Targeted Literature Review of Cost-Effectiveness Analyses in Sickle Cell Disease: Identifying the Optimal Modeling Approach for Therapies Targeting Sickle Hemoglobin Polymerization

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Background

- SCD is an inherited blood disorder characterized by the polymerization of deoxygenated HbS, which causes damage leading to rigid, sticky, sickled RBCs.[1,2]
  - RBC sickling can in turn lead to hemolytic anemia, acute complications, and chronic, multisystem organ damage.[1,3]
- Therapies targeting HbS polymerization, the molecular basis of SCD pathology, can impact multiple body systems and have been associated with >50 comorbidities and complications.[4]
- Consequently, health economic modeling of therapies targeting HbS polymerization in patients with SCD can be complex.

Objective

- To evaluate published cost-effectiveness analyses (CEAs) to identify the optimal type of modeling approach for therapies targeting HbS polymerization in SCD.

Methods

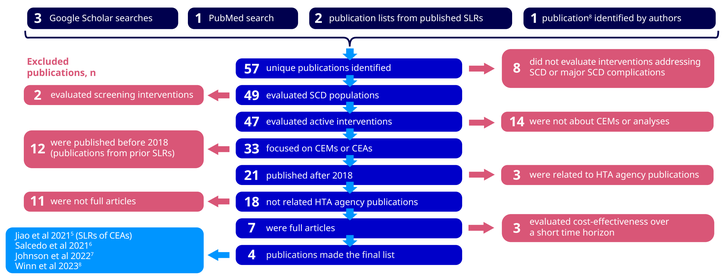
- A targeted literature review was conducted comprising:
  - 5 distinct structured searches (see Supplementary Material) for the period 2018–2023, and
  - Recent pertinent health economic evaluations performed or cited by ICER and NICE.
    - Additional details are in the Supplementary Material, downloaded using the QR code.
- The aims of the literature review were to:
  - Identify current methodologies employed to develop cost-effectiveness models of SCD treatments, and
  - Evaluate the suitability of each modeling approach to assess treatments targeting HbS polymerization in SCD specifically.

Results

STRUCTURED SEARCHES

- The structured searches identified 4 studies, including 1 SLR that reviewed the cost-effectiveness of treatment for SCD (**Figure 1**).

Figure 1: PRISMA flow diagram of structured searches



CEAS IDENTIFIED DURING THE TARGETED LITERATURE REVIEW

- In total, 12 unique CEAs evaluating the cost-effectiveness of treatments for SCD were identified during a targeted literature view, including:
  - 8 from structured searches (**Table 1**), and
  - 4 from HTA agency reports (**Table 2**).

Table 1: Overview of publications identified from structured searches

Study	General setting	Interventions	Model type	Health states
Jiao et al 2021[5] (SLR of CEAs)	• Multiple CEAs in a range of settings[a]	• Multiple CEAs assessing a range of interventions[b]	• 7 models[c] including: – 6 Markov – 1 DES	• Typically includes:[d] – Disease complications – Treatment complications
Salcedo et al 2021[6]	• US health care • Lifetime horizon	• Cell or gene therapy vs SoC[e]	• Markov cohort based	• Remission • Varying disease severities
Johnson et al 2022[7]	• US societal • Lifetime horizon	• Curative therapies vs SoC[f]	• Markov IPS	• Acute pain • Chronic pain • Chronic complications • SCD-related acute complications • Treatment-related complications
Winn et al 2023[8]	• US health care • Lifetime horizon	• Generic	• Markov IPS	• Acute complications • Chronic complications • Death

[a] Most commonly in the United States or United Kingdom, with a payer perspective. [b] Most commonly screening or treatments for SCD complications. [c] Includes 2 CEAs identified from structured searches.[6,10] [d] N/A for DES, which models time to prespecified events. [e] Includes antibiotics, vaccinations, analgesia, HU, and blood transfusions. [f] Includes HU and blood transfusions.

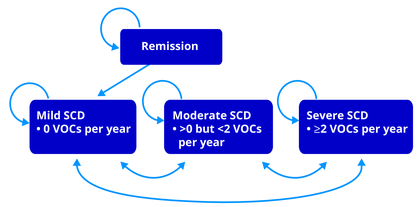
Table 2: Overview of relevant HTA agency reports

Report	General setting	Interventions	Model type	Health states
NICE 2020[9]	• UK NHS and PSS • Lifetime horizon • Patients aged ≥16 years	• Crizanlizumab vs SoC	• Markov cohort based	• 0 VOCs/year • 1–2 VOCs/year • ≥3 VOCs/year
ICER 2021[10]	• US health care and societal • Lifetime • Adults and children	• Crizanlizumab, voxelotor, and L-glutamine (each + SoC) vs SoC	• Markov cohort based	• Uncomplicated • Acute conditions • Chronic conditions • Acute on chronic conditions • Death
ICER 2023[11]	• US health care and societal • Lifetime horizon • Adults and children with severe SCD	• Gene therapies[a] vs SoC	• Markov cohort based	• No event • Acute complications • Chronic complications • Death
NICE 2023[12]	• UK NHS and PSS • Lifetime horizon • Patients aged ≥12 years	• Voxelotor ± HU vs HU, blood transfusions, or SoC	• DES	• N/A[b]

[a] Includes exagamglogene autotemcel and lovotibeglogene autotemcel. [b] DES models the time to prespecified events influenced by index Hb value and other covariates.

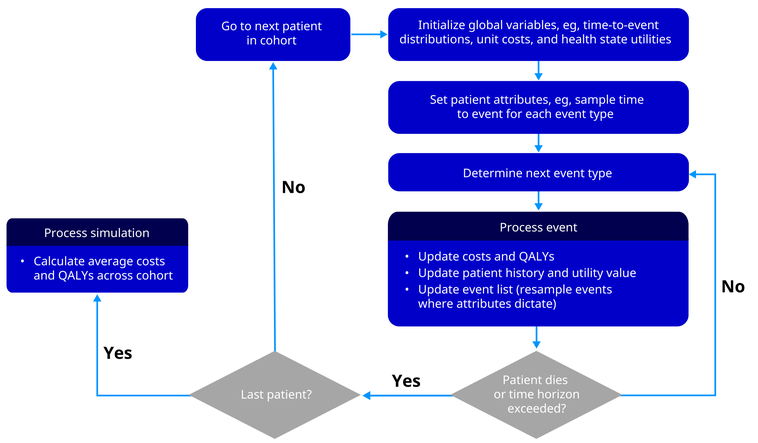
- The 12 CEAs were based on:
  - 8 Markov cohort–based models (**Figure 2**),
  - 2 Markov individual patient simulation (IPS) models (**Supplemental Figure**), and
  - 2 discrete event simulation (DES) models (**Figure 3**).
- An overview of each CEA is presented in either **Table 1** or **2**.
- Most Markov cohort–based models described the course of SCD by incorporating disease states using:
  - Annual numbers of VOCs, or
  - Aggregated acute and/or chronic complications.

Figure 2: Sample Markov cohort–based model based on annual number of VOCs in patients with SCD



Markov model for lifetime management of SCD. Death (not displayed) can occur from any state.
"Cost-effectiveness of a hypothetical cell or gene therapy cure for sickle cell disease" by Salcedo J, Bulovic J, Young CM, Sci Rep. 2021;11(1):10838, is licensed under CC BY 4.0.

Figure 3: Sample DES model for treating hemolytic anemia in SCD



Simplified DES algorithm.[12]

EVALUATION OF MODELS

- Markov cohort–based models are most frequently used in HTAs.
  - Although they do not preclude consideration of patients' medical histories, this can only be done by incorporating additional states, which may not be feasible for SCD as it impacts multiple body systems, requiring combinations and permutations of health impacts to be considered over time (**Table 3**).
  - In SCD, the risk of future acute and chronic complications can be influenced by a patient's medical history and Hb value, both of which may be altered by therapies targeting HbS polymerization.
- Patient-level simulations, encompassing both IPS (state-based) and DES (event-based) approaches, can explicitly model specific complications and/or co-occurring events, while considering patients' characteristics/medical histories.
- Markov IPS models present challenges because they are unable to manage competing risks/events within a cycle, and inefficiencies are introduced when processing event-free cycles.
  - DES models can overcome these challenges because they:
    - Place no restrictions on when events can occur limiting the need to apply arbitrary rules regarding the order in which events are processed, and
    - Can be more efficient, particularly during intervals when no events take place.
- A DES model developed to assess HbS polymerization inhibitor measured treatment effect through time-to-event equations and incorporated 15 distinct complications.[12]

Table 3: Evaluation of models in the literature

	Markov cohort–based model[5,6,9–11]	Markov IPS model[7,8]	DES-based model[5,12]
Overview	• Conceptualizes clinical outcomes as transitions between predefined states that occur at regularly spaced intervals (Markov cycles)	• Like cohort-based models, utilizes state-based conceptualization of events and fixed cycle length • Tracks events for each patient individually to overcome a memoryless approach[a]	• Conceptualizes clinical outcomes as a sequence of events experienced by individual patients: – Calculates when each event will occur, – Processes the first event, and – Recalculates time for remaining events continually until death or the model time horizon is reached
Precedent in HTAs for SCD	• Most frequently used	• None	• Limited (n=1)
Considers patient baseline characteristics	✓	✓	✓
Disease complications	• Limited to predefined, mutually exclusive states and fixed cycles – Difficult to assess competing risks and process multiple events within a cycle	• Limited to predefined states (not necessarily mutually exclusive) and fixed cycles – Difficult to assess competing risks, but multiple events can occur within a cycle	• Captures multiple or co-occurring complications
Events/medical history	• Memoryless approach[a] – Can be overcome by careful design at the expense of increased model complexity	• Tracks patient history • Inefficiencies in processing event-free cycles	• Tracks patient history • Efficient handling of event processing
Includes mortality	✓	✓	✓

[a] Incorporates a patient's current health state and excludes their past medical history when calculating transition probabilities.

Conclusions

- DES-based CEAs are preferred for modeling therapies targeting HbS polymerization in SCD because they:
  - Have the flexibility required to efficiently account for patient histories, and
  - Can accommodate multiple and/or co-occurring complications.
- Thus, they are optimally equipped to accurately reflect the unpredictable and heterogeneous course of SCD and its impact on individuals and health systems.

Electronic Poster and Supplementary Material

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If you do not have a smartphone, access the poster and supplementary material via the internet at: https://scientificpubs.congressposter.com/p/yybu9p0bzw632xz8.

References: **1.** Kato GJ, et al. Nat Rev Dis Primers 2018;4:18010. **2.** Li X, et al. J Biomech 2017;50:34–41. **3.** Piel FB, et al. N Engl J Med 2017;376:1561–73. **4.** Ericksen PN, et al. Authorea Preprint posted online March 12, 2024. doi:10.22541/au.171025471.18811984/v1 **5.** Jiao B, et al. Pharmacoeconomics 2021;39:1225–41. **6.** Salcedo J, et al. Sci Rep 2021;11:10838. **7.** Johnson KM, et al. PLoS One 2022;17:e0267448. **8.** Winn A, et al. Pharmaecon Open 2023;7:313–20. **9.** National Institute for Health and Care Excellence. Technology appraisal guidance. Crizanlizumab for preventing sickle cell crises in sickle cell disease. Accessed March 1, 2023. https://www.nice.org.uk/guidance/ta743 **10.** Institute for Clinical and Economic Review. Evidence report. Crizanlizumab, voxelotor, and L-glutamine for sickle cell disease: effectiveness and value. Accessed March 20, 2024. https://icer.org/wp-content/uploads/2021/02/ICER_SCD_Evidence-Report_031220-FOR-PUBLICATION.pdf **11.** Institute for Clinical and Economic Review. Final evidence report. Gene therapies for sickle cell disease. Accessed March 20, 2024. https://icer.org/wp-content/uploads/2023/08/ICER_SCD_Final_Report_FOR_PUBLICATION_082123.pdf **12.** National Institute for Health and Care Excellence. Single technology appraisal. Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]. Accessed March 20, 2024. https://www.nice.org.uk/guidance/gid-ta10505/documents/committee-papers-2.

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Abbreviations: CEA=cost-effectiveness analysis; CEM=cost-effectiveness model; DES=discrete event simulation; Hb=hemoglobin; HbS=sickle hemoglobin; HTA=Health Technology Assessment; HU=hydroxyurea; ICER=Institute for Clinical and Economic Review; IPS=individual patient simulation; N/A=not applicable; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSS= Personal Social Services; QALY=quality-adjusted life year; RBC=red blood cell; SCD=sickle cell disease; SLR=systematic literature review; SoC=standard of care; VOC=vaso-occlusive crisis

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