Low-Dose Prophylaxis Versus On-Demand Treatment for Children with Severe Hemophilia A in Indonesia: A Conceptual Model

Levina Chandra Khoe

Nur Atika

Dhia Ticha Pertiwi

Septiara Putri

Khoe *et al. Kesmas: Jurnal Kesehatan Masyarakat Nasional (National Public Health Journal).* 2026; 21 (1): 68-77
DOI: 10.7454/kesmas.v21i1.2476

Kesmas: Jurnal Kesehatan Masyarakat Nasional (National Public Health Journal)

Low-Dose Prophylaxis Versus On-Demand Treatment for Children with Severe Hemophilia A in Indonesia: A Conceptual Model

Levina Chandra Khoe[1,2*], Nur Atika[1,3], Dhia Ticha Pertiwi[1], Septiara Putri[1]

[1]Centre for Health Economics and Policy Studies, Faculty of Public Health, Universitas Indonesia, Depok, Indonesia
[2]Department of Community Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[3]Department of Health Policy and Administration, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia

Abstract

Hemophilia A is a rare bleeding disorder caused by a deficiency of clotting factor VIII, leading to recurrent bleeds, joint damage, and disability. Low-dose prophylaxis has been shown to achieve better clinical outcomes than on-demand treatment in reducing bleeding frequency. However, in Indonesia, access and affordability remain key challenges. This study aimed to develop a conceptual model for conducting a health economic evaluation of low-dose prophylaxis treatment for children with severe hemophilia A in Indonesia. This study followed the ISPOR-SMDM Modeling guidelines, outlining two-stage processes: conceptualization of the clinical problem and model development. A systematic literature review was conducted to identify relevant clinical and economic evidence on low-dose prophylaxis and on-demand treatment in pediatric hemophilia A. Indonesian clinical guidelines and expert input from two hematologists were incorporated to contextualize the model. Thirteen studies (three clinical and ten economic evaluations) consistently reported improved outcomes with low-dose prophylaxis. Most models applied health state transitions involving bleeding episodes, joint damage, complications, and death. Based on this review and discussion, the conceptual model was established to support the cost-effectiveness analysis of low-dose prophylaxis. A rigorous conceptual model serves as the key foundational step in developing a valid, health economic model for the Indonesian setting.

Keywords: conceptual model, hemophilia A, Indonesia, low-dose prophylaxis, on-demand

Correspondence*:
Levina Chandra Khoe,
Centre for Health Economics and Policy Studies, Faculty of Public Health, Universitas Indonesia, Depok, Indonesia.
levinachandramd@gmail.com

Received:
August 26, 2025
Accepted:
February 18, 2026
Published:
February 27, 2026

Section Editor:
Dwi Gayatri
Universitas Indonesia

Reviewers:
Reviewer 1:
Helen Andriani
Universitas Indonesia
Reviewer 2:
Adang Bachtiar
Universitas Indonesia

Introduction

Hemophilia is a hereditary bleeding disorder characterised by recurrent bleeding episodes, primarily into joints and muscles, which can result in long-term disability, particularly if left untreated.[1] Globally, 80% of individuals with hemophilia are diagnosed with hemophilia A (HA), a condition caused by a deficiency in coagulation factor VIII (FVIII).[2] Hemophilia A is classified according to severity degrees: mild (6-40% FVIII), moderate (2%-5% FVIII), and severe (<1% FVIII).[3] Clinical manifestations include hemarthrosis and intramuscular bleeding, which can significantly impair quality of life (QoL) and lead to chronic complications.[2,4]

The standard treatment for HA involves replacing the missing FVIII through infusions, administered either on-demand (OD) for acute bleeding episodes or prophylactically to prevent bleeding.[5] Prophylactic therapy has become the gold standard for patients with severe HA, as it reduces bleeding frequency and severity, improves QoL, and prevents long-term complications such as joint damage.[6] Evidence increasingly supports early initiation of low-dose prophylaxis (LDP) in children with severe HA to improve joint bleeding outcomes.[5,7,8] International guidelines from the World Federation of Hemophilia (WFH), the International Society on Thrombosis and Hemostasis (ISTH), and the National Hemophilia Foundation also recommend prophylactic FVIII therapy as the standard of care for severe HA.[9,10] The Indonesian Ministry of Health issued the National Guidelines for Clinical Services in February 2021, recommending LDP for children aged 3 to ≤12 years with severe HA.[11] However, implementation remains inconsistent due to budget constraints and limited healthcare resources. Access to LDP is only available in selected institutions, reflecting the broader challenge of resource-constrained healthcare systems,[12] as experienced in other Asian countries.[12–14]

In Indonesia, almost all HA patients are treated with OD therapy, covered by the National Health Insurance (NHI) scheme. Meanwhile, LDP has not been fully implemented in clinical practice due to affordability constraints. Evidence from other resource-constrained settings demonstrates that LDP is a cost-effective treatment option for children with hemophilia.[15,16] Nevertheless, local evidence on the cost-effectiveness of LDP in Indonesia remains limited. The financial demands of newer treatments often strain healthcare budgets, requiring rigorous evaluation to ensure interventions are both clinically effective and cost-effective.[17]

Economic evaluations are critical in addressing these challenges. Quantitative models provide a framework to estimate the costs and benefits of healthcare interventions, offering insights into their impact on healthcare systems. These models are particularly useful for analysing long-term outcomes, informing policy decisions, and complementing randomized controlled trials (RCTs), which are often costly and time-limited.[18] Economic models are widely used to inform policy decisions, but their credibility needs strengthening. A critical first step is developing a robust conceptual model to ensure analyses accurately reflect real-world systems.[19] This study aimed to develop such a model to evaluate the economic impact of LDP compared to OD in children with severe HA in Indonesia. This conceptual model will serve as a foundation for future cost-effectiveness analysis (CEA) of Hemophilia treatment.

Method

This study followed the guidelines of the International Society of Pharmacoeconomics and Outcomes Research-Society of Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practices Task Force,[19] emphasizing a two-stage process: (1) conceptualizing the problem involving translating healthcare processes into a problem representation and (2) model conceptualization determines the most suitable modeling types, attributes, data, and parameters. The initial step involved summarising clinical and treatment guidelines for HA, particularly in Indonesia. This summary described the disease progression, standard treatment practices, and gaps in current clinical practice.

A systematic literature review (SLR) was conducted to critically appraise clinical and economic evidence comparing prophylaxis to OD treatment in children with severe HA. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[20] guidelines for transparent reporting, a systematic search of databases includes EMBASE (Ovid), MEDLINE (Ovid), Cochrane, Google Scholar, York CRD, and the CEVR Tufts Medicine CEA Registry. The search targeted studies on LDP treatment in children with HA published between 2000 and 2024. To ensure comprehensive evidence synthesis, structured database queries were supplemented with grey literature searches and snowballing techniques (Supplementary Content 1).

Articles were selected based on inclusion and exclusion criteria (Table 1). Critical appraisal used the Mixed Methods Appraisal Tool (MMAT)[21] for clinical evidence and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[22] guidelines for economic studies (Supplementary Content 2). Data extraction was conducted independently by two reviewers. The whole review process for this SLR used the Covidence® software. The findings from the SLR provided base information for developing the conceptual health economic model.

Table 1. Inclusion Criteria for Systematic Review

PICOS Criteria	Inclusion	Exclusion
	Clinical Effectiveness	
Population	Children aged ≤12 years with severe HA	Adult population, not HA patients
Intervention	LDP; prophylaxis	
Comparator	OD treatment	
Outcome	Any reported clinical outcomes (i.e., bleeding, mortality, QoL)	Non-clinical outcome (i.e., admission, length of stay, insurance membership)
Study Design	RCT, non-randomized trial, single-arm trial, observational study (only cohort). Only English and full-text articles	Case study, animal testing, editorial/commentary, survey study, abstract
	Economic Evaluation	
Population	Children aged ≤12 years with severe HA	Adult population, not HA patients
Intervention	LDP	
Comparator	OD treatment	
Outcome	Incremental cost-effectiveness ratio, Net monetary benefit, Incremental Net Monetary Benefit	Non-monetary outcome
Study Design	Full economic evaluation study (CEA, CUA, Cost-Benefit Analysis). Model-based economic evaluation (decision analytic model, mathematical simulation)	Partial economic evaluation (cost analysis, economic burden of disease, healthcare tariff analysis. Systematic review of economic evaluation, editorial/commentary/ abstract

Notes: HA = hemophilia A, LDP = low-dose prophylaxis, OD = on-demand, QoL = quality of life, RCT = randomized controlled trial, CEA = cost-effectiveness analysis, CUA = cost-utility analysis.

The primary objective of health economic models is to guide policymakers in evaluating the cost-effectiveness of new interventions. The development of this conceptual model began with two rounds of structured discussions

involving two Indonesian hematologists, each with extensive experience in managing children with severe hemophilia. In the first meeting, an initial draft of the conceptual model (informed by the SLR) was presented. The goal was to align perspectives on the relevance of using cost-effectiveness modeling for LDP in Indonesia.

Before the second meeting, a structured discussion guide and questionnaire detailing key clinical and cost parameters were developed (Supplementary Content 3) and shared with the experts. The second meeting focused on validating and refining the revised conceptual model. Following this, the updated document was circulated for additional feedback, which was then incorporated. Additional discussions with the Medical Working Group of the Indonesian Hemophilia Society were also underway. These online consultations, facilitated via Zoom Meeting, provided valuable, broader insights into real-world clinical practice in Indonesia.

Results

Hemophilia A is an X-linked genetic disorder caused by a mutation in the F8 gene, resulting in a deficiency or dysfunction of clotting FVIII. This deficiency disrupts the coagulation cascade, particularly the intrinsic and common pathways, leading to prolonged and excessive bleeding.[23] In normal hemostasis, FVIII levels are above 50%, ensuring proper clot formation. However, in severe HA, FVIII levels drop below 1%, significantly reducing the body's ability to form stable blood clots. As a result, individuals with severe HA often experience spontaneous bleeding episodes, with symptoms typically appearing within the first months of life. In contrast, mild and moderate forms of HA may present later in life with less severe bleeding episodes.[24] The primary goal of HA treatment is to prevent and promptly manage acute bleeding episodes by replacing FVIII with FVIII concentrates, which can be either plasma-derived or recombinant. Both types are considered equally effective and safe, but recombinant products are often more expensive.[25]

Treatment strategies include OD therapy, administered after bleeding and prophylactic therapy, aimed at preventing bleeding. In Indonesia, due to cost and product availability constraints, OD therapy is more commonly used. However, OD treatment can face delays in accessing treatment, often exceeding the recommended two-hour window, leading to joint damage later in life.[11] For this and other reasons, the WFH recommends prophylaxis as the preferred treatment for severe HA. Prophylaxis treatment is initiated either after the first joint bleeding (primary prophylaxis), following multiple joint bleeds (secondary prophylaxis), or after the onset of joint disease (tertiary prophylaxis). For resource-limited settings, LDP is advised as an ethical and cost-effective alternative.[9-10]

The HA management in Indonesia aligns with the Decree of the Indonesian Ministry of Health Number HK.01.07/MENKES/243/2021, which endorses the administration of FVIII concentrates tailored to disease severity and clinical presentation. LDP of FVIII (10 IU/kg twice weekly) is recommended for patients with recurrent joint bleeding, as per WFH guidelines. The national clinical practice guideline incorporates regular evaluations every three months to assess the efficacy of prophylaxis.[11]

Tertiary prophylaxis is practiced in Indonesia for patients with existing joint damage. This approach aims to reduce the frequency of bleeding events, slow joint disease progression, and enhance the quality of life. A study comparing 12-month low-dose FVIII tertiary prophylaxis to OD treatment in Indonesian children with severe HA demonstrated that tertiary prophylaxis significantly reduced joint bleeding episodes and improved joint health scores.[8] However, the tertiary prophylaxis implementation in Indonesia is limited by resource constraints and the availability of clotting factor concentrates. However, fully addressing access challenges and aligning treatment with international standards to mitigate long-term complications is an altogether different conceptual problem. The literature search yielded 1,881 articles. After eliminating 235 duplicates, titles and abstracts were screened, yielding 127 articles for full-text review. Of these, 114 were excluded. Ultimately, three articles were included for clinical evidence review and ten for economic evaluation evidence (Figure 1).

The SLR included three clinical studies comparing OD treatment to LDP in children with severe HA (Table 2). All studies showed that prophylaxis significantly reduced bleeding events compared with OD treatment. Reductions in joint and total bleeds, along with improvements in joint health outcomes, were reported across studies.[8,26,27] Methodological quality, assessed using the MMAT, with scores of 80/100 for Chozie *et al*., (2019)[8] and Verma *et al*., (2016)[26] and 60/100 for Khayat *et al.,* (2021).[27]

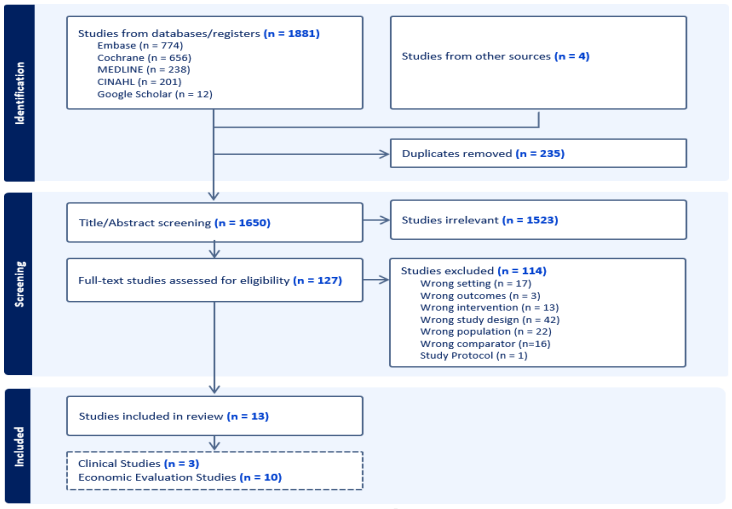

Figure 1. PRISMA Flow Diagram

Table 2. Characteristics of Studies Included in the Review

Author (Year)	Design/ Setting	Population	Intervention	Control	Inclusion Criteria	Bleeding Events	Clinical Joint Score	Safety Assessment
Verma *et al.*, (2016)[26]	Open-label, RCT/ India, single center	Children aged 1-10 years	pd monoclonal purified FVIII 10 IU/kg twice a week through peripheral vein on OPD basis	Patients on episodic treatment received FVIII concentrate at a nearby hospital at 25 IU/kg or more as early as possible after the joint bleed, followed by 25 IU/kg every 12–24 h until the joint bleeding resolved	Severe HA (FVIII levels <1%) and not having any measurable inhibitor	Overall bleeds/patient/month prophylaxis vs episodic: mean (SD) : 0.185 (0.183) vs 0.787 (0.457)* Joint bleeds/patient /month: 0.08 (0.13) vs 0.48 (0.34)*	Clinical score (HJHS 2.1) – at 6-month prophylaxis vs episodic: Median (range): 0 (0–3) vs 2 (0–4) Clinical score (HJHS2.1) – at end of study: 0 (0–5)* vs 4.5 (0–5)	Number of emergency visits to hospital prophylaxis vs episodic median (min-max) : 1 (0–7) vs 9 (1–15)
Chozie *et al.*, (2019)[8]	Open-label, RCT/ Indonesia, single center	Children aged 4-18 years	pdFVIII 10 IU/kg body weight, two times/ week for 12 months	Any bleeding episode was treated according to WFH guidelines for countries with resource constraints (10 IU/kg for 1-2 days for joint bleeding)	FVIII level <1%, history of repeated joint bleeds and previously received OD with human plasma-derived or recombinant FVIII (previously treated patients)	Total bleeds prophylaxis vs on-demand: Median (Q1;Q3): 8 (5.5;13.5) vs 25 (17;39.5)** Total joint bleeds: 3 (1;8.5) vs 9 (5;28.5)** Total non-joint bleeds: 3 (2;8) vs 10 (8;17)**	Δ HJHS (months 0-6) prophylaxis vs on-demand: 0 (−3.5;0) vs 0 (0;2)** Δ HJHS (months 0-12) −1 (−4;0) vs 2 (0;3.5)**	N/A
Khayat *et al.*, (2021)[27]	Open-label, non-RCT/ Multi countries, Multi-center	Male aged <12 years	pdVWF/FVIII 20-40 IU/kg body weight, every 2–3 days	Immediate treatment with pdVWF/FVIII of a non-surgical spontaneous or traumatic bleeding event, or a preventive treatment with p d VWF/FVIII to prevent an anticipated bleeding event	Severe HA (FVIII: C <1%) and had received previous FVIII treatment for a minimum of 20 EDs	NSB prophylaxis vs OD: 172 vs 318 Joint NSB prophylaxis vs OD: 143 vs 176	N/A	Treatment-emergent adverse events (TEAEs) prophylaxis vs on-demand: 66.7% reported 64 TEAEs vs 64.7% reported 33 TEAEs. Most reported: cough, pyrexia, rhinitis, FVIII inhibition, and rash

Notes: HA: Hemophilia A; NSB: Non-surgical bleedings; pd: plasma derived; RCT: randomized controlled trials; Δ HJHS: Median (Q1-Q3) Hemophilia Joint Health Score; N/A: not available; *: p-value <0.05; **: p-value <0.01

Table 3. Summary Characteristics of Economic Evaluation Studies

Author, Country	Intervention & Comparator	Dose (Prophylaxis)	Model Type, Model States	Time horizon, Cycle	Perspective	Discounting	Results	Sensitivity Analysis
Miners *et al.,*[28] UK	Primary prophylaxis (with clotting factor) vs on-demand	-	Markov alive, require major surgery, surgery, death	70 years, annual	UK societal	6% (cost)	Cost-effective (more likely to be cost effective of severe hemophilia B, compared to severe HA)	One-way SA
Risebrough *et al.,*[29] Canada	Prophylaxis (tailored prophylaxis, primary prophylaxis) vs OD	Standard Prophylaxis = 30 U/kg, 3x/week Escalating Dose 1 = 50 U/kg/week Escalating Dose 1 = 63 U/kg/week	Markov target joints, bleed, complication, joint bleed	5 years, 3 months	Societal	3% (cost and outcome)	Not cost-effective	One-way SA
Daliri *et al.,*[30] Iran	Prophylaxis vs OD	225.31 units/kg/month.	Retrospective chart review	6 months	Payer	-	Unclear	One-way SA
Miners *et al.,*[31] UK	Primary prophylaxis (with clotting factor) vs OD	25–40 IU/kg, 3x/week	Markov alive, require major surgery, surgery, death	70 years, annual	UK NHS	3.5 % (cost and outcome)	Cost-effective	PSA
Colombo *et al.,*[32] Italia	Primary prophylaxis with FVIII concentrates vs secondary prophylaxis, vs treatment OD, and vs a "hybrid" (primary prophylaxis followed by OD in adults)	30 UI/kg, 2.5x/week	Markov alive, require major surgery, surgery, death	Lifetime, annual	Health system	6% (cost)	Cost-effective	One-way SA
Farrugia *et al.,*[33] UK, US, Sweden	Prophylaxis vs OD	Cycles 1–2 = 25 IU/kg/week Cycles 3–20 = 59 IU/kg/week Cycles 21–100 = 35 IU/kg/week	Markov alive (non-inhibitor), alive (with inhibitor), death	Lifetime, annual	Health system	3.5% cost, 1.5% outcome	Cost-effective (UK, Sweden setting)	One-way SA, PSA
Castro Jaramilo *et al.,*[34] Colombia	Primary prophylaxis (with clotting factor) vs OD	25 IU/Kg, 3x/week	Markov alive (with & without arthropathy), bleeding, recover from bleeding, death	Lifetime, annual	Health system	3.5% cost, 1.5% outcome	Not cost-effective	One-way SA, PSA
Salinas-Escudero *et al.,*[35] Mexico	Prophylaxis vs OD	25 IU/Kg, 3x /week	Markov patients (with bleeding), patients (without bleeding), died	16 years, biweekly	Health system	5% (cost and outcome)	Cost-effective	One-way SA
Zahedi *et al.,*[36] Iran	Prophylaxis vs OD	20–30 units of plasma-derived FVIII/kg, 1–3 times/week	Markov alive, target joint, dead	70 years, annual	Societal	5% cost, 3% outcome	Cost-effective	PSA
Set *et al.,*[37] India	LDP vs OD	Intermediate prophylaxis 15–25 IU/kg, twice a week LDP = 10 IU/k, once/twice a week	Markov base state, joint disease, bleeding, death	Lifetime, annual	Societal	3.5% (cost and outcome)	Cost-effective	One-way SA, PSA

Notes: HA: hemophilia A; SA: Sensitivity Analysis; LDP: low-dose prophylaxis; OD: on-demand; PSA: Probabilistic Sensitivity Analysis

The systematic review identified 10 articles that performed full economic evaluations, including both CEA and cost-utility analysis (CUA). Eight studies used conventional health technology assessment (HTA) with model-based economic evaluations; one conducted a retrospective statistical analysis; and another applied an adaptive health technology assessment, a flexible, context-specific approach designed to assess low- and middle-income countries challenged by limited resources and data availability. In contrast, conventional HTA follows a systematic and rigorous framework typically used in resource-abundant settings.[38]

The articles spanned various countries, including the UK, Canada, Iran, Italy, Colombia, Mexico, India, and a multi-country analysis. Among these, only Seth *et al.* explicitly assessed LDP compared to OD treatment in a pediatric HA population.[37] Treatment dosages varied across settings, reflecting differences in healthcare practices and resource availability. Nine out of ten studies applied a multi-state transition model, primarily Markov models, to evaluate the cost-effectiveness of interventions for pediatric HA. Markov models are well-suited for chronic conditions, enabling individuals to progress through different health states over time. These models assessed the clinical and economic impacts of prophylaxis compared to OD treatment.

Most studies calculated the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) and adopted a long-term or lifetime horizon with annual cycles. Common health states included "alive," "requiring major surgery," "surgery," and "death." At the same time, one study focused on LDP versus OD treatment and incorporated health states such as "base state," "joint disease," "bleeding," and "death."[31] The design of health states was tailored to each study's objectives and policy questions.

The articles also adopted various perspectives, including societal, payer, and health system perspectives, aligning with policy goals and decision-making requirements in the system under study. Costs included direct medical costs (calculated in all studies), direct non-medical costs (e.g., transportation, meals), and indirect costs (e.g., productivity loss, emotional costs). Discounting was applied to both costs and outcomes, with rates ranging from 3% to 6% for costs and from 1.5% to 3.5% for outcomes. QoL utilities were primarily derived from the published literature and measured using generic tools that capture patients' health status. These were converted to QALY estimates, serving as the primary outcome in most evaluations.

While not all studies explicitly reported validation methods, most demonstrated strong face and internal validity. Sensitivity analysis, a key component of economic evaluations, was performed to test the robustness of results and identify influential factors. Deterministic sensitivity analysis (DSA), particularly one-way sensitivity analysis, was the most employed method. Four studies conducted both probabilistic sensitivity analysis (PSA) and DSA. Overall, most studies were well-reported and met the methodological requirements for economic evaluations. However, gaps were noted in addressing heterogeneity, distributional effects, and patient engagement, indicating areas for improvement in future research.

Regarding clinical management, hematologists agreed that LDP offered significant clinical advantages over OD treatment. The effectiveness of LDP was linked to patient-specific characteristics and risk factors, including age, weight, target joints, history or presence of rFVIII inhibitors, genetic factors, and disease severity. Key health outcomes investigated and found to favor LDP, including improved quality of life, reduced annual bleeding rates and joint bleeding rates, enhanced joint health scores assessed through physical or radiological evaluations, decreased episodes of breakthrough bleeding and inhibitor development, and improved patient compliance.

The questionnaire also underscored the economic burden of managing severe HA, detailing the total costs associated with treatment. These include the price of clotting FVIII concentrates for acute bleeding treatment in patients with or without inhibitors, in accordance with the WFH and National Guidelines for Clinical Services of Hemophilia.[11] Outpatient costs were highlighted, including expenses for consultations, laboratory monitoring for FVIII inhibitors, and radiological assessments such as ultrasound and magnetic resonance imaging. There were additional costs for hospital stays and surgeries for major bleeding episodes, particularly in patients with inhibitors. Indirect costs, such as transportation and meals during outpatient visits, were also necessary. The model identified complications and adverse events as significant challenges in HA management. Common issues included hemarthrosis, chronic synovitis, target joints, homophilic arthropathy, pseudotumors, fractures, and major bleeding. The development of inhibitors against FVIII was also a critical concern, as it incurred significant additional costs.

Ethical and equity issues emerged as pivotal concerns due to the difficulty in accessing treatment. Our discussion with experts also highlighted geographical and economic disparities that limit access to services. The results provided critical insights into the clinical, economic, and ethical dimensions of HA management, highlighting the importance of these considerations in developing a robust conceptual model. Also, by addressing these inputs, it ensures alignment with the local healthcare context and provides information for incorporating parameter considerations into a cost-effectiveness model.

Based on the discussion with hematologists, this study included the following key health states: "base state," "joint bleeding," "target joint," and "death." These health states reflected the disease's clinical trajectory and economic burden. The inclusion criteria for the model's cohort followed those of the previous clinical study.[8] In Markov models, the "base state" is defined as the state of health when the patient first receives a treatment (tertiary LDP). Patients have an estimated probability of progressing to another state, such as joint bleeding and the target joint. They also have a probability of remaining in their current health state. In a target joint state, there is a probability that patients will experience severe complications such as progressive cartilage loss and severe arthropathy. All states can transition to death (Figure 3). The initial model discussion focused solely on joint bleeding states, aligning with current trial reports. However, the scope was expanded to include the target joint as an additional state within the model structure.

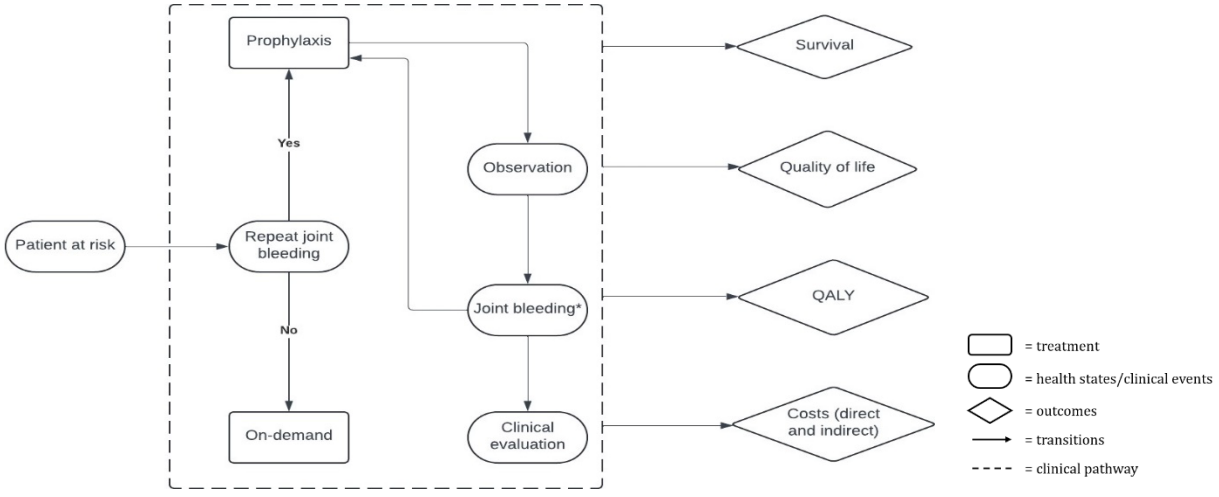

Figure 2. Conceptual Model

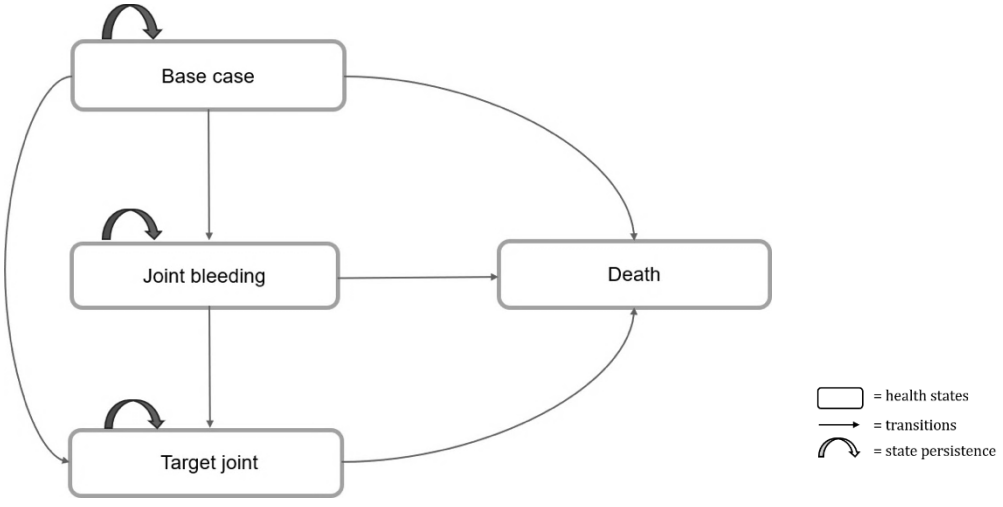

Figure 3. State Transition Model

Discussion

A conceptual health economic model comparing LDP versus OD for Indonesian children with severe HA was developed to ensure face validity and practical representation of treatment in Indonesia. The model incorporates existing evidence, current clinical practice, patient attributes, and local socio-political aspects to capture all appropriate variables before analysis begins. The SLR findings indicated that LDP substantially reduces bleeding episodes, improves joint health, and increases the quality of life. Evidence also revealed LDP as a cost-effective treatment, as compared to OD in children with HA. Overall, prophylaxis is a more cost-effective and beneficial option than on-demand treatment, underscoring its widespread use as a standard of care for hemophilia patients.[36] A previous study reported the same results: prophylaxis was cost-effective (ICER around ±USD 47,462) relative to accepted thresholds.[32] A separate analysis in the UK and Sweden mirrored these results, confirming better health outcomes at lower costs.[33]

While the clinical benefits of LDP are well established, a questionnaire administered to hematologists during conceptual model development highlighted significant challenges in Indonesia. In particular, budget constraints, obstacles to patients receiving timely treatment, and limited availability of FVIII concentrates make OD treatment difficult. Together, these difficulties need to be accounted for in the models as they have substantial and negative impacts on clinical outcomes and increased costs.

A Markov model is favored for an analytical approach. The number and types of health states patients should be well considered to reflect the course of disease, time horizons, and discounting. To operationalise, the clinical outcomes and treatment regimens should be based on the clinical study conducted in Indonesia,[8] while the utility values could be gathered from relevant published studies in broader settings. Most studies employ this approach for utility estimation and are considered acceptable. Initially, cost values will be gathered from the Indonesian NHI hospital tariff. However, these values were subject to adjustments as more comprehensive data becomes available. Additionally, this study plans to estimate direct non-medical and indirect costs using current local reimbursement rates as baseline values.

Conceptualizing a model is critical, yet often underutilized.[39,40] The problem conceptualization process and analytical model presented in this study followed best practices and ensured transparency across all stages. Several significant changes were made to the conceptual model compared to previously reported models. Specifically, instead of focusing solely on patients being in a healthy state regarding joint bleeding, the model structure in this study incorporated target joint bleeding and its associated complications in outcomes and treatments.

The described conceptualization of both clinical care issues and the associated economic model acknowledges certain limitations. First, expert consensus was gathered through a questionnaire rather than a Delphi panel, which may restrict the depth of discussion. A panel would be more likely to capture regional variations in Indonesia concerning clinical care, resource availability, and patient burden. Second, while the clinical study conducted in Indonesia provided essential baseline estimates for the model, this study recognized that the parameters for bleeding events, costs, and quality of life relied on published data from outside Indonesia. Therefore, the analytical model's conceptualization necessarily includes some data very close to the patient and other data at the meso- or macro-level.

This conceptual model provided a realistic, context-specific framework for evaluating the cost-effectiveness of hemophilia care in Indonesia. It did so by integrating local factors such as limited availability of LDP, NHI coverage, treatment practices, transportation, and caregiver costs with published data. The model serves as a valuable resource for Indonesian policymakers and may serve as a blueprint for other low- and middle-income countries developing evidence-informed health policies in resource-constrained settings.

Conclusion

The described conceptualization process serves as a rigorous framework for ensuring the credibility of results from a health economic model. Specifically, it provides a structured guide and documented justifications for comparing the cost-effectiveness of LDP versus OD treatment for children with severe HA within a cost-constrained nation such as Indonesia.

Abbreviations

HA: Hemophilia A; FVIII: factor VIII; QoL: Quality of Life; OD: On-Demand; LDP: Low-Dose Prophylaxis; WFH: World Federation of Hemophilia. ISTH: International Society on Thrombosis and Hemostasis; NHI: National Health Insurance; RCT: Randomized Controlled Trials; CEA: Cost-Effectiveness Analysis; SLR: Systematic Literature Review; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CUA: Cost-Utility Analysis; HTA: Health Technology Assessment; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year; DSA: Deterministic Sensitivity Analysis.

Ethics Approval and Consent to Participate
Not applicable.

Competing Interest
This study was funded by Grifols, but they had no influence over the study's design, execution, or conclusions. This study was conducted independently to maintain objectivity.

Availability of Data and Materials
The data used in this study is publicly available. The supplementary content can be accessed here.

Authors' Contribution
LCK and SP conceptualized the study and led the development of the conceptual model. LCK, SP, NA, and DTP conducted the literature review, contributed to the methodology design, reviewed clinical relevance, and provided expert input on hemophilia treatment strategies. SP supervised the overall research process, validated the model framework, and provided critical revisions to the manuscript. All authors reviewed and approved the final version of the manuscript.

Acknowledgment
The authors extend their heartfelt gratitude to Indonesian hematologists Dr. dr. Novie A. Chozie, Sp.A(K) and Dr. dr. Bambang Sudarmanto, Sp.A Subsp. H-Onk, MARS, FISQua for their invaluable contributions to the development of this conceptual model.

Declaration on the Use of Artificial Intelligence
The authors declare that artificial intelligence (AI) tools were utilized solely for language editing and grammatical refinement to improve the clarity and readability of the manuscript. The specific AI tool used is ChatGPT. AI was not involved in content generation, data analysis, interpretation, or any decision-making processes. All scientific content, interpretations, conclusions, and responsibilities related to the manuscript rest solely with the authors.

References

1. Berntorp E, Fischer K, Hart DP, et al. Hemophilia. Nat Rev Dis Primers. 2021; 7: 45. DOI: 10.1038/s41572-021-00278-x.
2. Mehta P, Reddivari AKR. Hemophilia. Treasure Island, FL: StatPearls Publishing: 2023.
3. Salen P, Babiker HM. Hemophilia A. Treasure Island, FL: StatPearls Publishing: 2023.
4. Franchini M, Mannucci P. Past, present and future of hemophilia: A narrative review. Orphanet J Rare Dis. 2012; 7: 24. DOI: 10.1186/1750-1172-7-24.
5. Munawar Ali R, Abid M, Zafar S, et al. Management of Severe Hemophilia A: Low-Dose Prophylaxis vs. On-Demand Treatment. Cureus. 2023; 15 (7): e41410. DOI: 10.7759/cureus.41410.
6. Berntorp E, Hermans C, Solms A, et al. Optimising prophylaxis in hemophilia A: The ups and downs of treatment. Blood Reviews. 2021; 50: 100852. DOI: 10.1016/j.blre.2021.100852.
7. Zhao Y, Xiao J, Yang R, et al. Efficacy of standard prophylaxis versus on-demand treatment with bayer's sucrose-formulated recombinant FVIII (rFVIII-FS) in Chinese children with severe hemophilia A. Pediatr Hematol Oncol. 2017; 34 (3): 146–56. DOI: 10.1080/08880018.2017.1313921.
8. Chozie NA, Primacakti F, Gatot D, et al. Comparison of the efficacy and safety of 12-month low-dose factor VIII tertiary prophylaxis vs on-demand treatment in severe hemophilia A children. Hemophilia. 2019; 25 (4): 633–639. DOI: 10.1111/hae.13770.
9. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Hemophilia. 2020; 26 (S6): 1–158. DOI: 10.1111/hae.14046.
10. Rezende SM, Neumann I, Angchaisuksiri P, et al. International Society on Thrombosis and Hemostasis clinical practice guideline for treatment of congenital hemophilia A and B based on the Grading of Recommendations Assessment, Development, and Evaluation methodology. J Thromb Hemost. 2024; 22 (9): 2629–2652. DOI: 10.1016/j.jtha.2024.05.026.
11. Menteri Kesehatan Republik Indonesia. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/Menkes/243/2021 Tentang Pedoman Nasional Pelayanan Kedokteran Tata Laksana Hemofilia. Jakarta: Kementerian Kesehatan Republik Indonesia; 2021.
12. Angchaisuksiri P, Amurao-Abiera M, Chou S, et al. Hemophilia care in Asia: Learning from clinical practice in some Asian countries. Hemophilia. 2024; 30 (3): 609–616. DOI: 10.1111/hae.14998.
13. Perolla A, Kalaja B. Improving Hemophilia Care in Low- and Middle-Income Countries: Addressing Challenges and Enhancing Quality of Life. Cureus. 2024; 16 (6): e62817. DOI: 10.7759/cureus.62817.
14. Moonla C, Sosothikul D, Pongtanakul B, et al. Practices and challenges for hemophilia management under resource constraints in Thailand. Orphanet J Rare Dis. 2023; 18: 110. DOI: 10.1186/s13023-023-02718-1.
15. Sidharthan N, Narayana Pillai V, Mathew S, et al. Low Dose Secondary/Tertiary Prophylaxis Is Feasible and Effective in Resource Limited Setting in South India for Children with Hemophilia. Blood. 2016; 128 (22): 2336. DOI: 10.1182/blood.V128.22.2336.2336.
16. Sidharthan N, Sudevan R. Low Dose Prophylaxis in Hemophilia Care. Indian J Hematol Blood Transfus. 2020; 36: 16–25. DOI: 10.1007/s12288-019-01147-0.
17. Hutasoit RH. World Hemophilia Day 2024, Hemophilia in Indonesia and Legal Safeguards. Jakarta: ARFP Lawyers; 2024.
18. Briggs AH, Weinstein MC, Fenwick EAL, et al. Model Parameter Estimation and Uncertainty Analysis: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group–6. Med Decis Making. 2012; 15 (6): 835–42. DOI: 10.1177/0272989X12458348.
19. Roberts M, Russell LB, Paltiel AD, et al. Conceptualizing a Model: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force–2. Med Decis Making. 2012; 32 (5): 678–689. DOI: 10.1177/0272989X12454941.
20. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. PLoS Med. 2021; 18 (3): e1003583. DOI: 10.1136/bmj.n71.
21. Hong QN, Pluye P, Fàbregues S, et al. Mixed Methods Appraisal Tool (Mmat) Version 2018: User Guide. Montreal; McGill University; 2018.
22. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. BMJ. 2022; 376: e067975. DOI: 10.1136/bmj-2021-067975.
23. Konkle BA, Fletcher SN. Hemophilia A Synonym: Factor VIII Deficiency. Seattle, WA: University of Washington; 2022.
24. Chaudhry R, Killeen RB, Babiker HM. Physiology, Coagulation Pathways. Treasure Island, FL: StatPearls Publishing; 2024.

25. Mannucci PM. Hemophilia treatment innovation: 50 years of progress and more to come. J Thromb Hemost. 2023; 21 (3): 403–412. DOI: 10.1016/j.jtha.2022.12.029.
26. Verma SP, Dutta TK, Mahadevan S, et al. A randomized study of very low-dose factor VIII prophylaxis in severe hemophilia – A success story from a resource limited country. Hemophilia. 2016; 22 (3): 342–348. DOI: 10.1111/hae.12838.
27. Djambas Khayat C, Iosava G, Romashevskaya I, et al. Efficacy, Efficacy, Safety and Pharmacokinetic Results of a Phase III, Open-Label, Multicenter Study with a Plasma-Derived Von Willebrand Factor (VWF)/Factor VIII (FVIII) Concentrate in Pediatric Patients <12 Years of Age with Hemophilia A (SWIFTLY-HA Study). J Blood Med. 2021; 12: 483–495. DOI: 10.2147/JBM.S299130.
28. Miners AH, Sabin CA, Tolley KH, et al. Cost-Utility Analysis of Primary Prophylaxis versus Treatment On-Demand for Individuals with Severe Hemophilia. PharmacoEconomics. 2002; 20: 759–774. DOI: 10.2165/00019053-200220110-00005.
29. Risebrough N, Oh P, Blanchette V, et al. Cost-utility analysis of Canadian tailored prophylaxis, primary prophylaxis and on-demand therapy in young children with severe hemophilia A. Hemophilia. 2008; 14 (4): 743–752. DOI: j.1365-2516.2008.01664.x.
30. Daliri AAK, Haghparast H, Mamikhani J. Cost-effectiveness of prophylaxis against on-demand treatment in boys with severe hemophilia A in Iran. Int J Technol Assess Healthcare. 2009; 25 (4): 584–587. DOI: 10.1017/S0266462309990420.
31. Miners A. Revisiting the cost-effectiveness of primary prophylaxis with clotting factor for the treatment of severe hemophilia A. Hemophilia. 2009; 15 (4): 881–887. DOI: 10.1111/j.1365-2516.2009.02019.x.
32. Colombo G, Matteo SD, Mancuso ME, et al. Cost utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. Clinicoecon Outcomes Res. 2011; 3: 55-61. DOI: 10.2147/CEOR.S16670.
33. Farrugia A, Cassar J, Kimber MC, et al. Treatment for life for severe hemophilia A– A cost-utility model for prophylaxis vs. on-demand treatment. Hemophilia. 2013; 19 (4): e228-e238. DOI: 10.1111/hae.12121.
34. Castro Jaramillo HE, Moreno Viscaya M, Mejia AE. Cost-Utility Analysis of Primary Prophylaxis, Compared With On-Demand Treatment, for Patients with Severe Hemophilia Type A In Colombia. Int J Technol Assess Healthcare. 2016; 32 (5): 337–347. DOI: 10.1017/S0266462316000544.
35. Salinas-Escudero G, Galindo-Suárez RM, Rely K, et al. Cost-effectiveness analysis of prophylaxis vs. "on demand" approach in the management in children with hemophilia A in Mexico. Bol Méd Hosp Infant México. 2013; 70 (4): 290–297.
36. Zahedi Z, Karimi M, Keshavarz K, et al. A cost-effectiveness analysis of the prophylaxis versus on-demand regimens in severe hemophilia A patients under 12 years old in southern Iran. Hematol. 2021; 26 (1): 240–248. DOI: 10.1080/16078454.2021.1885123.
37. Seth T, Garg K, Mandal PK, et al. Cost-effectiveness analysis of low-dose prophylaxis versus on-demand treatment for moderate-to-severe hemophilia A in India. Hematol. 2023; 28 (1): 2277497. DOI: 10.1080/16078454.2023.2277497.
38. Nemzoff C, Shah HA, Heupink LF, et al. Adaptive Health Technology Assessment: A Scoping Review of Methods. Value Health. 2023; 26 (10): 1549–1557. DOI: 10.1016/j.jval.2023.05.017.
39. Alemao E, Al MJ, Boonen AA, et al. Conceptual model for the health technology assessment of current and novel interventions in rheumatoid arthritis. PLoS ONE. 2018; 13 (10): e0205013. DOI: 10.1371/journal.pone.0205013.
40. Putri S, Ciminata G, Lewsey J, et al. The conceptualization of cardiometabolic disease policy model in the UK. BMC Health Serv Res. 2024; 24: 1060. DOI: 10.1186/s12913-024-11559-y.