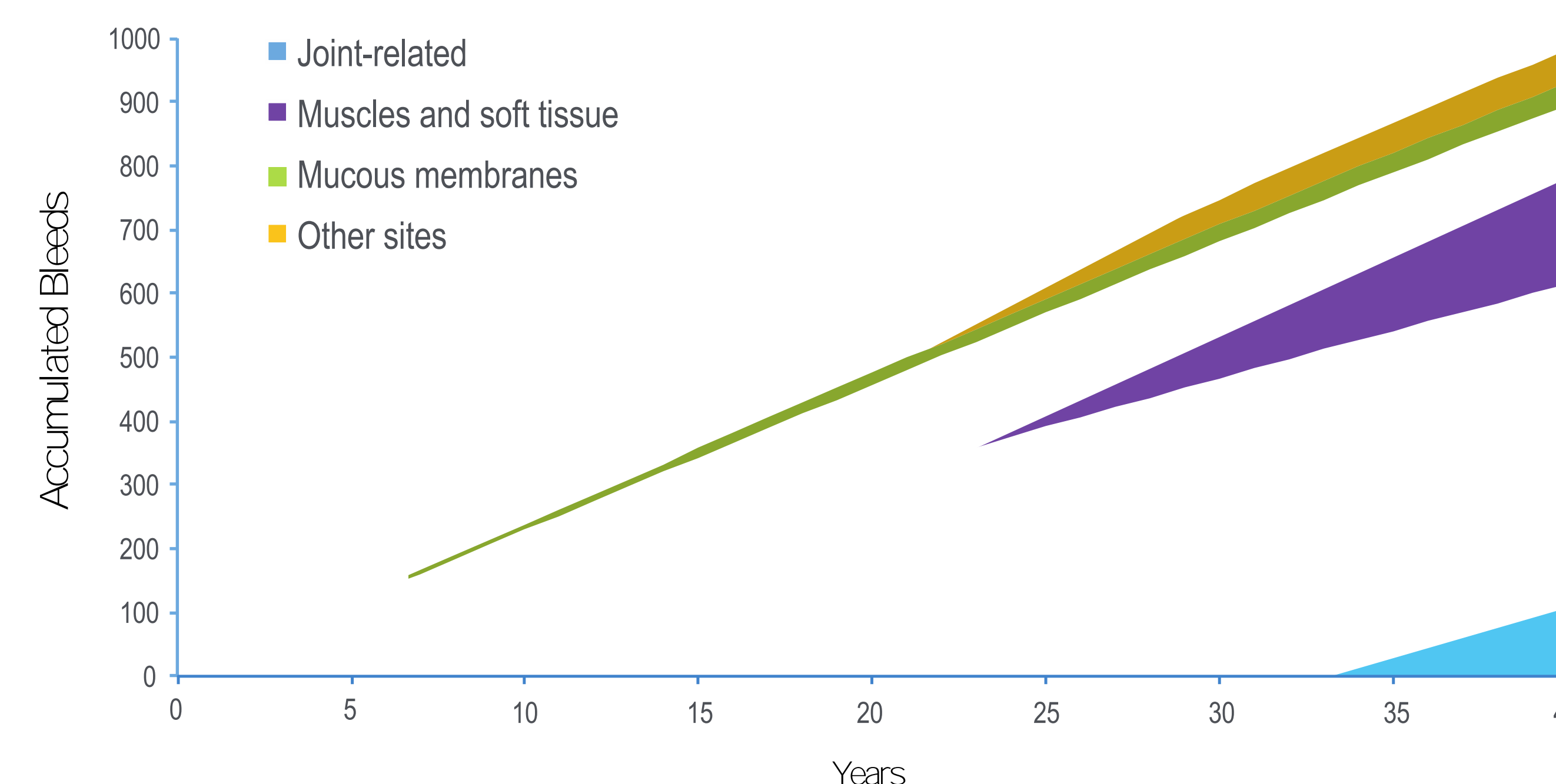
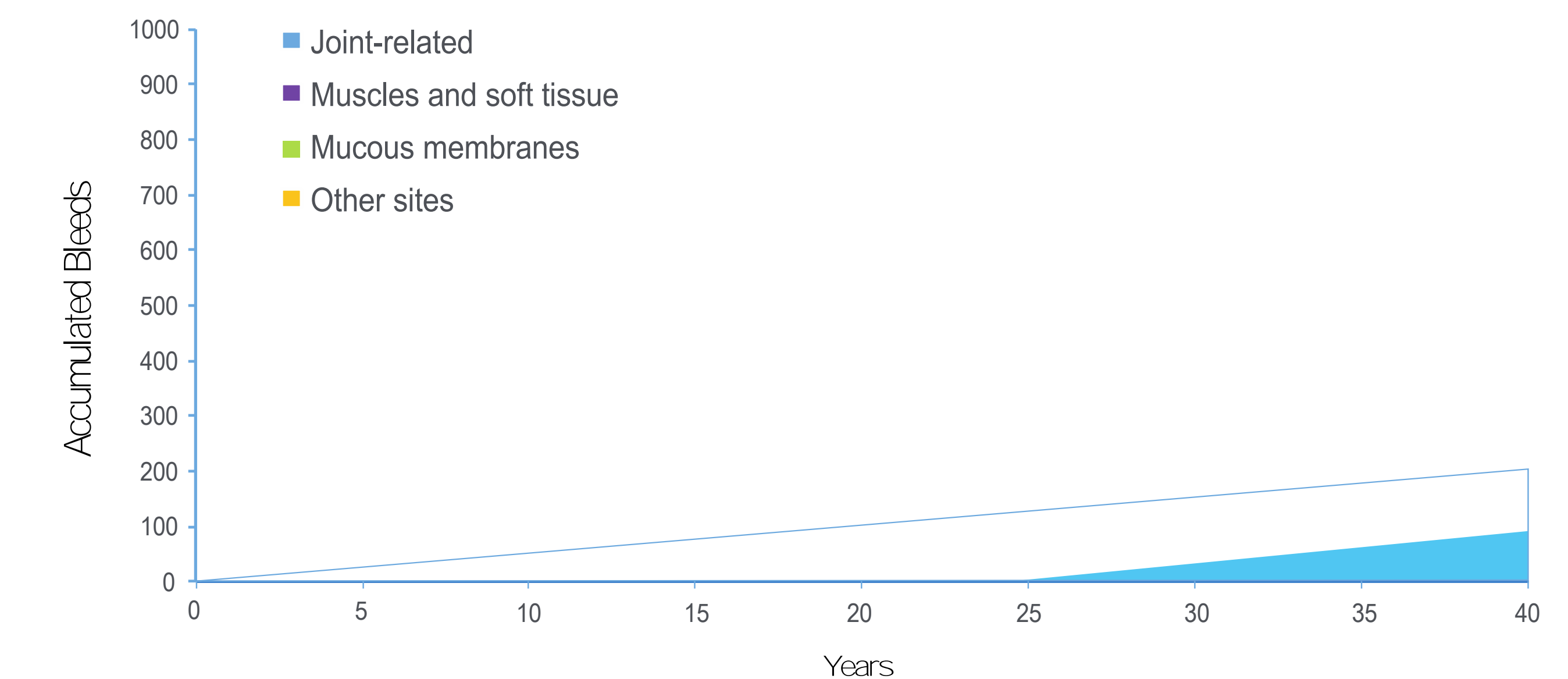


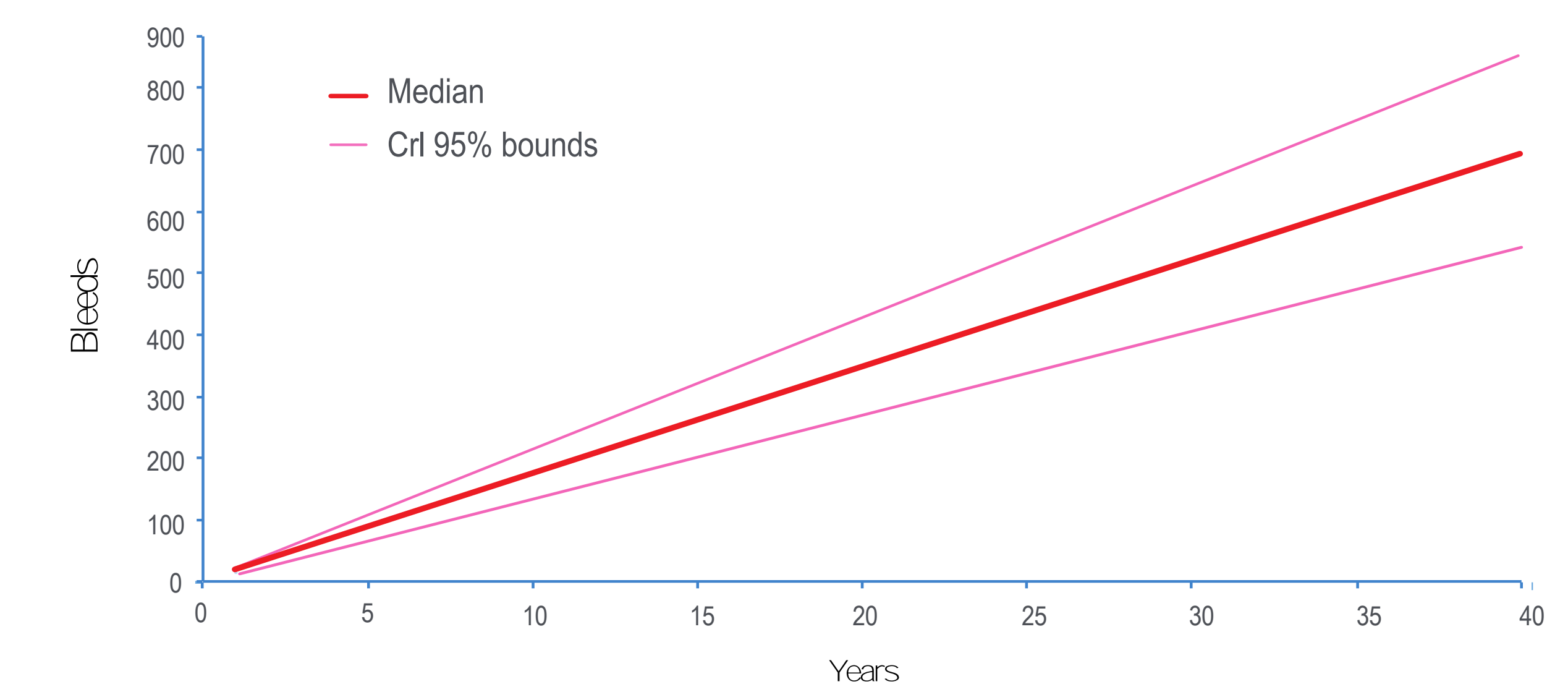
Figure 4. Bleeds frequency: patients treated with prophylaxis over time



### PSA analysis results

- From the 10,000 Monte-Carlo simulations, the median of bleeds avoided with prophylaxis strategy vs on-demand was 691 (95% CrI; 535-851) in 40 years. Avoided bleeds of prophylaxis strategy vs on-demand evolution during the 40 years of simulations is represented in Figure 5.
- Median of incremental QALYs gained with prophylaxis strategy vs on-demand was 11.65 QALYs (95% CrI; 3.79-19.6).

Figure 5. PSA of bleeds avoided (prophylaxis vs on-demand) over time



## CONCLUSION

- The results of the described modelling approach suggest that prophylaxis treatment regimen with aPCC would be associated with better long-term health outcomes as well as with a significant reduction in the number of bleeding events compared to on-demand treatment in patients with severe haemophilia A with inhibitors

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## DISCLOSURES

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