ECONOMIC ANALYSIS OF TRANSFUSION DEPENDENT THALASSAEMIA (TDT) AND DEFERASIROX FCT EFFICIENCY IN MALAYSIA

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by

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LIST OF ABBREVIATIONS

BIA	Budget impact analysis
BIM	Budget impact model
CEA	Cost effectiveness analysis
COI	Cost of illness
DFO	Deferoxamine
DFP	Deferiprone
DFX	Deferasirox
DFX FCT	Deferasirox (film coated tablet)
EE	Economic evaluation
EQ VAS	EuroQol Visual Analogue Scale
EQ-5D-3L	EuroQol
EXJADE	Deferasirox DT (dispersible tablet)
GDP	Gross domestic product
GI	Gastrointestinal
HRQOL	Health related quality of life
ICT	Iron chelation therapy
IOL	Iron overload
KOL	Key opinion leader
LYs	Life years
MATHAS	Malaysian Health Technology Assessment Section
MOH	Ministry of Health
MLR	Multiple linear regression

MTR	Malaysia Thalassaemia Registry
NTBI	Non-transferrin bound iron
QOL	Quality of life
RR	Rapid review
SAE	Serious adverse event
SFL	Serum ferritin level
TDT	Transfusion dependent thalassaemia
TDTHUS	Transfusion dependent thalassaemia health utilisation survey
WHO	World Health Organisation
WTP	Willingness-to-pay

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ANALISA EKONOMI TALASEMIA BERGANTUNG TRANSFUSI DAN KECEKAPAN DEFERASIROX FCT DI MALAYSIA

ABSTRAK

Talassemia merupakan sejenis penyakit keturunan di negara Malaysia di mana rawatan utama adalah transfusi darah dan rawatan penyingkiran zat besi (ICT). *Transfusion dependent thalassaemia* (TDT) merujuk kepada pesakit yang memerlukan transfusi darah > 100mL/kg setiap tahun. Malaysia mempunyai sekurang-kurangnya 4500 pesakit TDT. Namun demikian, data mengenai beban ekonomi dan keberkesaan formulasi baru Deferasirox (Exjade FCT) adalah terhad. Justeru itu, kajian ini bertujuan untuk mengkaji anggaran beban ekonomi, kos kecekapan serta impak bajet Exjade FCT (Desferasirox FCT) di negara Malaysia. Subkajian pertama menganggar jumlah kos rawatan sepanjang hayat pesakit TDT (TC1). Kos rawatan jangka hayat panjang pesakit TDT (TC2) disimulasi dengan menggunakan model *Markov*. Manakala kos perbelanjaan jangka hayat panjang yang ditanggung oleh pesakit TDT dan keluarga pesakit (TC3) dikumpul dengan menggunakan borang kaji selidik dengan kaedah keratan rentas. Kajian dijalankan secara pensampelan berperingkat dua di kalangan 13 pusat talassemia di negara Malaysia. Jumlah kos TDT sepanjang hayat pesakit (TC1) = TC2 +TC3. Subkajian kedua menilai kos kecekapan Exjade FCT berbanding dengan deferoxamine (DFO) yang merupakan rawatan piawai. Kos rawatan jangka hayat panjang pesakit dan hasil kesihatan (*quality adjusted life-years*, QALY) dianggar dengan menggunakan model *Markov*. Data kos diekstrak daripada data tempatan manakala data kualiti hidup dikumpul menggunakan soal selidik EQ-

5D-3L di kalangan pesakit TDT. Subkajian ketiga, menilai impak bajet penukaran tablet Exjade DT (*dispersible tablet*) kepada formulasi baru Exjade FCT (*film coated tablet*) dengan menggunakan model impak bajet. Anggaran jangka hayat pesakit TM adalah 57.7 tahun. Jumlah kos sepanjang hayat diunjurkan sebanyak MYR 2,469,128 bagi seorang pesakit TDT. Kos pembelian ubat serta kos transfusi darah merupakan kos utama. Kos per QALY adalah sebanyak MYR 266.640 apabila membandingkan formulasi Exjade FCT dengan DFO. Manakala, impak bajet menggantikan formulasi Exjade FCT dengan Exjade DT adalah MYR 790,801,301 selama 5 tahun dan penjimatan sebanyak 0.3 peratus dapat dicapai. Rawatan pesakit TDT memerlukan kos yang tinggi dan teleh menggunakan pecahan tinggi dalam belanjawan KKM tahunan yang sedia ada. Walaupun Exjade FCT didapati lebih berkesan, dengan profil keselamatan serta pematuhan rawatan yang lebih tinggi berbanding dari rawatan ICT lain yang sedia ada, namun ianya bukan pilihan terbaik untuk Malaysia disebabkan kos pembelian yang agak tinggi. Melihat dari sudut kemampuan semasa, penggantian rawatan pesakit kepada formulasi baru dijangka dapat menjimatkan bajet dengan mengurangkan kos rawatan komplikasi zat besi berlebihan dan kesan sampingan yang serius.

ECONOMIC ANALYSIS OF TRANSFUSION DEPENDENT THALASSAEMIA (TDT) AND DEFERASIROX FCT EFFICIENCY IN MALAYSIA

ABSTRACT

Thalassaemia is a common genetic disorder in Malaysia where the mainstay of supportive treatment is regular blood transfusion accompanied with iron-chelating therapy (ICT). Transfusion dependent thalassaemia (TDT) is defines as patient who requires blood transfusion >100mL/Kg annually. There are about 4500 patients in Malaysia who are suffering from TDT, however limited data is available on economic burden of this disease and also the efficiency of new formulated Deferasirox (Exjade FCT). Therefore, this study is designed to determine the economic burden of disease, cost effectiveness and budget impact of Exjade FCT in Malaysian context. Substudy one is to estimate the total lifetime cost of a TDT patient. Lifetime healthcare cost (TC2) was simulated using Markov model. Lifetime patient and family healthcare expenditure (TC3) was estimated through cross-sectional health survey approach. Survey was conducted using two-stage sampling method in 13 thalassaemia centers covering all regions in Malaysia. Total lifetime TDT cost (TC1) = TC2 + TC3. Substudy two to evaluate the cost effectiveness of Exjade FCT over the long standing gold standard treatment in TDT – Desferrioxamine. Costs and health outcome (quality adjusted life years) was estimated using Markov model. Costs data was extracted from local database and quality of life data was collected using EQ-5D-3L questionnaire among local thalassaemia patient. Lastly, substudy three, budget impact of converting

the current oral ICT- Deferasirox dispersible tablet (Exjade DT) to Exjade FCT was evaluated using budget impact model. Estimated life-years of a TDT patient was 57.7 years. Total lifetime cost was projected to be MYR 2,469,128 cost of drug acquisition and blood transfusion is the main cost driver. The cost per QALY gained when comparing Exjade FCT over DFO is MYR 266,640. The budget impact of having Exjade FCT in the market is MYR 790,801,301 for five years horizon, which give us a saving of 0.3% in the scenario to replace Exjade DT. TDT is an expensive chronic disease to treat which uptake a substantial fraction of our yearly total MOH budget to treat these patients. Although Exjade FCT has demonstrated improved efficacy, safety and compliance profile compare to all the others available ICTs in the market, it is not a cost effective option in local context due to the high acquisition cost. In terms of affordability, with the current share market of Exjade DT, to switch all patient to the newer formulation, budget saving is expected from management of IOL complications and SAEs.

CHAPTER 1

INTRODUCTION

1.1 Thalassaemia

Thalassaemia is the most common hereditary haemoglobin disorder in Malaysia (Jameela et al., 2011). The disorder was previously lethal from childhood especially for transfusion dependent group but in recent decade, it can be treated as chronic condition (Vassilis Ladis et al., 2011; Taher & Saliba, 2017).

In order to survive beyond childhood, optimum lifelong care is required by adopting good blood transfusion and chelation practices to prevent complications toward the vital organs. Optimum and appropriate treatment will improve patient's quality of life (QOL) by delaying complications to later years of life (Cappellini, Cohen, Porter, Taher, & Viprakasit, 2014; Ministry of Health Malaysia, 2009).

Well treated thalassaemia requires a trained and experienced physician/haematologist and cooperation from patient and family. Patient and family must deal with difficult and lifelong treatment schedule (regular blood transfusion and complex medication regimens) also equipped with strong coping mechanism with difficult lifestyle and social adjustments.

Thalassaemia carrier population was reported to be more than 270 million globally with more than three hundred thousand children born each year with thalassaemia syndrome. Thalassaemia is prevalent in Middle East, Mediterranean countries, Southeast Asian, Southeastern, North and Central Africa. However, due to mass migration of population from high prevalence areas, thalassaemia patients are encountered in many countries including USA, UK and European countries (Cappellini et al., 2014).

1.1.1 Classification of thalassaemia

The term “thalassaemia’ refers to a group of blood diseases characterised by decreased or absent synthesis of normal globin chains. The precise structure of globin chains is crucial to ensure prompt loading of oxygen in the lung alveoli and controlled gradual delivery to body tissues. Types of thalassaemia are named according to the chain whose synthesis is impaired such as α-, β-, γ-, δ -, δβ-, or εγδβ-thalassaemias .

Heterozygotes of either α- and β- thalassaemia are usually asymptomatic with no treatment required. On the other hand, homozygotes and compound heterozygotes of thalassaemia alleles will result towards thalassaemia syndrome. Other traits such as HbE, Hb C or Hb S with β-thalassaemia or Hb Constant Spring (Hb CS) with α-thalassaemia also give rise to various thalassaemia syndromes. The highest carrier frequency of β-thalassaemia is reported in Maldives (18%), Cyprus (14%), Sardinia (10.3%) and Southeast Asia (3-5%). α-thalassaemia on the other hand is commonly found in Southeast Asia and China. The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 globally and 1 in 10,000 in European countries (Cappellini et al., 2014; Galanello & Origa, 2010).

Thalassaemia syndromes can be phenotypically classified into two main groups (Figure 1.1), based on the clinical severity and transfusion requirement (Cappellini et al., 2014; Ministry of Health Malaysia, 2015a).

1. Transfusion dependent thalassaemia (TDT) and
2. Non-transfusion dependent thalassaemia (NTDT)

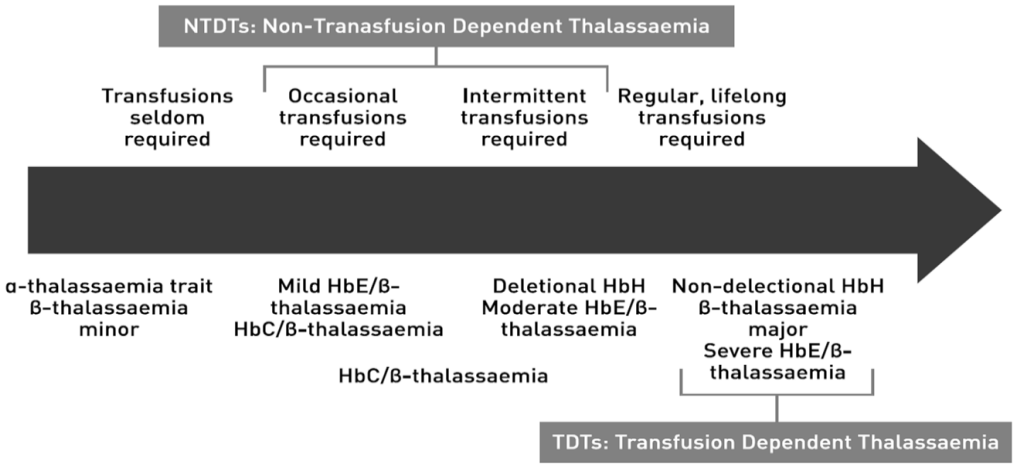

Figure 1.1: Spectrum of thalassaemia syndromes
(Source from Guidelines for Management of Transfusion Dependent Thalassaemia (TDT). 3rd edition. Thalassaemia International Federation. 2014. Page 16)

The TDT patient group (diagnosed with β-thalassaemia major, severe HbE/β-thalassaemia, transfusion dependent HbH diseases) requires regular blood transfusion to survive and without sufficient transfusion support, they would suffer from several complications leading to poor quality of life and short life span (Ministry of Health Malaysia, 2009).

Considering TDT patient group requires delicate and comprehensive medical management and support, they are the main focus of this present study.

1.1.2 Management of transfusion dependent thalassaemia (TDT)

In order to improve patient's quality of life (QOL) and prolong life span, TDT management include blood transfusion and assessment and treatment of iron overload (IOL).

1.1.2(a) Blood transfusion

Early and appropriate transfusion program is the pillar of care for TDT patient. The intention of blood transfusion therapy is to alleviate symptomatic anaemia, suppression of ineffective erythropoiesis, reduce iron loading by inhibition of

gastrointestinal iron absorption, improves growth and development and prolongs life (Galanello & Origa, 2010).

The decision to transfuse is often based on haemoglobin (Hb) concentration when Hb level is consistently (more than 2 weeks) below 6-7 g/dL and clinical characteristics of the child. Clinical characteristics include symptomatic anaemia, faltering of growth and development or clinically significant extramedullary haematopoiesis. When possible, the decision for chronic transfusion should start as early as second or third year of life to minimize the risk of alloimmunization (Chonat & Quinn, 2017; Galanello & Origa, 2010; Viprakasit, Lee-Lee, Chong, Lin, & Khuhapinant, 2009).

The recommended regime for TDT involves lifelong regular blood transfusion, usually administered every two to five weekly to maintain pre-transfusion Hb level of 9-10.5g/dL and post transfusion Hb level of 13-14g/dL. With this Hb target, patients could be prevented from growth impairment, bone deformities, organ damage and allowing normal activity and improves quality of life (Chonat & Quinn, 2017; Ministry of Health Malaysia, 2009).

The amount of blood to be transfused depends upon few factors including weight of patient, haematocrit of blood unit and target increase in Hb level. However, the amount of transfused packed red blood cell (PRBC) should not exceed 15-20 mg/kg/day (Cappellini et al., 2014; Galanello & Origa, 2010). Leukodepleted PRBC should be used to minimize non-haemolytic transfusion reactions and alloimmunization. The filtration can be done either in the blood bank or at the bedside before blood transfusion.

Although chronic transfusion has strong evidences to improve the survival and QOL of TDT individuals, transfusion does comes with unwanted effects which are consequential caused of morbidities and mortality. These include transfusion-transmitted infection primarily hepatitis B and C and iron overload (IOL) complications. (Chonat & Quinn, 2017; Malaysia Heath Technology Assessment Section Ministry of Health Malaysia, 2017).

1.1.2(b) Iron overload assessment

Human does not has effective mechanism to excrete excess iron accumulated from regular blood transfusion which has become major contribution of IOL. Beside transfusion, intestinal absorption of iron also increased in untransfused or under-transfused TDT patients. These non-transferrin bound iron (NTBI) promotes the production of toxic oxygen radicals which will deposit in vital organs such as heart, liver and endocrine glands and can be fatal within 10-20 years if left untreated (Cappellini et al., 2014; Galanello & Origa, 2010).

Monitoring of IOL is mandatory in TDT management. The crucial tests in IOL monitoring are serum ferritin level (SFL) and liver iron concentration (LIC). Measuring ferritin in blood serum is a straightforward method to monitor the levels of total body iron and would give good estimate on the risk of complications secondary to IOL (Birgens & Ljung, 2007; Ministry of Health Malaysia, 2009).

Total liver iron is a constant fraction of total body iron. Therefore LIC has been used as gold standard to reflect body iron load in the past. Values > 3-7 mg Fe/g dry weight for LIC and serum ferritin level of > 1000-1500 ng/mL would reflect the need of iron chelation therapy. MRI is now widely used as non-invasive measurement of iron in liver and heart. Reduction of myocardial iron level (< 20ms) in myocardial

T2* measurement reflects cardiac IOL (Chonat & Quinn, 2017; Ministry of Health Malaysia, 2009).

Iron overloaded patients should be monitored for hypogonadism (growth and sexual development and biochemical markers from age 10 years and above), diabetes mellitus (yearly OGTT), hypothyroidism, hypoparathyrodism and sequential monitoring of left ventricular ejection fraction (LVEF) to identify patient at high risk of developing cardiac failure (Cappellini et al., 2014; Ministry of Health Malaysia, 2009, 2015a).

1.1.2(c) Iron chelation therapy (ICT)

NTBI appears in plasma when plasma iron exceeds the transport capacity of circulating transferrin. As NTBI enters cardiomyocytes, hepatocytes, anterior pituitary cells and pancreatic β cells, it produces reactive oxygen species which causes cellular dysfunction, apoptosis and necrosis of the organs (Ballas, Zeidan, Duong, DeVeaux, & Heeney, 2018; Olivieri & Brittenham, 2013).

The most common IOL complications are cardiac disease, diabetes mellitus, hypogonadism, hypothyroidism, hypoparathyroidism and liver disease (see Figure 1.2). Therefore in order to prevent or delay the IOL complications, ICTs were introduced to remove the excess iron from the cells and reduce NTBI. ICT aims to balance iron accumulation from blood transfusion by increasing iron excretion in urine or faeces with chelators (Cappellini et al., 2014).

SFL should be kept below 1000ng/L as it is associated with less IOL complications and less than 2500ng/L significantly improve cardiac disease free survival. ICT should be initiated in all TDT patients. Figure 1.3 demonstrated the algorithm of ICT prescribing practice of TDT in Malaysia (Borgna-Pignatti & Gamberini, 2011; Cappellini et al., 2014; Ministry of Health Malaysia, 2009).

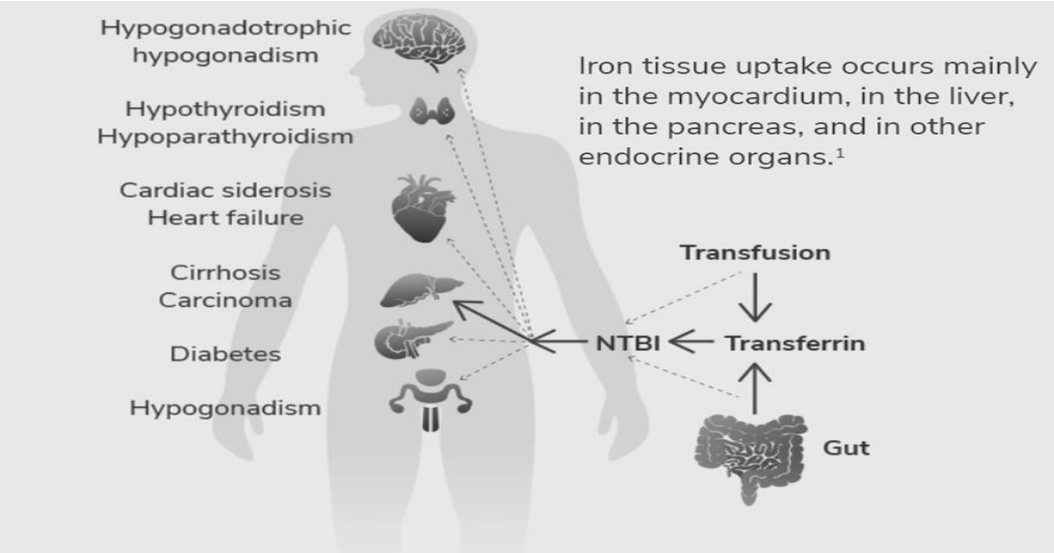

Figure 1.2: Iron loading mechanism in TDT and common IOL complications (Source from Guidelines for Management of Transfusion Dependent Thalassaemia (TDT). 3rd edition. Thalassaemia International Federation. 2014. Page 45.)

The aims of ICT are:

1. Prevention therapy – function as is the primary goal. To maintain iron balance in the body from blood transfusion.
2. Rescue therapy – to overcome condition where iron overload has accumulated as a result of blood transfusion.
3. Emergency therapy – when heart failure has developed and urgent action is required.

To date, there are three types of ICT licensed in the market worldwide. They are Desferrioxamine (DFO), deferiprone (DFP) and deferasirox (DFX) – see Table 1.1 for the pharmacological properties (Cappellini et al., 2014; Lee, von Riedemann, & Tricta, 2014; Viprakasit et al., 2009). All three ICT were claimed to have similar efficacy but different safety profile and mode of administration which make them distinctive. ICT regimen requires good compliance from patient in order to work effectively. Adjustment of dosing and treatment regimens is necessary according to routine iron load (see Figure 1.3) and chelator toxicity blood monitoring.

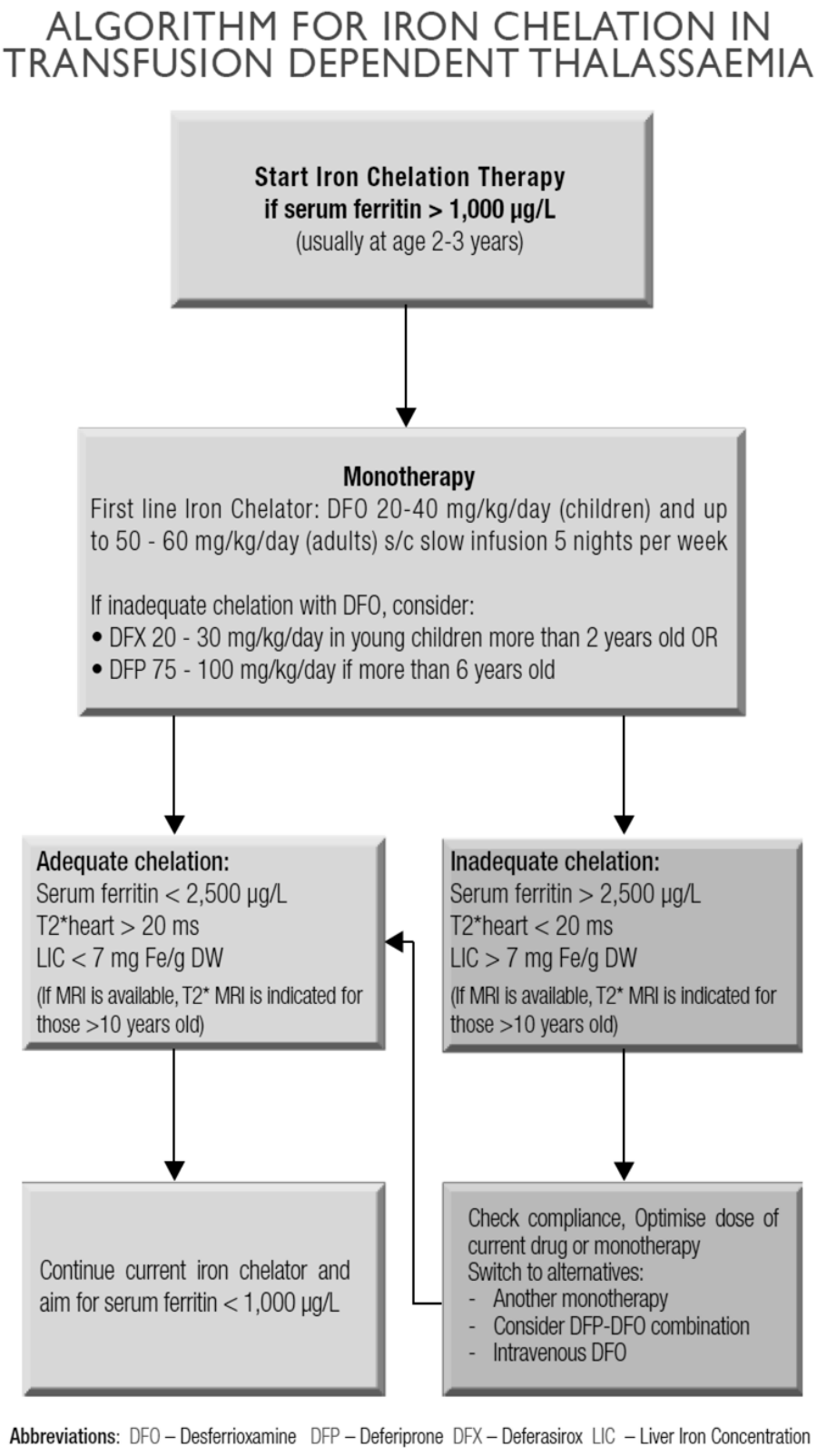

Figure 1.3: Algorithm to initiate ICT in TDT patient
(Source from: "Management of transfusion dependent thalassaemia". Copyright 2009 by Ministry of Health Malaysia. Page ix.)

Table 1.1: Pharmacological properties and characteristics of licensed chelator

Properties	Desferrioxamine (DFO)	Deferasirox (DFX)	Deferiprone (DFP)
Cost (MYR/mg)[2]	0.044	0.139	0.002
Stoichiometry (chelator : iron)	Hexadantate (1:1)	Tridentate (2:1)	Bidentate (3:1)
Age consideration	Not recommended for children, 3 years with low transfusional iron burden	Studied in children from aged 2 onwards.	No data in children under 6 years of age.
Route of administration	Subcutaneous or intravenous	Oral tablet	Tablet, oral solution
Plasma half life	20-30 minutes	3-4 hours	8-16 hours
Usual dose	25-50mg/kg/day, 8-12 hours 5days/week	20-40mg/kg/day once daily	75-100mg/kg/day in 3 divided doses
Ability to remove liver iron	+++	+++	++[1]
Ability to remove cardiac iron	++	++	+++
Adverse effects	Ocular, auditory, bone growth retardation, local reaction and allergy, pulmonary/ neurologic at high doses	Gastrointestinal (GI), rash, elevated creatinine and liver enzyme	Neutropenia/ agranulocytosis, gastrointestinal, arthralgia, elevated liver enzyme
Challenges	Compliance and extra cost due to parenteral administration.	Cost especially with higher doses. GI side effects limit optimal dosing.	Require frequent (weekly) blood count monitoring. Compliance (multiple dosing daily).

[1]reported of insufficient liver iron removal at 75mg/kg/day, higher dosing maybe effective for subjects with high transfusional iron burden.

[2] (Department of Pharmacy Hospital Kuala Lumpur, 2017)

Desferrioxamine (DFO)

DFO being the first marketed iron chelator has been the standard ICT option for TDT in the past 40 years. Large numbers of literatures have concluded DFO effectively control iron storage, reduce organ damage by delaying IOL complication and increase life expectancy in TDT patient. Therefore, DFO remains the acceptable active comparator in clinical studies with other newer iron chelators.

Despite of the good efficacy profile, main disadvantage of DFO is the poor bioavailability and short plasma half-life which require it to be administrated as slow subcutaneous or intravenous infusion over a period of 8- 12 hours for at least 5 times weekly. It is also costly having to purchase medical item/equipment to support the administration method. This results to suboptimal compliance due to discomfort and complexity associated with the administration regimen (Cappellini et al., 2014; Viprakasit et al., 2009). It was reported that the probability of survival by age was positively associated with the mean number of DFO infusions received per year. Higher number of infusion per year will have higher survival probability (Gabutti & Piga, 1996).

Due to the complexity of administration method which result to poor compliance and dose related complication (e.g. ocular and hearing problem, growth retardation), prescribing DFO compromises patient's QOL. Hence, this promotes the development of oral chelating agent which are DFP and DFX.

Deferiprone(DFP)

DFP was the first orally absorbed iron chelator, available in European Union, Asia and other countries in the late 1990s and recently in US, 2011. Due to relative short plasma half-life (three - four hours), DFP requires to be taken three times daily which

will interrupt with patient daily lifestyle resulting in suboptimal compliance as well. However studies has shown DFP has better compliance compared to DFO (Olivieri & Brittenham, 2013).

In terms of age consideration, there is limited data on the use of DFP in children between six to ten years of age and no data was available for children younger than six years of age. Based on Malaysia TDT clinical guideline (see Figure 1.3), DFP is recommended if patient is six years of age and above.

Another disadvantage of DFP is the poor safety profile. Serious adverse events (SAE) were reported such as neutropenia, including agranulocytosis. Hence, administrating DFP would require frequent blood monitoring (every week) especially absolute neutrophil count. Therapy should be interrupted if patient developed infection and neutrophil count to have monitored more frequently. In one trial, the risk of experiencing adverse event with DFP was two times of the risk with DFO (RR = 2.24) (Fisher et al., 2013).

Due to the poor safety profile and age consideration, DPF is limited to second-line therapy for treatment of iron load in many countries.

Deferasirox (DFX) Dispersible Tablet (Exjade DT)

Exjade dispersible tablet (DT) with the active ingredient of deferasirox (DFX) was approved by US FDA in October 2005 as first line use in adult and children two years of age and above. It was developed to overcome the complexity of DFO administration method. DFX is also available in most of the Asian countries before 2010 (Viprakasit et al., 2009).

DFX has long plasma half-life of 8-16 hours which means the drug is continually available to chelate NTBI and effective throughout 24 hours dosing period.

Data from a phase III trial comparing DFX and DFO for β-thalassaemia patient who are aged two and older, confirmed that efficacy and safety of DFX is non-inferiority to DFO in patients with baseline LIC ≥ 7mg Fe/g dw or higher (Cappellini, Cohen, & Piga, 2005).

A prospective patient reported outcome study was conducted to evaluate the preference of patient on DFO and DFX. Study has reported 96.9% preference for DFX over DFO with primary reason of more convenient to administer. As it does not involve injection-site soreness associated with DFO and less disruptive to day and sleep activities (Cappellini et al., 2007). Among adverse events reported, the events were transient and mild such as vomiting (8.3%), nausea (7.1%), and skin rash (7.5%) (Viprakasit et al., 2009).

Convenience and patient's QOL prescribed with DFX compare to other oral chelation agents are expected to be better and hence improve survival. In a large scale EPIC study, patients reported to have improved QOL and greater compliance to chelation therapy with DFX (Cappellini et al., 2014).

Deferasirox (DFX) Film Coated Tablet (Exjade FCT)

Exjade FCT also has active ingredient of Deferasirox but with new oral formulation – film coated tablet (FCT) approved in 2015 manufactured by Novartis. The formulation was developed and produced 10 years after the initial dispersible tablet (DT) formulation. The previous DT formulation though with once daily dosing has a rather complex oral administration instruction.

DT formulation require patient to administer at least 30 minutes prior to a meal, measuring specified amount of water, orange or apply juice according to the dose of DFX prescribed and stir the tablet(s) in suspension until completely dispersed and consume immediately (Novartis Pharmaceuticals Corporations, 2018).

The latter Exjade FCT formulation on the other hand requires to be taken in one simple instruction. The tablet can be swallowed with water or other beverages on an empty stomach or with light meal. The improved formulation does not contain lactose or sodium lauryl sulphate, which may result in fewer gastrointestinal side effect compared to Exjade DT (Novartis Pharmaceuticals Corporations, 2019a; Shah, 2017).

Patient receiving Exjade FCT has fewer frequency of severe events observed comparing to Exjade DT (19.5% vs 25.6%). Treatment compliance by pill count was higher with FCT formulation than DT (92.9% vs 85.3%) (Taher et al., 2016). A patient reported outcomes from a randomised controlled trial on TDT reported that FCT recipients have better compliance, greater satisfaction and fewer concern and limitation in daily activities (Taher et al., 2018).

These findings suggest that FCT formulation has better patient satisfaction and leads to better compliance. As a result, this may reduce or delay the development of IOL related complications.

1.1.2(d) Routine blood and instrument monitoring

In order to ensure optimal and safe iron chelation treatment was prescribed, series of blood and instrumental blood monitoring is mandatory regularly. Refer to Table 1.2 on the routine laboratory and instrumental test of each ICT recommended in Malaysia TDT clinical guidelines and nursing handbook in management of thalassaemia (Ministry of Health Malaysia, 2009, 2015a).

Table 1.2: Recommended blood and instrumental screening for TDT patient (Ministry of Health Malaysia, 2009, 2015a)

<table>
<tr><td colspan="2">Weekly</td></tr>
<tr><td colspan="2">Full blood count[1]</td></tr>
<tr><td colspan="2">Monthly</td></tr>
<tr><td colspan="2">• Full blood count
• Renal profile[2]
• Serum ferritin</td></tr>
<tr><td colspan="2">Three monthly</td></tr>
<tr><td colspan="2">• Liver function test
• Blood calcium and phosphate level</td></tr>
<tr><td colspan="2">Six monthly</td></tr>
<tr><td>• Renal profile
• Uric acid
Screening for transfusion associated infection:
• HIV serology
• Hepatitis B serology
• Hepatitis C serology
• Venereal disease research laboratory test (VDRL)</td><td>For patient > 10 years old, endocrine function assessment:
• Fasting blood sugar/2HPP (MGTT)
• Thyroid function test
• Serum oestradiol/testosterone
• Serum cortisol
• Serum zinc</td></tr>
<tr><td colspan="2">Annually</td></tr>
<tr><td colspan="2">• Eye assessment
• ENT assessment
For patient > 10 years old:
• Echocardiography
• MRI T2* of heart and liver
• DEXA bone scan</td></tr>
</table>

[1] for patient who is on DFP
[2] for patient who is on DFX

1.2 Burden of thalassaemia in Malaysia

1.2.1 Epidemiology of thalassaemia in Malaysia

Thalassaemia is global public health problem which affects 7% of the world population (Pauzy et al., 2018) and is prevalent in Asia notably in Southeast Asia, Bangladesh, India, and Mediterranean region (Figure 1.4) (Weatherall, 2011). Southeast Asia was estimated to have about 55 million carriers of thalassaemia among total population of 400 million (Azman et al., 2016; Viprakasit et al., 2009).

Malaysia is made up of Peninsular Malaysia which comprises of 11 states and two states in the Island of Borneo named as East Malaysia. Malaysia has a multi-ethnic population with over 32 million in 2018 of which 69.1% is Bumiputera, 23.0% of Chinese, 2.01% of Indian and 1.0% of other races (Department of Statistic Malaysia, 2018a).

Figure 1.4: Global distribution of thalassaemia
(Source from: D.J. Weatherall., 2011, p. 739)

From Malaysia Thalassaemia Registry (MTR) in April 2019, approximately 8964 patients with thalassaemia were registered, of which about 4590 were TDT patients. Sabah appears to have the highest incidence of TDT in Malaysia and mainly from Kadazadusuns ethnic (Ministry of Health Malaysia, 2019).

1.2.2 Economic burden of TDT in Malaysia

In the last decade it was reported 4.5% of the people in Malaysia are carrier of β-thalassaemia and are at estimated risk of producing 2.1/1000 birth with β-thalassaemia major annually (George, 2001). MTR was initiated in 2004 and the number of thalassaemia is increasing in trend up to present. In order to reduce the number of new TDT birth it is necessary to implement national birth preventive measure. This includes multi-disciplinary approach such as population screening, genetic counselling, prenatal diagnosis and the option of termination of affected pregnancies (Ministry of Health Malaysia, 2009; Thong, Tan, Tan, & Yap, 2005).

Developing a prevention programme is important in reducing the birth of TDT thus curbing the cost implications in the provision of optimal care. In Malaysia, prenatal diagnosis is not widely available and selective abortion of affected foetuses is not generally accepted due to cultural factors. The available prevention control is through voluntarily blood screening offered to secondary year 4 students implemented from year 2008 (Jameela et al., 2011). Unfortunately, we are not able to effectively reduce the numbers of TDT newborn.

Another reason for increasing incidence of TDT is mainly due to drop in TDT childhood mortality rates with improvement in public health and social conditions. Babies with TDT who would previously have died during early in life survived to

present with proper treatment and blood transfusion (Borgna-Pignatti et al., 2005; Weatherall, 2011).

1.2.3 Heathcare coverage of TDT management in Malaysia

Malaysia has long adopted universal health coverage, where every citizen is able to seek for medical advice/treatment from public hospital. Our public health system under Ministry of Health (MOH) is financed mainly through general revenue and taxation collected by federal government (World Health Organization, 2012).

Total MOH allocation was MYR 24.8 billion accounts for 9.4% of our national budget in year 2017 (Ministry of Health Malaysia, 2017). Total expenditure on health as a percentage of GDP was 4.24% with MYR 1,790 per capita and public health sector health expenditure was 51.15% of total health expenditure in 2017 (Malaysia National Health Account Section Ministry of Health, 2018).

Table 1.3 illustrated availability of different form of thalassaemia management gathered by Asian Thalassaemia Network (Weatherall, 2011). Malaysia is one of the countries among other Asian countries to have comprehensive different forms of management and treatment available. Free blood transfusion treatment is provided in all public hospital and treatment to all IOL complications experienced by TDT patients. To date, free supply of chelating agents are provided when serum ferritin > 1000µg/L as recommended by clinical guideline (see Figure 1.3).

Country	Transfusion	Iron Chelation			BMT	PND	National programme
		DFO	L1	Exjade			
Bangladesh	(+)	(+)	–	–	–	–	–
Cambodia	(+)	(+)	–	–	–	–	–
China: Guangxi	+	(+)	(+)		(+)	+	–
China: Hong Kong	+	+	+	(+)	+	+	+
China: Taiwan	+	+	+	(+)	+	+	+
India	+	(+)	(+)	–	(+)	(+)	*
Indonesia	+	(+)	(+)	–	–	(+)	–
Laos	(+)	(+)	–	–	–	–	–
Malaysia	+	+	+	(+)	+	+	+
Maldives	+	+	+	–	(+)	–	+
Myanmar	(+)	(+)	–	–	–	–	–
Philippines	+	(+)	–	(+)	–	––	–
Singapore	+	+	+	(+)	+	+	+
Sri Lanka	+	+	+	–	–	–	+
Thailand	+	+	+	(+)	+	+	+
Vietnam	(+)	(+)	(+)	–	(+)	–	–

DFO, desferrioxamine; L1, deferiprone; BMT, bone marrow transplantation; PND, prenatal diagnosis.
Last compiled with help of Dr Suthat Fucharoen and Asian Thalassaemia Network in 2009.
+Denotes availability.
(+)Denotes availability only to those who can afford it.
–Denotes complete lack of availability.

Figure 1.5: Current services and management of thalassaemia in Asian countries (Source from: D.J. Weatherall., 2011, p. 740)

Thalassaemia is a common public health problem in Malaysia and WHO has considered thalassaemia as a major economic burden to a country (Azman et al., 2016). In order to provide optimal care to TDT patient, availability of expertise, social, financial, government priorities and healthcare policies on management of TDT patient is very crucial.

1.2.4 Health related quality of life of TDT population

Thalassaemia is a chronic inborn illness. The disease manifestation of TDT is profound anaemia during the first few months of life and survival depends on regular blood transfusion and lifelong use of ICT agent to prevent iron accumulation (Cappellini et al., 2014; de Silva et al., 2000). Thalassaemia has been declared as a serious public health issues in many countries not only because of its economic implications, but also its great impact on the emotional and social well-being of patient and family especially in TDT group.

A study conducted in Malaysia found patients have difficulties with employers due to frequent days-off for hospital visits. About one-third of working mothers in urban area resigned from their job to take care of TDT child/children (Muhammad, Tan, Anne, George, & Ping, 2012). This is consistent with a qualitative study conducted among Jordanian mothers whereby three main themes emerged from the interview which are 'unprecedented psychosocial distress', 'additional financial burden' and 'deficiency of knowledge and source' (Abu Shosha & Al Kalaldeh, 2018).

While parent/caregiver of TDT child/children experiences challenges in psychosocial distress and financial burden, many studies also found that children with TDT are prone to significant physical, psychological and social stress. Malaysia TDT patients were found to have concerns and adverse impact on lower grades in education due to frequent hospital follow up visits, poor self-image due to short stature or growth failure as a consequence of IOL complications. Young adult patients who have difficulties in finding job as majority of them are only secondary educated. Besides, frequent time off taken for regular blood transfusion and other treatment has created tension with their employer and wages were exploited (Suzanah, Zulaiha, Faszrul, & Kamaruzaman, 2011).

Patient and family do experience challenges in coping lifestyle which has compromised their QOL. Type of iron chelator administered by patient also does affect HRQOL. Oral ICT has proven to have better HRQOL compared to subcutaneous/intravenous (Osborne et al., 2007; Weidlich, Kefalas, & Guest, 2016).

1.3 Problem statement

Healthcare financing is a key concern over the world today. The major factors which contributed to increase spending in healthcare are wasteful spending, prescription drugs, advancement in medical technology, ageing workforce and high administrative costs (Mack, 2016). In Malaysia, the healthcare expenditure is at increasing trend since year 1997 to 2017, from RM 4.36 billion to RM 29.34 billion solely from public healthcare provision (Malaysia National Health Account Section Ministry of Health, 2018).

According to the 11th Malaysia Plan and MOH Strategic Plan (2016-2020), the main theme is to enable Malaysia population to reach universal access to quality healthcare. The strategic objectives are listed below (Kementerian Kesihatan Malaysia, 2016):

1. Reduced health risks and improved health.
2. Improved access and equity in delivering healthcare services.
3. Improved responsiveness of the health care system.
4. Optimised used of resources
5. Enhanced adoption of healthy lifestyle.

Hence, in order to achieve the main objectives of 11th Malaysia Plan, it is crucial for the policy maker to optimise use of healthcare resources in order to improve the general healthcare delivery system to the Malaysian population.

Thalassaemia is a lifelong disease and its increasing prevalence is threatening to cause significant burden to both individual patient and society. Although chronic (or intermittent) transfusions have remarkably improved the survival and quality of life of individuals with thalassemia, transfusions do come at a cost. TDT patients are

expected to have the highest medical maintenance treatment cost compared non-transfusion dependent thalassaemia traits. Hence, it is necessary to consider the economic impacts associated with TDT to identify intervention that can reduce the burden of this disease.

Cost-of-illness study is considered to be an essential economic analysis in healthcare. By measuring and comparing the economic burdens of diseases to society, such studies provide more information to develop structure and economic requirements for the care and prevention services. At present, there is no economic study on thalassaemia disease in Malaysia. Estimating the lifetime cost of TDT patient provides important input to our local healthcare policy maker for TDT population.

With chronic/regular blood transfusion, TDT patients experienced high iron loading which leads to IOL complications. There is no other physiological mechanism within the body to excrete the excess of iron, hence ICT is required. All three ICTs deliver similar efficacy with different mode of administration and safety profile. In terms of cost, DFX exhibits the highest cost comparing to DFO and DFP (Department of Pharmacy Hospital Kuala Lumpur, 2017). Due to the complex administration method of DFO, poorer compliance is expected. This increases the risk of iron accumulation at vital organs leading to complications which compromise patient's QOL (Bentley, Gillard, Spino, Connelly, & Tricta, 2013; Delea, Sofrygin, et al., 2007; Karnon, Tolley, Vieira, & Chandiwana, 2012; Luangasanatip, Chaiyakunapruk, Upakdee, & Wong, 2011).

The complex consequences and costs of different ICT complicate healthcare prioritization for thalassemia. However, no study was found to have compared the cost effectiveness between oral and subcutaneous ICT in Malaysia. The result of cost

effectiveness analysis could provide insight to decision maker to provide efficient treatment to all patient.

CEA provides information on which intervention/drug is effective comparing the cost and outcome. However, with limited healthcare resources, it is essential to evaluate the affordability of the new intervention even if it is cost effective. Budget impact analysis (BIA) will provide useful information to healthcare policy maker tackling the new hurdle of “affordability” after having fulfilled hurdles of “safety”, “efficacy” and “added value” of new treatment over the existing ones.

BIA could estimate the feasibility and affordability of a new drug/technology for budgeting and forecasting purposes, in this case it would be Exjade FCT as it is the newest ICT on board and having the highest acquisition cost. BIA assesses financial consequences by introducing new technology to a specific setting in short to medium term and could estimate the effect of any offsetting savings.

1.4 Objective

To generate knowledge on economic impact of TDT population in Malaysia and to perform analysis on Exjade FCT efficiency from local healthcare perspectives.

1.4.1 Specific objectives

1. To estimate the total lifetime cost attributed to TDT patients from societal perspectives.
2. To assess cost effectiveness of new formulation Exjade FCT versus DFO among TDT population.
3. To estimate the budget impact of introducing Exjade FCT in Malaysia formulary.

CHAPTER 2

LITERATURE REVIEW

2.1 Theoretical foundations

2.1.1 Cost-of-illness (COI)

Cost-of-illness (COI) analysis is a technique to measure economic burden of illness. It is a descriptive study which provides information to support political process and management functions at different levels of healthcare organisations. Conducting such study design is able to capture the true cost of an illness to the society, incidence over total cost, estimating the main cost components by identifying the actual clinical management of illness and to explain cost variability (Tarricone, 2006). In order to evaluate the economic burden illness imposed on to the society, the fundamental step is to measure the consumption of healthcare resources and production losses.

2.1.1(a) Classification of cost

First of all, in order to measure the healthcare consumption, resources must be categorised accurately. Various terminologies have been used traditionally to account for economic cost, for example direct costs (related to healthcare cost), indirect costs (informal care by family/caregiver/productivity costs), intangible costs ("invisible" costs that are not directly measured) and total costs (sum of all costs) to classify the cost components. However, this classification of costs is often criticized due to confusion and overlapping definitions (Razzouk, 2017; Tarricone, 2006).

Recent literatures has adopted explicit terminologies suggested by (Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015) to classify healthcare resources/consumptions (see Table 2.1).

Table 2.1: Types of healthcare resources and definitions

Resources consumed	Definitions
Health sector	Costs of organizing and operating the programme, including variable costs (such as time of health professionals or supplies), fixed and overhead costs.
Other sector	Resources consumed from other public agencies or the voluntary sectors.
Patient/family	Any out-of-pocket expenses incurred by patient and family members or any values of resources they contributed to the treatment programme.
Productivity losses	Lose time from work while seeking treatment or participating in a health care programme.

2.1.1(b) Methods to conduct COI

Perspectives

The first step when conducting an economic evaluation is to define the study perspective. COI studies can be carried out from different perspectives and each perspective will include different cost items which in turn provide dissimilar and wide range of results for the same illness/service. Costs can be measured from society, public health provider, third-party payer/ private health provider (insurance), patient and family and employer. Table 2.2 presents the cost categories included in each perspective (Drummond et al., 2015; Razzouk, 2017).