10. ESTIMATING THE COST OF THALASSAEMIA CARE: TIF'S GLOBAL CONTRIBUTION

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INTRODUCTION

Health funders, including governments, social insurance funds and companies or even patients themselves, are now more than ever struggling to cover the increasing costs of medical treatments and especially novel ones, including gene- and cell- based therapies and other approaches targeting erythropoiesis for patients with thalassaemia. The cost of therapy does not though only include medication and blood transfusion costs but also hospitalisations, laboratory and diagnostic tests, medical consultations, treatment of side effects or complications and other indirect costs, such as travel expenses and loss of productive days.

Through this study, we aim to provide health funders, researchers, either academic or medical, and patients themselves with a cost model for thalassaemia that would contribute to better planning, allocation of resources and reduction of waste in health care. This would initiate a well-structured and evidence-based dialogue of patient associations with national health authorities to help them understand the rising needs of thalassaemia and the need for policy change.

This analysis would help national associations and patient advocates to justify: i) why affected countries should have a national prevention policy in place to control the number of new births and thus the economic costs of the disease; ii) why these countries should invest in the holistic (optimal) care of patients to help them achieve good health and thus contribute to society; and iii) why affected countries should assess the financial burden for better planning and management of available resources to avoid healthcare waste and determine whether access to novel (expensive) therapies would be possible.

METHODOLOGY

To elaborate a cost model for thalassaemia, we engaged both a highly qualified team of Health Economists from BCN Health, a small-sized enterprise based in Barcelona, Spain and a team of medical experts on thalassaemia from Cyprus and Greece. The project consisted of three (3) distinct stages:

1. **TARGETED LITERATURE REVIEW.** The team would first review existing literature to identify:
    i. which countries have already performed a cost-of-illness study on thalassaemia.
    ii. what components have been taken into consideration for the estimation of treatments costs.
2. **GENERIC COST-OF-ILLNESS MODEL.** The team would then prepare a cost-of-illness breakdown analysis in Excel format, reviewed by the team of medical experts.
3. **PILOTING.** The team would finally apply to the Model data collected from two (2) countries (one of the Western world and one of the Eastern world) to the cost-of-illness table.

More specifically:

1. **TARGETED LITERATURE REVIEW**
   Countries that have performed COI studies on thalassaemia

Cost analysis for thalassaemia therapy bears several limitations, including the diverse structure and organization of healthcare systems and social security services in high-prevalent and other countries across the world, the variable level and intensity of provided services, the different degree of healthcare coverage and the difficulty to estimate amount of out-of-pocket money that many patients and families have to pay in several countries. Evidence in the literature remains also limited and is based on diverse methods of cost calculation, a fact that renders comparisons among studies and countries problematic.

Cost analyses have focused either on the total cost of thalassaemia care or on the cost and, more often, the cost-effectiveness of specific treatment or prevention modalities, such as iron chelation, haematopoietic stem cell transplantation (HSCT) or prenatal screening. The findings of key studies on thalassaemia care cost in different parts of the world are summarized below.

General Cost of Thalassaemia Therapy

In the **UNITED STATES**, a retrospective matched-cohort study using payer claims estimated an average total healthcare costs per patient per year for regularly transfused patients of USD 128,062 (versus USD 5,438 for matched controls, p< 0.0001) [1, 2]. In **UNITED KINGDOM**, according to a model constructed on information obtained from literature review and clinicians, the estimated total healthcare expenditure for the management of thalassaemia was £483,454 ($720,201) at 2013-2014 prices over the first 50 years of patients' life [3, 4]. In **INDIA**, a survey performed in a tertiary hospital by interviewing patients' guardians estimated an average total expenditure per patient per year of US$ 1135, including direct and indirect costs, an amount representing 38.8% of the family income [5, 6]. In **SRI LANKA**, according to an analysis based on medical records, physicians' consultation and patients and families' interviews, the average total cost per patient year to the hospital was $US 2601, including direct and overhead costs, while the average household expenditure was $US 206 [7, 8]. In **IRAN (ISLAMIC REP. OF)**, a cost analysis from a social services perspective estimated an average cost per patient per year of $ 8321.8, including direct and indirect costs, plus another $ 1360.5 due to the distress caused by the disease [9, 10]. In **ISRAEL**, the total cost for treating one thalassaemia patients for 50 years was estimated at $1,971,380 [11, 12]. In a recent poster presentation from **EGYPT**, the total cost of treating thalassaemia is 1432 USD/patient/year; this takes into consideration direct, indirect and direct non-medical costs, with the highest cost going to medications and monitoring; the authors suggest that even with public sector insurance patients and families suffer a high financial burden due to co-payments, given the average salary which is 586 US Dollars per month [13, 14].

In the **UAE** a cost of illness study confirmed that direct medical costs and especially iron chelation are the most resource demanding features of thalassaemia management. The direct medical cost per annum was 131156 AED (35,709.11 USD) per patient per year. This is contrasted to the estimates from Egypt, even though there may be differences in the items included in the estimate. The authors of the UAE cost estimate included the following (Fig 1.)

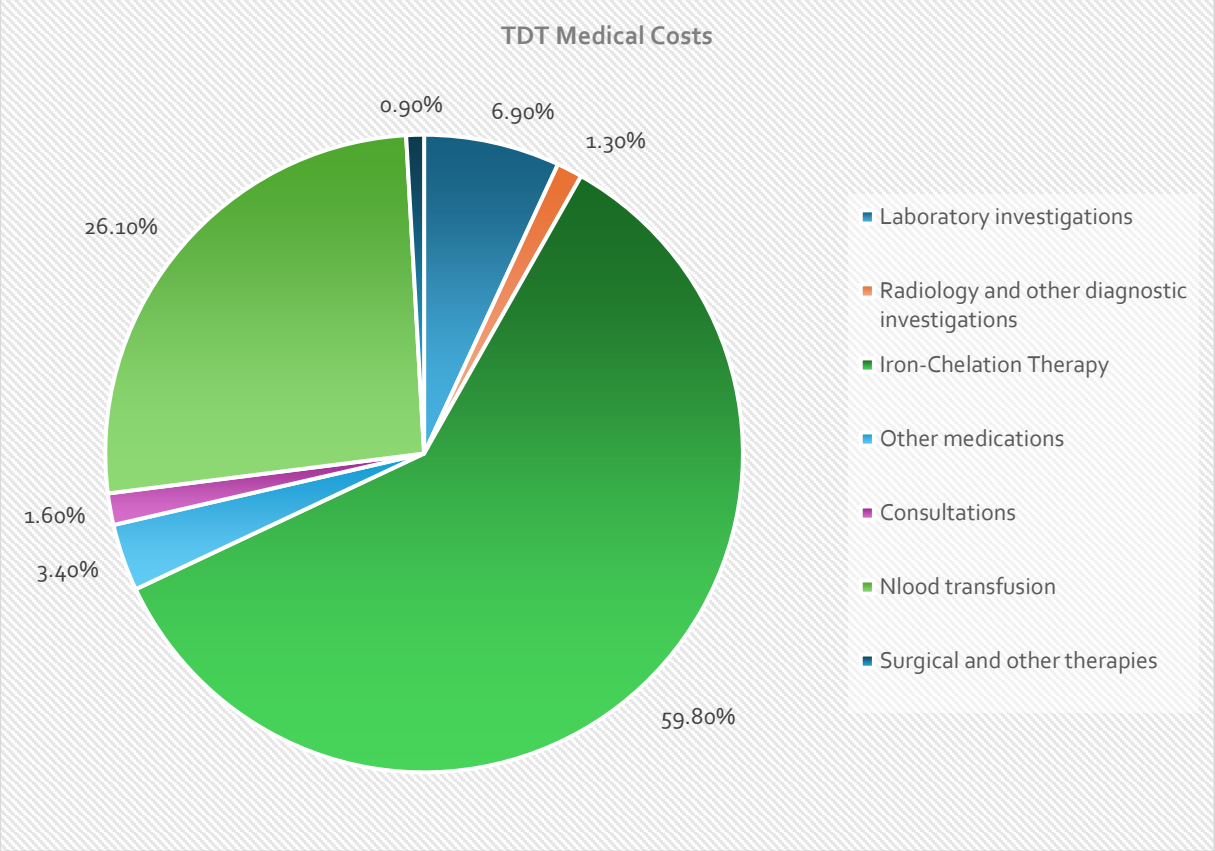


Figure 1. Distribution of the direct medical costs per TDT patient by medical service types, 2019

The median household annual income in the UAE is 26,137.38 USD (contrast to 7032 for Egypt). Over and above there are direct non-medical costs [15, 16]. The same authors also study productivity loss due to thalassaemia; they reported the annual total productivity loss cost at paid work among 79 employed patients was USD 4691, out of which absenteeism contributed USD2812 and presenteeism contributed USD 1879, whereas the annual total productivity loss cost at unpaid work was USD 1104 [2, 17].

Malaysia: The lifetime cost per TDT patient was calculated to be USD 606,665; this is the sum of lifetime healthcare cost and lifetime patient and family healthcare expenditure. This is based on information obtained from published literature and clinicians involved in managing TDT in Malaysia, while lifetime patients/family healthcare expenditure was derived through face-to-face interviews (a total of 574 patients were recruited) in a nationwide multi-centre cross-sectional study using a set of de novo questionnaires, in 12 major thalassemia centres covering all regions in Malaysia between May and September 2018. The costs included ICT drugs, blood transfusion, routine laboratory and instrumental monitoring tests, and iron overload complications. The annual cost to manage a TDT patient is substantial at USD 10,499 from a societal perspective while the monthly estimated mean total patient and family resource use is USD65.56. The Malaysia healthcare system is publicly funded; hence scarce resources limit the feasibility of meeting all patient requirements. This information is of interest to policymakers [4, 18].

Cost of Screening and Prevention

Applying population or premarital screening and prenatal diagnosis programmes was demonstrated to be a cost-effective strategy in other highly prevalent areas such as **IRAN (ISLAMIC REP. OF)**. Study reports savings of 7,825,000 USD in 10 years due to the screening programme applied in that country, considering 235

prevented cases in 10 years [6, 19]. In a more recent study from Iran, the costs of preventing the birth of each thalassaemia major patient were US$ 32 624 by screening techniques while the cost of managing a patient with thalassemia major is about US$ 136 532 per year. Incremental cost per QALY gained with screening as compared with managing thalassaemia major was US$ 11 571. In conclusion screening is a long-term value for money intervention that is highly cost effective and its long-term clinical and economic benefits outweigh those of managing thalassaemia major patients [8, 20]. In **CHINA** the savings in one year were HK$2651 in 2004 [10, 21] and US$356,499 in 2016 [22, 23]. A study from **ISRAEL** reported savings of $67,369 per birth prevented in 1998 [24, 25]. A more recent study also in Israel reported that the prevention of 45 affected newborns over a ten-year period represents a net saving of $88.5 million to the health budget. Even after deducting the cost of the prevention programme ($413.795/year), the programme still represents a benefit of $76 million over ten years [11, 12].

Cost of Specific Therapeutic Modalities

Estimating the cost of transfusion therapy may be challenging as there are several implicated processes. In **Australia**, the total cost per packed red cell unit, covering every step of the transfusion pathway for thalassaemia patients, was estimated at US$ 695.59 from a healthcare provider perspective [22].

Regarding iron chelation therapy, a series of studies performed in different countries including **United Kingdom**, **Italy**, **Iran (Islamic Rep. of)**, **China**, **Taiwan (China)**, **Thailand**, and **United States**, used Markov models to determine the lifetime cost and quality-adjusted life-years (QALYs) to compare the cost effectiveness of different iron chelators; results varied according to the time period of the study and the applied comparisons among available iron chelators [26, 27, 28, 29, 30, 31, 32, 33, 34, 35]. – which of these?

In what concerns curative therapies, the estimated average costs for HSCT and gene therapy in France were €215,571 and €608,086, respectively [36]. Using Markov modelling, two different studies in India and in Thailand showed that HSCT was a highly cost-effective strategy in the long-term compared with conventional transfusion-chelation therapy [37, 38].

IDENTIFICATION OF PARAMETERS TO ESTIMATE THE COST OF CARE

Treatment Costs

The β-thalassaemia treatment costs identified for different countries were estimated on the basis of the same set of components, namely:

a) Blood transfusion costs
b) Pharmaceutical drugs
c) Disposables
d) Iron load monitoring
e) Disease progression and complications
f) Laboratory testing
g) Medical consultations and multidisciplinary care
h) Infection management

Table 1 below summarises all parameters identified in literature with regard to treatment costs in general:

Table 1. Summary of parameters identified from the literature

Article	Country	Parameters
Weiss M, et al. 2019	USA	- Medication - Medical - Outpatient - Inpatient - ED - Other medical
Udeze C et al **J Med Econ 2023**	USA	Direct costs (as above) per patient/year
Weidlich D, et al. 2016 **(Transfusion)**	United Kingdom	- RBC transfusion - ICTs - Routine monitoring tests and regular visits to haematologists - Managing complications
Moirangthem A, et al. **(Ind J Pediatr 2018)**	India	- Hospital admission and BT - Travel related - Medications - Lab investigations - Mean annual income
Uchil A et al **(Natl Med J INDIA 2023)**	India	Direct costs
Reed-Embleton H, et al. 2020	Sri Lanka	Blood transfusion: - Number of transfusions - Staff Drug therapy: - ICT - Concomitant medication Overheads: - Indirect costs Household costs: - Transport and foods
Hossein et al **Orphanet J OF RARE DIS 2017**	Bangladesh	Direct costs annual
Safdar S et al **Pak J Med Res 2017**	Pakistan	Direct Indirect costs/ patient/year
Nhac-Vu HT et al **Plos One 2023**	Vietnam	Direct costs/patient/year
Zhen X et al **ORPHANET J OF RARE DIS 2023**	China	Mean annual direct costs
Shafie AA et al **BMC Pediatr 2020**	Malaysia	Direct costs Overhead costs
Atmakusuma TD et al **Int J of Gen Med 2021**	Indonesia	Cost/person /year
Esmaeilzadeh F, et al. 2016	Iran (Islamic Rep. of)	- Total costs per patient - Direct medical costs - Direct non-medical costs - Indirect costs

Article	Country	Parameters
Geitona M et al Value Health . 2014	Greece	Direct costs
Koren A et al Mediterr J Hematol Infect Dis . 2014	Israel	Lifetime costs
Antmen A et al Blood 2017	Turkey	Annual direct costs
Angelucci E et al Blood 2017	Italy	- Direct costs TDT - Direct costs NTDT
Alabbadi I et al Jord J Pharm Sci 2022	Jordan	- Direct and Indirect costs - Subsidised and unsubsidised

Blood Transfusion Services

Data about red blood cell (RBC) transfusion costs in beta-thalassaemia patients is scarce. We were able, though, to identify the main parameters involved in RBC transfusion costs, as outlined below in Table 2:

Table 2. Parameters of transfusion costs in beta-thalassaemia patients

Article	Country	Parameters
McQuilten ZK, et al. 2019	Australia	- Number of RBC units transfused - Staff costs - Consumables costs - Transfusion process costs - RBC procurement costs
Burns KE, et al. 2019	Australia	- Red blood cell (RBC) unit cost - Costs associated with clinical transfusion processes - Costs of laboratory transfusion (pathology) processes - Costs of full blood count and ferritin assays performed - Costs of clinical transfusion processes - Costs for management of iron overload - Medical therapy unit expenses and overheads
Ravangard R, et al. 2018	Iran (Islamic Rep. of)	Direct medical costs: - Medicine - Blood transfusion - Visit - Laboratory - Diagnostic and treatment services - Hospitalization Direct non-medical costs: - Transportation - Accommodation and food Indirect costs: - Potential production lost due to being absent from work to receive medical care

Iron Chelation

Most of the studies identified were cost-effectiveness or cost-utility studies comparing different chelators' cost and their effectiveness. Several studies (China, Italy, United Kingdom and Thailand) compared deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX). The parameters identified in literature to calculate the costs of the different chelation therapies are as follows:

Table 3. Parameters used to calculate costs of chelation therapies

Article	Country	Parameters
Saiyarsarai P, et al. 2020	Iran (Islamic Rep. of)	- Direct medical cost: included the cost of medicine and laboratory - Cost of medical equipment and infusion pump - Annual cost of cardiac complication - Indirect costs: transfusion time cost, cost of productivity loss
Li J, et al. 2020	China	- Chelator costs - DFO administration cost - Monitoring cost - Complications therapy cost
Pepe A, et al. 2017	Italy	- Drug costs - DFO administrations costs - Monitoring tests
Vekeman F, et al. 2016	USA	- Inpatient stays - Emergency room (ER) visits - Outpatient visits - All-cause healthcare costs - Disease-related healthcare costs
Bentley A, et al. 2013	United Kingdom	- Drug costs - Administration costs (DFO and combination therapy) - Monitoring tests - Managing treatment-related adverse events
Keshtkaran A, et al. 2013	Iran (Islamic Rep. of)	- Direct costs: drug, pump, transfusion kit cost and treatment of adverse events - Indirect costs: transfusion time cost
Ho WI, et al. 2013	Taiwan (China)	- Drug costs - Administration costs - Adverse events costs
Karnon J, et al. 2012	United Kingdom	- Chelation drug - Administration - Monitoring - Adverse events - Complications
Luangasanatip N, et al. 2011	Thailand	- Direct medical care *DFO costs: drug cost, cost of medical visit, cost of infusion pump and cost of injection set *DFP costs: drug cost, cost of medical visit, cost of complete blood count (CBC)

Article	Country	Parameters
		monitoring and cost of neutropenia treatment - DSX: drug cost and cost of medical visit - Direct non-medical care - Indirect costs
Zhang B, et al. 2011	USA	Treatment with DFO
Delea Te, et al. 2007	USA	- Drug costs - Administration costs - Complications
Lee Ta, et al. 2014	Worldwide	Drug costs
Li J, et al. 2019	Worldwide	Literature review that provides all the costs included in each study

Disease Progression – Complications

Thalassaemia syndromes lead to some complications in several systems including cardiopulmonary disorders, endocrine organ diseases, liver impairment and thromboses in different vascular beds. The main complications identified in the literature review were the following:

Table 4. Parameters of the costs of caring for complications of thalassaemia

Article	Country	Parameters
Farmakis D, et al. 2020	Worldwide	Cardiovascular disorders - Atherosclerotic cardiovascular disease - Atrial fibrillation - Aortic stenosis - Heart failure with preserved left ventricular ejection - Fraction - Supraventricular arrhythmias - Diastolic left ventricular dysfunction Hepatic disorders - Hepatocellular carcinoma - Hepatitis C infection - Hepatic epithelioid hemangioendothelioma (related to iron overload)
Demosthenous C, et al. 2019	Worldwide	- Epidemiology of renal complications - Renal manifestations - Tubular dysfunction - Glomerular dysfunction - Haematuria - Nephrolithiasis
Sinakos E, et al. 2017	Greece	- Chronic liver diseases, namely liver cirrhosis and hepatocellular

Article	Country	Parameters
		carcinoma, are currently the main causes of death in patients with b-TM. - CHC along with iron overload are the main reasons for the progression of liver disease in this population. - SVR could also lead to prolongation of life expectancy in b-TM patients.
Ozturk Z, et al. 2017	Turkey	- Hypozincaemia - Copper deficiency and toxicity - Deficiency of selenium - Hypomagnesaemia - Calcium
Karimi M, et al. 2018	Worldwide	- Osteoporosis (21.6%) - Hypogonadism (12.6%) - Central hypothyroidism (8.3%) - Non-insulin-dependent diabetes mellitus (7.8%) - Primary hypothyroidism (5.5%) - Insulin-dependent diabetes mellitus (4.2%) - Hypoparathyroidism (2.2%) - Growth hormone deficiency (1.1%) - Adrenal mass (1%) - Thyroid cancer (0.5%)
Fung Eb, et al. 2016		- Low bone mass: 60%–-85% of adults - Growth deficiency - Diabetes
Finianos A, et al. 2018		- Incidence of HCC: 1.02% - Risk factors for the development of HCC: iron overload and viral hepatitis with or without cirrhosis. - Recommendation of screening patients with: - Liver iron concentration (LIC) measurement by means of magnetic resonance imaging (MRI) - Liver ultrasound - HCC in thalassemia risk factors: hepatitis B, cirrhosis and iron overload. - Nontransferrin-bound free iron (NTBFI) and ferritin are associated with impaired immunity by impairing lymphocyte proliferation and tumoricidal activity of macrophages.

Article	Country	Parameters
		- There have been no randomised trials looking at HCC management interventions in thalassaemic patients.
Pepe A, et al. 2019	Italy	- Cardiac complications: 13.1% of the patients (heart failure, arrhythmias, pulmonary hypertension, myocardial infarction, angina, myo/pericarditis, peripheral vascular disease)
Yang G, et al. 2014	China	- Myocardial iron overload: 33.8% - Severe myocardial iron overload: 12.6% - Left Ventricle Ejection Fraction (LVEF): 64%
De Sanctis V, et al. 2019	Worldwide	- Central hypothyroidism: 4.8% (adults) 0.5 (children and adolescents) - Thyroid cancer: 0.44% (adults) - Latent hypocortisolism: 1.3% (adults) 4.4% (children and adolescents) - GH deficiency: 3.2%(adults) 4.5% (children and adolescents)
Farmakis D, et al. 20 1749	Worldwide	- Chronic haemolysis - Left ventricular dysfunction - Vascular disease - Myocardial ischaemia - Myocarditis - Pulmonary hypertension - Right ventricular dysfunction - Angina - Arrhythmias - Valvular abnormalities
Tartaglione I, et al. 2020	Italy	- Headache: 38.2% - No more common or severe than in the general population.
Mettananda S, et al. 2020	Sri Lanka	- Abnormal emotional: 18% - Conduct: 17% - Hyperactivity: 9% - Peer relationship symptom: 14%

Screening and Prevention

Screening and prenatal diagnosis are used to reduce the number of new thalassaemia births and the related costs. The following table summarises the parameters identified in the different studies:

Table 5. Parameters of prenatal screening and diagnosis

Article	Country	Parameters
Ahmadnezhad E, et al. 20 12	Iran (Islamic Rep. of)	- Cost of providing optimum care - Prevention costs - Cases prevented in 10 years - Savings
Bryan S, et al. 2011	United Kingdom	- Carrier test (woman) - Carrier test (father) - Carrier status counselling (woman only) - Carrier status counselling (couple) - PND - TOP counselling - TOP procedure
Leung Ky, et al. 2004	China	- Screening - Follow-up - Total screening programme - Savings
Yang Y, et al. 2016	China	- Non-invasive PND program - Invasive programme - Savings
Ginsberg G, et al. 1998	Israel	- Lifetime healthcare costs - Lost earnings - Premature mortality - Prevention program - Savings
Koren A, et al. 2014	Israel	- Cost of preventing one affected new-born - Treatment of a patient during 50 years

Curative Therapies

The curative therapies considered were the gene therapy and the HSCT. The average costs reported by the French study were €608,086 for patients treated by gene therapy and €215,571 for patients treated by HSCT. A study conducted in Thailand compared the costs of blood transfusion iron chelation therapy (BT-ICT) treated patients with reduced intensity HSCT (RI-HSCT). The results reported that the costs for BT-ICT were US$ 73,928 and costs for RI-HSCT were US$ 114,000.

Table 6. Parameters of assessing costs of curative therapies

Article	Country	Parameters
John Mj, et al. 2018	India	Hematopoietic Stem Cell Transplantation - Cost incurred after HSCT(MRD) - Cost incurred after HSCT(MUD) - Cost incurred in treating cGVHD Transfusion Chelation - Cost of managing cardiac complications - Cost of managing liver complications - Cost of managing endocrine complications
Coquerelle S, et al. 2019	France	Hospital professionals - Laboratory technician for production - Laboratory quality control technician - Nurse (FDI) - Laboratory engineer - Laboratory quality assurance manager (pharmacist) - Doctor - Laboratory director - Ambulatory medical consultations Tests performed - Haematological analysis - Genetic chimerism Treatments - Cyclosporine - Mycophenolate mofetil (Cellcept)
Sruamsiri R, et al. 2013	Thailand	- Direct medical cost - Direct non-medical cost - Indirect cost

Productivity Loss

There is a lack of data on measuring productivity loss in patients with thalassaemia. Only two abstracts were identified: one providing information about quality of life and one about productivity. The latter showed that 3% of thalassaemia population reported absenteeism, 30% presenteeism, work productivity loss of 38% and 50% of activity impairment.

Table 7. Parameters of assessing loss in work productivity

Article	Country	Parameters
Wong Jhy, et al. 2019	Malaysia	- Lifetime healthcare cost - Lifetime patient and family healthcare expenditure - Total lifetime transfusion dependent thalassaemia cost
Shah F, et al. 2019	United Kingdom	- EQ-5D-3L utility scores - EQ-5D-3L VAS scores - WPAI (%) - TranQoL - TranQoL domain scores

The components that contribute to the estimation of the cost of thalassaemia were defined taking into account the results of the literature review, as outlined further above. The most common parameters found for the different countries were selected to be included in a generic cost model and then validated by the team's medical experts.

Generic Cost-of-Illness Model

Following the targeted Literature Review, the team created a Generic Cost-of-Illness (CoI) Model (henceforth "the Model") on Microsoft Excel that would apply to all settings, whether local or national. The parameters identified were grouped and categorised to render the Model user friendly. The following seven tabs were created, the content of which will be analysed further below:

1. **AFFECTED POPULATION**
   - 1.1 Transfusion-Dependent Thalassaemias (TDT)
   - 1.2 Non-Transfusion-Dependent Thalassaemias (NTDT)

2. **MEDICAL CARE COSTS (OUTPATIENT SERVICES)**
   - 2.1 Blood Transfusion Services
   - 2.2 Pharmaceutical Drugs
   - 2.2.1 Iron Chelators
   - 2.2.2 Commonly Used Pharmaceutical Drugs
   - 2.2.3 Other Pharmaceutical Drugs
   - 2.3 Disposables
   - 2.4 Iron Load Monitoring
   - 2.5 Disease progression / Treatment-related testing
   - 2.6 Laboratory Testing
   - 2.7 Medical Consultations / Multidisciplinary Care
   - 2.8 Infection Management
     - i. Other Costs
     - ii. Indirect Costs / Productivity Loss
     - iii. Prevention Costs
     - iv. Summary of Results
     - v. References

3. **PILOTING**
   To verify that the Model is indeed comprehensive and useful for patient advocates and governments, the team applied data from two countries: the United Kingdom and Iran (Islamic Rep. of). The completed Model was then shared with TIF experts in both countries for validation purposes. No further modification or change was suggested.

RESULTS

The Generic COI Model

The Model is TIF's contribution in global patient advocacy, as the estimation of the annual costs of thalassaemia treatment and care will allow evidence-based policymaking in all countries affected with thalassaemia across the world. The Model consists of seven tabs with different colours to differentiate which need to be completed by the users. Tabs in **GREY** are informative; tabs in **GREEN** and **BLUE** need data input from the user; the tab in **RED** automatically calculates results and the last tab provides in **GREY** provides a space to note down data sources and other reference documents.

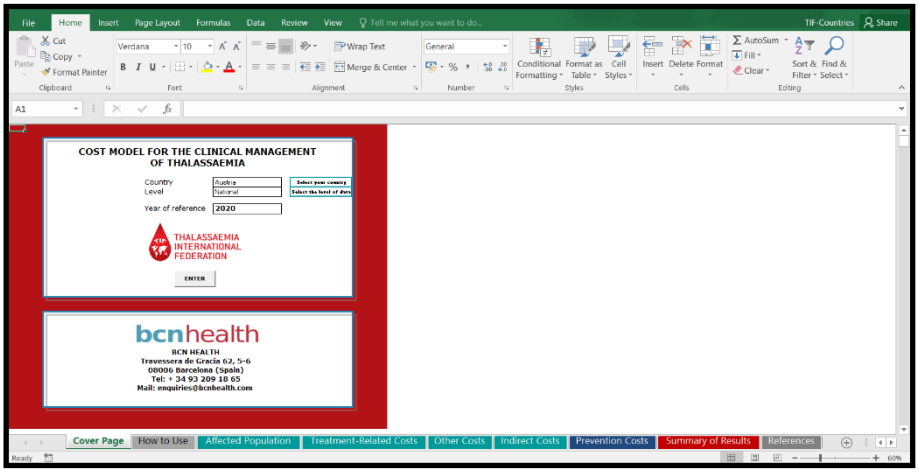


Figure 2. The CoI Model in Microsoft Excel

The Cover Page allows the user to select the country through a drop-down menu, the level of data, whether local, regional or national and the year of reference, as shown below:

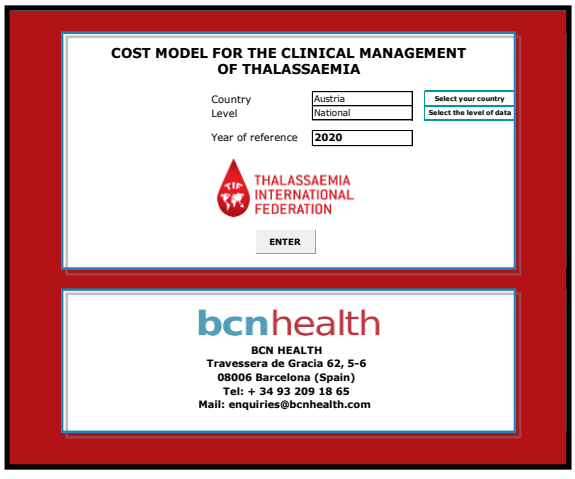


Figure 3. The CoI Model's Cover Page

The How-to-Use tab provides key information on the Model's content and the type of data needed to complete it:

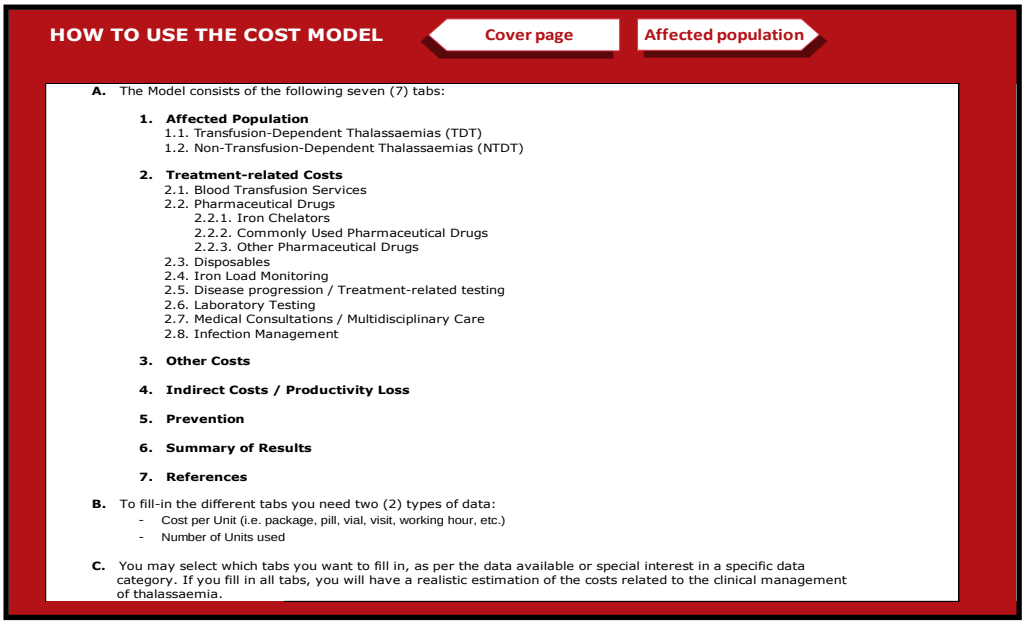


Figure 4. How to use the Cost Model

In the next tab, entitled "1. Affected Population", the user needs to introduce the number of transfusion- or non-transfusion-dependent thalassaemia patients taken into account for the estimation of costs. The Model uses the sum of the two values entered for calculation purposes:

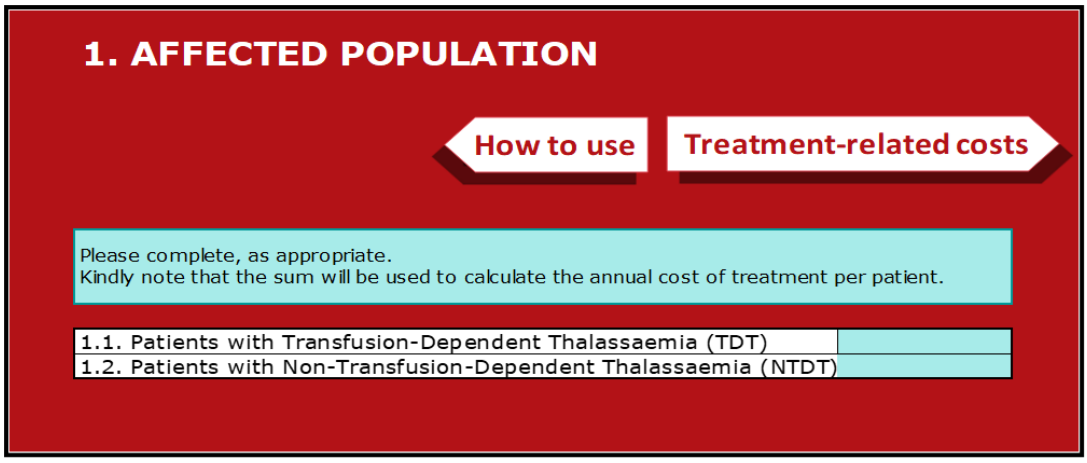


Figure 5. Affected population

Next, under "2. Treatment-related Costs", the user needs to fill in two different columns, one dedicated to costs (per unit, visit, package, etc.) and one dedicated to quantities used in a year. All data entered in the second column needs to be annual. To calculate the total cost per year per parameter, the Model multiplies the cost per unit (Column 1) with the corresponding quantities (Column 2). There is no need to fill in all parameters, as different parameters apply in each country. The Model lists all parameters that need to be present for the provision of optimal health care services to patients.

2. TREATMENT-RELATED COSTS

Affected population | Other costs

Please complete all highlighted /coloured cells, as appropriate.

NB:
- To calculate personnel costs, please insert a **median salary / wage** (monthly or annual) under "Cost per Unit".
- Please use information that is available and reliable in your setting.

2.1. Blood Transfusion Services	Cost per Unit	No of Units Used (per Annum)	Total Cost
2.1.1. ABO, Rh compatibility kits			0
2.1.2. Cross-matching donor/recipient			0
2.1.3. Red cell transfusion - Component separation			0
2.1.4. Pre-storage filtration			0
2.1.5. Bedside filtration			0
2.1.6. Washed red blood cells (e.g. cost of saline)			0
2.1.7. Test for TTIs (HCV, HBV, HIV, syphilis et al) - Serological (blood donor)			0
2.1.8. Test for TTIs (HCV, HBV, HIV, syphilis et al) - NAT testing (blood donor)			0
2.1.9. Transportation			0
2.1.10. Test for other TTIs (e.g. malaria, etc)			0
2.1.11. Storage (Addition of nutrients and additive solutions)			0
2.1.12. Personnel costs			0
2.1.13. Other [...]			0
2.1.14. Other [...]			0
TOTAL			0

2.2. Pharmaceutical Drugs	Cost per Package	No of Packages Used (Per Annum)	Total Cost
2.2.1. Iron Chelators			
2.2.1.1. Deferoxamine			
Deferoxamine (Desferal®) 500 mg			0
Deferoxamine (Desferal®) 2 g			0
Deferoxamine (generic) 500 mg			0
Deferoxamine (generic) 2 g			0
2.2.1.2. Deferiprone			
Deferiprone (Ferriprox®) 500 mg			0
Deferiprone (Ferriprox®) 1000 mg			0
Deferiprone (Ferriprox®) Oral Solution 100 mg/mL			0
Deferiprone (generic) 500 mg			0
Deferiprone (generic) 1000 mg			0
2.2.1.3. Deferasirox			
Deferasirox (Exjade® / Asunra®) 125 mg			0
Deferasirox (Exjade® / Asunra®) 250 mg			0
Deferasirox (Exjade® / Asunra®) 500 mg			0
Deferasirox New Formulation (EMA / Jadenu® FDA) 90 mg			0
Deferasirox New Formulation (EMA / Jadenu® FDA) 180 mg			0
Deferasirox New Formulation (EMA / Jadenu® FDA) 360 mg			0
Deferasirox (generic - e.g. Mylan, Accord)			0
Other [...]			0
Other [...]			0
TOTAL			0

2.2.2. Commonly Used Pharmaceutical Drugs			
Insulin			0
Folic acid			0
Hormone replacement therapy (HRT)			0
Calcium / Vitamin D			0
Other [...]			0
Other [...]			0
TOTAL			0

2.2.3. Other Pharmaceutical Drugs (e.g. Management of Complications)			
Other [...]			0
Other [...]			0
Other [...]			0
Other [...]			0
TOTAL			0

Figure 6. Treatment-related costs

2.3. Disposables	Cost per Unit	No of Units Used (Per Annum)	Total Cost
Infusion pump - Mechanical (deferoxamine-related)			0
Infusion pump - Balloon (deferoxamine-related) *Ongoing Costs			0
Infusion pump - Electronic (deferoxamine-related)			0
Injection kit (e.g. thalasets)			0
Other [...]			0
Other [...]			0
TOTAL			**0**

2.4. Iron Load Monitoring	Cost per Test	No of Tests Permormed (Per Annum)	Total Cost
MRI (Heart Measurements)			0
MRI (Liver Measurements)			0
Serum ferritin			0
Other [...]			0
Other [...]			0
TOTAL			**0**

2.5. Disease progression / Treatment-related testing	Cost per Unit	No of Tests Done	Total Cost
DEXA			0
Abdominal Ultrasound			0
Fibroscan			0
Echocardiogram			0
Other [...]			0
Other [...]			0
TOTAL			**0**

2.6. Laboratory Testing	Cost per Test	No of Tests Performed (Per Annum)	Total Cost
Complete Blood Count			0
Liver Function Tests (LFT)			0
Renal Function Tests (RFT)			0
T3, free T4, TSH			0
Parathyroid Hormone (PTH)			0
Calcium, ionized calcium			0
Fasting glucose			0
Glucose tolerance test			0
IGF-1, IGF BP-3			0
LH-ICMA			0
FSH			0
Estradiol			0
Vitamin D			0
Zinc test			0
Test for TTIs (HCV, HBV, HIV, syphilis et al) - Serological (Patients)			0
Test for TTIs (HCV, HBV, HIV, syphilis et al) - NAT testing (Patients)			0
Other [...]			0
Other [...]			0
TOTAL			**0**

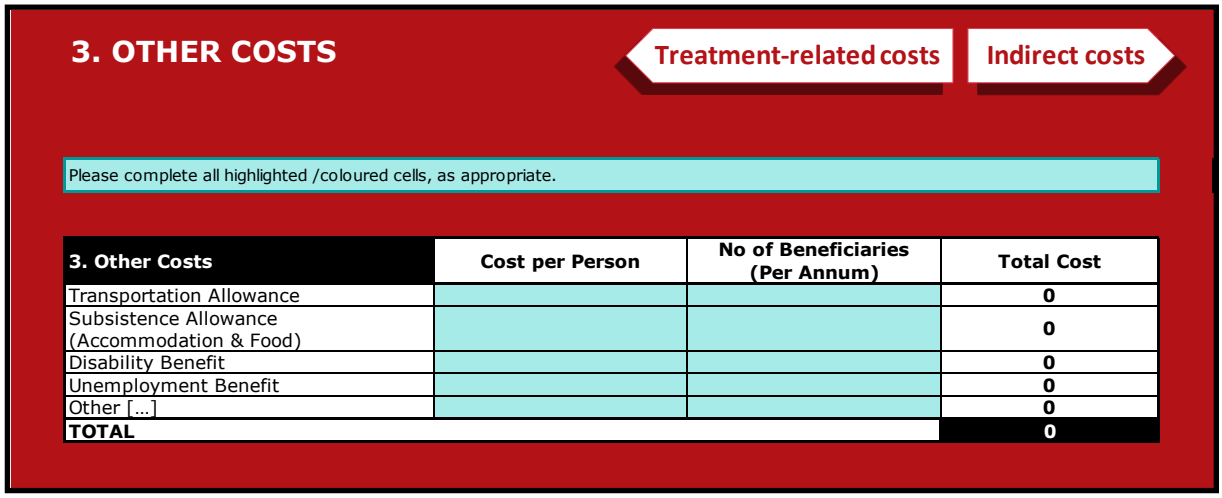
2.7. Medical Consultations / Multidisciplinary Care	Cost per Visit	No of Visits (Per Annum)	Total Cost
Cardiologist			0
Opthalmologist			0
ENT (Audiometry)			0
Endocrinologist			0
Hepatologist			0
Other [...]			0
TOTAL			**0**

2.8. Infection Management	Cost per Pill or Package	No of Pills or Packages Used (Per Annum)	Total Cost
Prophylactic antibiotics (e.g. penicillin)			0
Vaccine (Streptococcus pneumoniae)			0
Vaccine (Haemophilus influenzae type B)			0
Vaccine (Neisseria meningitides)			0
Vaccine (Influenza virus)			0
Other [...]			0
Other [...]			0
TOTAL			**0**

TOTAL TREATMENT-RELATED COSTS	0

Figure 7. Treatment-related costs (contd.)

Next, under "Other Costs", the user needs to enter data not directly related to treatment, such as any state-provided benefits or allowances:



3. OTHER COSTS

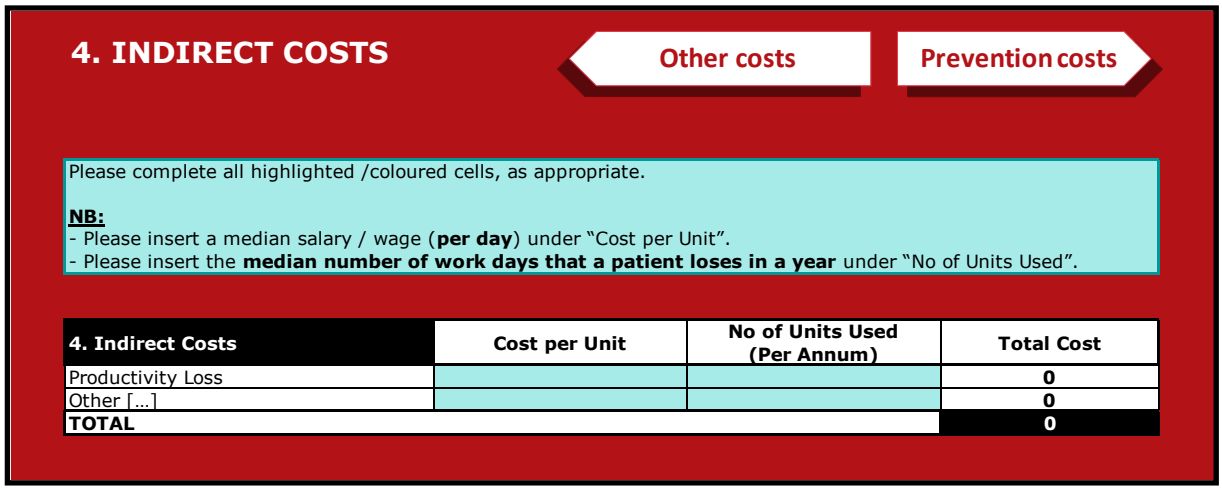
Treatment-related costs | Indirect costs

Please complete all highlighted /coloured cells, as appropriate.

3. Other Costs	Cost per Person	No of Beneficiaries (Per Annum)	Total Cost
Transportation Allowance			0
Subsistence Allowance (Accommodation & Food)			0
Disability Benefit			0
Unemployment Benefit			0
Other [...]			0
TOTAL			0

Figure 8. Other costs

Data on productivity loss needs to be entered under "4. Indirect Costs". To calculate productivity loss, the user needs to introduce under "Cost per Unit" the cost of a day of work and under "No of Units Used (per Annum)", the mean number of days that a patient with thalassaemia is absent from work. To calculate the total costs linked to productivity loss, the number of patients is multiplied by the number of days missed and then by the cost of a day of work.



4. INDIRECT COSTS

Other costs | Prevention costs

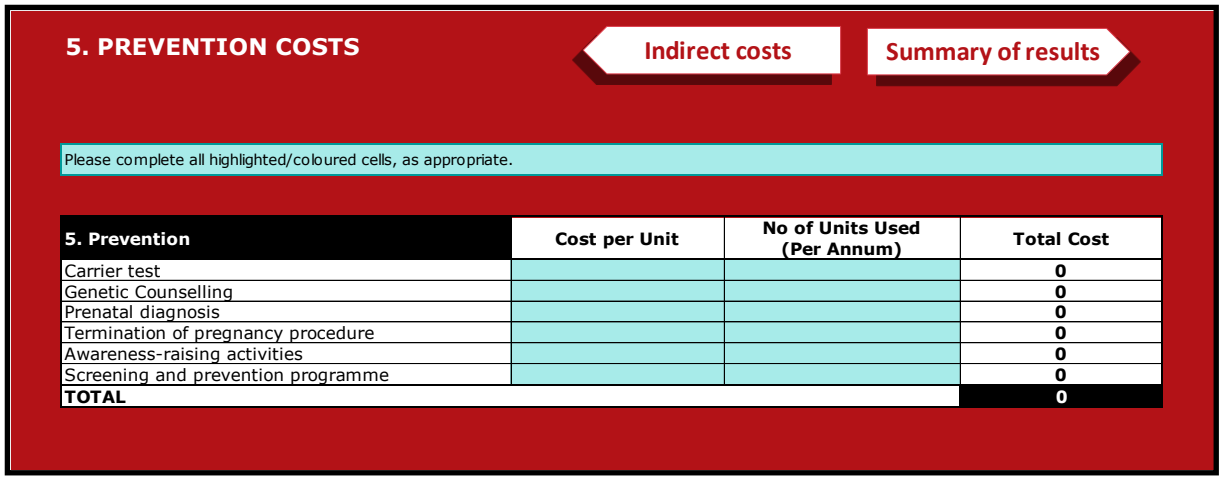
Please complete all highlighted /coloured cells, as appropriate.

NB:
- Please insert a median salary / wage (**per day**) under "Cost per Unit".
- Please insert the **median number of work days that a patient loses in a year** under "No of Units Used".

4. Indirect Costs	Cost per Unit	No of Units Used (Per Annum)	Total Cost
Productivity Loss			0
Other [...]			0
TOTAL			0

Figure 9. Indirect costs (productivity loss)

The CoI Model may also estimate the cost of prevention, under "5. Prevention Costs". This amount is not considered part of the cost of treatment calculations.



5. Prevention	Cost per Unit	No of Units Used (Per Annum)	Total Cost
Carrier test			0
Genetic Counselling			0
Prenatal diagnosis			0
Termination of pregnancy procedure			0
Awareness-raising activities			0
Screening and prevention programme			0
TOTAL			0

Figure 8. Prevention costs

The results are automatically calculated under "6. Summary of Results". Besides the totals for each parameter of costs, the user may also view an estimation of the annual cost of treatment per patient.

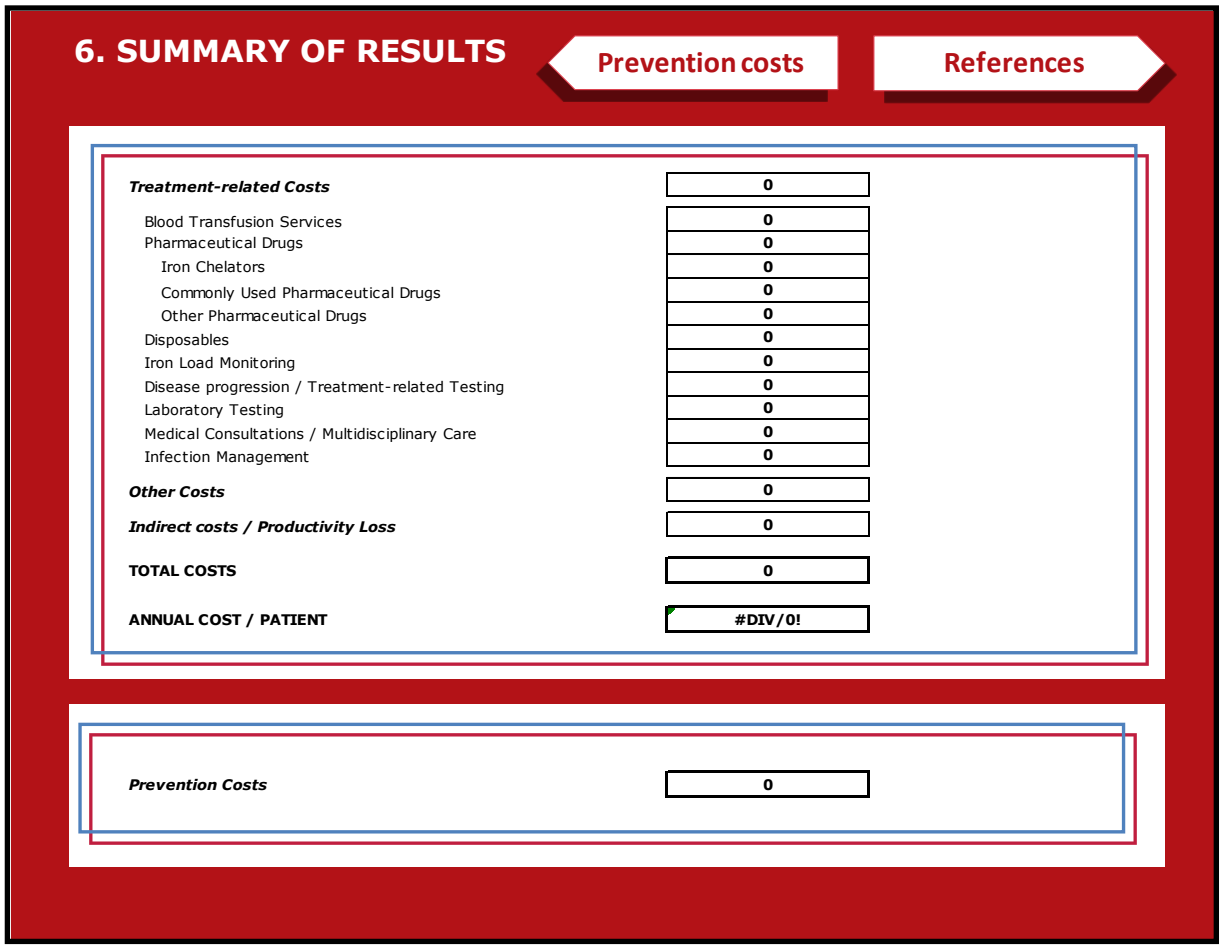


Figure 9. Summary of results

A last tab ("7. References) has been created to enter any reference documents or other details useful to the user or justifying the data used:

7. REFERENCES
(This can be used to create a table summarizing unit costs)

Summary of results | Cover page

Blood Transfusion Services	Unit Cost	Source
ABO, Rh compatibility kits	0.00	
Cross-matching donor/recipient	0.00	
Red cell transfusion - Component separation	0.00	
Pre-storage filtration	0.00	
Bedside filtration	0.00	
Washed red cells	0.00	
Test for TTIs (HCV, HBV, HIV, syphilis et al) 1. Serological	0.00	
Test for TTIs (HCV, HBV, HIV, syphilis et al) 2. NAT testing	0.00	
Transportation	0.00	
Test for other TTIs (e.g. malaria, etc)	0.00	
Storage (Addition of nutrients and additive solutions)	0.00	
Personnel costs	0.00	
Other [...]	0.00	
Other [...]	0.00	

Figure 10. References

Application of Data/Piloting

To verify that the Model is functional, the team entered published data found in literature for the United Kingdom and Iran (Islamic Rep. of). The two countries were selected based on geography and the amount of published data available. In the United Kingdom, the annual cost of thalassaemia care amounts to 81,796 GBP, while in Iran (Islamic Rep. of) this is estimated at 18,777 IRR (equal to 9,951.20 GBP).

	UK *in Pound Sterling (GBP)*	IRAN *in Iranian Rial (IRR)*
Affected Population	**1564**	**18777**
Treatment-related Costs	**109,230,917**	**247,596,902**
Blood Transfusion Services	**14,440,287**	**48,111,744**
Pharmaceutical Drugs	**53,617,048**	**182,991,254**
Iron Chelators	**53,617,048**	**182,991,254**
Commonly Used Pharmaceutical Drugs	**0**	**0**
Other Pharmaceutical Drugs	**0**	**0**
Disposables	**15,155,160**	**7,809,354**
Iron Load Monitoring	**0**	**0**
Disease progression / Treatment-related Testing	**0**	**0**
Laboratory Testing	**328,158**	**2,056,269**
Medical Consultations / Multidisciplinary Care	**18,705,440**	**6,628,281**
Infection Management	**6,984,824**	**0**
Other Costs	**0**	**3,049,573**
Indirect costs / Productivity Loss	**18,697,902**	**7,672,658**
TOTAL COSTS	**127,928,819**	**258,319,132**
ANNUAL COST / PATIENT	**81,796**	**13,757**

Figure 11. Comparative table – United Kingdom and Iran (Islamic Rep. of)

CONCLUSION

TIF proceeded to the development of a CoI Model for Thalassaemia to quantify the burden of thalassaemia on health systems and allow decision makers to translate the adverse effects of thalassaemia into monetary terms, the universal language of decision makers and the policy arena. **TIF anticipates that these estimates will be used to: i) define the magnitude of the disease in financial terms in different settings; ii) justify intervention programmes; iii) assist in the allocation of funding and resources on thalassaemia management; iv) provide a basis for policy and planning with regard to prevention and control; and v) provide an economic framework for the evaluation of existing thalassaemia control and management programmes** [39].

Such a model, simple in inception but powerful in execution, may be used to help affected countries include thalassaemia in policy planning and address the imminent research gap on this specific topic. It may also be used by health authorities, health partnerships and consortia both nationally and transnationally to identify needs and address them. Moreover, it is a powerful advocacy tool for the implementation of prevention strategies and the reduction of new affected births.

In comparative studies, it important to take into account a set of parameters that may affect the cost of the disease, including labour costs, equipment and supplies costs and the availability thereof. The comparison between the United Kingdom and Iran (Islamic Rep. of) may help a policy expert identify what works well and what not in each setting and what corrective measures need to be taken.

Such a model may also be of added value in any discussion on the introduction of new medicines or therapies into national essential or advanced medicines' lists and formularies. An estimation of the annual cost for the treatment of thalassaemia per patient is expected to allow governments to determine each product's or therapy's return in investment and thus the provision of access to such products or therapies would be informed and evidence-based, for the benefit of the patient.

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ANNEX

General Cost of Thalassaemia Therapy

SUMMARY TABLE OF COST OF TREATMENT ESTIMATES ACROSS COUNTRIES:			
Country	Total healthcare expenditure	Prices period	Reference
UK	$720,201 $14400/year	2013/14 prices over 50 years	Weidlich D et al. Transfusion. 2016
India	$1135/year	Poor state coverage 38% of family income	Moirangthem A, Phadke SR. Indian J Pediatr. 2018
India	$ 981/year direct costs		Uchil A et al Natl Med J India. 2023
Bangladesh	$1632-3960 direct costs/year according to age	No state coverage	Hossain et al. Orphanet Journal of Rare Diseases (2017)
Pakistan	$720 direct + indirect/p/y	Mixed Free gov but many private services	Safdar S, Pak J Med Res 2017
Vietnam	$426.7 (±294.0)/year	2019-2021.	Nhac-Vu HT et al. PLoS One. 2023
UAE	$35,713/year/patient direct	2019	Alshamsi S et al. BMC Health Serv Res. 2022
USA	$137,125/year	2010-2019. 33-times higher total annual costs than matched controls	Udeze C, et al. J Med Econ. 2023
USA	$128,062/patient/year	>18 years old	Weiss M et al Am J Hematol. 2019
China	mean annual direct medical cost estimated at $13,478 (95% CI: $11,538-$15,713)	September 1, 2021, and January 31, 2022,	Zhen X et al. Orphanet J Rare Dis. 2023
Sri Lanka	$2601/year of which $ 2092 direct costs and $509 overhead costs	Not fully supported Catastrophic expenditure for families	Reed-Embleton H et al. BMC Pediatr. 2020
Malaysia	$561,208 provider + $45,458 family =$606,665 lifetime cost $10,499 annual cost	2018/2019 prices mean age 17.3 years (SD = 10.6)	Shafie AA et al Orphanet J Rare Dis. 2021
Iran	$8321.8 per year medical $ 136 532 lifetime		Esmaeilzadeh F et al. Int J Health Policy Manag. 2022
Indonesia	$ 30,000/person/year		Atmakusuma TD et al. Int J of General Medicine 2021
Greece	€ 32,064/year for the whole period; reached 32564 in 2011	2009-2011	Geitona M, et al. 2014
Israel	$1971380 lifetime	Over 50 years	Koren A et al 2014
Turkey	$ 14,360 annual direct		Antmen A 2017
Thailand	$ 1434/TD p/year ($950 for the total patients mostly TI and children)	2005 prices	Riewpaiboon A et al BMC 2010
Italy	TM Direct: €31883 NTDT Direct: € 31183	2017 adult patients	Angelucci E et al. Blood 2017
Jordan	$4458.9 subsidised $7196.4 unsubsidised	Direct and indirect Age range 1-67, mean 18.55 years	Alabbadi I et al. Jord J Pharmaceutical Sciences 2022

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SELECTED ABSTRACTS

General Cost of Thalassaemia Therapy

Am J Hematol 2019 May;94(5):E129-E132.
doi: 10.1002/ajh.25429. Epub 2019 Feb 23.

Clinical and economic burden of regularly transfused adult patients with β-thalassemia in the United States: A retrospective cohort study using payer claims

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This retrospective matched-cohort study was performed using payer claims to analyze the clinical and economic burden of current disease management for regularly transfused patients with β-thalassemia in the United States over a 1-year period. Briefly, regularly transfused patients with β-thalassemia and matched non-thalassemia

controls were identified in the Truven Health MarketScan Research Databases between January 1, 2011 and September 30, 2015. A total of 50 regularly transfused patients were identified and matched to 250 controls. Average total healthcare costs per patient per year (PPPY) for regularly transfused patients were USD 128,062 versus USD 5438 for matched controls (P < 0.0001). Both treatment-related and medication costs were also significantly higher for patients with β-thalassemia versus matched controls (P < 0.0001). The major components of these costs for regularly transfused patients were iron chelation therapy (USD 61,974) and red blood cell (RBC) transfusion costs (USD 39,723). MRI and bone mineral density screenings cost an average of USD 2382 PPPY. The majority of costs in the "Other" category were laboratory tests (USD 16,209) and other medications (USD 4538). Overall, our study shows that ongoing comprehensive treatment of regularly transfused patients with β-thalassemia poses a substantial clinical and economic burden. Transfusion-dependent patients with β-thalassemia had significantly higher healthcare costs and significantly higher utilization of healthcare resources versus matched controls. Both treatment-related and medication costs were also significantly higher for regularly transfused patients versus matched controls and were primarily driven by RBC transfusion and iron chelation therapy costs.

Transfusion 2016 May;56(5):1038-45.
doi: 10.1111/trf.13513. Epub 2016 Apr 4.

Healthcare costs and outcomes of managing β-thalassemia major over 50 years in the United Kingdom

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Background: The objective was to estimate the incidence-based costs of treating β-thalassemia major (BTM) to the United Kingdom's National Health Service (NHS) over the first 50 years of a patient's life in terms of healthcare resource use and corresponding costs and the associated health outcomes.

Study design and methods: This was a modeling study based on information obtained from a systematic review of published literature and clinicians involved in managing BTM in the United Kingdom. A state transition model was constructed depicting the management of BTM over a period of 50 years. The model was used to estimate the incidence-based health economic impact that BTM imposes on the NHS and patients' health status in terms of the number of quality-adjusted life-years (QALYs) over 50 years.

Results: The expected probability of survival at 50 years is 0.63. Of patients who survive, 33% are expected to be without any complication and the other 67% are expected to experience at least one complication. Patients' health status over this period was estimated to be a mean of 11.5 discounted QALYs per patient. Total healthcare expenditure attributable to managing BTM was estimated to be £483,454 ($720,201) at 2013/14 prices over 50 years. The cost of managing BTM could be potentially reduced by up to 37% if one in two patients had a bone marrow transplant, with an ensuing improvement in health-related quality of life.

Conclusion: This analysis provides the best estimate available of NHS resource use and costs with which to inform policy and budgetary decisions pertaining to this rare disease.

Indian J Pediatr 2018 Feb;85(2):102-107.
doi: 10.1007/s12098-017-2478-y. Epub 2017 Nov 9.

Socio-demographic Profile and Economic Burden of Treatment of Transfusion Dependent Thalassemia (India)

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Objective: To compile the socio-demographic profile and estimate the economic burden of transfusion dependent thalassemia.

Methods: This cross-sectional descriptive study was conducted at a tertiary care hospital in north India. Transfusion dependent thalassemia patients on regular blood transfusion for at least a year were selected. Thalassemia diagnosis was based on

HPLC and/or mutation analysis results. Clinical and laboratory parameters were collected from electronic health records. Information regarding socio-economic profile and costs incurred, including indirect costs were collected by interviewing patients' guardians. The data was analyzed as a whole cohort and also in subgroups based on age.

Results: The data of 261 patients with a median age of 127 mo was collected. The median age at diagnosis was 9.8 mo. The total treatment expenses of a patient per year ranged from US$ 629 (INR 41,514) to US$ 2300 (INR 151,800), in the different age groups, at an average of US$ 1135 (INR 74,948). More than half (53%) of this was spent on medications. On an average, 38.8% of the family income was spent on the treatment of a thalassemia patient annually. Only 19 of 262 cases had an average pre-BT Hb ≥ 9 g/dl and serum ferritin ≤1500 ng/dl.

Conclusions: The treatment for transfusion dependent thalassemia is costly and mostly borne by the families in India. This study provides a realistic magnitude of this burden and will be useful in planning a thalassemia management program at the state or national level.

BMC Pediatr. 2020 May 27;20(1):257.
doi: 10.1186/s12887-020-02160-3.

A cost-of-illness analysis of β-Thalassaemia major in children in Sri Lanka - experience from a tertiary level teaching hospital

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Background: Sri Lanka has a high prevalence of β-thalassaemia major. Clinical management is complex and long-term and includes regular blood transfusion and iron chelation therapy. The economic burden of β-thalassaemia for the Sri Lankan healthcare system and households is currently unknown.

Methods: A prevalence-based, cost-of-illness study was conducted on the Thalassaemia Unit, Department of Paediatrics, Kandy Teaching Hospital, Sri Lanka. Data were collected from clinical records, consultations with the head of the blood bank and a consultant paediatrician directly involved with the care of patients, alongside structured interviews with families to gather data on the personal costs incurred such as those for travel.

Results: Thirty-four children aged 2-17 years with transfusion dependent thalassaemia major and their parent/guardian were included in the study. The total average cost per patient year to the hospital was $US 2601 of which $US 2092 were direct costs and $US 509 were overhead costs. Mean household expenditure was $US 206 per year with food and transport per transfusion ($US 7.57 and $US 4.26 respectively) being the highest cost items. Nine (26.5%) families experienced catastrophic levels of healthcare expenditure (> 10% of income) in the care of their affected child. The poorest households were the most likely to experience such levels of expenditure.

Conclusions: β-thalassaemia major poses a significant economic burden on health services and the families of affected children in Sri Lanka. Greater support is needed for the high proportion of families that suffer catastrophic out-of-pocket costs.

J Res Health Sci Summer 2016;16(3):111-115.

Economic Burden of Thalassemia Major in Iran, 2015

Firooz Esmaeilzadeh[1], Azita Azarkeivan[2], Sara Emamgholipour[3], Ali Akbari Sari[3], Mehdi Yaseri[4], Batoul Ahmadi[3], Mohtasham Ghaffari[5]

Background: Major Thalassemia is an autosomal recessive disease with complications, mortality and serious pathology. Today, the life expectancy of patients with major thalassemia has increased along with therapeutic advances. Therefore, they need lifelong care, and caring for them would incur many costs. Being aware of the patients' costs can be effective for controlling and managing the costs

and providing efficient treatments for the care of patients. Hence, this study was conducted to estimate the economic burden of the patients with major thalassemia.

Methods: Totally, 198 patients with major thalassemia were randomly selected from among the patients with major thalassemia in Tehran, Iran in 2015. The economic burden of the patients was estimated from a social perspective and through a bottom-up, prevalence-based approach.

Results: The average annual cost per patient was estimated $ 8321.8 regardless of the cost of lost welfare. Of this amount, $ 7286.8 was related to direct medical costs, $ 461.4 to direct non-medical costs, and $ 573.5 to indirect costs. In addition, the annual cost per patient was estimated $ 1360.5 due to the distress caused by the disease CONCLUSIONS: Considering the high costs of the treatment of patients with major thalassemia, adopting new policies to reduce the costs that patients have to pay seems necessary. In addition, making new decisions regarding thalassemia screening, even with higher costs than the usual screening costs, can be useful since the costs of treatment are high.

Health Policy 2015 Feb;119(2):239-43. doi: 10.1016/j.healthpol.2014.12.011. Epub 2014 Dec 19.

The effects of economic sanctions on disease specific clinical outcomes of patients with thalassemia and hemophilia in Iran

Mehran Karimi [1], Sezaneh Haghpanah [2]

Background: The sanctions applied by both the USA and the EU against Iran do not formally ban the exports of medicines; in practice, however, patients are experiencing great difficulty in securing the treatment. This article documents the impact of international sanctions on patients with thalassemia and hemophilia in southern Iran.

Methods: This survey examined the specific effects of external sanctions on the access of patients to their treatment between 2009 and 2012 from the point of view of patients with thalassemia (n=69) and congenital coagulation disorders (n=40) as well as related physicians (n=20). Also, clinical manifestation and laboratory data of patients were compared in the same period.

Results: Access to deferoxamine and Exjade as iron chelators in patients with thalasseamia, respectively, declined by almost 70% and half over this period. In addition, access to lyophilized coagulation factor VIII concentrate in hemophilia A dramatically dropped from 96.7% in 2009 to 3.3% in 2012. The clinical results showed a significant deterioration of arthropathy (P<0.001) in hemophiliac patients and a significant increase in serum ferritin levels in thalassemia patients (P=0.036).

Conclusion: Sanctions had significant effect on public health on patients with thalassemia and hemophilia.

BMC Health Services Research (2022) 22:304. https://doi.org/10.1186/s12913-022-07663-6

Healthcare resource utilization and direct costs of transfusion-dependent thalassemia patients in Dubai, United Arab Emirates: retrospective cost-of-illness study. Shaikha Alshamsi1, Samer Hamidi and Hacer Ozgen Narci

For this study, a retrospective prevalence-based cost-of-illness analysis based on the UAE healthcare system and patient perspectives was conducted among patients with TDT treated at the Dubai Thalassemia Center in 2019. Information regarding healthcare resource utilization and direct medical costs was collected from the billing system connected to the electronic medical record system. Patients and their families were interviewed for direct non-medical cost estimations.

A total of 255 patients with TDT were included in the study. The mean annual direct medical cost was estimated at $35,713 with the main driver of the medical cost for the participants being iron chelation therapy (59.8%), followed by blood transfusions, (26.1% of the total direct medical costs). The mean annual direct non-medical costs was ($605). In conclusion TDT poses a substantial economic burden on the healthcare system,

patients, and their families. Greater support is essential for families that suffer catastrophic out-of-pocket expenses.

In another study, the same authors found that TDT was associated with substantial productivity loss and indirect costs in the UAE. This amounted to 4691USD, out of which absenteeism contributed $2812 and presenteeism contributed USD 1879, whereas the annual total productivity loss cost at unpaid work was $1104. The annual mean total indirect cost for paid and unpaid work was $5795. [Alshamsi S, Hamidi S, Ozgen Narci H. Productivity Loss and Associated Costs Among Patients with Transfusion-Dependent Thalassemia in Dubai, United Arab Emirates. Clinicoecon Outcomes Res. 2021 Sep 29;13:853-862.doi: 10.2147/CEOR.S334724. PMID: 34616164]

Cost of specific therapeutic modalities

Blood transfusions

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The cost of blood: a study of the total cost of red blood cell transfusion in patients with β-thalassemia using time-driven activity-based costing

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Background: To accurately quantify the costs of care for patients with transfusion-dependent thalassemia (TDT), and to evaluate cost-effectiveness of new treatments, data are required on costs of regular red blood cell (RBC) transfusions. However, no previous studies have evaluated the costs of RBC transfusion specifically in chronically transfused patients.

Methods and materials: We performed a time-driven activity-based costing (TDABC) study using a health care provider perspective. This was performed over a 1-month period, capturing every step of the transfusion pathway for patients with TDT at a designated provider of specialist thalassemia services in Australia. Detailed process maps were developed to outline treatments and processes directly related to transfusion. For each process map, detailed data collection, including timing of activities, was performed multiple times to account for variation in practice. Costs associated with RBC transfusion were broken down into fixed, process, and RBC procurement costs.

Results: The total per-unit cost was US$695.59 (95% confidence interval, US$694.45-US$696.73). Approximately 40% of cost was for procurement of the RBC unit, with process costs accounting for 55%. The single largest contributor to process costs was attributed to iron chelation medication (approximately 80%). In sensitivity analyses, seniority of staff, time to perform processes, and probabilities of different processes occurring did not substantially influence the RBC transfusion cost; however the number of RBC units per transfusion episode did impact the overall cost per RBC unit.

Conclusions: We found significant costs associated with RBC transfusion for TDT, with the product cost contributing less than one-half of the total cost.

Transfus Med 2019 Feb;29(1):33-40.
doi: 10.1111/tme.12523. Epub 2018 Apr 10.

A time-driven, activity-based costing methodology for determining the costs of red blood cell transfusion in patients with beta thalassaemia major

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Objectives: To describe the methodology to estimate the total cost of administration of a single unit of red blood cells (RBC) in adults with beta

thalassaemia major in an Australian specialist haemoglobinopathy centre.

Background: Beta thalassaemia major is a genetic disorder of haemoglobin associated with multiple end-organ complications and typically requiring lifelong RBC transfusion therapy. New therapeutic agents are becoming available based on advances in understanding of the disorder and its consequences. Assessment of the true total cost of transfusion, incorporating both product and activity costs, is required in order to evaluate the benefits and costs of these new therapies.

Methods: We describe the bottom-up, time-driven, activity-based costing methodology used to develop process maps to provide a step-by-step outline of the entire transfusion pathway. Detailed flowcharts for each process are described. Direct observations and timing of the process maps document all activities, resources, staff, equipment and consumables in detail. The analysis will include costs associated with performing these processes, including resources and consumables. Sensitivity analyses will be performed to determine the impact of different staffing levels, timings and probabilities associated with performing different tasks.

Results: Thirty-one process maps have been developed, with over 600 individual activities requiring multiple timings. These will be used for future detailed cost analyses.

Conclusions: Detailed process maps using bottom-up, time-driven, activity-based costing for determining the cost of RBC transfusion in thalassaemia major have been developed. These could be adapted for wider use to understand and compare the costs and complexities of transfusion in other settings.

Hematology 2018 Aug;23(7):417-422. doi: 10.1080/10245332.2017.1404262. Epub 2017 Nov 21.

Blood transfusion versus hydroxyurea in beta-thalassemia in Iran: a cost-effectiveness study

Ramin Ravangard [1 2], Zahra Mirzaei [1 3], Khosro Keshavarz [2], Sezaneh Haghpanah [4], Mehran Karimi [4]

Introduction: Thalassemia intermedia is a type of anemia which has several treatments modalities. We aimed to study the cost effectiveness of two treatments, including blood transfusion and hydroxyurea, in patients with beta-thalassemia intermedia in south of Iran referred to a referral center affiliated to Iran, Shiraz University of Medical Sciences in 2015.

Materials and methods: This was a cost-effectiveness study which was conducted on 122 patients with beta-thalassemia intermedia. The indicator of effectiveness in this study was the reduction of growth disorder (normal BMI). Data analysis was done using SPSS 21, Excel 2010 and Treeage 2011. Finally, the one-way sensitivity analysis was performed to determine the robustness of the results.

Results: The average annual costs of blood transfusion and the use of hydroxyurea in 2015 were 20733.27 purchasing power parity (PPP)$ and 7040.29 PPP$, respectively. The effectiveness of blood transfusion was57.4% while in hydroxyurea group was 60.7%.

Conclusion: The results showed that the cost effectiveness of using hydroxyurea was more than that of blood transfusion. Therefore, it is recommended that the use of hydroxyurea in the treatment of patients with beta-thalassemia intermedia would become the first priority, and more basic and supplementary insurance coverage for treating such patients using hydroxyurea should be considered.

Iron chelation

Medicine (Baltimore) 2020 Jul 10;99(28):e20949. doi: 10.1097/MD.0000000000020949.

Cost-utility of new film-coated tablet formulation of deferasirox vs deferoxamine among major beta-thalassemia patients in Iran

Parisa Saiyarsarai [1] [2], Elahe Khorasani [1], Hasti Photogeraphy [1], Mohsen Ghaffari Darab [3], Meysam Seyedifar [4]

Objectives: Thalassemia is a hereditary disease, which caused economic burden in developing countries. This study evaluated the cost utility of new formulation of deferasirox (Jadenu) vs deferoxamine (Desferal) among B-Thalassemia-major patients from payer perspective in Iran.

Methods: An economic-evaluation through Markov model was performed. A systematic review was conducted in order to evaluate the clinical effectiveness of comparators. Because of chelating therapy is weight-dependent, patients were assumed to be 2 years-old at initiation in first and 18 years-old in second scenario, and model was estimated lifetime costs and utilities. Costs were calculated to the Iran healthcare system through payer perspective and measured effectiveness using quality-adjusted life years (QALYs). One-way sensitivity analysis and budget impact analysis was also employed.

Results: The 381 studies were retrieved from systematic searching through databases. After eliminating duplicate and irrelevant studies, 2 studies selected for evaluating the effectiveness. Jadenu was associated with an incremental cost-effectiveness ratio (ICER) of 1470.6 and 2544.7 US$ vs Desferal in first and second scenario respectively. The estimated ICER for Jadenu compared to generic deferoxamine was 2837.0 and 6924.1 US$ for first and second scenario respectively. For all scenarios Jadenu is presumed as cost-effective option based on calculated ICER which was lower than 1 gross domestic product per capita in Iran. Sensitivity analysis showed that different parameters except discount rate and indirect cost did not have impact on results. Based on budget impact analysis the estimated cost for patients using Desferal (based on the market share of brand) was 44,021,478 US$ in 3 years vs 42,452,606 US$ in replacing 33% of brand market share with Jadenu. This replacement corresponded to the cost saving of almost 1,568,872 US$ for the payers in 3 years. The calculated cost of using generic deferoxamine in all patients was 68,948,392 US$. The increase in the cost of using Jadenu for 10% of all patients in this scenario would be 934,427 US$ (1.36%) US$ at the first year.

Conclusions: Based on this analysis, film-coated deferasirox appeared to be cost-effective treatment in comparison with Desferal for managing child and adult chronic iron overload in B-thalassemia major patients of Iran.

Mediterr J Hematol Infect Dis 2020 May 1;12(1):e2020029.
doi: 10.4084/MJHID.2020.029. eCollection 2020.

Cost-Utility Analysis of four Chelation Regimens for β-thalassemia Major: a Chinese Perspective

Jialian Li [1], Peng Wang [1], Xue Li [1], Qiaoyu Wang [1], Jiayou Zhang [2], Yong Lin [1]

Objective: The Iron chelation is essential to prevent iron overload damage of vital organs, like heart, liver, and endocrine glands, in patients with transfusion-dependent thalassemia. The most common chelation regimens for β-thalassemia major (β-TM) patients used in China are a combination therapy of deferoxamine and deferiprone (DFO+DFP), deferoxamine (DFO) monotherapy, deferiprone (DFP) monotherapy and deferasirox (DFX) monotherapy. Such patients use iron chelators their whole lives, resulting in enormous treatment costs. This study analyses the cost-utility of these four regimens from the Chinese healthcare system perspective.

Methods: A Markov decision model was used over a 5-year time horizon and was populated using clinical data from a systematic literature review. We obtained utility data from local and previous research. Costs were estimated using Chinese national sources.

Results: From the base-case analysis results, DFP was the most cost-effective chelation regimen, followed by DFO, DFX, and DFO+DFP. DFP had 97.32%, 99.43%, and 58.04% likelihood of being cost-effective versus DFX, DFO+DFP, and DFO, respectively, at a payment threshold of 193,932.00 CNY/QALY (QALY, quality-adjusted life-year).

Conclusions: DFP was the most cost-effective chelation regimen for β-TM patients, followed by

DFO, DFX, and DFO+DFP. Using DFP as the primary treatment regimen may potentially result in cost-savings and QALY gains for the Chinese healthcare system. To increase these benefits, the Chinese government should take measures to lower DFX and DFO drug costs, and Chinese clinicians should choose the cheaper DFX and DFO, increase the utility of DFO+DFP and reduce mortality and morbidity of DFP. Changes in influential parameters easily affect the results of DFX versus DFO+DFP and of DFP versus DFO; clinicians should focus on such parameters and adjust the regimens accordingly.

Keywords: Cost-Utility analysis; Deferasirox; Deferiprone; Deferoxamine; β-thalassemia major.

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doi: 10.1007/s40261-017-0496-1.

Cost-Utility Analysis of Three Iron Chelators Used in Monotherapy for the Treatment of Chronic Iron Overload in β-Thalassaemia Major Patients: An Italian Perspective

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Purpose: Deferiprone (DFP), deferasirox (DFX) and deferoxamine (DFO) are used in thalassaemia major (TM) patients to treat chronic iron overload. We evaluated the cost-effectiveness of DFP, compared with DFX and DFO monotherapy, from an Italian healthcare system perspective.

Methods: A Markov model was used over a time horizon of 5 years. Italian-specific cost data were combined with Italian efficacy data. Costs and quality-adjusted life years (QALYs) were calculated for each treatment, with cost-effectiveness expressed as cost per QALY.

Results: In all scenarios modelled, DFP was the dominant treatment strategy. Sensitivity analyses showed that DFP dominated the other treatments with a >99% likelihood of being cost-effective against DFX and DFO at a willingness to pay threshold of €20,000 per QALY.

Conclusions: DFP was the dominant and most cost-effective treatment for managing chronic iron overload in TM patients. Its use can result in substantial cost savings for the Italian healthcare system.

J Med Econ 2016;19(3):292-303.
doi: 10.3111/13696998.2015.1117979. Epub 2015 Nov 30.

Adherence to iron chelation therapy and associated healthcare resource utilization and costs in Medicaid patients with sickle cell disease and thalassemia

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Background: Sub-optimal patient adherence to iron chelation therapy (ICT) may impact patient outcomes and increase cost of care. This study evaluated the economic burden of ICT non-adherence in patients with sickle cell disease (SCD) or thalassemia.

Methods: Patients with SCD or thalassemia were identified from six state Medicaid programs (1997-2013). Adherence was estimated using the medication possession ratio (MPR) of ≥0.80. All-cause and disease-specific resource utilization per-patient-per-month (PPPM) was assessed and compared between adherent and non-adherent patients using adjusted incidence rate ratios (aIRR). All-cause and disease-specific healthcare costs were computed using mean cost PPPM. Regression models adjusting for baseline characteristics were used to compare adherent and non-adherent patients.

Results: A total of 728 eligible patients treated with ICT in the SCD cohort, 461 (63%) adherent, and 218 in the thalassemia cohort, 137 (63%) adherent, were included in this study. In SCD patients, the adjusted rate of all-cause outpatient visits PPPM was higher in adherent patients vs non-adherent

patients (aIRR [95% CI]: 1.05 [1.01-1.08], p < 0.0001). Conversely, adherent patients incurred fewer all-cause inpatients visits (0.87 [0.81-0.94], p < 0.001) and ER visits (0.86 [0.78-0.93], p < 0.001). Similar trends were observed in SCD-related resource utilization rates and in thalassemia patients. Total all-cause costs were similar between adherent and non-adherent patients, but inpatient costs (adjusted cost difference = -$1530 PPPM, p = 0.0360) were lower in adherent patients.

Conclusion: Patients adherent to ICT had less acute care need and lower inpatient costs than non-adherent patients, although they had more outpatient visits. Improved adherence may be linked to better disease monitoring and has the potential to avoid important downstream costs associated with acute care visits and reduce the financial burden on health programs and managed care plans treating SCD and thalassemia patients.

Pharmacoeconomics 2013 Sep;31(9):807-22.
doi: 10.1007/s40273-013-0076-z.

Cost-utility analysis of deferiprone for the treatment of β-thalassaemia patients with chronic iron overload: a UK perspective

Anthony Bentley [1], Samantha Gillard, Michael Spino, John Connelly, Fernando Tricta

Background: Patients with β-thalassaemia major experience chronic iron overload due to regular blood transfusions. Chronic iron overload can be treated using iron-chelating therapies such as desferrioxamine (DFO), deferiprone (DFP) and deferasirox (DFX) monotherapy, or DFO-DFP combination therapy.

Objectives: This study evaluated the relative cost effectiveness of these regimens over a 5-year timeframe from a UK National Health Service (NHS) perspective, including personal and social services.

Methods: A Markov model was constructed to evaluate the cost effectiveness of the treatment regimens over 5 years. Based on published randomized controlled trial evidence, it was assumed that all four treatment regimens had a comparable effect on serum ferritin concentration (SFC) and liver iron concentration (LIC), and that DFP was more effective for reducing cardiac morbidity and mortality. Published utility scores for route of administration were used, with subcutaneously administered DFO assumed to incur a greater quality of life (QoL) burden than the oral chelators DFP and DFX. Healthcare resource use, drug costs (2010/2011 costs), and utilities associated with adverse events were also considered, with the effect of varying all parameters assessed in sensitivity analysis. Incremental costs and quality-adjusted life-years (QALYs) were calculated for each treatment, with cost effectiveness expressed as incremental cost per QALY. Assumptions that DFP conferred no cardiac morbidity, mortality, or **morbidity and mortality benefit were also explored in scenario analysis.**

Results: DFP was the dominant strategy in all scenarios modelled, providing greater QALY gains at a lower cost. Sensitivity analysis showed that DFP dominated all other treatments unless the QoL burden associated with the route of administration was greater for DFP than for DFO, which is unlikely to be the case. DFP had >99 % likelihood of being cost effective against all comparators at a willingness-to-pay threshold of £20,000 per QALY.

Conclusions: In this analysis, DFP appeared to be the most cost-effective treatment available for managing chronic iron overload in β-thalassaemia patients. Use of DFP in these patients could therefore result in substantial cost savings.

Transfusion 2013 Aug;53(8):1722-9.
doi: 10.1111/trf.12024. Epub 2012 Dec 12.

Cost-utility analysis of oral deferasirox versus infusional deferoxamine in transfusion-dependent β-thalassemia patients

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Background: Deferasirox (DFX) is a novel iron chelator that has been shown to have similar

efficacy and safety compared with deferoxamine (DFO) in patients with β-thalassemia. The aim of this study was to determine the cost utility of DFX versus DFO in β-thalassemia major patients from Iran's society perspective.

Study design and methods: A Markov model has been developed to determine lifetime cost and quality-adjusted life-years (QALYs) of patients. To estimate the annual cost of each method, a cross-sectional study was conducted among two groups of patients who received DFO and DFX (n = 100 and n = 45, respectively). Also a time trade-off method was used to estimate the utility of two strategies. Finally a one-way and probabilistic sensitivity analysis was conducted to examine the strength of the results.

Results: Our base-case analysis showed that estimated total lifetime costs per patient for DFX and DFO were 47,029 international dollar ($Int) and $Int143,522, respectively, while the estimated total discounted QALYs per person were 12.28 and 7.76, respectively. Calculated incremental cost-effectiveness ratio showed that DSX is a dominant therapy and its estimated lifetime net monetary benefit was $Int273,528.

Conclusion: We conclude that the use of DFX instead of DFO represents a cost-effective use of resources for treatment of iron overload in patients with β-thalassemia from Iran's society perspective.

J Formos Med Assoc 2013 Apr;112(4):221-9.
doi: 10.1016/j.jfma.2011.08.020. Epub 2012 Apr 30.

A pharmaco-economic evaluation of deferasirox for treating patients with iron overload caused by transfusion-dependent thalassemia in Taiwan

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Background/purpose: The newly available iron chelator deferasirox (Exjade, Novartis) is expected to provide better long-term clinical outcomes and improved quality of life for patients with thalassemia than its predecessor, deferoxamine (Desferal, Novartis), because of its oral tablet form.

Methods: We used the Markov model to estimate total additional lifetime costs and quality-adjusted life years (QALYs) gained with deferasirox versus deferoxamine in patients with transfusion-dependent thalassemia. Patients were assumed to be 2 years of age at initiation of chelation therapy. Clinical outcomes in terms of morbidity and mortality from associated complications and life expectancy for the study population were estimated using the databases of the Bureau of National Health Insurance and the Health and Vital Statistics of Taiwan. Treatment costs were based on analyses of health insurance claims for patients with transfusion-dependent thalassemia. Utilities in terms of quality of life were also included in the model. The incremental cost-utility ratio of deferasirox versus deferoxamine was defined by the ratio of the difference in expected lifetime costs to the difference in QALYs. One-way sensitivity analyses were performed to examine the robustness of the results to key assumptions.

Results: Patients treated with deferasirox are expected to experience a lower incidence of associated complications and obtain 2.3 QALYs (discounted) at an additional lifetime cost of US$36,291 per patient (US$15,596 per QALY). Sensitivity analyses showed that the unit drug cost of deferasirox had the greatest impact on the incremental cost-utility ratio. In addition, the incremental cost-utility ratio will increase by delaying the starting age (2 years of age in our study) of chelation therapy.

Conclusion: Compared with infusional deferoxamine, oral deferasirox improved clinical outcomes and quality of life in terms of iron chelation in transfusion-dependent patients with thalassemia at a reasonable cost from a healthcare perspective.

Clin Drug Investig 2012 Dec;32(12):805-15.
doi: 10.1007/s40261-012-0008-2.

Lifetime cost-utility analyses of deferasirox in beta-thalassaemia patients with chronic iron overload: a UK perspective

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Background and objectives: Regular blood transfusions for beta-thalassaemia patients lead to the accumulation of iron deposits in the body. In order to remove such deposits, iron chelation therapy is required. Subcutaneously administered deferoxamine has been the gold standard chelation therapy for over 40 years. Deferasirox is a newer chelation therapy that is taken orally once daily. The objective of this study was to estimate the long-term costs and quality-adjusted life-years (QALYs) associated with deferoxamine and deferasirox in a cohort of transfusion-dependent beta-thalassaemia patients from a UK health service perspective.

Methods: A 50-year annual cycle state transition model comprised three core health states: alive without cardiac complications, alive with cardiac complications, and dead, as well as representing other chronic complications of iron overload: diabetes, hypogonadism, hypoparathyroidism and hypothyroidism. The model was calibrated to identify sets of convergent input parameter values that predicted observed overall survival by mean lifetime compliance with chelation therapy. A pivotal non-inferiority trial informed the main estimates of the effectiveness of deferasirox, which were applied to the calibrated model. Using cost values for the year 2011, costs and utilities were summed over patients' lifetimes to estimate lifetime costs and QALY gains.

Results: Mean lifetime treatment costs for patients receiving deferoxamine were £70,000 higher than deferasirox. Drug acquisition costs were £100,000 higher for deferasirox, but administration costs associated with deferoxamine were £170,000 higher. Higher compliance associated with oral deferasirox administration led to fewer complications. Combined with the quality-of-life effects of an oral mode of administration, an average gain of 4.85 QALYs for deferasirox was estimated. In the base case, deferasirox dominates deferoxamine, i.e., costs less and patients gain more QALYs. The key parameter is the proportion of deferoxamine patients using balloon infusers. Sensitivity analyses showed that even when the proportion of patients using balloon infusers is decreased from 79 to 25 %, the incremental cost per QALY gained remains well under £20,000.

Conclusion: Higher drug acquisition costs for deferasirox are offset by the avoidance of infusion-related equipment costs. Combined with health benefits derived from an oral mode of administration and improved compliance, deferasirox has a high probability of being a cost-effective intervention compared with deferoxamine.

Clin Drug Investig 2011;31(7):493-505.
doi: 10.2165/11587120-000000000-00000.

Iron-chelating therapies in a transfusion-dependent thalassaemia population in Thailand: a cost-effectiveness study

Nantasit Luangasanatip[1], Nathorn Chaiyakunapruk, Nilawan Upakdee, Peerapon Wong

Background and objective: β-Thalassaemia is a major public health problem in Thailand. Use of appropriate iron-chelating agents could prevent thalassaemia-related complications, which are costly to the healthcare system. This study aimed to evaluate the cost effectiveness of deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX) in Thai transfusion-dependent β-thalassaemia patients from the societal perspective.

Methods: A Markov model was used to project the life-time costs and outcomes represented as quality-adjusted life-years (QALYs). Data on the clinical efficacy and safety of all therapeutic options were obtained from a systematic review and clinical trials. Transition probabilities were derived from published studies. Costs were obtained from the Thai Drug and Medical Supply Information Center, Thai national reimbursement rate information and other Thai literature sources. A discount rate of 3% was used. Incremental cost-effectiveness ratios (ICERs) were presented as year 2009 values. A base-case analysis was performed for thalassaemia patients requiring regular blood transfusion therapy, while a separate analysis was performed for patients requiring low (i.e. symptom-dependent, less frequent) blood transfusion therapy. A series of sensitivity analysis and cost-effectiveness acceptability curves were constructed.

Results: Compared with DFO, using DFP was dominant with lifetime cost savings of $US91 117. Comparing DFX with DFO, the incremental cost was $US522 863 and incremental QALY was 5.77 with an ICER of $US90 648 per QALY. When compared with DFP, the ICER of DFX was $US106 445 per QALY. A cost-effectiveness analysis curve showed the probability of DFX being cost effective was 0% when compared with either DFO or DFP, based on the cost-effectiveness cut-off value of $US2902 per QALY. When compared with DFP, DFX was cost effective only if the DFX cost was as low as $US1.68 per 250 mg tablet. The results of the analysis in patients requiring low blood transfusion therapy were not different from those of the base-case analysis.

Conclusions: Our findings suggest that using DFP is cost saving when compared with conventional therapy, while using DFX is not cost effective compared with either DFO or DFP in Thai patients with transfusion-dependent β-thalassaemia. Policy-makers and clinicians may consider using such information in their decision-making process in Thailand.

Pharmacoeconomics 2011 Jun;29(6):461-74.
doi: 10.2165/11589250-000000000-00000.

Pharmacoeconomic considerations in treating iron overload in patients with β-thalassaemia, sickle cell disease and myelodysplastic syndromes in the US: a literature review

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Patients with β-thalassaemia, sickle cell disease (SCD) and myelodysplastic syndromes (MDS) require chronic blood transfusions, which can lead to iron overload and substantial morbidity and mortality. To reduce the excess iron and its deleterious effects, available iron chelation therapy (ICT) in the US includes oral deferasirox or infusional deferoxamine (DFO). The aim of this study was to review and synthesize the available pharmacoeconomic evidence on ICT in patients with β-thalassaemia, SCD and MDS in the US. We systematically identified and reviewed pharmacoeconomic studies of ICT in patients with β-thalassaemia, SCD and MDS that either were published in MEDLINE-indexed, English-language journals from 1999 to 2009, or appeared in medical society websites and scientific meeting abstracts. We assessed available cost-of-illness, cost-of-treatment, cost-consequence, cost-effectiveness, utility and patient-satisfaction studies. The majority of the 20 identified studies assessed cost of treatment, mainly focusing on acquisition and administration costs of ICTs. Gaps in the published literature include current data on direct medical costs for patients with MDS, direct medical costs associated with complications of iron overload, direct non-medical costs, indirect costs and patient utilities. Different underlying model assumptions, methodologies and comparators were found in the cost-effectiveness studies, which yielded a broad range of incremental cost-effectiveness ratios for different ICTs. Comprehensive cost-of-illness studies are needed to address data gaps in the published literature regarding the economic burden of iron overload. Comparative-effectiveness studies that evaluate clinical, economic and patient-reported outcomes would help the medical community to better understand the value of different ICTs.

Pharmacoeconomics 2007;25(4):329-42.
doi: 10.2165/00019053-200725040-00005.

Cost effectiveness of once-daily oral chelation therapy with deferasirox versus infusional deferoxamine in transfusion-dependent thalassaemia patients: US healthcare system perspective

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Background: Deferasirox is a recently approved once-daily oral iron chelator that has been shown to reduce liver iron concentrations and serum ferritin levels to a similar extent as infusional deferoxamine.

Objective: To determine the cost effectiveness of deferasirox versus deferoxamine in patients with

beta-thalassaemia major from a US healthcare system perspective.

Methods: A Markov model was used to estimate the total additional lifetime costs and QALYs gained with deferasirox versus deferoxamine in patients with beta-thalassaemia major and chronic iron overload from blood transfusions. Patients were assumed to be 3 years of age at initiation of chelation therapy and to receive prescribed dosages of deferasirox and deferoxamine that have been shown to be similarly effective in such patients. Compliance with chelation therapy and probabilities of iron overload-related cardiac disease and death by degree of compliance were estimated using data from published studies. Costs ($US, year 2006 values) of deferoxamine administration and iron overload-related cardiac disease were based on analyses of health insurance claims of transfusion-dependent thalassaemia patients. Utilities were based on a study of patient preferences for oral versus infusional chelation therapy, as well as published literature. Probabilistic and deterministic sensitivity analyses were employed to examine the robustness of the results to key assumptions.

Results: Deferasirox resulted in a gain of 4.5 QALYs per patient at an additional expected lifetime cost of $US126,018 per patient; the cost per QALY gained was $US28,255. The cost effectiveness of deferasirox versus deferoxamine was sensitive to the estimated costs of deferoxamine administration and the quality-of-life benefit associated with oral versus infusional therapy. Cost effectiveness was also relatively sensitive to the equivalent daily dose of deferasirox, and the unit costs of deferasirox and deferoxamine, and was more favourable in younger patients.

Conclusion: Results of this analysis of the cost effectiveness of oral deferasirox versus infusional deferoxamine suggest that deferasirox is a cost effective iron chelator from a US healthcare perspective.

Expert Rev Pharmacoecon Outcomes Res 2014 Oct;14(5):651-60. doi: 10.1586/14737167.2014.927314. Epub 2014 Jun 11.

Cost-utility of chelators in transfusion-dependent β-thalassemia major patients: a review of the pharmacoeconomic literature

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In the inherited hematologic disorder β-thalassemia major, patients receive regular, lifelong blood transfusions, which carry excess iron that the body is unable to eliminate. Chelation therapy (deferoxamine, deferiprone, deferasirox or deferoxamine-deferiprone combination) is required to reduce iron accumulation in target organs and the associated morbidity and mortality. Each chelation regimen has a distinct safety/efficacy profile and particular costs associated with its use. This review aims to provide an overview of published cost-utility analyses of currently used chelation regimens, and to comment on the potential relevance of their findings in the USA market, where deferiprone has recently been introduced.

Mediterr J Hematol Infect Dis 2019 Jul 1;11(1):e2019036. doi: 10.4084/MJHID.2019.036. eCollection 2019.

Economic Evaluation of Chelation Regimens for β-Thalassemia Major: a Systematic Review

Jialian Li [1], Yong Lin [1], Xue Li [1], Jiayou Zhang [2]

Background: Deferoxamine (DFO) or Deferiprone (DFP) or Deferasirox (DFX) monotherapy and DFO and DFP combination therapy (DFO+DFP) were four commonly implemented now chelation regimens for the iron overloaded of β-thalassemia major. This systematic review aims to determine the cost-effectiveness of four chelation regimens and provide evidence for the rational use of chelation regimens for β-thalassemia major therapy in the clinic.

Methods: A systematic literature search in MEDLINE, EMBASE, the Cochrane Library, China Biology Medicine, China National Knowledge Infrastructure, VIP Data, and WanFang Data was conducted in April 2018. In addition, a manual

search was performed. Two researchers, working independently, selected the papers, extracted the data, and assessed the methodological quality of the included documents. Each included paper was evaluated using a checklist developed by Drummond et al.

Results: The number of records was initially 968, and eight papers met the final eligibility criteria. All the included eight papers were cost-utility analyses, and their methodological quality was fair. In these eight papers, nineteen studies were present. Nine studies of DFX versus DFO had contradictory results. Out of the nineteen studies, three studies of DFX versus DFP established that using DFP was cost-effective. Three studies of DFP versus DFO proved that using DFP was cost-effective. One survey of DFO+DFP versus DFO found that using DFO was cost-effective. One study of DFO+DFP versus DFP found that using DFP was cost-effective. Moreover, there were two studies of DFO+DFP versus DFX, but we cannot be sure which one of two chelation regimens was cost-effective.

Conclusion: In brief, DFP is cost-effective, followed by DFO or DFX, when an iron chelator is to be used alone for β-thalassemia iron overload treatment. All studies that compared DFO+DFP with DFO (or DFP) monotherapy established that the DFO+DFP was not cost-effective. Existing studies about DFO+DFP versus DFX could not prove which one of two chelation regimens was cost-effective. However, due to the low number of DFO+DFP versus DFO (or DFP or DFX) monotherapy studies, more extensive, high-quality research is required for further analysis and confirmation of our findings. Moreover, the cost-effectiveness is not an absolute issue when in different countries (regions) the results are opposite for other countries (regions). As a result, the local/national context had a substantial influence on the results of the pharmacoeconomic evaluation.

Curative therapies: HSCT and Gene therapy

Biol Blood Marrow Transplant 2018 Oct;24(10):2119-2126.
doi: 10.1016/j.bbmt.2018.04.005. Epub 2018 Apr 16.

Cost Effectiveness of Hematopoietic Stem Cell Transplantation Compared with Transfusion Chelation for Treatment of Thalassemia Major

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Hematopoietic stem cell transplantation (HSCT) is the only cure for thalassemia major (TM), which inflicts a significant 1-time cost. Hence, it is important to explore the cost effectiveness of HSCT versus lifelong regular transfusion-chelation (TC) therapy. This study was undertaken to estimate incremental cost per quality-adjusted life-year (QALY) gained with the intervention group HSCT, and the comparator group TC, in TM patients. A combination of decision tree and Markov model was used for analysis. A hospital database, supplemented with a review of published literature, was used to derive input parameters for the model. A lifetime study horizon was used and future costs and consequences were discounted at 3%. Results are presented using societal perspective. Incremental cost per QALY gained with use of HSCT as compared with TC was 64,096 (US$986) in case of matched related donor (MRD) and 1,67,657 (US$2579) in case of a matched unrelated donor transplantation. The probability of MRD transplant to be cost effective at the willingness to pay threshold of Indian per capita gross domestic product is 94%. HSCT is a long-term value for money intervention that is highly cost effective and its long-term clinical and economic benefits outweigh those of TC.

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doi: 10.1089/hum.2018.178. Epub 2019 May 3.

Innovative Curative Treatment of Beta Thalassemia: Cost-Efficacy Analysis of Gene Therapy Versus Allogenic Hematopoietic Stem-Cell Transplantation

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Boquet [5], Stéphane Blanche [6], Semir Benaouadi [6], Thomas Brice [6], Caroline Tuchmann-Durand [5], Jean Antoine Ribeil [6], Elisa Magrin [5], Etienne Lissillour [6], Lise Rochaix [4 8], Marina Cavazzana [5 9 10], Isabelle Durand-Zaleski [1 3 11]

Seventy-five percent of patients with beta thalassemia (β-thalassemia) do not have human leukocyte antigen-matched siblings and until recently had no access to a curative treatment. Gene therapy is a promising treatment that can be proposed to these patients. This study estimates its cost and efficacy. In a monocentric retrospective study and cost-efficacy analysis, this study compared the two-year outcomes and costs of patients with β-thalassemia treated by gene therapy and hematopoietic stem-cell transplantation (HSCT). Grade III and grade IV complications, hospitalizations, and length of stay were extracted from the hospital discharge data. Costs were estimated from hospital accounting information and national cost studies. A total of seven patients with β-thalassemia treated between 2009 and 2016 were included, of whom four received gene therapy. Patients treated by gene therapy were older and had fewer complications and hospital admissions. Infectious complications were three times more frequent for patients treated with HSCT than for gene therapy. Average costs were €608,086 for patients treated by gene therapy and €215,571 for HSCT. The total cost of the vector was 48% of the total cost of gene therapy. Gene therapy as a curative alternative for patients lacking human leukocyte antigen-matched donors was costlier but resulted in fewer complications than HSCT.

BMC Health Serv Res 2013 Feb 5;13:45.
doi: 10.1186/1472-6963-13-45.

Cost utility analysis of reduced intensity hematopoietic stem cell transplantation in adolescence and young adult with severe thalassemia compared to hypertransfusion and iron chelation program

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Background: Hematopoieticic stem cell transplantation is the only therapeutic option that can cure thalassemia disease. Reduced intensity hematopoietic stem cell transplantation (RI-HSCT) has demonstrated a high cure rate with minimal complications compared to other options. Because RI-HSCT is very costly, economic justification for its value is needed. This study aimed to estimate the cost-utility of RI-HSCT compared with blood transfusions combined with iron chelating therapy (BT-ICT) for adolescent and young adult with severe thalassemia in Thailand.

Methods: A Markov model was used to estimate the relevant costs and health outcomes over the patients' lifetimes using a societal perspective. All future costs and outcomes were discounted at a rate of 3% per annum. The efficacy of RI-HSCT was based a clinical trial including a total of 18 thalassemia patients. Utility values were derived directly from all patients using EQ-5D and SF-6D. Primary outcomes of interest were lifetime costs, quality adjusted life-years (QALYs) gained, and the incremental cost-effectiveness ratio (ICER) in US ($) per QALY gained. One-way and probabilistic sensitivity analyses (PSA) were conducted to investigate the effect of parameter uncertainty.

Results: In base case analysis, the RI-HSCT group had a better clinical outcomes and higher lifetime costs. The incremental cost per QALY gained was US $3,236 per QALY. The acceptability curve showed that the probability of RI-HSCT being cost-effective was 71% at the willingness to pay of 1 time of Thai Gross domestic product per capita (GDP per capita), approximately US $4,210 per QALY gained. The most sensitive parameter was utility of severe thalassemia patients without cardiac complication patients.

Conclusion: At a societal willingness to pay of 1 GDP per capita, RI-HSCT was a cost-effective treatment for adolescent and young adult with severe thalassemia in Thailand compared to BT-ICT.

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Economic evaluation of betibeglogene autotemcel (Beti-cel) gene addition therapy in transfusion-dependent β-thalassemia

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Background: Standard of care (SoC) for transfusion-dependent β-thalassemia (TDT) requires lifelong, regular blood transfusions as well as chelation to reduce iron accumulation. Objective: This study investigates the cost-effectiveness of betibeglogene autotemcel ('beti-cel'; LentiGlobin for β-thalassemia) one-time, gene addition therapy compared to lifelong SoC for TDT.

Study design: Microsimulation model simulated the lifetime course of TDT based on a causal sequence in which transfusion requirements determine tissue iron levels, which in turn determine risk of iron overload complications that increase mortality. Clinical trial data informed beti-cel clinical parameters; effects of SoC on iron levels came from real-world studies; iron overload complication rates and mortality were based on published literature. The study was conducted in the USA from the commercial payer perspective. The participants were TDT patients aged 2–50 years.

Results: The model predicts beti-cel adds 3.8 discounted life years (LYs) or 6.9 QALYs versus standard od care. Discounted lifetime costs were $2.28 M for beti-cel ($572,107 if excluding beti-cel cost) and $2.04 M for SoC, with a resulting ICER of $34,833 per QALY gained.

Conclusion: Beti-cel is cost-effective for TDT patients compared to SoC. This is due to longer survival and cost offset of lifelong SoC. Beti-cel has the potential to transform patients' lives and its benefits are shown to be cost-effective or cost-saving in the one-time treatment of TDT.

Cost effectiveness of screening and prevention

Screening and Prenatal diagnosis

Int J Prev Med 2012 Oct;3(10):687-92.

Evaluation and cost analysis of national health policy of thalassaemia screening in west-azerbaijan province of Iran

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Background: Thalassaemia is one of the most common Mendelian disorders in Mediterranean area. Iran has about 26,000 Thalassaemic patients, so it is one of the most affected countries. The aim of this study was to evaluate the screening program and cost analysis of Thalassaemia prevention program in West-Azerbaijan province of Iran.

Methods: This study evaluated the efficacy of Health system's Thalassaemia prevention program with a sensitivity analysis for its costs. The second five years of the program was evaluated. The economic burden of Thalassaemia is determined by the birth prevalence of the affected infants and the cost that is accrued to treat the infected individuals and was compared with the total cost of screening the couples for thalassemia trait.

Results: The average incidence rate of major Thalassaemia was 19.8 per 100,000 live births and mean coverage rate of program was 74%. The rate of canceling the marriage among carrier couples was 53%. Cost analysis showed that the cost of screening and prenatal diagnosis program was much lower than the cost of treatment in potential thalassaemic patients.

Conclusions: The prevention program of Thalassaemia including a premarital and pre-natal screening in west Azerbaijan province is demonstrated to be cost-effective. Taking some actions in order to increase the coverage of pre-marital screening, providing pre-natal diagnosis in private and public sector, complete insurance

coverage for the high-risk couples to perform the investigations more easily, were recommended.

Br J Gen Pract 2011 Oct;61(591):e620-7.
doi: 10.3399/bjgp11X601325.

Screening for sickle cell and thalassaemia in primary care: a cost-effectiveness study

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Background: Haemoglobinopathies, including sickle cell disease and thalassaemia (SCT), are inherited disorders of haemoglobin. Antenatal screening for SCT rarely occurs before 10 weeks of pregnancy.

Aim: To explore the cost-effectiveness of offering SCT screening in a primary care setting, during the pregnancy confirmation visit.

Design and setting: A model-based cost-effectiveness analysis of inner-city areas with a high proportion of residents from ethnic minority groups.

Method: Comparison was made of three SCT screening approaches: 'primary care parallel' (primary care screening with test offered to mother and father together); 'primary care sequential (primary care screening with test offered to the mother and then the father only if the mother is a carrier); and 'midwife care' (sequential screening at the first midwife consultation). The model was populated with data from the SHIFT (Screening for Haemoglobinopathies In First Trimester) trial and other sources.

Results: Compared to midwife care, primary care sequential had a higher NHS cost of £34,000 per 10,000 pregnancies (95% confidence interval [CI] = £15,000 to £51,000) and an increase of 2623 women screened (95% CI: 1359 to 4495), giving a cost per additional woman screened by 10 weeks of £13. Primary care parallel was dominated by primary care sequential, with both higher costs and fewer women screened.

Conclusion: The policy judgement is whether an earlier opportunity for informed reproductive choice has a value of at least £13. Further work is required to understand the value attached to earlier informed reproductive choices.

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Cost-effectiveness of prenatal screening for thalassaemia in Hong Kong

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Objectives: To determine the cost effectiveness of a universal prenatal screening program for alpha- and beta-thalassaemia.

Methods: We retrospectively reviewed our program from 1998 to 2002, and calculated the direct and indirect costs of various components.

Results: 18,936 women were screened at our prenatal clinic and 153 couples were subsequently referred to our Prenatal Diagnostic Centre for counselling and further investigations. In addition, there were 238 tertiary referrals and 157 self-referrals. After investigations, 84 fetuses were at risk of beta-thalassaemia major/beta-E thalassaemia, 19 of them were affected and 18 were aborted. The total expenditure on our program (HK 10.0 million dollars) would be less than the postnatal service costs (HK 40.4 million dollars) for 18 beta-thalassaemia major fetuses if they were born. Of 361 women at risk of carrying a homozygous alphao-thalassaemia fetus, 311 (86.2%) opted for the indirect approach (using serial ultrasound examinations to exclude Hb Bart's disease), and 76 (24.5%) subsequently underwent an invasive test for a definitive diagnosis. The sensitivity and false positive rate of this indirect approach was 100.0% and 2.9% respectively.

Conclusion: It is cost effective to run a universal prenatal screening program in an area where both beta-thalassaemia and alpha-thalassaemia are

prevalent. The indirect approach can effectively avoid an invasive test in unaffected pregnancies.

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A Program on Noninvasive Prenatal Diagnosis of α-Thalassemia in Mainland China: A Cost-Benefit Analysis

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The aim of the present study was to determine the cost effectiveness of a noninvasive prenatal diagnosis (PND) program for α-thalassemia (α-thal) using ultrasound scan. During a 5-year period, 1923 pregnancies at-risk for homozygous α(0)-thal were recruited into the noninvasive PND program. There were 1452 women who avoided invasive testing because of a normal ultrasound scan. The remaining 471 showed abnormal fetal ultrasonographic findings, and invasive testing was recommended. The overall cost of running the noninvasive PND program was US$213,383, while the cost of running the invasive program would have been US$554,810. The total savings were estimated at US$356,499 for women with an unaffected pregnancy with a net saving of US$246 per capita. This study demonstrated that it is cost effective to run a noninvasive PND program for α-thal in an area where the disease is prevalent, and therefore effectively avoiding an invasive test in unaffected pregnancies.

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NESTROFT - A Valuable, Cost Effective Screening Test for Beta Thalassemia Trait in North Indian Punjabi Population

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Background and objectives: Beta-thalassemia continues to be a cause of significant burden to the society, particularly in the poorer developing countries. The objective of the present study was to evaluate the validity of "NESTROFT" (Naked Eye Single Tube Red Cell Osmotic Fragility Test) as a useful screening tool in the diagnosis of beta thalassemia trait.

Material and methods: The present study was conducted on 150 subjects in the department of haematology in a tertiary health care center in north Indian state of Punjab. In group I, 111 cases diagnosed as microcytic hypochromic anaemia were selected. In group II, 39 individuals (the family members of known cases of beta thalassemia major) were selected. Complete haemogram, NESTROFT and HbA2 levels by electrophoresis were done and the results were tabulated and analyzed statistically.

Results: Of the 111 cases in group I, 20 (18%) gave positive results with NESTROFT while 91 cases (82%) tested negative. In group II, out of 39 cases, 30 (76.92%) tested positive with NESTROFT while 9 gave a negative result. In group I, out of 20 NESTROFT positive cases, only 3 had HbA2 levels more than 3.5%. In group II, all the 30 NESTROFT positive cases had HbA2 levels more than 3.5%. The test showed a sensitivity of 100%, specificity of 85.47%, a positive predictive value of 66% and a negative predictive value of 100%.

Conclusion: Thus, NESTROFT is a valuable, cost-effective screening test for beta thalassemia trait and appears to be a valid test in rural setting with financial constraints.

Prevention programmes

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Cost-benefit analysis of a national thalassaemia prevention programme in Israel

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Objective: In Israel (population 5.7 million) there are around 200 known living subjects with

thalassaemia major, of whom around 80% are from the northern district. This study aims at examining the costs and benefits of a national screening programme to prevent thalassaemia in Israel.

Measurements and main results: The lifetime healthcare costs of caring for a person born with thalassaemia major are $284,154. The costs of the home infusion service (33.1%) actually exceed the costs of the chelating agent itself (22.1%). The remaining 44.8% of costs are due to stay in hospital, operations, outpatient visits, laboratory tests, therapists, etc. Lost earnings and premature mortality costs account for a further $51,843 and $141,944 respectively for each case. A national screening programme would cost $900,197 and prevent around 13.4 homozygotes being born, at a cost of $67,369 for each birth prevented. The benefit-cost ratio of the programme to the health services is 4.22:1, which increases to 6.01:1 when a societal perspective is taken. However, around 13.0 homozygote births are still expected to occur, the majority owing to lack of compliance of patients at various stages in the screening process. The addition of a national health education programme for the higher risk non-Jewish population either nationally or in selected regions will incur extra costs, which may be covered by increased benefits as a result of better compliance with the screening programme.

Conclusion: Israel should start to provide a nationwide thalassaemia screening programme as the monetary benefits to society (and even to the health services alone) will exceed the screening programmes costs.

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Prevention of β Thalassemia in Northern Israel - a Cost-Benefit Analysis

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Background: β Thalassemia major is characterized by hemolytic anemia, ineffective erythropoiesis and hemosiderosis. About 4% of the world population carries a Thalassemia gene. Management includes blood transfusions and iron chelation. However, this treatment is costly, and population screening may be significantly more cost beneficial.

Purpose: The purpose of the current study is to analyze the cost of running a prevention program for β Thalassemia in Israel and to compare it to the actual expenses incurred by treating Thalassemia patients.

Methods: THREE COST PARAMETERS WERE ANALYZED AND COMPARED: the prevention program, routine treatment of patients and treatment of complications. An estimation of the expenses needed to treat patients who present with complications was calculated based on our ongoing experience in treating deteriorating patients.

Results and conclusions: The cost of preventing one affected newborn was $63,660 compared to $1,971,380 for treatment of a patient during 50 years (mean annual cost: $39,427). Thus, the prevention of 45 affected newborns over a ten-year period represents a net saving of $88.5 million to the health budget. Even after deducting the cost of the prevention program ($413.795/year), the program still represents a benefit of $76 million over ten years. Each prevented case could pay the screening and prevention program for 4.6 years.