

A Microsimulation Experiment Study

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BACKGROUND

- Hemophilia B (HB), or coagulation factor IX (FIX) deficiency, is a rare X-linked recessive bleeding disorder. Patients with moderate-to-severe HB frequently experience spontaneous bleeding, often leading to chronic joint damage and pain^[1].
- China's first approved novel adeno-associated virus (AAV) gene therapy** for the treatment of moderate to sever adult hemophilia B patients, **dalnacogene ponparvovec**, recently published the results of its key clinical trial that 26 patients achieved the factor IX level of 55 IU/dL at 52 weeks post-infusion^[2].

OBJECTIVE

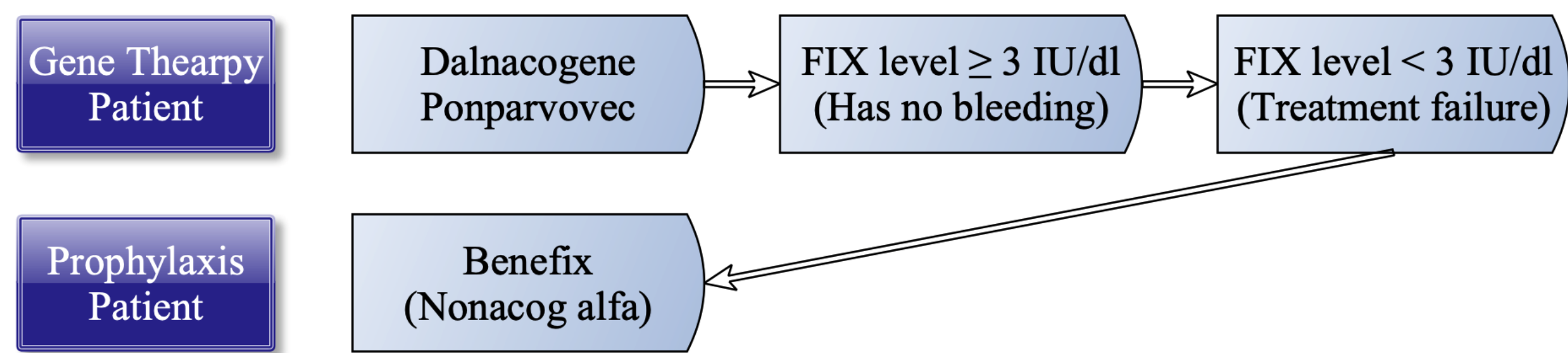
- This study aimed to assess the potential cost-effectiveness of Dalnacogene Ponparvove compared to routine prophylaxis infusions of standard half-life recombinant Factor IX(SHL rFIX) from the perspective of the healthcare system in China.

METHODS

Intervention

- Although dalnacogene ponparvovec enabled sustained FIX expression, declining FIX activity over time may lead to **treatment failure**. The treatment failure threshold was defined as the minimum FIX activity level sufficient to prevent spontaneous bleeding episodes.
- The failure threshold was set at 3 IU/dL, with FIX activity projected to decline by 1 IU/dL annually from the 52-week post-infusion mean, consistent with previous study^[3].
- Gene thearpy patients deemed to treatment failure will switch to standard half-life prophylactic FIX replacement therapy.

Figure 1. Treatment Sequence



Comparator

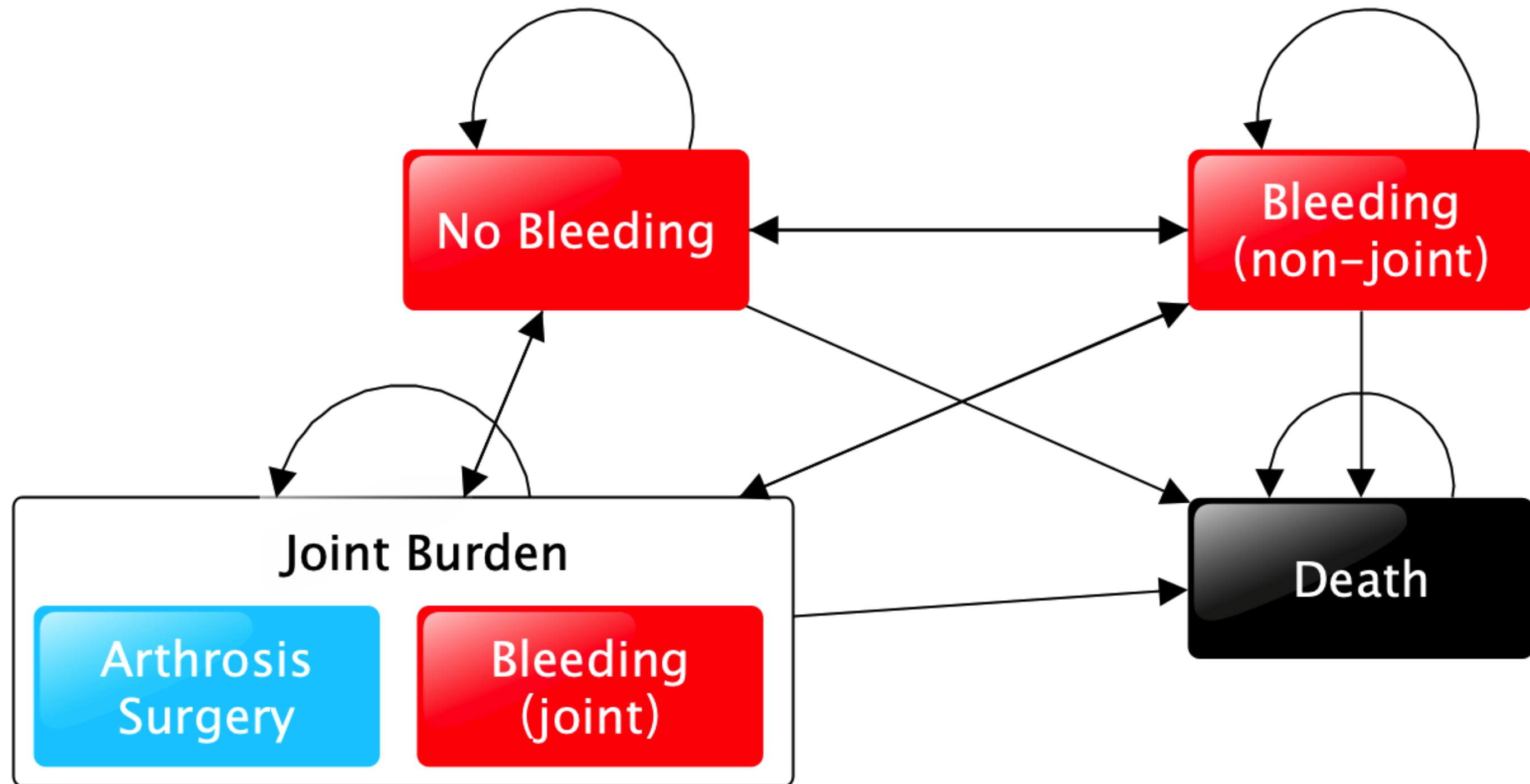
- The nonacog alfa (Benefix) is currently the only approved SHL rFIX thearpy in China and served as the comparator in this study.
- Although nonacog alfa prescribing information recommends 40 IU/kg twice weekly (used as the base-case analysis), real-world evidence^[4] and expert review indicated that Chinese patients rarely sustain this regimen for routine prophylaxis due to financial constraints.
- Scenario analyses therefore evaluated reduced dosing regimens (15 IU/kg), while conservatively assuming comparable efficacy to the standard 40 IU/kg dose.

METHODS (Continued)

Model Structure

- A lifetime, five-state Markov model was developed. The cycle length was one week(except the “Arthrosis Surgery” state have a length of 4 weeks), and all the patients started from the “No Bleeding” start at 18 years old.

Figure 2. Markov Model



Probability of Bleeding

- Annualized bleeding rate (ABR) and annualized joint bleeding rate (AJBR) are key efficacy endpoints derived from systematic review data. Adult hemophilia B patients receiving routine prophylaxis of nonacog alfa at a dose of 40 IU/kg producing ABR and AJBR of 2.55 and 2, respectively^{[6][7]}.
- A widely used function^[5] for converting rate to ratio was applied in this study.

i.e. Probability of joint bleeding in each week= $1 - e^{-AJBR/52}$,
Probability of non-joint bleeding in each week= $1 - e^{-(ABR-AJBR)/52}$

Table 1. Weekly Probability of Bleeding

From \ To	No Bleeding	Bleeding (non-joint)	Bleeding (joint)	Death
No Bleeding	1 - others	1.05%	3.76%	General death rate
Bleeding (non-joint)	1 - others	1.05%	3.76%	General death rate
Bleeding (joint)	1 - others	1.05%	3.76%	General death rate
Death	-	-	-	1

Probability of Arthrosis Surgery, Pettersson Score

- Arthrosis surgery represents joint replacement operation to treat joint damage from cumulative bleeding episodes.
- To evaluate the association between joint bleeding history and arthroplasty, the Pettersson score, a radiographic index, was used as a quantitative link between cumulative bleeding frequency and surgical intervention in hemophilia patients.

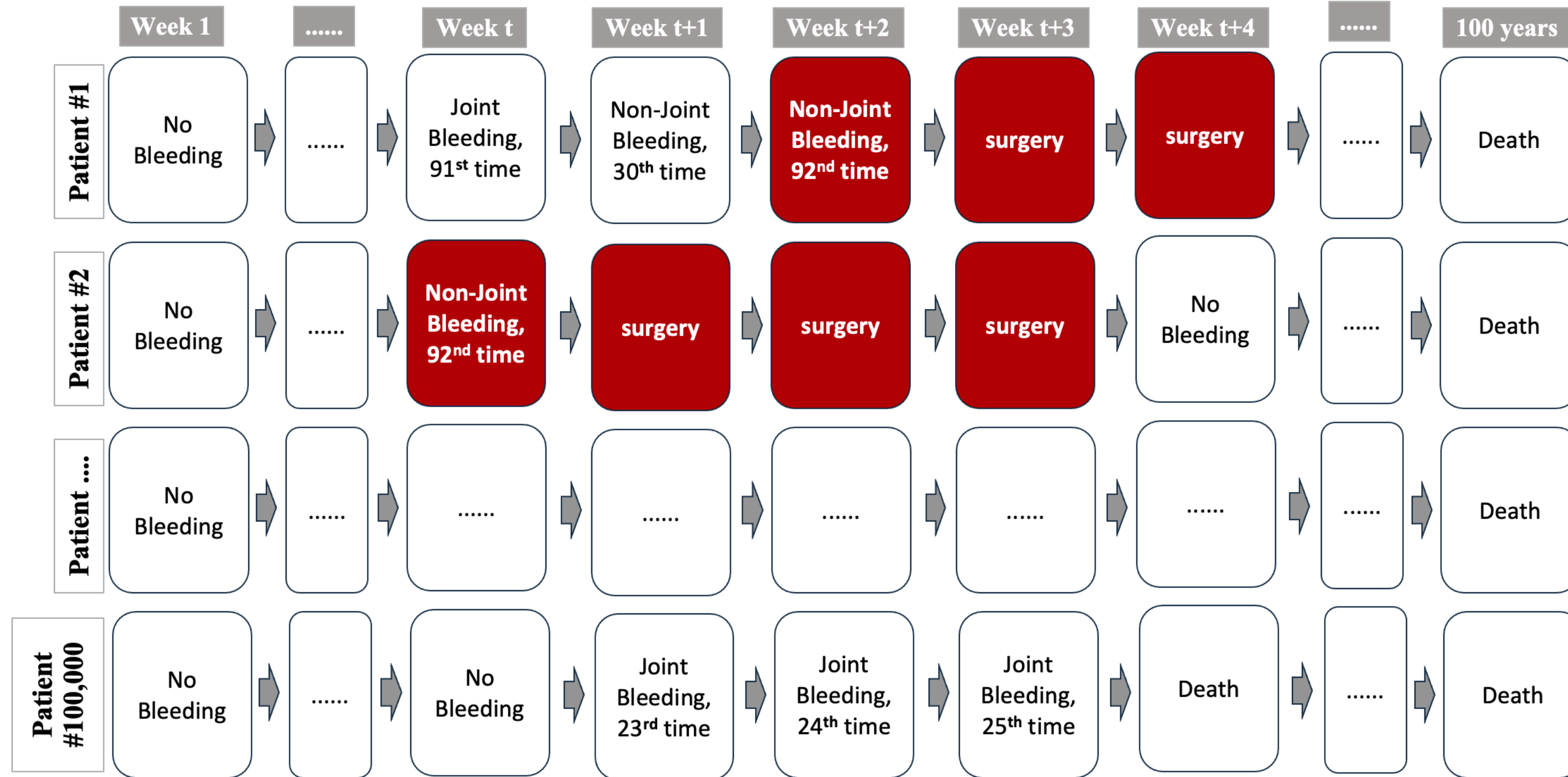
i.e. start pettersson score=14, 6.52 joint bleedings = +1 pettersson score^[8],
28 pettersson score = surgery^[9]

METHODS (Continued)

Probability of Arthosis Surgery, Microsimulation

- 100,000 patients was simulated in R to replicate the Markov model using microsimulation.
- Individual bleeding histories were tracked, with patients undergoing 4 weeks of arthroplasty upon reaching the joint bleeding threshold (92nd times) .
- The probability of arthrosis surgery per cycle was incorporated into the Markov model.

Figure 3. Microsimulation



PARAMETERS

- Cost parameters included drug costs, disease administration costs, and surgery costs.
- Utility parameters incuded disutility of injection, disutility of non-joint bleeding, disutility of joint bleeding, disutility of surgery, and utility of no bleeding.

RESULTS

- Compared to prophylaxis infusion of nonacog alfa, dalnacogene ponparvovec demonstrated higher quality-adjusted life years (QALYs) gains due to a lower frequency of injection and surgery, along with cost savings of avoiding routine prophylaxis injection twice a week, resulting in a **dominant** outcome.
- At prices of USD\$2,770,000 and USD\$1,385,000, dalnacogene ponparvovec remained dominant compared to nonacog alfa prophylaxis at doses of 40 IU/kg and 15 IU/kg, respectively.

CONCLUSION

- Dalnacogene ponparvovec was shown to be an economically dominant alternative, offering lower costs and higher QALYs, compared to SHL rFIX for hemophilia B patients in China.

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