# A COST-UTILITY AND BUDGET IMPACT ANALYSIS OF DRUG TREATMENTS IN PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONGENITAL HEART DISEASE

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ABSTRACT

The objectives of this study were to assess the cost-utility and the budget impact of drug treatments in patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) when included on the National List of Essential Medicines (NLEM). The study population was patients with PAH-CHD in WHO Functional class II and III. Cost-utility analysis was used to compare the alternatives for both first-line and second-line treatments. The first-line treatment compared beraprost and sildenafil with standard treatment. The second-line treatment compared sildenafil combined with iloprost and sildenafil combined with bosentan with sildenafil switched to standard treatment in cases of no response to sildenafil as the first-line treatment. A Markov model was constructed to estimate the costs and health outcomes over lifetimes using a societal perspective. The health outcome was quality adjusted life years (QALYs) gained. Probabilistic sensitivity analyses (PSA) were performed to investigate the effect of parameter uncertainty.

At the initial treatment, the costs and quality adjusted life years (QALYs) were not significantly different between patients who had PAH-CHD in Functional class II and III. As the first-line treatment, both beraprost and sildenafil were close to being cost-effective. Sildenafil significantly increased one to three QALYs when compared with beraprost. Therefore, if the price of sildenafil (20 mg) was decreased to 19-26 baht, it would be cost-effective in the Thai context. Moreover, the budget impact was approximately 12 million THB. If the price of sildenafil was decreased to the cost-effective price, the budget impact would be approximately 7.5 million THB. Furthermore, in cases of no response to sildenafil as the first-line treatment, all second-line treatments were not cost-effective in the Thai context. Sildenafil should be used as the first-line treatment in PAH-CHD patients in Functional class II or III if its price was reduced to be cost-effective.

KEY WORDS: COST-UTILITY ANALYSIS / PULMONARY ARTERIAL HYPERTENSION/ CONGENITAL HEART DISEASE / BUDGET IMPACT ANALYSIS

88 pages

การประเมินต้นทุนอรรถประโยชน์และผลกระทบทางด้านงบประมาณของการรักษาผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูงที่เกี่ยวกับโรคหัวใจพิการแต่กำเนิด

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บทคัดย่อ

วัตถุประสงค์ของการศึกษาเพื่อประเมินต้นทุนอรรถประโยชน์ และประเมินผลกระทบด้านงบประมาณของการรักษาผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูงที่เกี่ยวกับโรคหัวใจพิการแต่กำเนิด โดยพิจารณาการเริ่มรักษาที่ระดับความรุนแรงของโรค Functional class (FC) II และ III ในการเสนอพิจารณาบรรจุการรักษาเข้าสู่บัญชียาหลักแห่งชาติ การศึกษานี้เปรียบเทียบทางเลือกของการรักษาทั้งยาทางเลือกแรกและยาทางเลือกที่สอง โดยพิจารณาตามแนวทางการรักษาผู้ป่วยดังต่อไปนี้ การเปรียบเทียบยาทางเลือกแรก ได้แก่ sildenafil และ beraprost เปรียบเทียบกับการรักษามาตรฐาน และการเปรียบเทียบยาทางเลือกที่สอง ได้แก่ sildenafil ร่วมกับiloprost และ sildenafil ร่วมกับ bosentan เปรียบเทียบกับ sildenafil เป็นยาทางเลือกแรกแต่ผู้ป่วยไม่ตอบสนองจึงเปลี่ยนเป็นการรักษามาตรฐาน การวิเคราะห์ต้นทุนและผลลัพธ์ของการรักษาที่เกิดขึ้นตลอดชีวิตของผู้ป่วยด้วยแบบจำลองทางเศรษฐศาสตร์ Markovโดยใช้มุมมองทางสังคม ผลลัพธ์ทางสุขภาพในงานวิจัยนี้ คือ ปีสุขภาวะ การประเมินผลกระทบของความไม่แน่นอนของค่าตัวแปรที่ใช้ในแบบจำลองใช้วิธีการวิเคราะห์ความไวแบบ Probabilistic sensitivity analysis

ผลการศึกษาพบว่า การเริ่มรักษาผู้ป่วยที่ระดับความรุนแรงของภาวะความดันหลอดเลือดแดงในปอดสูงที่เกี่ยวกับโรคหัวใจพิการแต่กำเนิดใน FC II หรือ III มีค่าต้นทุนและปีสุขภาวะไม่แตกต่างกัน ซึ่งยาทางเลือกแรกในการรักษาที่มีค่าใกล้เคียงกับความคุ้มค่าในบริบทของประเทศไทย คือ beraprost และ sildenafil แต่เมื่อเปรียบเทียบกับ beraprost พบว่าการรักษาโดย sildenafil สามารถเพิ่มปีสุขภาวะได้อย่างมีนัยสำคัญ กล่าวคือทำให้ผู้ป่วยมีปีสุขภาวะเพิ่มขึ้นคิดเป็น1-3 ปีสุขภาวะ ดังนั้นหากลดราคายา sildenafil 20 mg ลงเหลือประมาณ 19-26 บาทก็จะทำให้ยา sildenafil มีความคุ้มค่า ในส่วนของผลกระทบทางด้านงบประมาณของยา sildenafil ที่เริ่มรักษาใน FC II หรือ III มีภาระงบประมาณเท่ากับ 12 ล้านบาท และหากลดราคายาลงมา ณ จุดที่ยามีความคุ้มค่าจะมีภาระงบประมาณเท่ากับ 7.5 ล้านบาท นอกจากนี้ ผลการศึกษาการรักษาทางเลือกที่สอง พบว่าไม่มีความคุ้มค่าในทุกกรณี จากข้อมูลผลการศึกษาราคาต่อรองของยา sildenafil พบว่า sildenafil ควรจะเป็นยาทางเลือกแรกในการรักษาภาวะความดันหลอดเลือดแดงในปอดสูงที่เกี่ยวกับโรคหัวใจพิการแต่กำเนิดใน FC II หรือ III ตามบริบทของประเทศไทย

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| CBA | Cost-benefit analysis |
| CEA | Cost-effectiveness analysis |
| CMA | Cost-minimization analysis |
| CUA | Cost-utility analysis |
| ICER | Incremental cost-effectiveness ratio |
| NLEM | National List of Essential Medicines |
| NHSO | National Health Security Office |
| PSA | Probabilistic sensitivity analysis |
| PAH-CHD | Pulmonary arterial hypertension associated with Congenital heart disease |
| QALY | Quality adjusted life years |
| SD | Standard deviation |
| SE | Standard error |
| STD | Standard treatment |
| THB | Thai Baht |
| WTP | Willingness to pay |
| WHO | World Health Organization |

# CHAPTER I
# INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare condition with narrowing coronary arteries in the lungs. The major symptoms such as swelling, syncope and angina can be worsening as the disease progressed and right heart failure developed. If the progression of the disease becomes advanced, it can be fatal to the patient. Patients with moderate or severe disease progression will have high risk mortality. The disease can be classified as either idiopathic PAH (iPAH) or PAH caused by other health problems such as connective tissue disease (PAH-CTD), congenital heart disease (PAH-CHD) which is a major cause of PAH in Thailand base on expert opinion. Before the specific medications were discovered for treating PAH. Anticoagulation therapy, diuretics, oxygen and digoxin were prescribed to PAH patients with the aim for standard care. It was found that a median survival of PAH patients receiving standard care ranged from 2 to 3 years after treatment (1).

Recently, new drugs specifically licensed for treating PAH have become available in Thailand. These drugs include inhaled iloprost, bosentan, beraprost and sildenafil. They can reduce pulmonary arterial pressure and result in improve functional class, quality of life (QOL), and survival of patients. However, these drugs are very expensive, ranging from approximately 600 to 20,000 THB per day (2). This, therefore, can lead to financial difficulty for patients accessing to drug.

Currently, in Thailand, only sildenafil is a pulmonary selective drug included in the National List of Essential Medicines (NLEM) as the first line treatment, while others such as iloprost and bosentan have been proposed for the inclusion in the NLEM as the second-line treatment. Nevertheless, in this country there has been no economic evaluation information related to these drugs available. Therefore, economic evaluation and budget impact analysis are needed in order to provide evidence to inform decision makers for the consideration of drugs to be included in the NLEM.

## Objectives

1. To assess the cost-utility of drug treatments in patients with PAH-CHD in Thailand
    - To evaluate the cost-utility of drug treatments as the first line treatments in patients with PAH-CHD
    - To investigate which functional class is the most cost-effective for patients with PAH-CHD for starting the treatments
    - To assess the cost-utility of drug treatments as the second line treatments in patients with PAH-CHD in cases of unresponsiveness to the first line treatments
2. To assess the budget impact of treating patients with PAH associated with congenital heart disease in Thai setting.

## Expected outcomes and benefits

The results from this study could be used as the useful information for the National List of Essential Medicines (NLEM) Committees to make decision whether drug treatments (i.e., iloprost and bosentan) for PAH associated with CHD should be included in the NLEM.

## Conceptual Framework

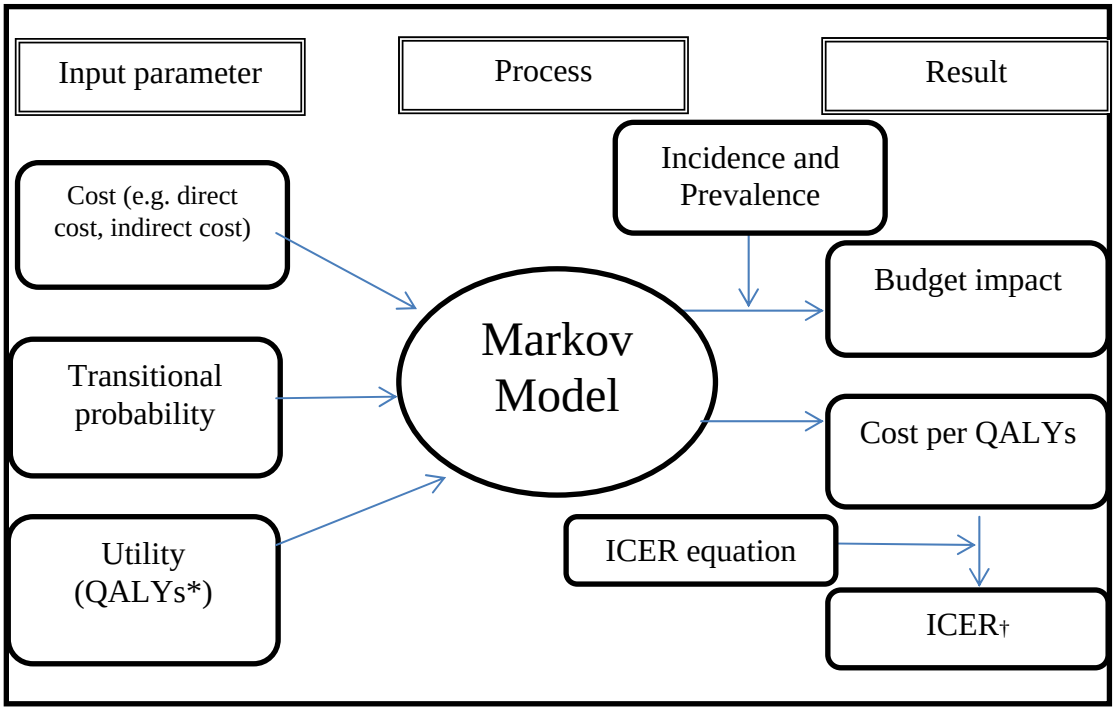


**Figure 1.1 The conceptual framework of the cost-utility and budget impact analysis**

***QALYs: quality adjusted life years

† ICER: Incremental cost-effectiveness ratio

## Definition of term

**Cost utility analysis (CUA)** is one of economic evaluation method which costs are measured in a monetary unit and outcomes are measured as quality adjusted life years (QALY).

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**Informal care** is the care given to dependent persons such as the sick and elderly outside the framework of organized, paid and professional work. Attention to the importance of informal care has increased with the adoption of community care policies which place increasing reliance on care provided by family, relatives, and friends, often women. Scientists with different disciplinary backgrounds do research on distinct issues regarding informal care. Sociologists and psychologists measure and describe the burden of informal caregiving. Economists model the supply of informal care and try to value informal care (3).

**Incremental cost-effectiveness ratio (ICER)** is calculated by incremental cost divided by incremental effectiveness. The lower positive value of this ratio is higher priority of the intervention on terms of maximized the benefit achieved from a given expenditure.

**Second line treatment in PAH CHD** is sildenafil combined with iloprost or bosentan (combination therapy) and used in cases of unresponsiveness to sildenafil as the first line treatment.

**Standard treatment** is a usual care to treat PAH patients including oral anticoagulants, diuretics, oxygen and digoxin based on clinical sign of an individual patient.

# CHAPTER II
# LITERATURE REVIEW

The literature reviews in this study is divided into five parts as follows.

Pulmonary arterial hypertension (PAH)

Epidemiology of PAH and burden to the society

Treatment for PAH diseases

Clinical effectiveness of pulmonary selective drugs

Economic evaluation of drug therapies

Economic evaluation of PAH treatments

## Pulmonary arterial hypertension (PAH)

Pulmonary arterial hypertension (PAH) is a subset of pulmonary hypertension (PH). PAH is a condition in which there is a narrowing of the coronary arteries in the lungs. The major symptoms such as peripheral edema (swelling around the ankles and feet), shortness of breath, fatigue, syncope and angina can worsen as the disease progresses and right heart failure develops. The patients who have disease progression to moderate or severe will have high risk mortality in the short term. Several pathogenic pathways have been related to the development of PAH, including those at the molecular, genetic levels, in the smooth muscle, endothelial cells and connective tissue. The imbalance in the vasoconstrictor/vasodilator of blood vessel has served as the basis for current medical therapies, although it is increasingly recognized that PAH also involves an imbalance of proliferation and apoptosis (1, 4, 5).

***Classification***

In 1973, a meeting organized by the World Health Organization was the first to attempt to establish the classification of pulmonary hypertension. A distinction was made between primary and secondary PH. A second conference in 1998 at Evian les Bains also addressed the causes of secondary PH (i.e. those due to other medical conditions). In 2003, the third World Symposium on PAH was convened in Venice to modify the classification based on new understandings of disease mechanisms. The revised system developed by this group provided the current framework for understanding PH. The system included several improvements over the former 1998 Evian Classification system. Risk factor descriptions were updated, and the classification of congenital systemic-to pulmonary shunts was revised. A new classification of genetic factors in PH was recommended, but not implemented because available data were judged to be inadequate. After that, in 2008 the fourth World symposium on PAH was convened in Dana Point, USA. The experts and physicians in this meeting summarized data from the third and fourth symposium as ungroup PH in order to avoid possible confusion between the terms of PH and PAH. This meeting also proposed to add a new technical term called "Pre-PAH" in patients with mean pulmonary arterial pressure, (mPAP) between 20 to 25 mmHg in order to make the diagnosis in the early stage but not included in the classification of the WHO. Pre-PAH also does not affect the treatment plan. In addition, the revised clinical classification was performed and divided into five different groups as follows (1, 5).

1. Idiopathic (iPAH) with unknown cause

2. Familial (FPAH) often resulted from a mutation in the bone morph genic protein receptor-2 (BMPR2). It is inherited as an autosomal dominant disease with incomplete penetrance and genetic anticipation.

3. Associated with other diseases (APAH)

3.1 PAH associated with connective tissue disorder (PAH-CTD) such as scleroderma, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and mixed connective tissue disorder

3.2 Congenital systemic-to-pulmonary shunts with high blood pressure in pulmonary arteries of the patients with congenital heart diseases (PAH-CHD). The development of PAH-CHD and subsequent reversal of shunt flow occur more frequently when blood flow is extremely high and the shunt exposes the pulmonary vasculature to systemic level pressures in several specific types such as occurs with a ventricular septal defect (VSD), patent ductus arteriosus (PDA), or truncus arteriosus. However, PAH-CHD may also occur with low pressure-high flow abnormalities such as with atrial septal defects.

4. Associated with significant venous or capillary involvement with high blood pressure in pulmonary arterial as a result of fibrosis in the wall of the pulmonary artery and thickness of the vessel wall. Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH), the two groups of patients have similar initial symptoms, thus the two groups are classified into the same group.

5. Persistent pulmonary hypertension of the newborn is that the high blood pressure occurs in the pulmonary artery in newborn. The blood vessel in the lungs which is fewer and smaller than normal and thickness of the wall muscles make artery stenosis.

***Screening and Diagnostic Assessment***

Echocardiogram (ECG) is the most appropriate assessment to obtain in patients suspected with PH in addition to history, physical examination and chest x-ray (CXR). ECG is the evaluation for other potential etiologies such as thromboembolic disease and is appropriate in all patients suspected of having PAH. The diagnosis of PAH requires confirmation with a complete right heart catheterization (RHC). PAH is diagnosed when a mean pulmonary artery pressure (mPAP) >25 mmHg at rest or >30 mmHg during exercise, in the presence of a pulmonary capillary wedge pressure (PCWP) ≤15 mmHg and high pulmonary vascular resistance and a pulmonary vascular resistance (PVR) >3 Wood units/$m^2$) with a normal or reduced cardiac output.

Acute vasodilator testing which involves the administration of pharmacologic agents to test the presence of pulmonary vasoreactivity has prognositic value and should be performed in all PAH patients who might be considered potential candidates for long-term calcium-channel blocker therapy. Those with overt right heart failure or hemodynamic instability should not undergo acute vasodilator testing. The definition of an acute responder is a reduction in mPAP of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output. Vasodilator testing should be performed by centers with experience in the administration of these agents and the interpretation of the results (1, 5).

**PAH associated with congenital heart disease (PAH-CHD)**

The condition of congenital systemic-to-pulmonary shunts is a major cause of PAH-CHD in Thailand and can also be represented as PAH associated with congenital heart disease (PAH-CHD). Therefore, the condition of congenital systemic-to-pulmonary shunts was focused (4).

Congenital heart disease (CHD) was the cause of increasing in the volume of blood to lung. The changing of the blood vessels in lung may occur in unborn child which PAP also may reduce slower than usual. Intracardiac shunt patients were deceased PVR due to two reasons (i.e., pathology of disease and natural condition) which can lead to have heart failure symptoms, especially fatigue and hyperventilation. Infants who have septal heart puncture always show symptoms of heart failure at the age of about 6-8 weeks. If CHD patients have not been resolved at the time of surgery, the pathology will irreversible damages. The study of animal experiments have demonstrated that pulmonary arteries with a diameter less than 5 mm result in the thickness of the artery wall significantly when compared with the control group (6). Therefore, if patients get operated when thickness of artery occurs, they will increasingly have cardiovascular risk including PAH after surgery.

The pathogenesis of CHD will give PAH formation prior to PAH complications, so that pediatricians and cardiologists will play an important role in determining whether CHD patients should be operated at an appropriate time. The patients with non-complex heart disease such as VSD and PDA they should get operated before the age of 2 years because pulmonary arterial pressure (PAP) usually

returns to normal after surgery. Nowadays, CHD surgery is developed to reduce risk of surgery. The incidence of PAH associated with CHD may be reduced.

However, for older children with CHD and PAH complications who have no surgery still have problems. The evaluation of these patients is very important and necessary, because the pathogenesis of PAH in the lung are found. Surgical pathology of the lung cannot be resolved (irreversible) and will not change the prognosis. In some cases, although the PAP is not very high but high PVR (less than 6-8 unit * m2), it may change the pulmonary artery back to normal after surgery (reversible), especially when the patients respond to vasodilators (pulmonary vasoreactivity test) before surgery (7). In practice, CHD patients with PAH who were older children or adults should receive cardiac catheterization.

## Epidemiology of PAH and burden to the society

The exact prevalence of all types of PH in Thailand and the World is unknown. Based on the information from the American Thoracic Society in the US, the number of American patients is certainly in the hundreds of thousands with many undiagnosed patients (8). Although there is no reported incidence and prevalence of idiopathic cause in Thailand, the study in other countries indicating the incidence rate and prevalence are 0.48 per million per year and 2.1 per million, respectively (9). In Thailand, the respective incidence rate and prevalence of PAH associated with scleroderma which accounts for the majority of PAH associated with CTD are 0.36 per million per year and 2.5 per million, respectively (10). Moreover, the respective incidence rate and prevalence of PAH associated with CHD is 0.4 per million per year and 2 per million based on expert opinion in Thailand.

Patients with PH as a primary or secondary diagnosis had about 200,000 hospitalizations occurred annually in the US. About 15,000 deaths per year are due to PH, although this is certainly a low estimate (8). In addition, the treatment expenses of PAH are costly ranging from approximately 600 to 20,000 baht per day (2).

## Treatment for PAH diseases

The severity of PAH is characterized by the symptoms that are associated with the ability to do daily activities at different levels. The severity of PAH classified by WHO functional class is similar to the assessment of the severity of heart disease based on New York Heart Association (NYHA). Functional classes are divided into four levels (4).

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Treatments of PAH according to the guidelines of the U.S.ACC/AHA 2009 (1) and the guidelines of ESC/ERS (5) can be summarized that divided into three parts as below.

**1. General care**

Patients with PAH require reasonable advice about general activities of daily living and need to adapt to the uncertainty associated with a serious chronic life-threatening disease. The diagnosis usually indicates a degree of social isolation. Patients and their family members should be encouraged to gain knowledge of general care that can be positive effects on an increase in the confidence in their lives.

1.1 Physical activity and supervised rehabilitation

Patients should be suggested to exercise within physical limitation. Therefore patients should avoid excessive physical activity that leads to worsening symptoms, but when physically deconditioned may consult

physiotherapists to have rehabilitation exercise. Although, one recent study has demonstrated an improvement in exercise capacity in patients with PAH who took part in a training program (11), more data were required before appropriate recommendations could be made. In addition, there is growing evidence supporting loss of peripheral muscle mass in patients with advanced PAH, and this may be corrected by a defined rehabilitation program.

1.2 Pregnancy, birth control, and post-menopausal hormonal therapy

According to the WHO and existing guidelines, pregnancy is associated with 30–50% mortality in patients with PAH. Thus, patients with PAH should avoid getting pregnant. In addition, they should know about birth control (i.e. oral contraceptive, fertility awareness, and condom). However, those patients who have strong desire to become pregnant should be treated with pulmonary selective drugs, planned elective delivery and needed close monitoring between obstetricians and the special physicians in PAH.

Data supports about use of hormonal therapy in post-menopausal women are not clear (12-14). It may be depend on intolerable menopausal symptoms and physician diagnosis.

1.3 Travel

Patients with PAH in WHO-FC III and IV usually have hypoxia which is a major symptom, thus patients should avoid going to altitudes above 1500–2000 m without supplemental oxygen. It is suggested that in-flight oxygen administration should be considered for patients and local PAH clinics should be available nearby their visiting places.

1.4 Psychosocial support

Almost PAH patients have stressful emotion with this chronic life threatening disease which leads to anxiety and depression. The important way to cope this problem is that patients should participate in a patient support group which they can share an accurate and up to date information.

1.5 Elective surgery

Elective surgery is predicted to have an increase risk in patients with PAH. Patients may continue receiving oral therapy. It is not clear as to which form of anesthesia is preferable but epidural is probably better tolerated than general anesthesia.

## 2. Standard treatment

Several medicines can be used as a usual care to treat PAH patients but there have been a few clinical trials supporting the efficacy of these medicines. Standard treatments are consisted of four major parts as follows.

2.1 Oral anticoagulants

Patients with iPAH may found abnormalities in vascular system which is a high risk factor for venous thromboembolism, heart failure and immobility (15-18). Thus, oral anticoagulants are necessary to be used in iPAH. Nevertheless, the potential benefits of oral anticoagulation should be aware against the risks in patients with other types of PAH especially when there is an increase risk in bleeding. Further studies indicated that patients should receive oral anticoagulation (15, 19). Suggested target international normalized ratio (INR) in patients with IPAH varies from 1.5–2.5 in most centers of North America (1) to 2.0–3.0 in European centers (5). Furthermore, existing guidelines recommend that anticoagulation should be used in patients with more advanced diseases or long-term intravenous therapy such as intravenous prostaglandins in the absence of contraindications (5).

2.2 Diuretic

The worsening symptom of PAH leads to heart failure which occurs in several kinds of fluid retention such as peripheral edema, pulmonary edema and ascites. Based on physicians' clinical experiences, diuretics is beneficial to be used despite of lacking data support. Aldosterone antagonists which have no side effect of hypokalemia should be chosen. However, serum electrolytes and renal function should be closely monitored.

### 2.3 Oxygen

Hypoxemia which is the insufficient oxygenation of arterial blood usually occurs in PAH patients. Thus, oxygen administration should be required especially in patients with PAH associated with CHD and pulmonary-to-systemic shunts. Although there have been no clinical trial data suggesting that long-term oxygen therapy has advantage, most experts in the USA recommend to use oxygen supplementation to maintain oxygen saturation above 90% and the experts in Europe recommend to follow the treatment guidelines for patients with COPD, when arterial blood oxygen pressure is continually less than 8 kPa (60 mmHg). Patients should receive oxygen to achieve arterial blood oxygen pressure of 8 kPa for at least 15 hours per day. Ambulatory O2 may be considered when there is evidence of symptomatic benefit and correctable desaturation on exercise.

### 2.4 Digoxin

Digoxin is always used in the treatment of various conditions including PAH. This drug can reduce the ventricular rate in patients with PAH who develop atrial tachyarrhythmia and increases the strength of heart muscle contractions, although its efficacy is unknown when administered long-term therapy. PAH patients may be more sensitive than most patients to digitalis toxicity and require close monitoring.

**3. Pulmonary selective drugs**

Pulmonary selective drugs have, in particularly, a direct effect on pulmonary artery pressure. The criteria of starting pulmonary selective drugs are depended on the response with acute vasodilator testing at the time of RHC (right heart catheterization) or the severity of WHO functional class. If a patient responds to RHC testing, they can start with calcium channel blockers (CCBs). In contrast if patients do not respond to RHC testing, physicians should evaluate patients depended on the severity of WHO functional class and patient should start with pulmonary selective drugs except calcium channel blocker. All of pulmonary selective drugs can be classified as follows.

3.1 Calcium channel blockers (CCBs) have been a traditional medicine for the treatment of PAH patient since the mid-1980s. PAH patients must have RHC testing before starting CCB.

CCBs which have been recommended to use in reported studies are nifedipine, diltiazem, and amlodipine. Due to its potential negative inotropic effects, verapamil should be avoided. The choice of CCBs is based upon the patient's heart rate at baseline nifedipine and amlodipine are recommended for patients with a relative bradycardia, while diltiazem. is suggested for those with a relative tachycardia. The daily doses of these drugs which were shown to be effective in iPAH are very high, 120–240 mg for nifedipine, 240–720 mg for diltiazem, and up to 20 mg for amlodipine. The recommended starting doses are low doses such as 30 mg of slow release nifedipine twice a day, 60 mg of diltiazem three times a day or 2.5 mg of amlodipine once a day and doses can be increased cautiously and progressively to the maximum tolerated dose. Limiting factors for a dose increase are usually systemic hypotension and lower limb peripheral edema. Patients with iPAH who meet the criteria for a positive vasodilator response and are treated with a CCB should be followed closely for both safety and efficacy with an initial reevaluation after 3–4 months of therapy including RHC. If the patient does not show an adequate response, defined as being in WHO-FC I or II and with a marked hemodynamic improvement, additional PAH therapy should be given. Thus, CCBs are useful only in patients with a severe degree of functional class I and II. Patients who have not undergone a vasoreactivity test or those with a negative response should not be started on a CCB

because of potential severe side effects (e.g. hypotension, syncope and RV failure). Vasodilator responsiveness does not appear to predict a favorable long-term response to CCB therapy in patients with PAH in the setting of CTD, and high dose CCBs are often not well tolerated in such patients.

3.2 Inhale nitric oxide (iNO) may cause problems with the treatment of patients with long-term. For example, the toxicity of NO2 pressure lung increased immediately after stopping the iNO -rebound phenomenon and some patients had no significant response to treatment-non responder phenomenon.

3.3. Prostacyclin

The mechanism of action of prostacyclin (or $PGI_2$) is to inhibit platelet activation and act as an effective vasodilator. Nowadays, there are four commercially available prostanoids, i.e. epoprostenol, treprostinil, iloprost and beraprost. However, prostacyclins in Thailand have been registered only two drugs – iloprost and beraprost which used to treat patients with functional class III to IV and functional class II, respectively.

3.4 Phosphodiesterase 5 inhibitor (PDE5I)

The mechanism of action of phosphodiesterase 5 inhibitor (PDE5I) is to block the degradative action of phosphodiesterase type 5 on cyclic GMP in the smooth muscle within the lungs which lead to the vasodilatory effects. PDE-5 inhibitors, such as sildenafil and tadalafil, may therefore be expected to enhance or prolong the effects of these vasodilating (and perhaps antiproliferative) cyclic nucleotides. Nevertheless, only sildenafil is currently available in Thailand and used to treat patients with functional class II and class III, because tadalafil and vardenafil are approved to treat only erectile dysfunction indication.

3.5 Endothelin receptor antagonist (ERA)

Endothelin-1 is a vasoconstrictor and a smooth muscle mitogen that may contribute to the development of PAH. Attempting to treat PAH by endothelin receptor blockade is a promising approach supported by evidence of the pathogenic role of endothelin-1 in PAH. Endothelin receptor antagonists (ERA) block both endothelin-A receptors and endothelin-B receptors in the pulmonary vascular smooth muscle cells. Bosentan is currently available in Thailand and used to treat patients with functional class II to III. However, ambrisentan and sitaxsentan are not registered in Thailand.

Table 2.1 demonstrates the summary of guidelines in Thailand based on U.S.ACC/AHA 2009 (1) classified the treatment based on the risk of patients (1, 4). Figure 2.1 presents PAH treatment algorithm which manages drug treatment depending on determinants of risk (1, 4).

**Table 2.1 Determinants of Prognosis PAH**

| Determinants of Risk | Lower Risk (Good Prognosis) | Higher Risk (Poor Prognosis) |
|---|---|---|
| Clinical evidence of RV failure | No | Yes |
| Progression of symptoms | Gradual | Rapid |
| WHO class | II, III | IV |
| 6MW distance | Longer (greater than 400 m) | Shorter (less than 300 m) |
| CPET | Peak VO2 greater than 10.4 mL/kg/min | Peak VO2 less than 10.4 mL/kg/min |
| Echocardiography | Minimal RV dysfunction | Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement |
| Hemodynamics | RAP less than 10 mm Hg, CI greater than 2.5 L/min/m2 | RAP greater than 20 mm Hg, CI less than 2.0 L/min/m2 |
| BNP | Minimally elevated | Significantly elevated |

6MW indicates 6-minute walk; BNP, brain natriuretic peptide. CI, cardiac index; CPET, cardiopulmonary exercise testing; peak VO2, average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; and WHO, World Health Organization.

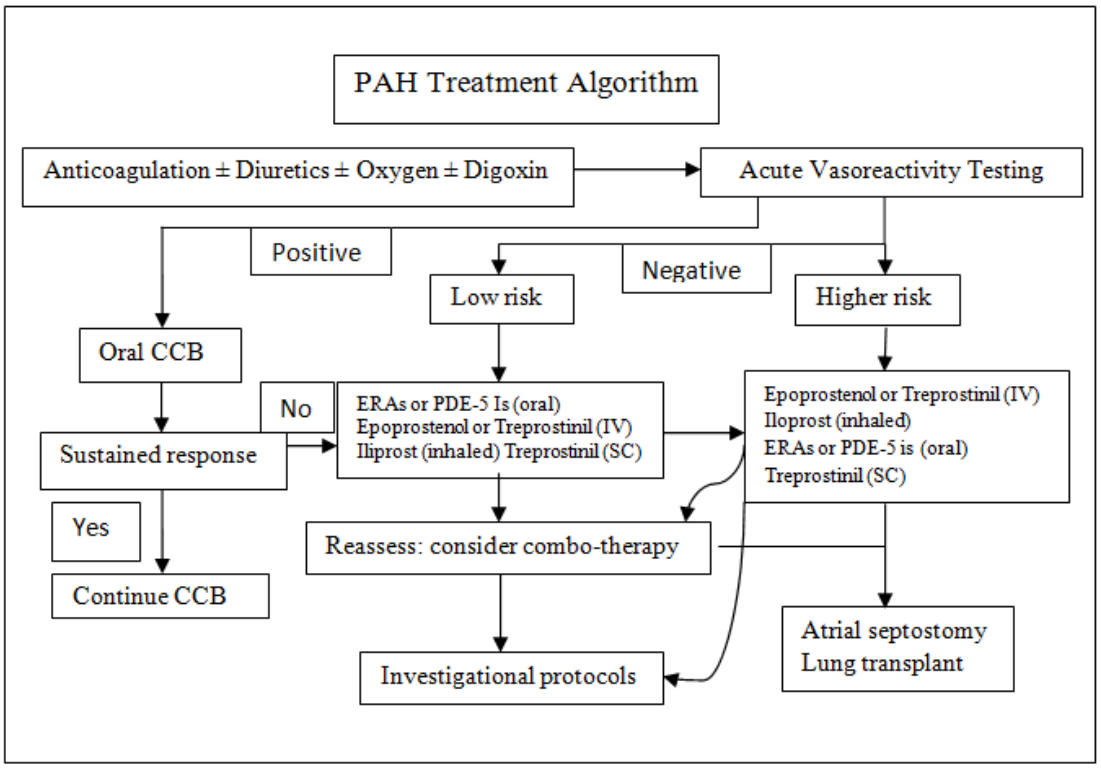


**Figure 2.1 Presented PAH treatment Algorithm**

## Clinical effectiveness of pulmonary selective drugs

According to a systematic review and meta-analysis of pulmonary selective drugs, several studies which support clinical effectiveness of pulmonary selective drugs were found and evaluated. In this part, we emphasized only drugs which are currently registered in Thailand.

### Prostacyclin

### Iloprost

Iloprost is a chemically stable prostacyclin analogue available for only aerosol administration in Thailand. Iloprost could be delivered by an adaptive aerosol device that was studied in a 12-week, multicenter, placebo-controlled, randomized trial of 207 functional class III and IV patients with either iPAH, PAH associated with scleroderma spectrum of diseases or appetite suppressants, or PH related to inoperable

chronic thromboembolic disease (20). Daily doses of iloprost inhalations (6–9 times, 2.5–5 mg/inhalation, median 30 mg daily) were compared with placebo inhalation. The study showed that long-term inhaled administration of aerosolized iloprost, a stable analogue of prostacyclin, improved a clinically important combined secondary end point consisting of exercise capacity, NYHA class, and clinical deterioration in patients with PAH. Furthermore, iloprost also improved primary end points that were found a significant effect of treatment in favor of iloprost (P=0.007). The estimated odds ratio of an effect in the iloprost group as compared with the placebo group was 3.97 (20).

The study of 24 iloprost-treated iPAH patients who received aerosolized iloprost at a daily dose of 100 or 150 microgram reported sustained benefits in exercise capacity and pulmonary hemodynamics at 1 year (21). More recently, Opitz et al. reported that event-free survival at 3, 12, 24, 36, 48, and 60 months was 81, 53, 29, 20, 17 and 13%, in IPAH patients treated with iloprost mono-therapy, respectively(22). Common side effects of inhaled iloprost included cough, headache, flushing, and jaw pain. Iloprost has been approved by the FDA since 2004 for the treatment of PAH patients with functional class III and IV.

**Beraprost**

Beraprost is the first chemically stable and orally active prostacyclin analogue. The randomized controlled trail in Europe (23) and the other in the US (24) of this compound showed the improvement in exercise capacity that unfortunately persisted only up to 3–6 months. There were no hemodynamic benefits. The most frequent adverse events were headache, flushing, jaw pain and diarrhea.

**Phosphodiesterase 5 inhibitor (PDE5I)**

PDE5 inhibitor is the drug used to block the degradation action of phosphodiesterase type 5 on cyclic GMP in the smooth muscle within the lungs. PDE-5 inhibitors such as sildenafil might therefore be expected to enhance or prolong the effects of these vasodilation and also exert anti-proliferative effect.

**Sildenafil**

Sildenafil is a specific PDE5 inhibitor that has been utilized previously for the treatment of erectile dysfunction. The SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension) study was a randomized, double-blind, placebo controlled trial that assigned 278 patients with PAH (either IPAH or PAH-CTD or with repaired congenital systemic-to-pulmonary shunts) to placebo or sildenafil (20, 40, or 80 mg) orally 3 times daily for 12 weeks. This study has confirmed favorable results on exercise capacity, symptoms, and hemodynamics (25). The 6MW test significantly increased from baseline in all sildenafil groups, with mean placebo-corrected treatment effects of 45, 46, and 50 m for 20, 40, and 80 mg doses of sildenafil, respectively. This appeared to be entirely related to improvements with active therapy, as there was little change in 6MW test in the placebo group. All sildenafil doses reduced the mPAP and improved functional class. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil versus placebo. Long-term data available only at a dose of 80 mg 3 times daily in 222 patients completing one year of treatment with sildenafil mono-therapy showed sustained improvement from baseline at one year in the 6MW test (51 m). A post hoc analysis of 84 PAH associated with CTD patients receiving sildenafil in the SUPER-1 trial revealed improved exercise capacity, hemodynamic parameters, and functional class at 12 weeks when compared with placebo (26). Based on the US FDA and European guidelines, approved dose of sildenafil in patients with PAH is 20 mg administered orally 3 times daily but in clinical practice, up-titration beyond 20 mg three times/day (mainly 40–80 mg three times/day) is needed quite frequently. Therefore, there has been considerable discussion as to whether higher doses might confer additional hemodynamic benefit, but such doses continue to be “off-label” (27). Most side effects of sildenafil were mild to moderate which usually related to vasodilation symptom include headache, flushing, dyspepsia and epistaxis.

**Endothelin receptor antagonists**

Endothelin-1 exerts vasoconstrictor and mitogenic effects by binding to two distinct receptor isoforms (i.e., endothelin-A and endothelin-B receptors) in the pulmonary vascular smooth muscle cells. Endothelin receptor antagonist (ERA) is a drug that blocks endothelin receptors which lead to reduce pulmonary arterial pressure. However, potential efficacy in each blocker receptor is also being comparable.

**Bosentan**

Bosentan is an oral active dual endothelin-A and endothelin-B receptor antagonist and the first molecule of its class that was synthesized. Bosentan was used in PAH (idiopathic, associated with CTD, and Eisenmenger's syndrome) in five randomized controlled trails (RCTs) (28-32) and the improvement in exercise capacity, functional class, hemodynamics, echocardiographic and Doppler variables and time to clinical worsening was found. Two RCTs enrolled exclusively patients with WHO-FC II (31) or patients with Eisenmenger's syndrome (32). This resulted in regulatory authority approval for the use of bosentan in the treatment of PAH patients in WHO-FC II and also in patients with PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome.

In an initial effort to evaluate bosentan in PAH patients, a relatively small, randomized, double-blind, placebo-controlled, multicenter study of 32 functional classes III or IV IPAH or scleroderma spectrum of diseases associated patients was conducted. Patients were randomized to receive bosentan versus placebo (2:1 ratio) (28). After 12 weeks, the 6MW test improved by 70 m in the bosentan arm, whereas no improvement was seen with placebo at week 12. The median change from baseline was 51 m with bosentan versus -6 m with placebo. The mean difference between treatment arms in the 6MW test was 76 in favor of bosentan (95% confidence interval: 12 to 139; p=0.021). Bosentan improved cardiac index and reduced mPAP and pulmonary vascular resistance (PVR). Functional class improved in patients treated with bosentan.

A second double-blind, placebo-controlled study evaluated bosentan in 213 patients with WHO functional classes III to IV PAH (either idiopathic or associated with connective tissue disease) was performed. Patients were randomized to

receive placebo or bosentan 125 or 250 mg twice daily for a minimum of 16 weeks (62.5 mg twice daily for 4 weeks, then target dose) (29). The primary end point was a change in exercise capacity (assessed by 6MW test), and secondary end points included changes in Borg dyspnea index, WHO functional class, and time from randomization to clinical worsening. After 16 weeks, bosentan improved the 6MW test by 36 m, whereas deterioration (-8 m) was seen with placebo, and the difference between treatment groups in the mean change in 6MW test was 44 m in favor of bosentan (95% confidence interval: 21 to 67 m, p=0.0002). No dose response for efficacy could be ascertained, although the placebo corrected improvement in 6MW test for the currently FDA-approved dose of 125 mg twice daily was 35 m. This study was the first to assess time to clinical worsening, a composite morbidity and mortality end point. Time to clinical worsening was defined in this study as time to death, lung transplantation, hospitalization for PH, lack of clinical improvement or worsening leading to discontinuation, need for epoprostenol therapy, or atrial septostomy. The risk of clinical worsening was reduced by bosentan compared with placebo (p=0.0015).

Longer-term data regarding bosentan therapy have been more recently published. This study (33) reported that bosentan treatment was started at the dose of 62.5 mg twice daily and up titrated to 125 mg twice daily after 4 weeks. In pediatric patients, doses were reduced according to the body weight. Side effects of bosentan were syncope, flushing, increasing in hepatic aminotransferases and/or aspartate aminotransferase occurred in approximately 10% of the subjects which found to be dose dependent and reversible after dose reduction or discontinuation (33). For these reasons, liver function test should be performed monthly in patients receiving bosentan. In addition, reductions on hemoglobin levels and impaired spermatogenesis should be observed.

**Combination therapy**

The term combination therapy describes the simultaneous use of more than one PAH-specific class of drugs e.g. ERAs, phosphodiesterase type-5 inhibitors and prostanoids. Combination therapy has become the standard of care in many PAH centres, although long-term safety and efficacy have not yet been explored. Numerous case series have suggested that various drug combinations appear to be safe and effective (30, 34-37). In one series, a step-wise use of combination therapy according to predefined treatment goals was associated with an improved outcome compared with a historical control group (38). Results of a few RCTs evaluating combination therapy for PAH have been published. The relatively small BREATHE-2 study (30) showed a trend to a better hemodynamic effect of the initial combination epoprostenol-bosentan as compared to epoprostenol alone.

The STEP-1 study (39) addressed the safety and efficacy of 12 week therapy with inhaled iloprost in addition to bosentan and found a marginal increase in the post-inhalation 6 min walk distance by +26m (P=0.051). When measured at pre-inhalation, the placebo-corrected improvement in 6 min walk distance was +19 m (P = 0.14). There was no improvement in pre-inhalation hemodynamics in the iloprost group after 12 weeks of treatment, but time to clinical worsening was significantly prolonged in the iloprost group (0 events vs. 5 events in the placebo group, P = 0.02). In contrast, another RCT, Combination therapy of Bosentan and aerosolized Iloprost in idiopathic pulmonary arterial hypertension (COMBI), which also studied the effects of inhaled iloprost added to bosentan, was stopped prematurely after a planned futility analysis. It did not show an effect on 6 min walking distance or time to clinical worsening (40).

Another RCT called TRIUMPH (41) studied the effects of inhaled treprostinil in patients treated with bosentan or sildenafil. The primary endpoint (i.e., change in 6MWT at peak exposure) improved by 20 m compared with placebo (P< 0.0006). At trough exposure, i.e. after 0.4 h post-inhalation, the difference was 14 m in favor of the treprostinil group (P< 0.01). There were no significant differences in Borg dyspnea index, functional class and time to clinical worsening. In addition, the PACES trial (42) addressed the effects of adding sildenafil to epoprostenol in 267 PAH patients. The most pertinent findings of this study were significant improvements after 12

weeks in 6MWT and time to clinical worsening. Importantly, seven deaths in the placebo group occurred in this trial.

Additional data from the RCTs were available for the combination of ERAs and phosphodiesterase type-5 inhibitors. In the subgroup of patients enrolled in the EARLY study (31) (bosentan in WHO-FC II PAH patients) who were on the treatment with sildenafil, the hemodynamic effect of the addition of bosentan was comparable with that achieved in patients without background sildenafil treatment. A pharmacokinetic interaction was described between bosentan and sildenafil, which acted as inducers or inhibitors of cytochrome P450 CYP3A4, respectively. The co-administration of both substances resulted in a decline of sildenafil plasma levels and in an increase in bosentan plasma levels (43). Until now there has been no indication that these interactions are associated with reduced safety (44) but the issue of whether the clinical efficacy of sildenafil is significantly reduced is still under debate. No pharmacokinetic interactions have been reported between sildenafil and the two other available ERAs, sitaxentan and ambrisentan. In the PHIRST study (45) the combination of tadalafil and bosentan resulted in an improvement of exercise capacity of borderline statistical significance (subgroup analysis).

There are many open questions regarding combination therapy including the choice of combination agents, the optimal timing [initial combination (in naive patients) or sequential combination (according to the response to the first drug)], when to switch, and when to combine. When combination therapy is considered, patients should be treated within clinical trials or registries whenever possible. Combination therapy of established PAH drugs is recommended for patients not responding adequately to mono-therapy, but combination therapy should be given by experts only. Whether the response to mono-therapy is sufficient or not, it can only be decided on an individual basis. The safety and efficacy of tyrosine kinase inhibitors in PAH must be further evaluated and at present the use of these drugs should be restricted to RCTs.

## Economic Evaluation of Drug Therapies

Economic issues involved in healthcare have been recognized worldwide as being very important. The growth of both public and private healthcare sectors in recent years implies that there is an increasing demand for health economic expertise. The appraisal of health care programs is increasingly necessary for health professionals, health services management and industries related to healthcare. Evaluation of health care programs may be divided into evaluation of efficacy, effectiveness, efficiency and availability. Efficiency is a key concept in economics. The evaluation of efficiency is more commonly known as economic evaluation. Economic evaluation may be defined as 'the comparative analysis of alternative courses of action in terms of both their costs and outcomes (46).

### Costs

These have broad definitions in health economics, which may base in part on the perspective or viewpoint. Perspective requires from whose point of view is the study conducted. Health care payers are only interested in the direct costs of health care, while society considers that both direct and indirect costs (i.e., loss of productivity) are also important. In practical, the societal perspective is considered as the most appropriate perspective, but health care managers with a limited budget may be interested in only the costs that fall on their own budget. Costs therefore can be classified as below:

**Direct costs** are the costs from the perspective of the healthcare funder including staff costs, capital costs and drug acquisition costs.

**Indirect costs** are the costs incurred from the loss of earnings, loss of productivity, loss of leisure time, due to the illness. This would include not just the patient themselves but also their families and society as a whole. Many of these are difficult to measure, and there are some controversies over how to value these.

### Outcomes

The Outcome that can expect from an intervention might be measured in

Natural units - e.g. years of life saved, Myocardial infarction prevented

Utility units - utility is word for satisfaction of people, or sense of well-being, and is an attempt to evaluate the quality of a state of health. Utility estimates can be obtained through direct measurement (using techniques such as time trade off or standard gambles, or by EQ-5D questionnaire). They are often measured in different disease states. The Quality Adjusted Life Year (QALY) is widely used to integrate both quality and the quantity of life.

### Methods of Economic Evaluation

Economic evaluation is the formal process of weighing outcomes and costs in an incremental analysis. It is essentially a framework which draws up a balance sheet between costs and benefits to assist decision making. There are four common methods of economic evaluation (Table 2.2)(46, 47).

**Table 2.2 Economic evaluation methods**

| Method | Measurement of outcome | Result |
|---|---|---|
| Cost minimization analysis (CMA) | Assumed to be equivalent in comparable groups | Additional costs of therapy A relative to B |
| Cost effectiveness analysis (CEA) | Health outcomes across therapies are measured in similar natural units (i.e., Life year gained, LYG). | ICER (cost per LYG) |
| Cost utility analysis (CUA) | Health outcomes across therapies are valued in utility based on individual preferences (i.e., Quality adjusted life year, QALY gained) | ICER (cost per QALY gained) |
| Cost benefit analysis (CBA) | Measured in similar or different units and are always valued in monetary units. | Net benefit, Benefit to cost ratio, Return on investment (ROI) |

Cost minimization analysis (CMA)

CMA involves measuring only costs and is applicable only where the outcomes are identical. An example would be prescribing a generic preparation instead of the brand drug when we assume lower cost but same health outcomes.

Cost effectiveness analysis (CEA)

The term cost effectiveness is often used to refer to a particular type of evaluation, in which the health benefit can be defined and measured in natural units (e.g. years of life saved) and the costs are measured in money. Therefore it compares therapies with qualitatively similar outcomes in a particular therapeutic area. CEA is the most commonly applied form of economic analysis in the literature, and especially in drug therapy. It does not allow comparison to be made between two totally different areas of medicine with different outcomes. The key measure is the incremental cost effectiveness ratio (ICER).

Cost utility analysis (CUA)

This is similar to cost-effectiveness analysis which costs are measured in monetary unit and the outcomes which outcomes are measured in a unit of utility (i.e., a QALY). CUA can in theory compare more than one area of interventions such as cost per QALY of coronary artery bypass grafting versus cost per QALY for erythropoietin in renal disease. In practice this is not so easy since the QALY is not a well-defined fixed unit transferable from study to study.

Cost benefit analysis (CBA)

The benefit is measured as the associated economic benefit of an intervention which both costs and benefits are expressed in money unit. However the virtue of this analysis is that it may allow comparisons to be made between very different areas, and not just medical interventions such as cost-benefit of expanding high school education (benefits of improved education and productivity) compared to establishing office syndrome service (enhancing productivity by returning patients to work). This approach is not widely used in health economics. Economists argue that health should be another commodity, and not necessarily valued more than other possible uses of the resources.

All most studies are often complex and require use of economic models. Decision-analytic modeling is commonly used as the framework for meeting these requirements. The two most common forms of model used in decision analysis for economic evaluation are decision tree and Markov models.

**Decision tree**

The decision is commonly structure for decision models in economic evaluation. It represents individual's prognoses, following some sort of interventions, by a series of pathways. The decision can be used to describe a series of general features with model structure as shown in figure 2.2 (47).

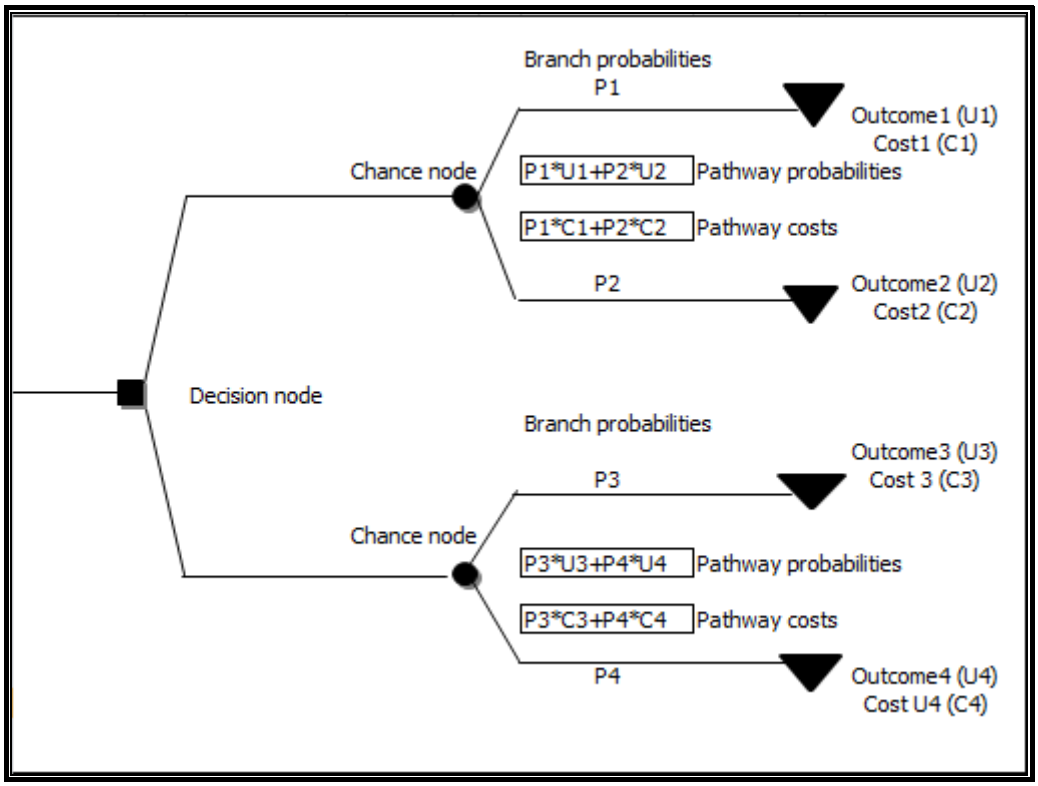


**Figure 2.2 Model structure of decision tree**

Decision nodes- The square box at the start of decision tree is a decision node and represents the decision being addressed in the model.

Chance node- Coming out of the decision node is the range of possible pathway that characterizes the effects of the alternative therapies. The pathways are built up through a series of branches representing particular events.

Branch probabilities- The branches issuing from a chance node represent the possible events patients in term of branch probabilities.

Pathways-The combination of the different branches in the tree determines a series of pathways along which patients can pass in the tree.

Pathway probabilities-To the right of the decision tree is a series of column of numbers. These probabilities are calculated by multiplying the initial branch probability by subsequent conditional probabilities.

Pathway costs-Each pathway in the tree also has costs associated with it. These represent the sum of costs of each events a patient experience in that pathway.

Expected cost and outcome can be calculated by weighing each pathway cost and outcome. Then sum across all the pathways.

### Markov model

Markov models assume that there are exactly numbers of defined health states and at any time each patient should be assigned to only one (mutually exclusive) health state. At the end of each cycle, there is a risk of a patients moving from one state of health to another, defined by transition probabilities. The probabilities of moving from one state to all other possible states should always add up to 1 (47).

## Economic evaluation of PAH treatments

A systematic literature was conducted to identify economic evaluation studies of drug treatments (i.e., bosentan, iloprost, beraprost and sildenafil) in pulmonary arterial hypertension (PAH) published from January 1990 to October 2012 and searched from electronic databases including PubMed and the Cochrane Library. Searching terms used for PubMed database were as follows: "Hypertension, Pulmonary/drug therapy"[Mesh] AND "Cost-Benefit Analysis"[Mesh] AND ("sildenafil" OR "bosentan" OR "iloprost" OR "beraprost"). Key words used for Cochrane database were as follows**:** "Hypertension, Pulmonary "[Mesh] AND "Cost-Benefit Analysis"[Mesh] OR "iloprost" OR "bosentan" OR "sildenafil" OR "beraprost"

The following inclusion criteria were used to select relevant studies. Original study with full-text of full economic evaluations (i.e., cost-effectiveness or cost-utility analyses) studies related to PAH treatments in English language were included. Therefore, studies evaluating only costs (i.e., cost of illness or cost analysis) or clinical outcomes of the interventions were excluded. Figure 2.3 shows the systematic review process.

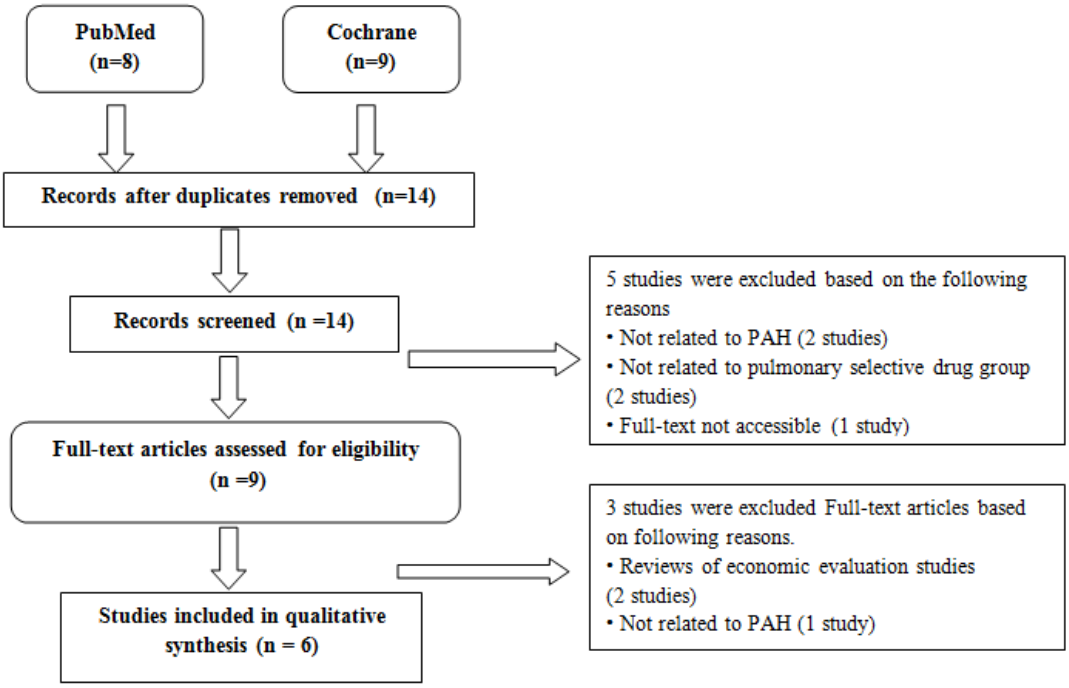


**Figure 2.3 Systematic review process**

The authors screened titles and abstracts of studies based on the inclusion and exclusion criteria. Selected studies were included for the full review. Data were extracted using data extraction form in Microsoft Excel 2010. Data included study characteristic, citation, publication year, setting, objective study population, intervention, comparator, perspective, time horizon, model used, clinical effectiveness, type of cost, discounting, results and sensitivity analysis.

According to the systematic review of economic evaluation of drug treatments in PAH, seventeen articles were reviewed and only six full text articles were included (2, 48-52). Table 2.3 present six articles in details. Six studies were conducted in the United Kingdom (UK)(2, 51), the United State (US)(48, 50), Australia and Spain(49, 52). Target populations in two studies were specific to iPAH and PAH-CTD (49, 51), while the other studies did not mention about type of PAH. Perspective used in these studies was healthcare payer (3 studies) (48-50) and healthcare system (3 studies) (2, 51, 52). Compared interventions included sildenafil, iloprost and bosentan. Nevertheless, beraprost was not found as a compared intervention in any economic evaluation studies. Time horizon used in these studies was 1 year (2 studies) (48, 50), 3 years (1 study) (52), 15years (1 study) (49) and

lifetime period (2 studies) (2, 51). The cost-effective analysis (CEA) (1 study) (49) and cost-utility analysis (CUA) (5 studies) (2, 48, 50-52) were mostly used. Markov model (5 studies) and Monte-Carlo simulation (1 study) (49) were applied to evaluate cost and outcome. Only direct medical costs were estimated in accordance with perspective used. In term of clinical effectiveness, most studies showed that bosentan and sildenafil were more effective than iloprost. Costs have been discounted at the rate of 3% (1 study)(52) , 3.5% (2 studies) (2, 51) or 5% (1 study)(49) per annum. Probabilistic sensitivity analysis (PSA) (1 study) (52) and one-way sensitivity analysis (5 studies) were used.

Results of cost-effectiveness analysis were presented in Table 2.3 All studies reported both cost and clinical outcome in terms of incremental cost-effectiveness ratio (i.e., cost per quality-adjusted life year (ICER/QALY) or cost per life year gained (ICER/LYG), or cost saving (per 100 patients/year). The results showed that bosentan and sildenafil were likely to be less costly and resulted in a greater increase in QALYs gained when compared to other drugs. Moreover, the ICER results of bosentan compared to other drugs were A $55,927/LYG (49), £27,000/QALY (2) and £30,000/QALY (51). Three studies in the UK, USA, and Australia indicated that bosentan was more cost-effective compared with other drugs in their contexts. In addition, one study demonstrated that bosentan was cost saving (US$3,631,900 per 100 patients/year) (48). In addition, two studies revealed that the ICER results of sildenafil compared with other drugs were dominant meaning that the intervention was more effective and less costly than other drugs and also cost-effective in the UK and USA(2, 50).

**Table 2.3 Results of systematic review**

| Data | Highland et al. (2003)(48) | Wlodarczyk et al. (2006)(49) | Chen et al. (2009)(2) | Garin et al. (2009) (50) | Stevenson et al.(2009)(51) | Roman et al. (2012)(52) |
|---|---|---|---|---|---|---|
| **Conduct study** | USA | Australia | UK | USA | UK | Spain |
| **Study population** | PAH in (FC) III or IV | iPAH | PAH of (FC) III | PAH of (FC) III or IV | iPAH or PAH-CTD (FC) III | PAH of (FC)III |
| **Intervention** | bosentan | bosentan | epoprostenol, iloprost, bosentan,sitaxentan and sildenafil | bosentan, treprostinil, epoprostenol, iloprost, sildenafil, sitaxentan and ambrisentan | bosentan | iloprost,epoprostenol, treprostinil |
| **Comparator** | treprostinil ,epoprostenol | supportive care | supportive care | other treatments | supportive care | other treatments in prostacyclin group |
| **Perspective** | Healthcare payer | Healthcare payer | Healthcare system | Healthcare payer | Healthcare system | Healthcare system |
| **Method** | Cost-utility (Markov model) | Cost-effectiveness (First-order Monte Carlo simulation) | Cost-utility (Markov model) | Cost-utility (Markov model) | Cost-utility (Markov model) | Cost-utility (Markov model) |
| **Time horizon** | 1 year | 5,10,15 years | Life time | 1 year | Life time | 3 years |

**Table 2.3 Results of systematic review (cont.)**

| Data | Highland et al. (2003) (48) | Wlodarczyk et al. (2006) (49) | Chen et al. (2009)(2) | Garin et al. (2009) (50) | Stevenson et al.(2009)(51) | Roman et al. (2012)(52) |
|---|---|---|---|---|---|---|
| **Discounting** | - | 5% | 3.50% | - | 3.50% | 3% |
| **Sensitivity analysis** | one-way sensitivity analysis | one-way sensitivity analysis | one-way sensitivity analysis | one-way sensitivity analysis | one-way sensitivity analysis | one-way sensitivity and probabilistic analysis |
| **Outcome** | QALYs | ICER* | QALYs | QALYs | QALYs | QALYs |
| **Result** | Bosentan was less costly (cost savings of US$3,631,900) and resulted in greater gain in 11 QALYs than epoprostenol and treprostinil.for 100 patients in cohort study | ICER at 15 years of A$55,927 dollars for each LYG | Epoprostenol = ICER £277,000/ QALY for FCIII and £343,000/QALY for FCIV patients. In FCIII patients. iloprost = £101,000/QALY, bosentan= £27,000/ QALY and sitaxentan =£25,000/QALY | Treatment with sildenafil was less costly, resulted in a greater gain in QALYs and ICER of sildenafil was dominant compared with other treatments.. | The cost per QALY of bosentan compared with palliative care alone became £30,000 (a potential cost-effectiveness threshold used in the United Kingdom). | ICER of epoprostenol versus iloprost and treprostinil were much above the threshold commonly used in Spain. Iloprost was dominant compared with treprostinil. |

# CHAPTER III
# METHODOLOGY

The methodology of this study was consisted of eight parts as follows.

Study design

Perspective

Economic evaluation (Model structure)

Time horizon

Discount rate

Parameters

Transitional probability

Cost measurement

Utility

Uncertainty analysis

Budget impact analysis

## Study design

A cost-utility analysis was conducted using Markov model which simulated the disease progression and compared lifetime costs and health outcome with three months cycle length. The analysis was focused on treatment options for patients with PAH associated with CHD in WHO Functional class II and III. Furthermore, the budget impact analysis of the cost-effective options on the governmental viewpoint was estimated for five years.

**1. Population / patients and study site**

**Population/patients**

Study populations were the patients with PAH associated with CHD who started the treatment for PAH in Functional class II and III. PAH patients were classified into two groups (i.e., PAH-CHD patients aged ≤ 30 years and PAH-

CHD patients aged > 30 years). In addition, PAH patients were also divided by the severity of functional class II to III at the start of the treatment.

**Study site**

This study site was the university hospitals, namely Ramathibodi hospital and Siriraj hospital where could provide medical treatments for pulmonary selective drugs should perform cardiac catheterization laboratories, pulmonary vasodilator test laboratories, heart ultrasound images, laboratory of clinical chemistry and 6-minute walk test (6MWT) for the diagnosis and identification of the cause based on the requirement of the National List of Essential Medicines (NLEM) Committees.

**Comparison of alternatives**

Table 3.1 presents the available choices of treatment for the patients with PAH associated with CHD who started PAH treatment in Functional class II and III.

**Table 3.1 Treatment options**

| Alternative | Initial treatment | In case of unresponsive to first line treatment | Treatment guideline |
|---|---|---|---|
| **1** | standard treatment | standard treatment | First line treatment |
| **2** | sildenafil | standard treatment | First line treatment |
| **3** | beraprost | standard treatment | First line treatment |
| **4** | sildenafil | sildenafil + iloprost | Second line treatment |
| **5** | sildenafil | sildenafil + bosentan | Second line treatment |

This study evaluated the alternatives for both first and second line treatments in accordance with the treatment guidelines and the practices of medical professionals as follows (4):

First line treatment:

Sildenafil was compared with standard treatment as alternative option 2 compared with 1 in Table 3.1.

Beraprost was compared with standard treatment as alternative option 3 compared with 1 in Table 3.1.

Second line treatment:

In cases of unresponsiveness to sildenafil as the first line treatment, sildenafil combined with iloprost (combination therapy) was compared with standard treatment as alternative option 4 compared with 2 in Table 3.1.

In cases of unresponsiveness to sildenafil as the first line treatment, sildenafil combined with bosentan (combination therapy) was compared with standard treatment as alternative option 5 compared with 2 in Table 3.1.

**2. Health outcomes**

Health outcomes were Quality adjusted life year (QALY) calculated from life (Life years) multiplied by a utility score.

## Perspective

According to the recommendations of the Thai Health Technology Assessment Guideline, societal perspectives was used in this study (53).

# Economic evaluation

## Model structure

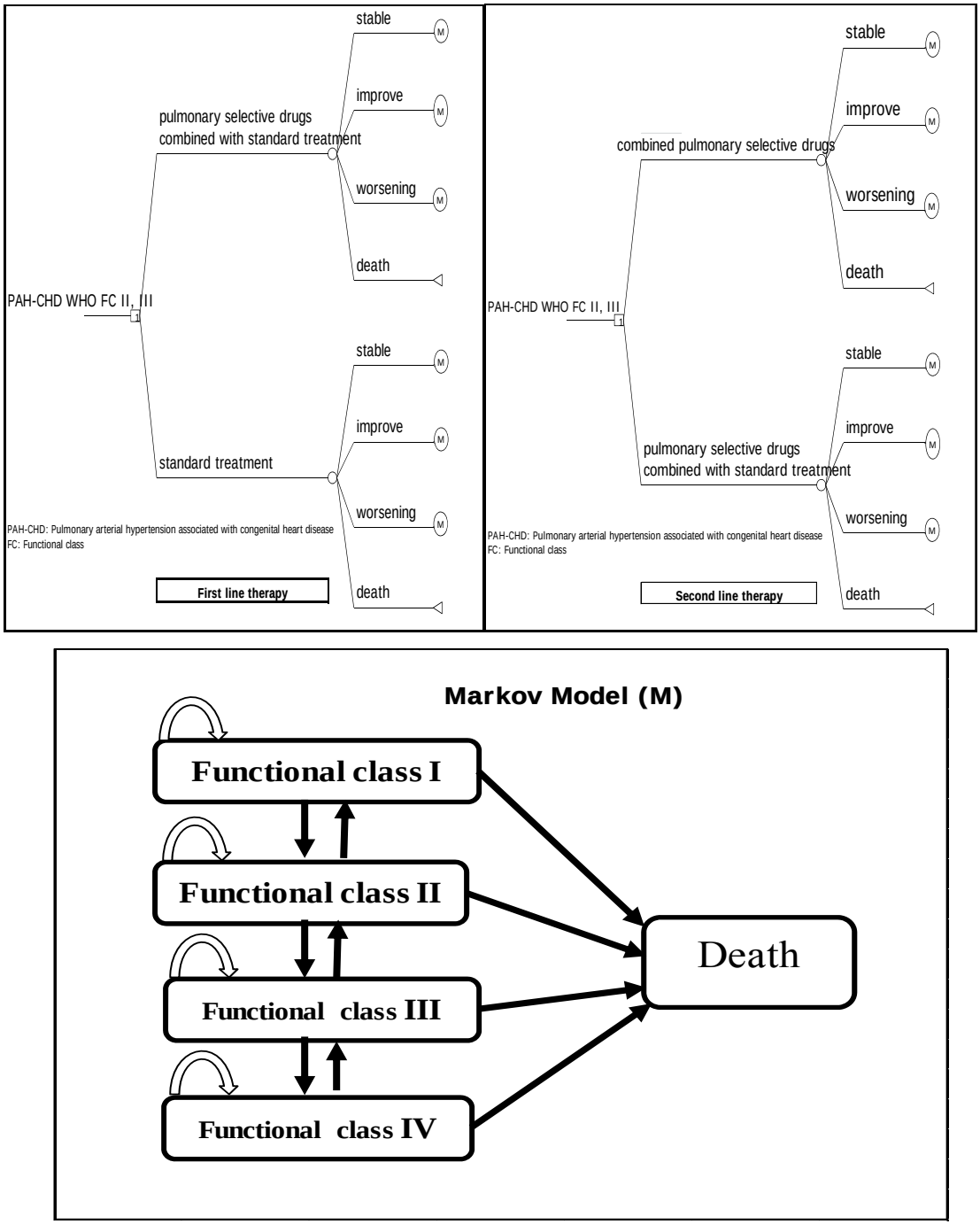


**Figure 3.1 Diagram of the decision tree and Markov model**

Figure 3.1 shows decision tree and Markov model. There are five health states including 1) functional class I state, 2) functional class II state, 3) functional class III state, 4) functional class IV state and 5) death state. Patients with functional class II or III would start the treatment. If the patients' condition would be improved and diagnosed by specialist doctors, they patients would move to functional class I or II state. On the other hand, if patients' condition gets worse using the same criteria as functional class improvement. They would move to functional class III or IV state. Patients could stay at the same state or could move back to the previous functional class state. Patients in each state could move to death state. The arrows in model show the probability of transition from one state to another state called transitional probability for a cycle length of 3 months.

**Model assumptions**

Currently, there has been no enough evidence found to confirm efficacy of combination treatment in PAH base on alternative options in this study (i.e., sildenafil plus iloprost, sildenafil plus bosentan). Thus, it was assumed that efficacy of combination therapy would be equal to that of the second line treatment for patients with unresponsiveness to the first line treatment.

## Time horizon

Markov model was used to assess the expected lifetime horizon.

## Discount rate

Since the time horizon of this study was lifetime period, all costs and outcomes in future values were adjusted to the present values with the discount rate of 3% based on the recommendations of the Thai Health Technology Assessment Guidelines.

## Parameters

The parameters used in this study were consisted of three main parameters which are transitional probability, cost and utility.

### 1. Transitional probability

### Probability of Death

The data of survival in PAH-CHD were obtained from the study of Panichwattana (54) which was the only one cohort study in Thai PAH-CHD patients. Clinical data were collected from medical chart in 81 PAH-CHD patients who were classified by WHO functional class during 2009-2010. All cases were diagnosed with right heart catherization or echocardiogram. Six patients were dead in one year after diagnosis and there was a significant difference in mortality among patients with different severity based on WHO classification.

According to the results of this study, probability of death was calculated. Rate is the spontaneous potential for the occurrence of an event and expressed in number of patients at risk per time. Probability represents the likelihood of an event happening over a specific period of time. It is possible to convert a spontaneous rate to a probability over a particular time period, if the rate is assumed to be constant over that period. The formula is shown as follows (47).

$$p= 1- \exp[-rt]$$

Where p is the probability, r is the rate and t is the time period. In addition, it is possible to convert a probability over a period of time to a (constant) spontaneous rate as follows.

$$r=-[\ln(1-p)]/t$$

Table 3.2 demonstrates probability of death parameters. Parametric survival method (Weibull distribution) was not applied in this study due to the limited data of population and death event. It was assumed that probability of death was directly related to patient severity based on WHO classification, but not related to efficacy of intervention. This assumption was tested on the Markov model for Model validation. The validation analysis was performed in PAH-CHD (mean age 24 years) who classified the severity of the disease by WHO Functional class I to IV, as shown in Figure 3.2.

**Table 3.2 Probability of death parameters**

| Parameter (Probability of dying) | Distribution | Mean | SE | Ref |
|---|---|---|---|---|
| **Probability of death of PAH-CHD ( Standard treatment and Pulmonary selective drug )** | | | | |
| probability of death in FC I | Beta | 0.002 | 0.009 | (54) |
| probability of death in FC II | Beta | 0.013 | 0.009 | |
| probability of death in FC III | Beta | 0.016 | 0.011 | |
| probability of death in FC IV | Beta | 0.240 | 0.065 | |

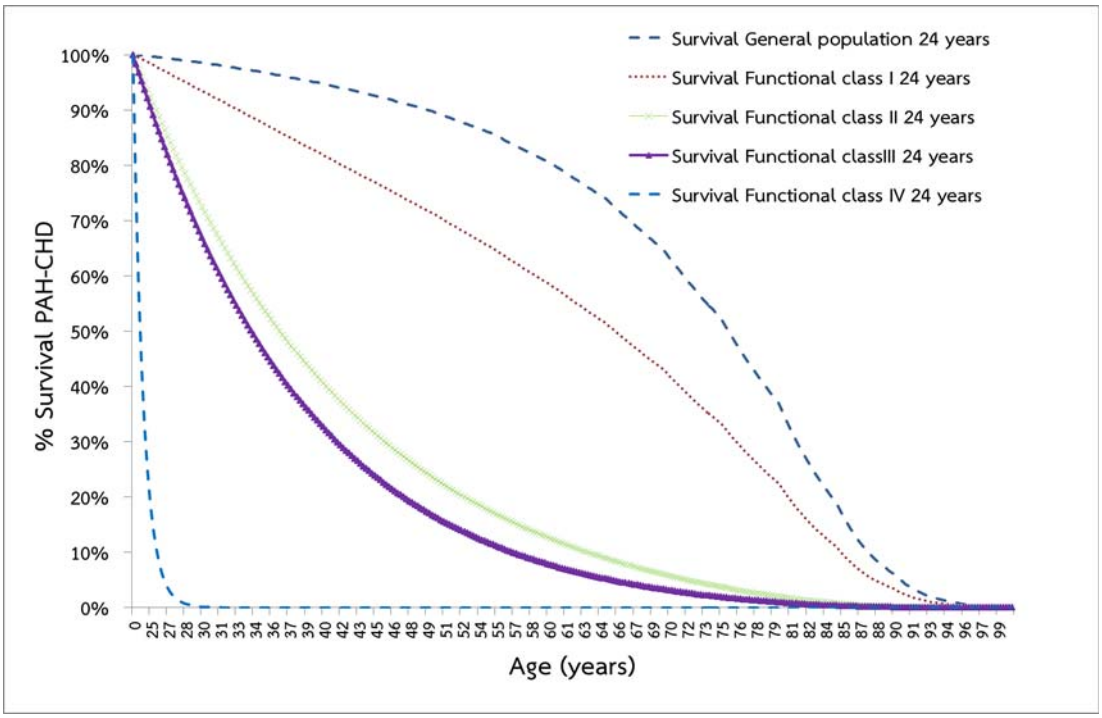


**Figure 3.2 Survival rate of patients with PAH-CHD with mean aged 24 years**

**Transitional probability in each functional class**

Transitional probability data in patients receiving standard treatment were obtained from systematic review and meta-analysis studies during 1980 – 2007 (2) as presented in Table 3.3.

Transitional probability data in patients receiving pulmonary selective drugs were obtained from the relative risk (RR) adjusting for the probability of a change in functional class of patients who received standard therapy. There is an existing systematic review which considered studies from 1980 to 2007 (2). Therefore, in this study, we searched the database from 2007 up to 2012. A systematic literature review and meta-analysis was performed through PubMed during March 1, 2007 to May 8, 2012 to investigate the efficacy of standard treatment and pulmonary selective drugs. Key words were as follows: ("Pulmonary arterial hypertension" OR "Pulmonary artery hypertension") AND ("iloprost" OR "bosentan" OR "sildenafil" OR "beraprost"). The inclusion criteria were the studies related to randomize controlled trial, meta-analysis, or systematic review and the studies with patients with PAH associated with CHD in functional class II and III. The studies with non-English or without full-text available were excluded. Flow chart of systematic reviews on clinical efficacy studies selection presents in Figure 3.3.

Meta-analyses were conducted using Ravman program. Separate analyses were performed for each of the interventions. The results were presented as relative risk for "FC improved or worsening" at 12 weeks to be used in the economic evaluation. Heterogeneity between studies was assessed with the chi-squared test and $I^2$. The $I^2$ is a measure of inconsistency in studies' results in meta-analysis. It shows the percentage of the total variation across studies meaning that 0% (no observed heterogeneity) and 100% (significant heterogeneity). The chi-squared tests were used to investigate the inconsistency in studies. If p-value $\leq 0.10$, it means that the result has heterogeneity (55).

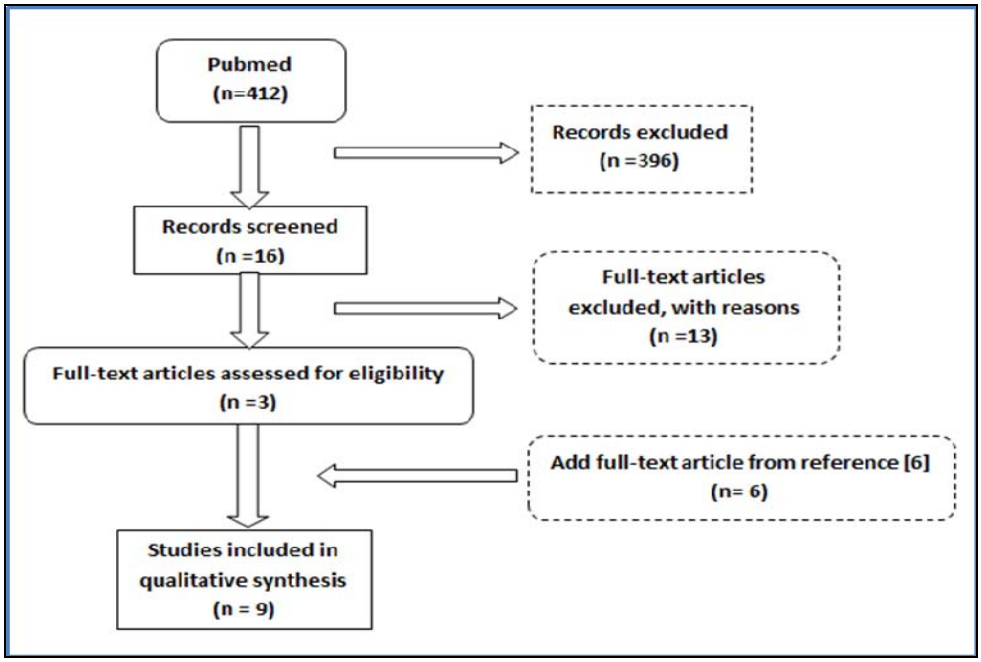


**Figure 3.3 Flow chart of systematic reviews on clinical efficacy studies selection**

Based on the results of systematic review, 412 studies were found (Figure 3.3). There were 396 studies excluded, therefore only sixteen studies were selected according to inclusion and exclusion criteria. In summary, nine studies were included in the analysis. The relative risk (RR) values of functional class worsening and improvement were analyzed for each pulmonary selective drug compared with placebo as shown in Table 3.3. The RR values of changing functional class for each pulmonary selective drug compared with placebo were obtained from meta-analysis. It was found that there was no significant heterogeneity found in this meta-analysis. Based on the RR of functional class worsening, patients receiving pulmonary selective drugs (i.e., iloprost, sildenafil, beraprost, and bosentan) could reduce the risk of functional class worsening by 24%, 57%, 90%, and 71%, whereas they were more likely to improve functional class approximately 1.94, 4.23, 0.93, and 1.39 times compared to placebo, respectively.

**Table 3.3 Parameters of transitional probability**

| Parameter (Transitional probability) | Distribution | Mean | SE | Ref |
|---|---|---|---|---|
| **Probability of switching FC in PAH-CHD patient who treated with standard treatment in 3 months** | | | | |
| Probability of switching from FC2 to FC1 | Beta | 0.125 | 0.033 | (2) |
| Probability of switching from FC1 to FC2 | Beta | 0.127 | 0.043 | |
| Probability of switching from FC3 to FC2 | Beta | 0.125 | 0.033 | |
| Probability of switching from FC2 to FC3 | Beta | 0.127 | 0.043 | |
| Probability of switching from FC3 to FC4 | Beta | 0.094 | 0.029 | |
| Probability of switching from FC4 to FC3 | Beta | 0.025 | 0.022 | |
| **Relative risk (RR) of Pulmonary selective drugs** | | | | |
| Worsening / Improvement (compare with standard treatment) | | | | |
| iloprost | Gamma | 0.76 /1.94 | 0.467/0.645 | (20) |
| sildenafil | Gamma | 0.43 /4.23 | 0.380/2.043 | (26),(25) (24) |
| beraprost | Gamma | 0.10/0.93 | 0.199/0.612 | (28),(32),(31),(56),(29) |
| bosentan | Gamma | 0.29/1.39 | 0.145/0.260 | |

**2. Cost measurement**

**Direct medical costs**

Direct medical costs (e.g., costs of medicine, medical services, and monitoring, etc.) were retrieved from the hospital database during the years 2002-2012 at Ramathibodi hospital. The patients were identified by diagnosis code by International Classification of Diseases (ICD) version 9 and 10 (i.e., primary pulmonary hypertension (ICD-10 I27.0), other secondary pulmonary hypertension (ICD-10 I27.2), Eisenmenger syndrome (ICD-10 I27.8), echocardiography (ICD-9 CM. 88.72) and right heart cardiac catheterization (ICD-9 CM 37.21). All costs were adjusted to values in 2012 using consumer price index and charges were adjusted to cost using the cost to charge ratio equal to 0.69 (57). The total of direct medical cost was calculated from outpatient cost and hospital admission cost per visit multiplied by the average number of visits in each service between the functional class I to IV. The average numbers of visits were obtained from interviewing patients using questionnaire at Ramathibodi and Siriraj hospitals (see detail in Appendix A). The ethical approval of this study was granted by the Ethics Committee of the two institutions.

However, direct medical cost data could not be classified into two groups (i.e., patients receiving standard treatment and those treating with pulmonary selective drug) due to the limitation of a hospital database. Therefore, it was assumed that these two groups had the same outpatient costs. Table 3.4 presents direct medical cost parameters used in this study.

**Table 3.4 Parameters of direct medical cost**

| | Distribution | Mean | SE | Ref. |
|---|---|---|---|---|
| **Direct medical cost of PAH-CHD patient receiving with standard treatment during 3 months (Baht)** | | | | |
| cost of outpatient visits (supportive care for 3 months) | Gamma | 1,063 | 873 | Database of Ramathibodi hospital |
| cost of hospital admission (supportive care for 3 month) | Gamma | 4,828 | 2,616 | |
| **Direct medical cost of PAH-CHD patient who receiving pulmonary selective drugs during 3 months (Baht) (excluded drug cost)** | | | | |
| cost of outpatient visits (supportive care for 3 months) | Gamma | 1,063 | 873 | Database of Ramathibodi hospital |
| cost of hospital admission (supportive care for 3 month) | Gamma | 24,226 | 15,316 | |

In addition, the cost of pulmonary selective drugs that pharmaceutical industries submitted to the subcommittee of the NLEM using the average dose used in adults were shown in Table 3.5 .

**Table 3.5 Drug price of pulmonary selective drug**

| Drug name | Dose | Price per dose (Baht) | Price per day (Baht) |
|---|---|---|---|
| beraprost | 20 mcg four times/day | 21.4 | 21.4*4=85.6 |
| sildenafil | 20 mg three times/day | 46.01 | 46.01*3=138.03 |
| bosentan | 125 mg once daily | 1,203.75 | 1,203.75 |
| iloprost | 5 mcg NB 6-9 times/day | 353.10 | 353.1*7.5=2,648.25 |

**Direct non-medical costs**

Direct non-medical costs (e.g., travel cost, food, costs of informal care etc.) were collected from interviewing patients and caregivers who received the services at Ramathibodi and Siriraj hospitals using the data collection forms (see details in Appendix A). The ethical approval of this study was granted by the Ethics

Committee of the two institutions. Table 3.6 presents the parameters of direct non-medical costs.

**Indirect costs**

Indirect cost (i.e., productivity lost due to illness) was calculated using human capital approach. Income loss from the average income classified by age and sex in 2009 was obtained from the National Statistical office. Number of days that patients missed work due to the illness was collected from interviewing patients and caregivers who received the services at Ramathibodi and Siriraj Hospitals using the data collection forms (see details in Appendix A). Twenty-one PAH-CHD patients were interviewed at Ramathibodi (15 patients) and Siriraj hospital (6 patients). Patients in FC I (2 patients), FC II (16 patients), FC III (2 patients) and FC IV (1 patient) were included in the analysis.

The ethical approval of this study also was granted by the Ethics Committee of the two institutions. Mortality cost was not included in order to avoid double counting because it was taken into account in the calculation of QALYs. Table 3.6 shows parameters of indirect costs.

**Table 3.6 Parameters of direct non-medical and indirect costs**

| Variable | Distribution | Mean | SE | Ref |
|---|---|---|---|---|
| **Direct non-medical cost and indirect cost during 3 months (Baht)** | | | | |
| direct non-medical cost and indirect cost in FC I | Gamma | 3,323 | 649 | Interviewing patients in Ramathibodi and Siriraj hospital using questionnaire |
| direct non-medical cost and indirect cost in FC II | Gamma | 8,268 | 2,212 | |
| direct non-medical cost and indirect cost in FC III | Gamma | 10,787 | 200 | |
| direct non-medical cost and indirect cost in FC IV | Gamma | 8,477 | 8,477 | |

**3. Utility**

The utility data were also collected from interviewing patients and caregivers who received the services at Ramathibodi and Siriraj Hospitals using the EQ-5D (European Quality of Life Measure) Thai version questionnaire in order to measure a quality of life (see details in Appendix B). The EQ-5D includes questions about health status in five dimensions including mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Each dimension has three levels (i.e., no problem, moderate problem and especially problematic). The data from measurement were converted to utility values using the coefficients of Thai population (58). Twenty one patients with PAH-CHD patients were interviewed at Ramathibodi (15 patients) and Siriraj hospital (6 patients). All patients were classified into FC I (2 patients), FC II (16 patients), FC III (2 patients) and FC IV (1 patient). Utility of PAH-CHD in FC IV equal 0. Even though the negative value of utility score was found, it was assumed that the utility value was equal to zero. Table 3.7 shows the parameters of utility.

**Table 3.7 Parameters of utility**

| Utility | Distribution | Mean | SE | Ref |
|---|---|---|---|---|
| utility of FC I | Beta | 0.68 | 0.046 | Interviewing patients in Ramathibodi and Siriraj hospital by EQ-5D questionnaire |
| utility of FC II | Beta | 0.67 | 0.044 | |
| utility of FC III | Beta | 0.67 | 0.2 | |
| utility of FC IV | Beta | 0* | - | |

## Result presentation

The Incremental Cost-Effectiveness Ratios (ICER) in THB per QALY gained were presented and calculated using the formula below.

$$ICER = (C_A - C_B)/(E_A - E_B)$$

Whereas;
$C_A$= Cost of intervention A $E_A$ = effectiveness of intervention A
$C_B$ = cost of intervention B $E_B$ = effectiveness of intervention B

## Uncertainty analysis

The aim of probabilistic modeling is to test the uncertainty of the input parameters such as cost, effectiveness, etc. in the model. One-way sensitivity analysis was performed to examine the uncertainty surrounding each parameter individually (e.g., discounting rate at 0% and 6% per annum, utility, direct medical costs, probability of death etc.) and results were presented using a tornado diagram. In addition, probabilistic sensitivity analysis (PSA) was performed to examine the effect of all parameter uncertainty simultaneously using a second order Monte Carlo simulation by the Microsoft Office Excel 2010 program. The second order Monte Carlo simulation was run for 1,000 iterations to show the interval of probable values of total costs, health outcomes, and incremental cost–effectiveness ratios (ICERs)

From 1,000 simulations of each outcome, the maximum expected net monetary benefit (NMB) was calculated for each cost-effectiveness threshold ratio value (i.e., the value that society would be willing to pay (WTP) for the intervention yielding one QALY gained). Results of the PSA were presented as cost-effectiveness acceptability curves, which showed the probability of each treatment option being cost-effective at different values of WTP per QALY gained. Moreover, threshold sensitivity analysis was carried out to determine the maximum price of a cost-effective pulmonary selective alternative at a Thai ceiling threshold of 120,000 Thai baht per QALY gained(59).

## Budget impact analysis

The model compared especially direct medical costs for only treatment option which would be the most cost-effective at one time of gross domestic product (GDP) per QALY gained (120,000 THB) (59) compared with standard treatment (first-line treatment) and with standard treatment in cases of unresponsiveness to sildenafil as the first line treatment (second-line treatment). In addition, threshold analysis was conducted to find the cost-effective price and compared results of current price and negotiated price in the most cost-effective option. Budget impact was calculated from the total number of patients with PAH associated CHD and total cost per patient incurred during five year period based on the governmental perspective. The number of PAH-CHD patients was obtained from the incidence and prevalence base on expert opinion in Thailand (i.e., 27 and 134 per year) that were calculated from the total of Thai population (i.e., 67 million), respectively.

# CHAPTER IV
# RESULTS

The results of this study were divided into three parts as follows:

1. Cost-utility analysis
2. Uncertainty analysis
3. Budget impact analysis

## Part one: Cost-utility analysis

The cost-utility analysis results were divided into two sub-groups as follows.

1. PAH-CHD patients aged ≤ 30 years (Mean age = 24 years)
2. PAH-CHD patients aged > 30 years (Mean age =49 years)

***First-line therapy***

1. PAH-CHD patient ≤ 30 years (Mean age = 24 years)

The cost-utility analysis estimated lifetime costs and health outcomes (i.e., QALYs) of the first line therapy according to treatment options based on a societal perspective. The probabilistic results of total costs and outcomes of sildenafil and beraprost compared with standard treatment classified by functional class for PAH-CHD patients aged ≤ 30 years are shown in Table 4.1. It showed that the costs were the highest for sildenafil (FC III) (2,600,134 THB), followed by sildenafil (FC II) (2,231,411 THB), whereas standard treatment (FC III) (336,305 THB) incurred the lowest cost when compared with all interventions. The QALYs of sildenafil (FC III) (13.33 QALYs) were the highest, followed by sildenafil (FC II) (12.28 QALYs) and beraprost (FC II) (12.17 QALYs), respectively. In contrast, the QALYs were the lowest for standard treatment (FC III) (3.35 QALYs), followed by standard treatment (FC II) (4.98 QALYs).

The ICER results of PAH-CHD patients who had pulmonary selective drugs were compared with standard treatment (Table 4.2). The ICERs of beraprost compared standard treatment in FC II and III were 192,752 and 201,308 THB per QALY gained, respectively. The ICERs of sildenafil compared standard treatment in FC II and III were 249,770 and 226,802 THB per QALY gained, respectively.

2. PAH-CHD patient > 30 years (Mean age =49 years)

Table 4.1 presents the total costs and outcomes of sildenafil and beraprost compared with standard treatment as the first-line therapy classified by functional class for PAH-CHD patients aged > 30 years. The total costs were the highest for sildenafil (FC III) (1,597,286 THB), followed by sildenafil (FC II) (1,456,502 THB), whereas standard treatment (FC III) (316,114 THB) incurred the lowest cost when compared with all interventions. The QALYs of sildenafil (FC III) (9.74 QALYs) were the highest, followed by sildenafil (FC II) (9.35 QALYs) and beraprost (FC II) (9.16 QALYs), respectively. In contrast, the QALYs were the lowest for standard treatment (FC III) (3.15 QALYs), followed by standard treatment (FC II) (4.63 QALYs).

The ICER results of PAH-CHD patients who had pulmonary selective drugs were compared with standard treatment and the ICER results (Table 4.2). The ICERs of beraprost compared standard treatment in FC II and III were 183,813and 194,244 THB per QALY gained, while the ICERs of sildenafil compared standard treatment in FC II and III were 228,531and 194,384 THB per QALY gained.

**Table 4.1 Total costs and health outcomes of the first-line treatments classified by patient age groups and functional class**

| Subgroup Analysis | Total costs (million THB) | | | Quality adjusted life years QALYs | | |
|---|---|---|---|---|---|---|
| | STD* | beraprost | sildenafil | STD | beraprost | sildenafil |
| **Subgroup Age ≤ 30 years** | | | | | | |
| Start FC II | 408,584 | 1,794,440 | 2,231,411 | 4.98 | 12.17 | 12.28 |
| Start FC III | 336,305 | 1,806,999 | 2,600,134 | 3.35 | 10.65 | 13.33 |
| **Subgroup Age >30 years** | | | | | | |
| Start FC II | 375,850 | 1,207,880 | 1,456,502 | 4.63 | 9.16 | 9.35 |
| Start FC III | 316,114 | 1,257,685 | 1,597,286 | 3.15 | 8.00 | 9.74 |

STD* = standard treatment

**Table 4.2 Incremental cost-effectiveness ratios (ICERs) of the first line treatments classified by patient age groups and functional class**

| Subgroup Analysis | Incremental cost | | Incremental QALY | | ICERs of | |
|---|---|---|---|---|---|---|
| | beraprost VS STD | sildenafil VS STD | beraprost VS STD | sildenafil VS STD | beraprost VS STD | sildenafil VS STD |
| **Subgroup Age ≤ 30 years** | | | | | | |
| Start FC II | 1,385,857 | 1,822,828 | 7.19 | 7.30 | 192,752 | 249,770 |
| Start FC III | 1,470,694 | 2,263,830 | 7.31 | 9.98 | 201,308 | 226,802 |
| **Subgroup Age >30 years** | | | | | | |
| Start FC II | 832,030 | 1,080,652 | 4.53 | 4.73 | 183,813 | 228,531 |
| Start FC III | 941,570 | 1,281,172 | 4.85 | 6.59 | 194,244 | 194,384 |

***Second line treatment***

According to above results of the first-line treatment, literature reviews and expert opinions, it was summarized that only sildenafil should be used as the first-line treatment, because it yielded higher QALYs than beraprost. Base on the progression of PAH-CHD, the second-line plus the first-line treatments should be preferred, whereas for other types of PAH (e.g. PAH-CTD), switching to the second-

line or the first-line plus the second-line treatments will depend on clinical progression.

1. PAH-CHD patient ≤ 30 years (Mean age = 24 years)

The cost-utility analysis estimated lifetime costs and health outcomes (i.e., QALYs) of the second line therapy according to treatment options based on societal perspective. The probabilistic results of total costs and outcomes of sildenafil plus iloprost and sildenafil plus bosentan compared with standard treatment in cases of unresponsiveness to sildenafil as the first line treatment classified by functional class for PAH-CHD patients aged ≤ 30 years are shown in Table 4.3. The total costs were the highest for sildenafil plus iloprost (FC II) (4,925,951 THB), followed by sildenafil plus bosentan (FC II) (3,836,462 THB), whereas sildenafil switch to standard treatment (FC II) (2,231,411THB) incurred the lowest cost compared with all interventions. The QALYs of sildenafil plus bosentan (FC II) (14.27 QALYs) were the highest, followed by sildenafil plus iloprost (FC II) (14.15 QALYs) and sildenafil plus iloprost (FC III) (13.47 QALYs) which the average health outcomes were between 13-15 QALYs. In contrast, the QALYs were the lowest for sildenafil switch to standard treatment (FC II) (12.28 QALYs), followed by sildenafil switch to standard treatment (FC III) (13.33 QALYs) but these results were slightly different from the highest of QALYs.

The ICER results of PAH-CHD patients who had sildenafil plus iloprost and sildenafil plus bosentan were compared with sildenafil switch to standard treatment in Table 4.4. The ICERs of sildenafil plus iloprost compared sildenafil switch to standard treatment in FC II and III were 1,440,409 and 3,298,720 THB per QALY gained, respectively. The ICERs of sildenafil plus bosentan compared sildenafil switch to standard treatment in FC II and III were 805,528 and 2,147,137 THB per QALY gained, respectively.

2. PAH-CHD patient > 30 years (Mean age =49 years)

The total costs and outcomes of sildenafil plus iloprost and sildenafil plus bosentan compared with sildenafil switch to standard treatment classified by functional class for PAH-CHD patients aged > 30 years are shown in Table 4.3. The

total costs were the highest for sildenafil plus iloprost (FC II) (3,081,920 THB), followed by sildenafil plus bosentan (FC II) (2,374,242 THB), whereas sildenafil switch to standard treatment (FC II) (1,456,502 THB) incurred the lowest cost when compared with all interventions. . The QALYs of sildenafil plus bosentan (FC II) (10.47 QALYs) were the highest, followed by sildenafil plus iloprost (FC II) (10.39 QALYs) and sildenafil plus iloprost (FC III) (9.83 QALYs) which the average health outcome were between 10-11 QALYs. In contrast, the QALYs were the lowest for sildenafil switch to standard treatment (FC II) (9.36 QALYs), followed by sildenafil switch to standard treatment (FC III) (9.74 QALYs) but these results were slightly different from the highest of QALYs as the same in previous subgroup (i.e. PAH-CHD patient ≤ 30 years).

The ICER results of PAH-CHD patients who had sildenafil plus iloprost and sildenafil plus besentan were compared with sildenafil switch to standard treatment in Table 4.4. The ICERs of sildenafil plus iloprost compared sildenafil switch to standard treatment in FC II and III were 1,567,582 and 4,292,518 THB per QALY gained, respectively. The ICERs of sildenafil plus bosentan compared sildenafil switch to standard treatment in FC II and III were 827,283 and 2,699,191 THB per QALY gained, respectively.

**Table 4.3 Total costs and health outcomes of the second-line treatments classified by patient age groups and functional class**

| | **Total costs (million THB)** | | | **Quality adjusted life years QALYs** | | |
|---|---|---|---|---|---|---|
| **Subgroup Analysis** | **sildenafil switch to STD** | **sildenafil+ iloprost** | **sildenafil+ bosentan** | **sildenafil switch to STD** | **sildenafil+ iloprost** | **sildenafil+ bosentan** |
| **Subgroup Age ≤ 30 years** | | | | | | |
| Start FC II | 2,231,411 | 4,925,951 | 3,836,462 | 12.28 | 14.15 | 14.27 |
| Start FC III | 2,600,134 | 3,076,153 | 2,844,343 | 13.33 | 13.47 | 13.44 |
| **Subgroup Age >30 years** | | | | | | |
| Start FC II | 1,456,502 | 3,081,920 | 2,374,242 | 9.36 | 10.39 | 10.47 |
| Start FC III | 1,597,286 | 1,996,592 | 1,796,971 | 9.74 | 9.83 | 9.81 |

**Table 4.4 Incremental cost-effectiveness ratios (ICERs) of the second-line treatments classified by patient age groups and functional class at start of treatment**

| Subgroup Analysis | Incremental cost | | Incremental QALY | | ICERs | |
|---|---|---|---|---|---|---|
| | sildenafil+iloprost vs sildenafil switch to STD | sildenafil+bosentan vs sildenafil switch to STD | sildenafil +iloprost vs sildenafil switch to STD | sildenafil +bosentan vs sildenafil switch to STD | sildenafil+iloprost vs sildenafil switch to STD | sildenafil+bosentan vs sildenafil switch to STD |
| **Subgroup Age ≤ 30 years** | | | | | | |
| Start FC II | 2,694,540 | 1,605,050 | 1.87 | 1.99 | 1,440,409 | 805,528 |
| Start FC III | 476,020 | 244,209 | 0.14 | 0.11 | 3,298,720 | 2,147,137 |
| **Subgroup Age >30 years** | | | | | | |
| Start FC II | 1,625,418 | 917,740 | 1.04 | 1.11 | 1,567,582 | 827,283 |
| Start FC III | 399,306 | 199,685 | 0.09 | 0.07 | 4,292,518 | 2,699,191 |

## Part two: Uncertainty analysis

Threshold analysis of cost-effective drug prices in PAH-CHD

Table 4.5 shows drug price that would be cost-effective in Thai context at the willingness to pay (WTP) threshold of 120,000 THB per QALY gained. Prices of drugs could decrease the ICER values to be equal to or less than 120,000 THB per QALY gained. The prices of sildenafil 20 mg should be equal to 19 and 20 THB for the PAH treatment in patients younger than 30 years with, Functional class II and III, respectively. The prices of sildenafil 20 mg should be 23 and 26 THB for the PAH treatment in patients older than 30 years, respectively. We could not calculate cost-effective prices of bosentan and iloprost, since their ICER values were much higher than the WTP threshold in Thailand.

**Table 4.5 Negotiated price using threshold analysis**

| **Drug name** | **Regimen** | **Price per dose (THB)** | **Maximum price of drugs at the cost-effective threshold** | **Maximum price of drugs at the WTP threshold** |
|---|---|---|---|---|
| | | | Start treatment FCII | Start treatment FCIII |
| **sildenafil** | 20 mg 3 times/day | 46.01 | **19.39-22.77** | **20.20-26.12** |
| **bosentan** | 125 mg once daily | 1,203.75 | bosentan was not cost-effective | bosentan was not cost-effective |
| **iloprost** | 5 mcg inhale 6-9 times/day | 353.10 | iloprost was not cost-effective | iloprost was not cost-effective |

### One-way sensitivity analysis

Figure 4.1 shows a tornado diagram presenting one-way sensitivity analysis results of sildenafil compared with standard treatment, which was the most cost-effective intervention, classified by functional class for PAH-CHD patients aged ≤ 30 years. It was found that when altering the value of each parameter, the ICER per QALY gained was the most sensitive to changes in the discount rate of 0% and 6% per annum, followed by changes in probability of switching from FCII to FCIII (standard treatment), utility in FCI, changes in probability of switching from FCIII to FCIV (standard treatment), costs of sildenafil and probability of switching from FCI to FCII (standard treatment). It was noted that the ICER were more sensitive to changes in the transition probabilities of switching from each functional class, changes in cost of sildenafil and changes in utility in some functional class.

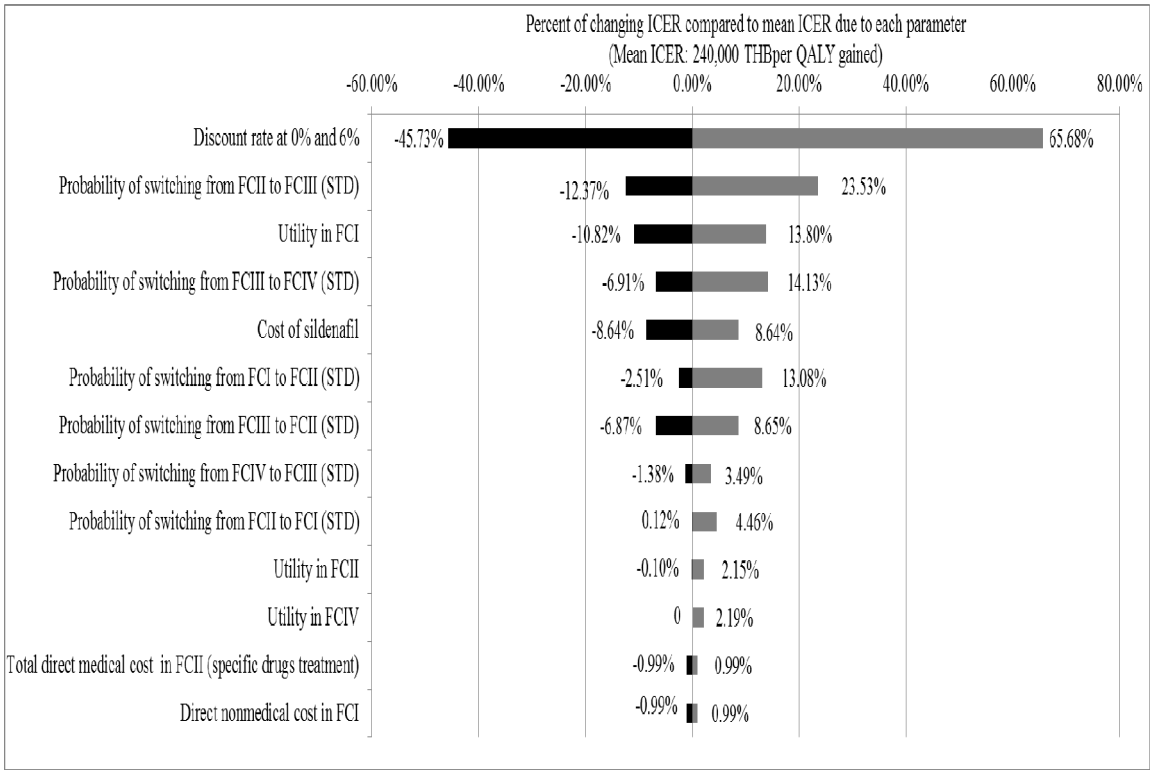


**Figure 4.1 Tornado diagram**

**Probabilistic sensitivity analysis (PSA)**

PSA was performed to investigate the impact of the uncertainty of input parameters based on a societal perspective. According to the Thai Subcommittee for Development of the National List of Essential Drugs, the willingness to pay (WTP) threshold for a QALY gained for the adoption of health technologies and interventions is between one and three times the Thai GDP (i.e., approximately 120,000 to 360,000 THB) (59). The cost-effectiveness acceptability curves representing the relationship between the willingness to pay (WTP) and probability of each treatment being cost-effective are shown by in Figures 4.2-4.5.

***First line treatment***

1. PAH-CHD patient ≤ 30 years (Mean age = 24 years)

Figure 4.2 displays the cost-effectiveness acceptability curves based on the PSA results among PAH-CHD patients aged ≤ 30 years who had the first line treatment classified by functional class. At a WTP threshold of 120,000 THB per QALY gained, this figure shows that the probabilities that standard treatment (FC II) and standard treatment (FC III) would be cost-effective were 92% and 6%, respectively. At the WTP threshold of 360,000 THB (approximately three times the GDP per capita) shows that the probabilities that beraprost (FC II), followed by standard treatment (FC II), sildenafil (FC II) would be cost-effective were 62%, 14% and 10 %, respectively.

2. PAH-CHD patient > 30 years (Mean age =49 years)

Figure 4.3 displays the cost-effectiveness acceptability curves based on the PSA results among PAH-CHD patients aged > 30 years who had the first line treatment classified by functional class. At the WTP threshold of 120,000 THB per QALY gained, this figure shows that the probabilities that standard treatment (FC II), beraprost (FC II), standard treatment (FC III) would be cost-effective were 87%, 9% and 4%, respectively. At the WTP threshold of 360,000 THB (approximately three times the GDP per capita) shows that the probabilities that beraprost (FC II), followed by sildenafil (FC II), sildenafil (FC III) would be cost-effective were 55%, 18% and 13 %, respectively.

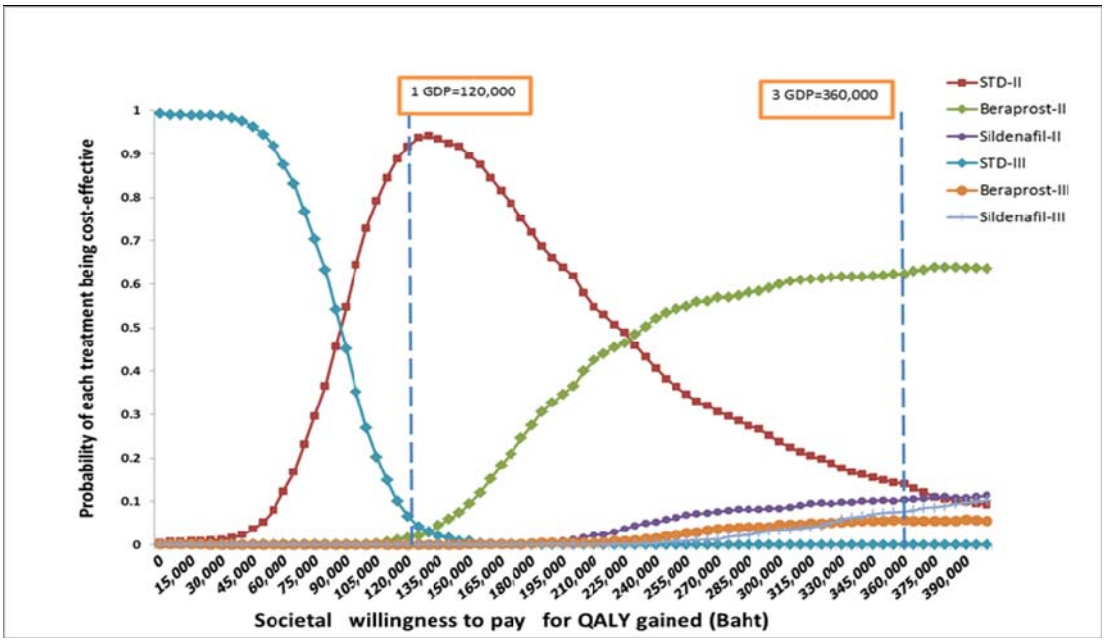


**Figure 4.2 Cost-effectiveness acceptability curves for PAH-CHD patients who had first line treatment in patient ≤ 30 years (Mean age = 24 years) classified by functional class at start treatment**

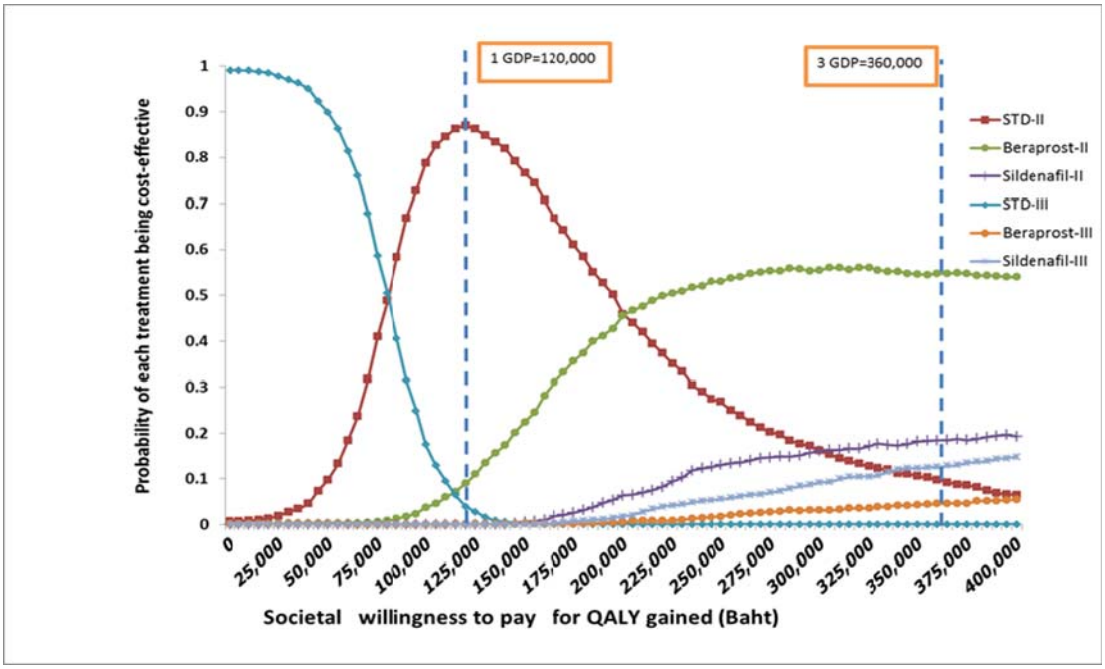


**Figure 4.3 Cost-effectiveness acceptability curves for PAH-CHD patients aged > 30 years (Mean age = 49 years) who had first line treatment classified by functional class**

***Second line treatment***

1. PAH-CHD patient ≤ 30 years (Mean age = 24 years)

Figure 4.4 displays the cost-effectiveness acceptability curves based on the PSA results among PAH-CHD patients aged ≤ 30 years who had the second line treatment classified by functional class. At the WTP threshold of 120,000 THB per QALY gained, this figure shows that the standard treatment for patients not responding to sildenafil in patients (FC II) was 90%, followed by the standard treatment for patients not responding to sildenafil in patients (FC III) was 10%. At the WTP threshold of 360,000 THB (approximately three times the GDP per capita) shows that the standard treatment in patients not responding to sildenafil (FC II) was 60 %, followed by standard treatment in patients not responding to sildenafil in patients with (FC III) was 40 %.

2. PAH-CHD patient > 30 years (Mean age =49 years)

Figure 4.5 displays the cost-effectiveness acceptability curves based on the PSA results among PAH-CHD patients aged > 30 years who had the second line treatment classified by functional class. At the WTP threshold of 120,000 THB per QALY gained, this figure shows that the standard treatment for patients not responding to sildenafil in patients (FC II), the most cost-effective, was 87%, followed by the standard treatment for patients not responding to sildenafil in patients (FC III) was 14%. At the WTP threshold of 360,000 THB (approximately three times the GDP per capita) shows that the standard treatment in patient not responding to sildenafil in patients (FC II) was 64 %, followed by standard treatment in patients not responding to sildenafil in patients with (FC III) was 36 %.

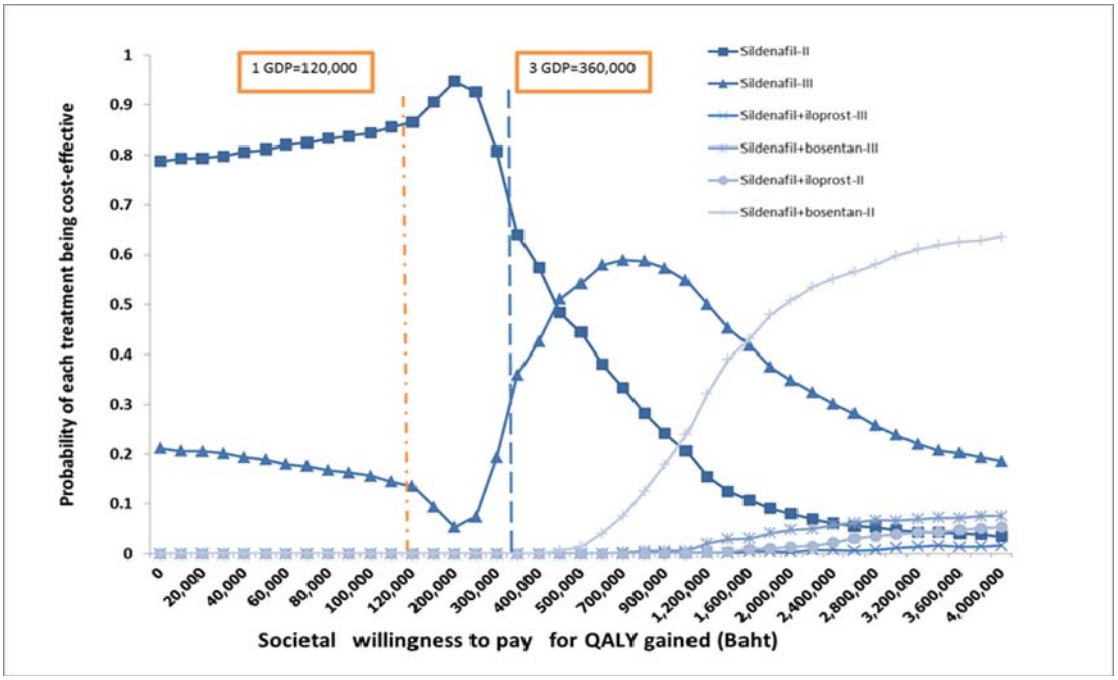


**Figure 4.4 Cost-effectiveness acceptability curves for PAH-CHD patients aged ≤ 30 years (Mean age = 24 years) who had second line treatment classified by functional class**

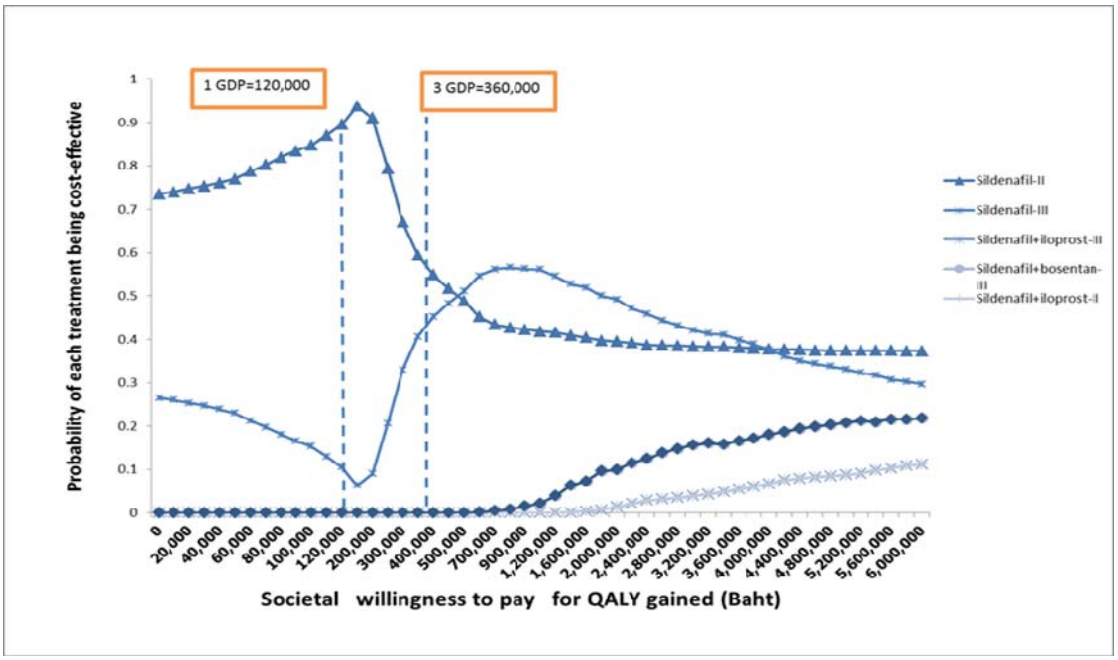


**Figure 4.5 Cost-effectiveness acceptability curves for PAH-CHD patients aged > 30 years (Mean age = 49 years) who had second line treatment classified by functional class**

## Part three: Budget impact analysis

From the results of cost-utility analysis, the use of sildenafil (FC II, III) as the first-line treatment was nearly to be a cost-effective option at the WTP 120,000 THB per QALY gained. As a result, threshold analysis was conducted to find the cost-effective price. The budget impact analysis shows how much burden on future expenditures due to current and negotiated prices if sildenafil is included in the benefit package of UC scheme base on NHSO perspective. Moreover, the total budget of sildenafil (FC II, III) as the first-line treatment was calculated to compare with that of standard treatment (first-line treatment) in order to present how much additional budget would be required for an alternative treatment.

The total budget of sildenafil (FC II, III) as the first-line treatment on the governmental budget during fiscal years 2012 to 2016 is presented in Table 4.6. The average budget between current and negotiated prices in each year classified by functional class was approximately 12 and 7.5 million THB. In addition, the total budgets during five years of sildenafil with normal and negotiated prices were approximately 60 and 38 million THB, respectively. Thus, the incremental budget between current and negotiated prices was approximately 22 million during five years which is the amount that the government could save due to price negotiation.

In contrast, the average budget between sildenafil (FC II, III) with current price and standard treatment (FC II, III) as first-line treatment in each year classified by functional class was approximately 12 and 3 million THB. In addition, the total budgets in five years of sildenafil with current price and standard treatment were approximately 60 and 16 million THB, respectively. Thus, the incremental budget between these two options was approximately 44 million THB during five years. Moreover, if a negotiated price of sildenafil was implemented, the government could reduce the additional budget approximately 20 million THB.

**Table 4.6 Estimated total budget (million THB) during fiscal years 2012 to 2016 of PAH-CHD patients treating with sildenafil and standard treatment classified by functional class**

| | Budget impact of treating in PAH-CHD patients with sildenafil (million baht) | | | | | |
|---|---|---|---|---|---|---|
| **Year** | **1** | **2** | **3** | **4** | **5** | **Total** |
| **Normal price of sildenafil as the first-line treatment (46 baht per 20 mg)** | | | | | | |
| Functional class II | 11.8 | 9.5 | 10.74 | 11.9 | 13 | 57.03 |
| Functional class III | 14.6 | 10.4 | 11.36 | 12.59 | 13.86 | 62.83 |
| Average budget in each year | | | 11.97 | | | |
| **Negotiated price of sildenafil as the first-line treatment** | | | | | | |
| Functional class II (19-23 baht per 20 mg) | 7.65 | 5.56 | 6.24 | 6.89 | 7.52 | 33.87 |
| Functional class III (20-26 baht per 20 mg) | 10.77 | 6.76 | 7.18 | 7.87 | 8.6 | 41.19 |
| Average budget in each year | | | 7.50 | | | |
| **Standard treatment (first-line treatment)** | | | | | | |
| Functional class II | 2.84 | 2.68 | 2.91 | 3.08 | 3.21 | 14.73 |
| Functional class III | 3.91 | 3.44 | 3.20 | 3.09 | 3.07 | 16.72 |
| Average budget in each year | | | 3.14 | | | |

# CHAPTER V
# DISCUSSION

The discussion of this study was divided in to three parts as follows:

Cost-utility analysis
Budget impact analysis
Limitations of study

This study was the first to perform the cost-utility and budget impact analysis of drug treatments in PAH-CHD in Thailand. Although several studies suggested that efficacy and safety of pulmonary selective drugs for the treatment of PAH-CHD was better than standard treatment, patients with PAH-CHD still cannot get an access to the use of these drugs due to a very high price. In Thailand, there has been no economic evaluation information related to these drugs available. Therefore, the National List of Essential Medicines (NLEM) subcommittees requested the cost-effectiveness information for making decision whether which drug treatment for PAH associated with CHD should be included in the NLEM. The results of cost-utility analysis and budget impact analysis as well as limitations of study were discussed as follows.

## Cost-utility analysis

The results of this study presented that at the initial treatment, the costs and quality adjusted life year (QALYs) were not significantly different between patients who had PAH associated with CHD in functional class II and III as well as between patients aged less than 30 years (mean age 24 years) and patients aged more than or equal 30 years (mean age 49 years). Although sildenafil as the first line treatment was not cost-effective in Thai context (i.e., incremental cost-effectiveness ratio less than 120,000 THB per QALY) due to its high price, it significantly increased

one to three QALYs when compared with beraprost. Cost of sildenafil could significantly affect to its cost-effectiveness. Therefore, if the price of sildenafil 20 mg was decreased to 19-20 THB, it would be a cost-effective option.

Furthermore, in cases of unresponsiveness to sildenafil as the first line treatment, all interventions as the second line treatment (i.e., sildenafil combined with iloprost, sildenafil combined with bosentan) were not cost-effective in Thai context. This study could not analyze a cost-effective price, because its ICER was much greater than the cost-effectiveness threshold in Thailand.

When compared the results in this study with other studies in the United States, Australia, the United Kingdom and Spain. All studies only compared the first line treatment (2, 48-52), while our study compared both first and second line treatments (i.e., iloprost and bosentan) using combination treatment when the patient did not respond to first line treatment. Most studies compared epoprostenol which is not currently registered in Thailand for the treatment of PAH in patients in Functional class IV (2, 50, 52). In addition, all previous studies only focused in healthcare payer and health care system perspectives (2, 48-52), while our study used the societal perspective. Target populations of PAH from previous studies were not clearly identified, but study population in this study were PAH-CHD patients. Moreover, the functional class to start the treatment was not studied in all previous published studies (2, 48-52), whereas our study evaluated which functional class would be the most cost-effective to receive the initial treatment.

When compared with previous studies, this study showed different cost-effectiveness results on sildenafil and bosentan. In Australia bosentan was cost-effective compared with standard treatment with the incremental cost-effectiveness ratio of A$55, 927 dollars (1,704,431 THB, 1 A$ = 30.48 THB) for one life year gained (49). Moreover, in the United Kingdom, compared with standard treatment bosentan was more expensive and yielded greater amount of QALYs, resulting in an ICER of £27,000 (1,200,312 THB, 1£ = 44.46 THB) per QALY gained, whereas sildenafil was less costly and more effective (2). In contrast, the results of this study suggested that bosentan and sildenafil would be not cost-effective based on the cost-effectiveness threshold of 120,000 THB in Thai context.

## Budget impact analysis

The actual budget impact of health insurance scheme should be estimated from the real number of PAH-CHD. Unfortunately, Thai PAH registry, which represents number of PAH-CHD patients, is still in a developing process. Therefore, this study used data of incidence and prevalence based on expert opinion that expected incidence and prevalence to be 27 and 134 patients per year, respectively

The results of this study presented that the budget impact of sildenafil at first-line treatment for patients with PAH associated with CHD in functional class II or III during fiscal years 2012 to 2016 was approximately 12 million THB. If the price of sildenafil was decreased to the cost-effective price, the budget impact would be approximately 7.5 million THB which the government could save this incremental budget due to a negotiated price.

## Limitations of study

This study has several limitations as follows:

1. There has been no enough evidence found to confirm the efficacy of combination treatment in PAH base on alternative options in this study (i.e., sildenafil plus iloprost and sildenafil plus bosentan). Thus, this study assumed efficacy of combination therapy equal to the second line treatment for patients with unresponsiveness to the first line treatment.
2. Based on a systematic literature review and meta-analysis, it was found that there was no sufficient data on the relative risk and efficacy of the PAH treatment. Therefore, we assumed that patients in each WHO functional class equally improved and got worsen.
3. There is the lack of evidence on the effectiveness of pulmonary selective drugs in long term period. In most previous studies, effectiveness of treatment was monitored within 3 months. Therefore, this study assumed that the probability of the functional class improvement and worsening was the same through lifetime period.
4. Since we lack data on the probability of death in PAH-CHD patients receiving standard treatment and pulmonary selective drugs. Therefore, we assumed the

probability of death were only related to WHO classification of patients, but not related to efficacy of intervention.

5. Based on literature review, the study found no data of utility in PAH-CHD in Thailand. So, this study collected data from interview patients using EQ5D questionnaire that could convert to the utility. However, the data were not cover the number of patients in each Functional class due to limitation of time and accessing the target patients.

# CHAPTER VI
# CONCLUSIONS

The conclusions of this study were divided into two parts as follows:

Recommendations for policy decision making

Recommendations for the further studies

## Recommendations for policy decision making

1. Patients who have PAH associated with CHD can be treated at the severity level both functional class II and III.

2. In the use of sildenafil as the first line treatment for patients with PAH, it is proposed that the price of sildenafil should be negotiated based on the results of this study.

3. The second line treatments (i.e., iloprost and bosentan) should not be included on the NLEM because it slightly increased in effectiveness but significantly increased in costs, compared with sildenafil. Therefore, these drugs would not be cost-effective in the Thai context.

## Recommendations for the further studies

1. Regarding to the result of one-way sensitivity analysis, the utility of PAH-CHD patients was sensitive to a change in the ICER values. Therefore, the utility should be explored from Thai data in sufficient number of patients in each functional class in order to represent real situation.

2. The efficacy data of a combination treatment on patients' survival were presented in term of relative risk (RR). The relative risk (RR) was adjusted for the probability of a change in functional class of patients who received standard therapy. According to the result of one-way sensitivity analysis, it showed that transitional

probability of PAH-CHD patients was the most sensitive to a change in the ICER values, but there is no efficacy data of combination treatment on patients' survival. Therefore, efficacy data should be investigated in further studies.

3. Further studies should perform the economic evaluation and budget impact analysis of PAH in other types such as iPAH and PAH-CTD.

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# APPENDICES

# APPENDIX A

**แบบสอบถามต้นทุนในผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูง**

**ชื่อโครงการ** "การประเมินต้นทุนอรรถประโยชน์และผลกระทบทางด้านงบประมาณของการรักษาผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูง"

ผู้สัมภาษณ์: อธิบายวัตถุประสงค์ของการศึกษาวิจัยแก่ผู้ถูกสัมภาษณ์

ชื่อผู้สัมภาษณ์ .....

วัน เดือน ปี (พ.ศ.) ที่สัมภาษณ์ □□/ □□/ □□□□

ผู้ให้ข้อมูล □ 1. ผู้ป่วย □ 2. ญาติ มีความสัมพันธ์กับผู้ป่วยโดยเป็น ..... ของผู้ป่วย

**ส่วนที่ 1: ข้อมูลทั่วไปของผู้ป่วย**

1. เพศ □ 1.หญิง □2.ชาย อายุ.....ปี

2. ศาสนา □ 1.พุทธ □2. อิสลาม □ 3.คริสต์ □4.อื่นๆระบุ .....

3. สถานภาพสมรส □ 1.โสด □ 2.คู่ □ 3.หย่า □4. หม้าย

4. อาชีพหลัก

□ 1.ข้าราชการ □ 2.พนักงานรัฐวิสาหกิจ □ 3.พนักงานบริษัทเอกชน

□ 4.ค้าขาย/เจ้าของกิจการ □ 5.เกษตรกรรม (ทำนา, ไร่, สวน) □ 6.แม่บ้าน

□ 7.เกษียณ □ 8.ผู้ใช้แรงงาน/รับจ้างทั่วไป □ 9.ไม่ได้ประกอบอาชีพ

□ 10.อื่นๆ ระบุ.....

5. รายได้จากอาชีพหลัก ..... บาทต่อเดือน

6. ปัจจุบันที่อยู่อาศัยของผู้ป่วยอยู่บริเวณใด

□ 1.อยู่ในเขตกรุงเทพฯ □2. ต่างจังหวัด ระบุ.....ในเขตเทศบาล

□ 3.ต่างจังหวัด ระบุ.....อยู่นอกเขตเทศบาล

7. ระดับการศึกษาสูงสุด

☐ 1.ไม่ได้เรียนหนังสือ ☐2.ประถมศึกษา 3.มัธยมศึกษาหรือเทียบเท่า

☐4.อนุปริญญา/ประกาศนียบัตร☐ 5.ปริญญาตรีหรือเทียบเท่า 6. ปริญญาโทหรือเทียบเท่า

☐ 7.อื่นๆ ระบุ.....

8. สิทธิการรักษา

☐ 1.ประกันสุขภาพถ้วนหน้า ☐ 2.ประกันสังคม ☐ 3.ข้าราชการ/รัฐวิสาหกิจ

☐ 4.ทหารผ่านศึก ☐ 5.ประกันสุขภาพบริษัทเอกชน

☐ 6.ชำระค่าใช้จ่ายเอง ☐ 7.อื่นๆ ระบุ.....

9. โรคประจำตัว 1.ภาวะความดันหลอดเลือดแดงในปอดสูงโดยไม่ทราบสาเหตุ

2.ภาวะความดันหลอดเลือดแดงในปอดสูง ประเภทที่เกิดสัมพันธ์กับโรคที่เกิดจากเนื้อเยื่อเกี่ยวพัน

3.ภาวะความดันหลอดเลือดแดงในปอดสูง ประเภทที่เกิดกับผู้ป่วยโรคหัวใจพิการแต่กำเนิด

10. ระดับความรุนแรงของโรค (Functional Class: FC)

1. FC I 2. FC II 3. FC III 4. FC IV

11. จากข้อ 9 ระยะเวลานับจากการวินิจฉัยว่าเป็นโรค.....ปี.....เดือน (ดูคำอธิบายเพิ่มเติม)

12. วิธีการรักษา ☐1.beraprost☐ 2.iloprost☐ 3.bosentan☐ 4.sildenafil☐ 5.รักษาประคับประคอง

13.จากข้อ 12 ระยะเวลานับจากการได้รับการรักษา .....ปี.....เดือน (ดูคำอธิบายเพิ่มเติม)

14.นอกจากโรคในข้อ 9 ผู้ป่วยมีโรคประจำตัวใดอีกบ้าง (ตอบได้มากกว่า 1 ข้อ)

☐ 1.ไม่มี ☐ 2.โรคความดันโลหิตสูง ☐ 3.โรคหัวใจ

☐ 4.โรคตับอักเสบ ☐ 5.โรคหอบหืด☐ 6.โรคปอด

☐ 7.โรคลมชัก☐ 8.โรคเบาหวาน ☐9. อื่นๆ ระบุ .....

**ส่วนที่ 2: ข้อมูลด้านต้นทุนของผู้ป่วย**

**2.1 ต้นทุนของผู้ป่วยนอก**

15.ในช่วงระยะเวลา 3 เดือนที่ผ่านมา ( เดือนมกราคม2555 ถึง เดือนมีนาคม 2555)ผู้ป่วยต้องมารับการรักษาโรคที่โรงพยาบาลนี้เป็นจำนวน ..... ครั้ง

16. ระยะเวลาที่ใช้ในการมารับการรักษาโรคในครั้งนี้ (เช่น 3 ชั่วโมง 1 วัน).....

17. การมารับการรักษาโรคในครั้งนี้ ผู้ป่วยเสียค่าใช้จ่ายด้านที่พักหรือไม่

☐ 1.ไม่เสียค่าใช้จ่าย☐ 2.มีค่าที่พักคิดรวมเป็นจำนวนเฉลี่ย ..... บาท

18. ค่าใช้จ่ายในการเดินทางไป-กลับของผู้ป่วย ระหว่างที่พักและโรงพยาบาลเพื่อมารับการรักษาโรคในครั้งนี้เป็นจำนวนเฉลี่ย ..... บาท (ดูคำอธิบายเพิ่มเติม)

19. ค่าอาหารที่**เพิ่มขึ้น**ในการมาโรงพยาบาลของผู้ป่วยเพื่อมารับการรักษาโรคในครั้งนี้

เป็นจำนวนเฉลี่ย ..... บาท (ดูคำอธิบายเพิ่มเติม)

20. ค่ารักษาพยาบาลที่ต้องจ่าย**เพิ่มเติม**จากสิทธิการรักษาในครั้งนี้เป็นจำนวนเฉลี่ย.....บาท

21.การมารับการรักษาโรคในครั้งนี้ ผู้ป่วยต้องมีญาติเพื่อพามารับการรักษาที่โรงพยาบาลหรือไม่

☐ 1.ไม่มี (ข้ามไปทำข้อ22) ☐ 2.มี จำนวน..... คน โปรดระบุรายละเอียดค่าใช้จ่าย

| | จำนวน (ในครั้งนี้) | | |
|---|---|---|---|
| | คนที่ 1 | คนที่ 2 | คนที่ 3 |
| อายุ | | | |
| เพศ | | | |
| ระยะเวลาที่ใช้ทั้งหมดเพื่อพาผู้ป่วยมารับการรักษา เช่น 2 ชั่วโมง | | | |
| ค่าที่พัก | | | |
| ค่าเดินทางไป-กลับ | | | |

| | จำนวน (ในครั้งนี้) | | |
|---|---|---|---|
| | คนที่ 1 | คนที่ 2 | คนที่ 3 |
| ค่าอาหาร(ที่เพิ่มขึ้น) | | | |
| อื่นๆ ระบุ..... | | | |

22.ในช่วงเวลาระยะเวลา 3 เดือนที่ผ่านมา นอกเหนือจากผู้ป่วยมารับการรักษาโรคที่โรงพยาบาลนี้แล้วได้ไปรับการรักษาจากสถานที่อื่นที่หรือไม่

☐ 1.ไม่ ☐ 2.ใช่ โปรดระบุรายละเอียด

| สถานที่ | จำนวนครั้ง | จำนวนเงินเฉลี่ยที่จ่ายต่อครั้ง |
|---|---|---|
| ☐ โรงพยาบาลอื่นๆ ระบุ ..... | | |
| ☐ คลินิก | | |
| ☐ ศูนย์บริการสาธารณสุข | | |
| ☐ อื่นๆ ระบุ ..... | | |

23.ในช่วงเวลาระยะเวลา 3เดือนที่ผ่านมา ผู้ป่วยได้ซื้อยาหรือผลิตภัณฑ์เสริมอาหารเองเพื่อการรักษา หรือบรรเทาอาการที่เกิดจากโรคเองหรือไม่

☐ 1.ไม่ ☐2. ใช่ โปรดระบุรายละเอียด

| รายการ | ชื่อหรือชนิดของยาหรือผลิตภัณฑ์เสริมอาหาร | ระยะเวลาที่ใช้ยาหรือผลิตภัณฑ์เสริมอาหาร | ราคา |
|---|---|---|---|
| | | | |

| | | | |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |

24.ในช่วงเวลาระยะเวลา 3เดือนที่ผ่านมาผู้ป่วยต้องอาศัยญาติในการทำกิจกรรมการดูแลอย่างไม่เป็นทางการหรือไม่ (ดูคำอธิบายเพิ่มเติม) 1.ไม่ (ข้ามไปทำข้อ 25) □ 2.ใช่ โปรดระบุรายละเอียด

| | จำนวน | | |
|---|---|---|---|
| | คนที่ 1 | คนที่ 2 | คนที่ 3 |
| อายุ | | | |
| เพศ | | | |
| ความถี่ของการช่วยเหลือ (เช่น ทุกวัน สัปดาห์ละ...ครั้ง) | | | |
| ระยะเวลาต่อครั้ง (เช่น 2 ชั่วโมง) | | | |
| เป็นระยะเวลาต่อเนื่องนานเท่าใด | | | |

25.จากข้อ 24 ญาติของผู้ป่วยพักอยู่บ้านเดียวกับผู้ป่วยหรือไม่

□ 1.ใช่

□ 2.ไม่ และต้องเสียค่าใช้จ่ายในการเดินทางไป-กลับเป็นจำนวนเฉลี่ย..... บาทต่อการมาบ้านผู้ป่วย 1 ครั้ง

**2.2 ต้นทุนของผู้ป่วยใน**

26. ในช่วงระยะเวลา1 ปีที่ผ่านมา (เดือนมีนาคม 2554 ถึง เดือนมีนาคม 2555) ผู้ป่วยต้องมาพักรักษาตัวในโรงพยาบาลนี้เป็นจำนวนเฉลี่ย..... ครั้ง (ดูคำอธิบายเพิ่มเติม)

27. จากข้อ 26 ผู้ป่วยต้องพักรักษาตัวในโรงพยาบาลในแต่ละครั้งเป็นจำนวนเฉลี่ย.....วัน

28. ค่ารักษาพยาบาลที่ต้องจ่าย**เพิ่มเติม**จากสิทธิการรักษาเป็นจำนวนเฉลี่ย.....บาท

29.ในการเข้ารับการรักษาตัวในโรงพยาบาล ผู้ป่วยต้องมีญาติเพื่อมาดูแลระหว่างนอนโรงพยาบาลหรือไม่

□ 1.ไม่มี (ข้ามไปทำข้อ30)□

2.มี จำนวน..... คน โปรดระบุรายละเอียดค่าใช้จ่าย

| | จำนวน | | |
|---|---|---|---|
| | คนที่ 1 | คนที่ 2 | คนที่ 3 |
| อายุ | | | |
| เพศ | | | |
| ความถี่ของการช่วยเหลือ (เช่น ทุกวัน สัปดาห์ละ...ครั้ง) | | | |
| ระยะเวลาต่อครั้ง (เช่น 2 ชั่วโมง) | | | |
| ค่าที่พัก | | | |
| ค่าเดินทางไป-กลับ | | | |
| ค่าอาหาร(ที่เพิ่มขึ้น) | | | |
| อื่นๆ ระบุ..... | | | |

30. ในช่วง 3เดือนที่ผ่านมาท่านเคยมีอาการป่วย จนต้องได้รับการดูแลเป็นพิเศษที่บ้านหรือหยุดงานเพื่อพักรักษาตัวที่บ้านหรือไม่

☐ 1.ไม่เคย (ข้ามไปทำข้อ 31) ☐ 2.เคย จำนวน .....วันในรอบ 3 เดือนโดยที่

☐ 1) มีคนคอยดูแลทุกวัน ☐ 2) ไม่ได้มีคนคอยดูแลทุกวัน จำนวนวันที่มีคนคอยดูแล.....วัน

31. ตั้งแต่ผู้ป่วยเกิดโรค ผู้ป่วยหรือญาติจัดหาสิ่งต่อไปนี้หรือไม่ โปรดระบุรายละเอียด

☐ 1.ไม่ ☐2. ใช่ โปรดระบุรายละเอียด

| รายการ | จำนวนเงิน |
|---|---|
| ☐ ผู้ดูแลผู้ป่วย(ระบุอัตราจ้างต่อเดือน) | |
| ☐ ผู้ดูแลทำงานบ้านหรือคนรับใช้ เนื่องจากการเจ็บป่วยของผู้ป่วยทำให้ไม่สามารถทำเองได้(ระบุอัตราจ้างต่อเดือน) | |
| ☐ ผู้ดูแลบุตรหรือบุพการีของผู้ป่วยเนื่องจากการเจ็บป่วยของผู้ป่วยทำให้ไม่สามารถทำเองได้(ระบุอัตราจ้างต่อเดือน) | |
| ☐ อื่นๆ ( เช่น รถเข็น ถังออกซิเจน ) ระบุ ..... | |

32.ในปัจจุบันผู้ป่วยได้รับเงินช่วยเหลือ จากการเจ็บป่วย หรือไม่

☐ 1.ไม่ได้

☐ 2.ได้ โปรดระบุแหล่งที่มา.....

จำนวน …….....บาทต่อเดือน

ข้อคิดเห็น: ……

# APPENDIX B

**แบบประเมินคุณภาพชีวิต ณ วันนี้**

**แบบประเมินคุณภาพชีวิต EQ-5D**

**กรุณาทำเครื่องหมาย ✓ลงในช่องสี่เหลี่ยมของคำถามแต่ละข้อที่ตรงกับภาวะสุขภาพของท่านในวันนี้มากที่สุด**

1. การเคลื่อนไหว

❑1.ข้าพเจ้าไม่มีปัญหาในการเดิน

❑2.ข้าพเจ้ามีปัญหาในการเดินบ้าง

❑3.ข้าพเจ้าไม่สามารถไปไหนได้ และจำเป็นต้องอยู่บนเตียง

2. การดูแลตนเอง

❑1.ข้าพเจ้าไม่มีปัญหาในการดูแลตนเอง

❑2.ข้าพเจ้ามีปัญหาในการอาบน้ำหรือการแต่งตัวบ้าง

❑3.ข้าพเจ้าไม่สามารถอาบน้ำหรือแต่งตัวด้วยตนเองได้

3. กิจกรรมที่ทำเป็นประจำ (เช่น การทำงาน, การเรียนหนังสือ, การทำงานบ้าน การทำกิจกรรมในครอบครัว หรือการทำกิจกรรมยามว่าง)

❑1.ข้าพเจ้าไม่มีปัญหาในการทำกิจกรรมที่ทำเป็นประจำ

❑2.ข้าพเจ้ามีปัญหาในการทำกิจกรรมที่ทำเป็นประจำอยู่บ้าง

❑3.ข้าพเจ้าไม่สามารถทำกิจกรรมที่ทำเป็นประจำได้

4. ความเจ็บปวด/ความไม่สุขสบาย

❑1.ข้าพเจ้าไม่มีอาการเจ็บปวดหรืออาการไม่สุขสบาย

❑2.ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สุขสบายปานกลาง

❑3.ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สุขสบายมากที่สุด

5.ความวิตกกังวล/ ความซึมเศร้า

❑1.ข้าพเจ้าไม่รู้สึกวิตกกังวลหรือซึมเศร้า

❑2.ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้าปานกลาง

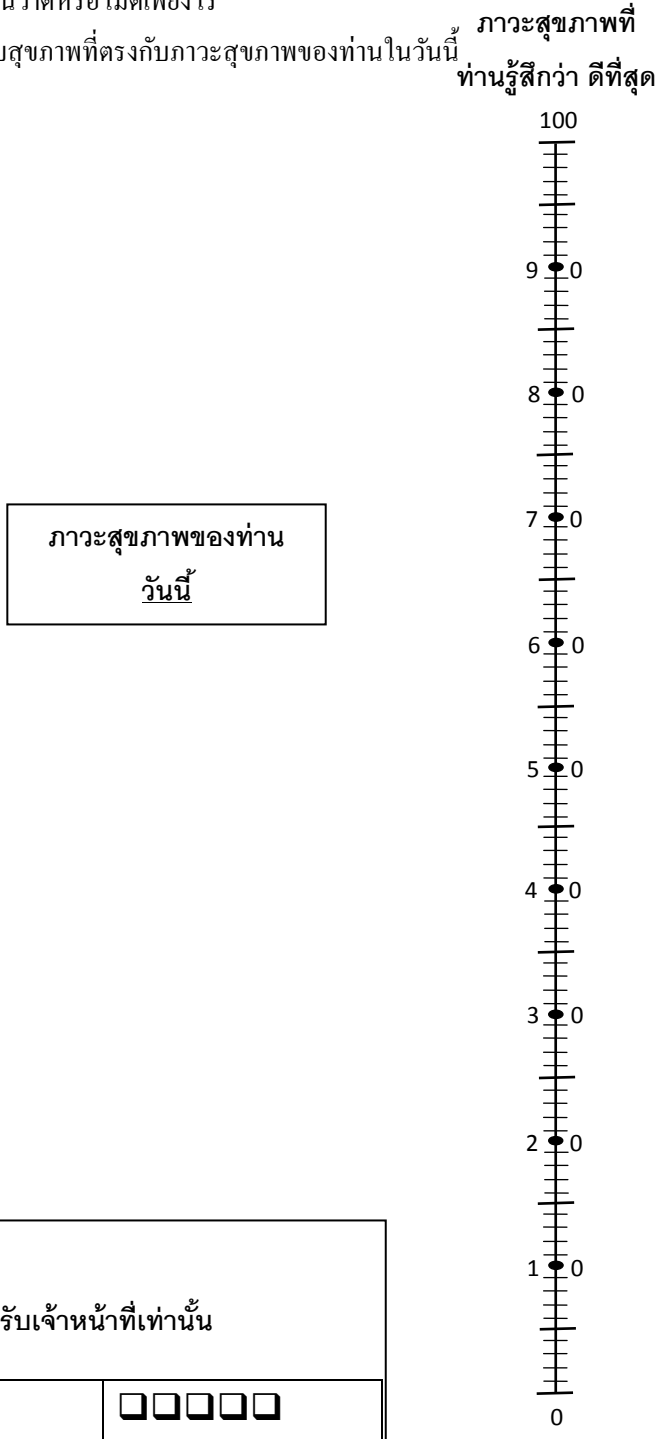
❑3.ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้ามากที่สุด

**แบบประเมินคุณภาพชีวิต VAS**

**เพื่อช่วยในการประเมินภาวะสุขภาพของท่าน ทางเราได้จัดทำสเกลวัดระดับสุขภาพขึ้น เริ่มตั้งแต่ระดับ 0 ถึง 100 โดยที่ 100 หมายถึงภาวะสุขภาพที่ดีที่สุด และ 0 หมายถึง ภาวะสุขภาพที่แย่ที่สุด ตามความคิดของท่าน**

กรุณาประเมินภาวะสุขภาพของท่านในวันนี้ว่าดีหรือไม่ดีเพียงไร

โดยทำเครื่องหมาย X ทับบนสเกลวัดระดับสุขภาพที่ตรงกับภาวะสุขภาพของท่านในวันนี้




**สำหรับเจ้าหน้าที่เท่านั้น**

| | |
|---|---|
| $EQ\text{-}5D_{index}$ | ❑❑❑❑❑ |
| $EQ\text{-}5D_{vas}$ | ❑❑❑ |

**ข้อมูลสำหรับผู้สัมภาษณ์**

**คำชี้แจง**

การศึกษานี้เป็นการศึกษาวิจัยเรื่อง “การประเมินต้นทุนอรรถประโยชน์และผลกระทบทางด้านงบประมาณของการรักษาผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูง”โดยการวิจัยนี้มีความจำเป็นต้องใช้ข้อมูลด้านต้นทุนที่เกิดขึ้น ทั้งต้นทุนทางตรงและต้นทุนทางอ้อมของผู้ป่วย เพื่อใช้ในการประเมินความคุ้มค่าของทางเลือกในการรักษาโรคด้วยวิธีต่างๆต่อไป

**การเก็บข้อมูล**

1. ก่อนเก็บข้อมูล ผู้สัมภาษณ์ต้องประเมินว่าผู้ป่วยที่จะให้ข้อมูลต้องมีลักษณะดังต่อไปนี้

1.1 ได้รับการวินิจฉัยว่าเป็นผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูงโดยไม่ทราบสาเหตุ / ผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูงประเภทที่เกิดในผู้ป่วยที่มีความผิดปกติของโรคที่เกิดจากเนื้อเยื่อเกี่ยวพัน/ผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูง ประเภทที่เกิดกับผู้ป่วยโรคหัวใจพิการแต่กำเนิด

1.2 เคยได้รับการรักษาโรคด้วยยาที่มีผลโดยตรงต่อความดันเลือดในปอดโดยเฉพาะ ได้แก่ beraprost iloprost bosentan sildenafil หรือได้รับการรักษาแบบมาตรฐาน

1.3 กรณีที่เป็นญาติหรือผู้แทนที่ตอบแบบสอบถาม จะต้องสามารถตอบคำถามได้ครบทุกข้อ

2. ผู้สัมภาษณ์จะต้องอธิบายวัตถุประสงค์ วิธีการศึกษาและประโยชน์ของการศึกษาวิจัยแก่ผู้ถูกสัมภาษณ์
3. ผู้ถูกสัมภาษณ์จะต้องลงนามในหนังสือแสดงความยินยอมการเข้าร่วมโครงการวิจัยก่อนการสัมภาษณ์
4. เมื่อเสร็จสิ้นการสัมภาษณ์ ผู้สัมภาษณ์จะต้องตรวจสอบว่าผู้ถูกสัมภาษณ์ได้ตอบคำถามครบทุกหัวข้อ

**รายละเอียดแบบสอบถาม**

แบบสอบถามแบ่งเป็น 2 ส่วน

**ส่วนที่ 1 ข้อมูลทั่วไป**

<u>คำอธิบายเพิ่มเติม</u>

ข้อ 11 และ 13 จะกำหนดระยะเวลานับจากเดือนที่ผู้ป่วยเริ่มต้นจนถึงสิ้นเดือนมีนาคม พ.ศ. 2555

**ส่วนที่ 2 ข้อมูลด้านต้นทุน**

เป็นข้อมูลด้านต้นทุนของผู้ป่วยที่เกี่ยวข้องกับการรักษาภาวะความดันหลอดเลือดแดงในปอดสูงโดยไม่ทราบสาเหตุ /ผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูงประเภทที่เกิดในผู้ป่วยที่มีความผิดปกติของโรคที่เกิดจากเนื้อเยื่อเกี่ยวพัน/ผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูง ประเภทที่เกิดกับผู้ป่วยโรคหัวใจพิการแต่กำเนิด

**1.1 ต้นทุนของผู้ป่วยนอก**

คำอธิบายเพิ่มเติม

1. ข้อ 18 หากเดินทางโดยรถส่วนตัว ให้ผู้ถูกสัมภาษณ์ประมาณค่าใช้จ่ายในการเดินทาง ( เช่น ค่าน้ำมัน ค่าทางด่วน ) หากญาติพักหรือเดินทางร่วมกับผู้ป่วยไม่คิดค่าใช้จ่ายในส่วนนี้ เช่น เดินทางโดยรถส่วนตัวหรือแท็กซี่ร่วมกัน
2. ข้อ 19 ค่าอาหารที่เพิ่มขึ้น คิดค่าใช้จ่ายเฉพาะส่วนที่เพิ่มจากค่าอาหารปกติในแต่ละวันที่ไม่ได้มาโรงพยาบาล
3. ข้อ 24 กิจกรรมการดูแลผู้ป่วยอย่างไม่เป็นทางการ เนื่องจากการเจ็บป่วยของผู้ป่วยทำให้ไม่สามารถทำเองได้

3.1 กิจกรรมภายในบ้าน เช่น ทำความสะอาดบ้าน ล้างจาน ซักเสื้อผ้า ถูบ้าน เป็นต้น

3.2 กิจกรรมการดูแลรักษาที่บ้าน เช่น การเตรียมยา เป็นต้น

3.3 กิจวัตรประจำวันที่บ้าน เช่น การรับประทานอาหาร การอาบน้ำ-แต่งตัว การขับถ่าย เป็นต้น

3.4 กิจกรรมนอกบ้าน เช่น การไปธนาคาร การไปพบแพทย์ เป็นต้น

**2.2 ต้นทุนของผู้ป่วยใน**

คำอธิบายเพิ่มเติม

1. ข้อ 26 ผู้ป่วยเข้ารับการรักษาตัวในโรงพยาบาลด้วยอาการที่เกี่ยวข้องกับภาวะความดันหลอดเลือดแดงในปอดสูงโดยไม่ทราบสาเหตุ /ผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูงประเภทที่เกิดในผู้ป่วยที่มีความผิดปกติของโรคที่เกิดจากเนื้อเยื่อเกี่ยวพัน/ผู้ป่วยภาวะความดันหลอดเลือดแดงในปอดสูง ประเภทที่เกิดกับผู้ป่วยโรคหัวใจพิการแต่กำเนิด
2. ข้อ 29 หากญาติค้างคืนกับผู้ป่วยที่โรงพยาบาลไม่คิดค่าใช้จ่ายในส่วนของค่าที่พักและค่าเดินทาง

# BIOGRAPHY

| | |
|---|---|
| **NAME** | Miss Watsamon Thongsri |
| **DATE OF BIRTH** | September 10, 1984 |
| **PLACE OF BIRTH** | Udonthani, Thailand |
| **INSTITUTIONS ATTENDED** | Silpakorn University, 2002-2007: Bachelor of Science in Pharmacy<br>Mahidol, University, 2011-2013: Master of Science in Pharmacy (Pharmacy Administration) |
| **HOME ADDRESS** | 355/1741 M.15 T.Kookod A. Lumlooka Pathumthani province |
| **EMPLOYMENT ADDRESS** | Pharmacy departments in Bhumiphol hospital, Bangkok (temporary employee) and Pharmacy departments in Phyathai 2 hospital, Bangkok (temporary employee)<br>Position: Pharmacist<br>E-mail: hyde_nut@hotmail.com |