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Conceptual Framework for Economic Evaluations in β-Thalassemia

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Introduction

- β-thalassemia is a genetic hematologic disorder associated with ineffective erythropoiesis and anemia
- Transfusion-dependent patients receive regular red blood cell transfusions (RBCT), supported by iron chelation therapy (ICT) to control serum iron levels
- Lentiglobin and luspatercept were recently approved by the European Medicines Agency and the US Food and Drug Administration, changing the treatment landscape of β-thalassemia
- As the number of available treatments increases, there is a growing need for economic evaluations to assess the cost-effectiveness of different therapies
  - Use of consistent frameworks will allow for valid comparisons across analyses

Objective

- To establish a conceptual framework regarding the treatment of β-thalassemia that accurately captures long-term effects and resource use

Methods

- A targeted review of the literature was conducted for β-thalassemia
- Central cost drivers and value drivers were identified
- Additional cost and quality of life (QoL) considerations were provided by expert hematologists, health economists, and market access experts
- Clinical and safety outcomes, health states, technical assumptions (e.g. time horizon), costs, and economic endpoints were also considered
- Different sets of assumptions were tested using a semi-Markov model
- With all β-thalassemia-related inputs, a conceptual framework for economic evaluations was developed from the US payer perspective with the goal of accurately capturing long-term costs and benefits related to novel treatments
- Key value drivers were identified to help optimize future models and facilitate valid comparisons between future economic analyses
- The conceptual framework and clinical rationale were validated by expert hematologists

Results

Overview and structure

- A lifetime horizon was considered appropriate as patients with β-thalassemia often require regular RBCTs over the long term, which lead to iron loading and morbidity
  - Iron loading is associated with long-term complications, high costs, reduced QoL, and early mortality[1]
  - A lifetime horizon permits the use of age-related increases for complication rates and captures the long-term benefits of key therapies (curative or otherwise)
- 6 health states accurately captured the patient lifetime journey: transfusion independence, low transfusion burden (TB), medium TB, high TB, treatment discontinuation, and mortality
  - Low, medium, and high TB were defined as 0–6, 6–12, and > 12 RBC units per 12 weeks, respectively; however, precise definitions should reflect trial data[2]
- These health states enable the inclusion of response status defined in terms of TB and treatment discontinuation in 3 different periods:
  - Within-trial period: where the within-trial uptake is applied
  - Response threshold: where non-responders discontinue
  - Extrapolation period: where the outcomes are extrapolated beyond the duration of the trial
- It was assumed that:
  - A treatment could improve a patient's health state until the response threshold, after which no improvements could occur
  - Patients could discontinue treatment or experience mortality during any of the 3 periods at any treatment cycle
- In future economic models, cycle lengths that reflect drug cycles should be used to drive patients between health states over time

Semi-Markov model

- A semi-Markov concept permitted the use of state and/or time dependency, which allowed a dynamic transition rate between health states, meaning that transition rates between health states differed for each set of treatment cycles over each of the 3 responder threshold-defined periods[3]
- Separate transition rates between health states within each threshold period should be considered separately for responders and non-responders
- The mortality rate should consider both disease-related mortality and complication-related mortality, in addition to natural mortality
- Trial data should be used to determine response for each treatment, and the state of responders and non-responders at baseline and during the within-trial response
- For the extrapolation period, evidence-based rationale should be presented for the stabilization, improvement, or worsening of patients
- This semi-Markov structure permits the inclusion of clinical trial data and related overall response rate, which is generally a key outcome in β-thalassemia (**Figure 1**)

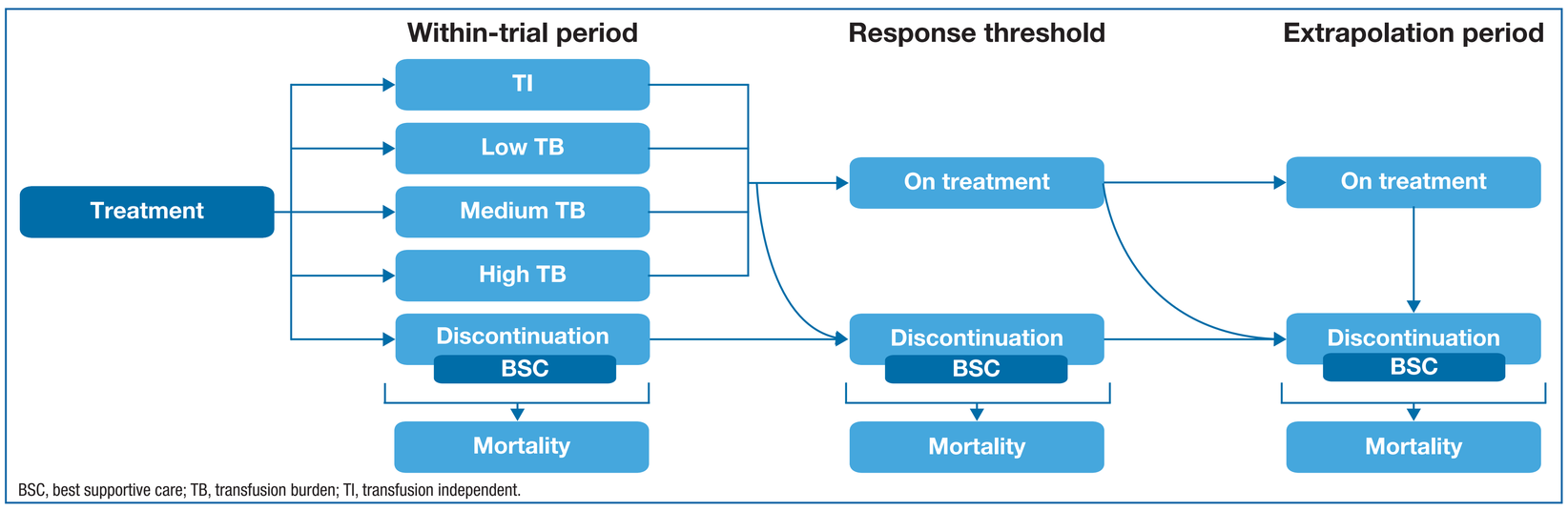
Costs

- Across cost categories, central cost drivers in each category, rationale, economic impact, and supporting evidence are shown in **Table 1**
- ICT was assumed to be a central cost driver and a viable target for reducing the economic burden associated with β-thalassemia
  - As TB increases across health states, it was assumed that ICT would be used more frequently to counteract iron overloading
  - 1 US-based costing study found the average annual cost of ICT in TD β-thalassemia to be USD 52,718 per patient, and combined with the cost of transfusion, annual costs were USD 75,000[4]
- Disease-related costs were expected to increase over a lifetime horizon due to the number of hospitalizations

Quality of life

- Factors expected to influence QoL are presented in **Table 2**
- As β-thalassemia is a chronic disease, a longitudinal approach that assesses the risk of complications and mortality over time is necessary to accurately reflect the disease
- Complications and early mortality would be reflected in quality-adjusted life year (QALY) and life year (LY) effectiveness measures

Figure 1. Semi-Markov concept



BSC, best supportive care; TB, transfusion burden; TI, transfusion independent.

Table 1. β-thalassemia costs

Cost category	Central cost drivers	Rationale	Economic impact	Supporting evidence
Primary therapy	• Novel treatments • Administration (e.g. SCT, IV)	In the USA, novel therapies are typically the primary driver of costs in economic evaluations	High	• Expert opinion • US Department of Health and Human Services, 2018[7]
AE	• Hospitalizations for severe AEs • Physician visit for less severe AEs	Hospitalizations are costly; however, frequency of severe AEs is generally expected to be low for most approved therapies	Low-medium	• Expert opinion
Routine care	• Physician visits • Diagnostic testing	Patients are expected to regularly undergo diagnostic tests for complications and visit their physician, both of which have relatively low costs	Low	• Expert opinion • CMS 2019 physician fee schedule[8]
Secondary therapy	• ICT • RBCT	BSC with regular ICT and RBCT for TD patients can be costly	Medium-high	• Expert opinion • Paramore et al., 2017[4]
Complications	• Hospitalizations for complications related to iron overload	Regular RBCTs will lead to complications over a lifetime horizon that will require hospitalizations, which are potentially costly	Medium-high	• Expert opinion • Chuncharunee et al., 2019[6]
Mortality	• Early mortality	Early mortality related to iron overloading and β-thalassemia is a one-time event	Low	• Expert opinion
Indirect	• Work absence and lost wages	Transfusion dependency was assumed to result in 1.3 work days lost PPPM	Low	• Expert opinion • Sattari et al., 2012[9]

AE, adverse event; BSC, best supportive care; CMS, Center for Medicare & Medicaid Services; ICT, iron chelation therapy; IV, intravenous; PPPM, per patient per month; RBCT, red blood cell transfusion; SCT, stem cell transplantation; TD, transfusion dependent.

Table 2. β-thalassemia QoL modifiers

QoL category	Rationale	QoL impact	Supporting evidence
Treatment	Response to treatments is expected to drive patients into different TB health states, which will affect QoL	High	• Expert opinion
AE	Severe AEs are expected to produce disutility, negatively affecting patients' QoL	Low-medium	• Bentley et al., 2013[10]
Complications	Complications related to iron overloading are expected to negatively affect patients' QoL over time	Low-medium	• Expert opinion • John et al., 2018[11] • Sruamsiri et al., 2013[12]
Mortality	Iron overloading and β-thalassemia are associated with early mortality	High	• Expert opinion • Hassanzadeh et al., 2018[13]

AE, adverse event; QoL, quality of life; TB, transfusion burden.

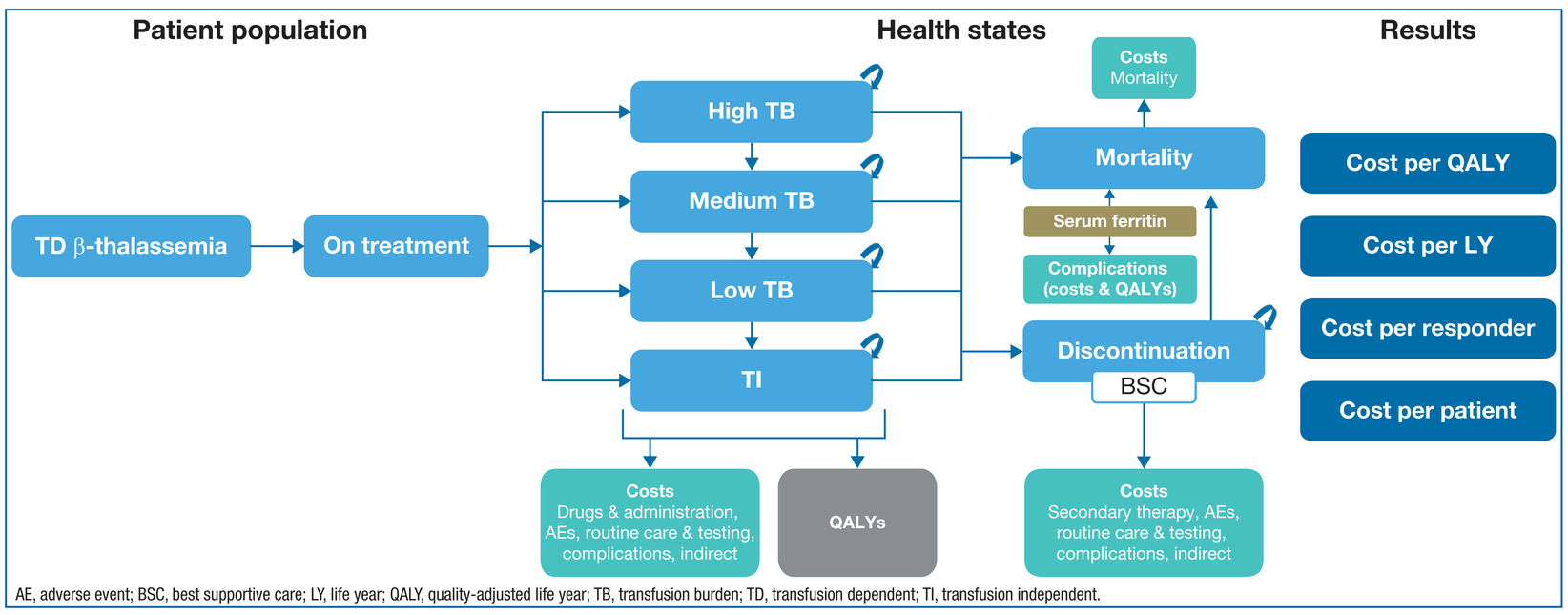
Serum ferritin

- Serum ferritin may increase over time for patients in TB health states due to RBCTs, and could be used as a marker for iron overloading due to increased RBCT demand[5,6]
  - Higher levels of serum ferritin would be associated with relatively higher risk of complications and early mortality, affecting both costs and QoL, and should therefore be included in the modelling framework

Conceptual framework

- Key economic endpoints that quantify value in β-thalassemia include: incremental cost per QALY, per LY, and per responder; and total cost per patient
- The conceptual framework for β-thalassemia, which comprehensively includes health states, key cost categories, key effectiveness measures, endpoints, and serum ferritin, is presented in **Figure 2**

Figure 2. β-thalassemia conceptual framework



AE, adverse event; BSC, best supportive care; LY, life year; QALY, quality-adjusted life year; TB, transfusion burden; TD, transfusion dependent; TI, transfusion independent.

Conclusions

- As β-thalassemia treatment evolves, there is a growing need to evaluate novel treatments and optimize resource use
- This novel conceptual framework will allow future cost-effectiveness analyses to accurately capture the long-term effects of β-thalassemia, including increased iron loading and its impact on complications and mortality
- The findings of this analysis could be used to critically assess future economic evaluations, evaluate their robustness, and validate their findings

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Disclosures

G.T., D.T.: Purple Squirrel Economics – employment. E.M., R.C.: BMS – employment.

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