การวิเคราะห์ผลกระทบเชิงงบประมาณ: กรณีศึกษาของกลูโคซามีนในการรักษาข้อเข่าเสื่อม

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BUDGET IMPACT ANALYSIS:
AN ILLUSTRATIVE CASE OF GLUCOSAMINE IN KNEE OSTEOARTHRITIS

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ในปัจจุบันการแข่งขันของยาใหม่เพื่อจะอยู่ในบัญชียายังคงเป็นที่สนใจของผู้ตัดสินใจเชิงนโยบายโดยทั่วไป นอกจากการพิจารณาถึงความคุ้มค่าทางเศรษฐศาสตร์ของยาใหม่แล้วปัจจัยเรื่องความสามารถในการจ่ายยังเป็นปัจจัยสำคัญอีกปัจจัยหนึ่งที่จะต้องคำนึงถึง ด้วยเหตุนี้ แนวคิดของการวิเคราะห์ผลกระทบเชิงงบประมาณจึงสามารถใช้เป็นเครื่องมือในการช่วยตัดสินใจในกรณีนี้ได้เป็นอย่างดี การศึกษานี้เป็นการวิเคราะห์ผลกระทบเชิงงบประมาณของกลูโคซามีนในการรักษาข้อเข่าเสื่อมโดยใช้มุมมองของโรงพยาบาล รูปแบบพัฒนาโครงสร้างการวิเคราะห์เป็นการกรอบแนวคิดโดยใช้โรคที่ศึกษา และ กรอบการวิเคราะห์โดยใช้ข้อบ่งใช้ของยา ข้อมูลที่ใช้นำมาจากฐานข้อมูลการใช้ยาและกลุ่มวินิจฉัยโรคร่วมของโรงพยาบาล รวมถึงจากงานวิจัยต่าง ๆ และ การประมาณค่าโดยผู้เชี่ยวชาญ ข้อมูลดังกล่าวนี้ถูกนำมาวิเคราะห์โดยอาศัยการจำลองสถานการณ์จริงของค่าต่าง ๆ ที่เป็นไปได้บนตัวแปรด้วยวิธีมอนติคาโล เมื่อกลูโคซามีนเป็นยาในบัญชียาของโรงพยาบาล ผลการวิเคราะห์พบว่า มีผู้ป่วยที่เป็นผู้ใช้ยานี้เพิ่มขึ้น โดยเมื่อเปรียบเทียบข้อมูลปี 2006 และ 2009 กับข้อมูล ปี 2004 ซึ่งเป็นปีที่กลูโคซามีนถูกนำในโรงพยาบาลปีแรก พบว่า ผลกระทบเชิงงบประมาณด้านยาเพิ่มขึ้นเป็นเงิน 0.8, 0.6, 0.5 และ 0.2 ล้านบาท ในปี 2006-2009 ตามลำดับ ค่าเฉลี่ยของงบประมาณเฉพาะค่ายาต่อปีมีค่าเท่ากับ 0.43 ล้าน ซึ่งมีค่าโดยประมาณเท่ากับค่ารักษาผ่าตัดเปลี่ยนเข่าผู้ป่วยจำนวน 5 คน อัตราเพิ่มของค่าใช้จ่ายด้านยาและค่ารักษาข้อเข่าเสื่อมในช่วงดังกล่าว มีค่าน้อยกว่าอัตราเพิ่มในช่วงที่กลูโคซามีนยังไม่เป็นยาในบัญชีโรงพยาบาล ตัวแปรที่มีความไวมากที่สุดได้แก่ ค่ายากลูโคซามีน และค่ายาเซเลค็อกซิบ โดยสรุปแล้ว ผลกระทบเชิงงบประมาณของกลูโคซามีนในการรักษาข้อเข่าเสื่อมไม่ได้ทำให้ค่าใช้จ่ายด้านยาและค่ารักษาข้อเข่าเสื่อมมีค่าเพิ่มขึ้นไปกว่าอัตราเพิ่มปกติ หากยานี้สามารถชะลอการดำเนินโรคได้ในระยะยาว การลงทุนนำยานี้เข้ามาใช้ในโรงพยาบาลโดยพิจารณาจากผลกระทบเชิงงบประมาณมีความเป็นไปได้ที่จะคุ้มค่า อย่างไรก็ตาม เพื่อที่จะทำให้ผลการศึกษามีความแน่นอนมากขึ้น ควรจะได้มีจัดการกับตัวแปรที่มีความไวด้วยการติดตามต่อไป

สาขาวิชา เภสัชศาสตร์สังคมและบริหาร ลายมือชื่อนิสิต.....

ปีการศึกษา 2549 ลายมืออาจารย์ที่ปรึกษา.....

4676968833: MAJOR SOCIAL AND ADMINISTRATIVE PHARMACY
KEY WORD: BUDGET IMPACT / MONTE CARLO SIMULATION / KNEE OSTEOARTHRITIS /GLUCOSAMINE

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Competition among new pharmaceutical products for formulary inclusion continues to dominate the concern of healthcare decision makers. Affordability became an importance issue in line with cost-effectiveness. The budget impact model provides a comprehensive result to aid the decision-making process in such case. In this study, a budget impact model was aimed at estimating the effect of introducing glucosamine usage in patients with knee osteoarthritis. The model was developed based on the disease-based framework and the indication-based analysis. The analysis was conducted based on the hospital perspective. Data inputs were obtained from historical utilization data, literatures, and physicians' opinions. Probabilistic analysis by using the Monte-Carlo simulation was used to determine the probable drug budget and total budget of knee osteoarthritis treatments after glucosamine has been listed in the hospital formulary. Analysis results showed that glucosamine has gradually penetrated the share of drug uses. Comparing to 2004, the impact on the hospital budget affected by glucosamine were gradually increased from 0.8, 0.6, 0.5 and 0.2 million baht in 2006-2009 respectively. An average of drug budget increased was 0.43 million baht per year which approximately equated to the healthcare expenses of 5 knee replacement patients. The growth rates of drug budget and total budget of knee osteoarthritis treatment in these years were lower than the regular growth rate seen in 2003-2004. Costs of glucosamine and costs of celecoxib were the most two sensitive variables in the forecast model. In brief, based on the analysis results, to include glucosamine into hospital formulary might be worthy of note if glucosamine can effectively delay progression in patients. However, in order to make the results less uncertain, key sensitive variables should be further investigated and re-calculation of budget impact was also recommended.

Field of study: Social and Administrative Pharmacy Student's signature.....
Academic year 2006 Advisor's signature.....

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CHAPTER I
INTRODUCTION

Rationale

In an increasing number of new healthcare interventions especially pharmaceuticals, they must present not only clinically effective, but also cost effective before they are listed on formularies. This increased importance on indicating value of money has arisen to assure the efficiency in healthcare resource allocation under budget constraint atmosphere. Cost-effectiveness of medicine has been widely labeled as the *'fourth hurdle'* to market in addition to the traditional 3 hurdles of safety, efficacy, and quality.[1] Indeed, the results of cost-effectiveness analysis can well assist the prioritization of interventions even it is not sufficient to predict affordability of an intervention with given resources. Affordability can then be viewed as the '*fifth hurdle*' to market, which requires a comprehensive assessment of economic evaluations and budget impact analysis.[2-4]

Budget impact analysis (BIA), while addressing the issue of affordability, estimates the impact on annual healthcare use and costs for the first, second, and subsequent years after the introduction of the new product for a national or health plan population. It provides an estimate of the financial impact of a drug based on its rate of uptake as well as the magnitude and timing of which on healthcare utilization and costs.[5] All budget impact models have taken into account the special factors as following: whether or not to include the impacts of the new drug on all healthcare costs or just those related to disease of interest, market diffusion, current mix of treatment, and increased number of seeking care patients. Additionally, BIA considers associated population characteristics of those with or at-risk for the condition of interest since the impacts of new drug may vary across population subgroups through the short and long period of time.

BIA is already being requested by healthcare decision-makers in many countries to help inform judgments on introducing new treatment to formulary.[6-8] Decision makers need such estimates for basic financial planning. Also, knowing the impacts of a new drug on annual healthcare service utilization at the system level enables the decision-makers to clearly understand how the new drug will impact the system in terms of service provision.

The published literature presenting population budget impacts is small, however there is a much larger published literature of cost studies that present the annual, 2-year, 3-year or lifetime costs for a cohort group of people or a representative individual being started on different treatments.[8] There are limited publications of budget impact estimates and the methods used vary considerably. These studies attempted to estimate explicitly the financial and healthcare service impacts of a new drug for a well-defined national or health plan population.[8-12]Most of them do not clearly how they incorporated all special factors for BIA as described above. There is then a need to conduct the study on budget impact analysis according to the recent guideline proposed, by which takes into account every possible special factors and at the same time, can present the results in the practically understandable format for healthcare decision makers.

In this study, osteoarthritis (OA) of the knee is chosen as a case study to model budget impact with two major rationales. Firstly, concerning the disease itself and secondly, the new pharmacologic agent used in OA interestingly presents the uncharacteristic model comparator in economic evaluation.

The first rationale for osteoarthritis involves the disease complexity and incompletely understanding of etiology including its remarkable economic impact on both society and individual. Due to the rapidly aging population today, OA is now considered as one major public health issue in many countries. It is the most common form of arthritis with a high prevalence in the adult population, and often associated with significant disability and impaired quality of life. Accurate figures for the clinical prevalence are hard to obtain since the correlation between clinical features and objective parameter is weak, but available data estimates up to 10% of the world population suffering from OA.[13] Similar picture has also been found in Thailand as of a recent study reporting the prevalence of knee OA around 34.5-45.6%.[14] The economic burden from arthritis symptoms are significant to both society and patient.[15, 16] Additionally, suffering patients whose functions were limited by severe pain reported a substantial diminution of their quality of life as shown in those patients with coronary health failure, a serious chronic condition with a poor prognosis.[17]

In OA, the cartilage, that protects the ends of the bones breaks down, is not completely understood in its etiology. OA affects many joints, with diverse clinical patterns. The knee is a dominantly affected site.[18] Major clinical manifestation of OA of the knee is pain, which is usually related to activity, and around the joint that is typically worse with weight-bearing.[19] The symptoms are highly varied across population, and might be static, relapsing, or progressive.[20] OA progresses slowly over years and is rarely predictable since its symptoms correlate poorly with clinical and radiological signs. Diagnosis then rests on the clinical recognition of the common patterns and the exclusion of alternatives.

Conventional goals of treatment are to control pain and improvement in function and health-related quality of life, with avoidance, if possible, of toxic effects of therapy.[21] Delaying progression of disease is an additional advanced treatment objective.[22] These objectives have laid the groundwork for the second rationale in choosing OA. glucosamine, which is considered as effective particularly in delaying progression, becomes a challenging illustration once it is introduced to the formulary.

Treatment of OA needs a comprehensive approach of pharmacologic and non-pharmacologic methods. Most patients with osteoarthritis seek medical attention because of pain. Accordingly, various currently available medical therapies primarily address the treatment of joint pain in patients with osteoarthritis.[23] The American College of Rheumatology (ACR) guidelines emphasize the use of acetaminophen as first-line treatment for osteoarthritis of the hip and knee.[21] If pain relief is inadequate, oral non-steroidal anti-inflammatory drugs or intra-articular injections of Hyaluronic acid like products should be considered. Intra-articular corticosteroid injections may provide short-term pain relief in disease flares. Alleviation of pain does not alter the underlying disease. Attention must also be given to non-pharmacologic measures such as patient education, weight loss and exercise. Concurrently, all co-morbid conditions such as cardiac disease, hypertension, peptic ulcer disease, or renal disease must be considered, without exception on the patient's needs and expectations.

The recognition that pain in osteoarthritis is not necessarily due to inflammation has led to an increased awareness of the role of simple analgesics in the treatment of this disease. Besides most analgesics including traditional and cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (NSAIDs) have been questioned about their safety associated with gastrointestinal adverse events and particularly, in the recent reports of increased cardiovascular risks.[24-26]

Evidences supporting the new perspective in the management of osteoarthritis which is structure modification in knee thus become a focal point of current OA treatment. The dietary supplement of glucosamine has been advocated as safe and effective option for the OA management in this case. It acts as a chondroprotective agent in osteoarthritis. A meta-analysis of studies evaluating the efficacy of glucosamine for osteoarthritis suggested potential benefit from this agent but raised questions about the scientific quality of the studies.[27] Two long-term studies already included in this meta-analysis, showed the significant improvement of the joint space narrowing in patients taking glucosamine comparing to placebo group. It is therefore proposed that this agent might be effective in delaying disease progression eventually.[28, 29] However, recently, the large multi-centre, well designed, controlled study of glucosamine and chondroitin sulfate, which is another chondroprotective agent, reported their substantial effects only in the patients with moderate-to-severe pain.[30] The authors emphasized that the continuing research is needed to establish the potential efficacy and increase the understanding of biology, pharmacology, and pharmacokinetics of these agents.

Even there are conflicting results of using glucosamine in osteoarthritis, it is still of interest and considered as of value in OA treatment since current treatments available so far have many adverse events especially in the elderly patients who suffer from OA the most. Conclusively, the knee osteoarthritis, with a consideration of its complexity as well as the interesting choice of treatment nowadays, is of merit to be an illustrative case for budget impact analysis.

In an initial attempt to address the importance of budget impact analysis, this research was then conducted with the research objectives and expected benefits as following.

Research objective

To analyze budget impacts of adding glucosamine to the formulary

Expected benefits

(1) Analysis results of budget impact model can effectively aid decision-makings concerning drugs addition on formulary.

(2) Importance of budget impact analysis has been addressed to and realized by involved stakeholders. Its benefits as a comprehensive economic evaluation of cost-effectiveness analysis could have clear implementation in practice.

CHAPTER II
LITERATURE REVIEW

This chapter is divided into 2 major parts. The first part shows the clinical details of disease of interest, osteoarthritis and its current treatment approaches. Details of clinical consequences as well as treatment approaches were conceptually structured in decision tree models. Subsequently, the concept of budget impact analysis was presented including the key structures related to standard economic evaluation by modeling technique.

1. Osteoarthritis of the knee

1.1 Pathogenesis and disease progression

Recent study showed that approximately 25 percent of persons 55 years of age or older in US have had knee pain on most days in a month, and about half of them have radiographic osteoarthritis of the knee, a group considered to have symptomatic osteoarthritis.[31] Many without radiographic osteoarthritis of the knee probably have osteoarthritis that is not yet visible on radiograph, which is an imaging procedure insensitive to early disease.[19]

Osteoarthritis affects all structure within a joint. Not only is hyaline articular cartilage lost, but bony remodeling occurs, with capsular stretching and weakness of periarticular muscle. However, the tissue that has attracted most attention in relation to the pathogenesis of this disease is still articular cartilage. The main pathological characteristics of OA are loss of cartilage, more progressively than naturally formation process, with associated underlying bony changes consisting of sclerosis, subchondral bone collapse, bone cysts, and osteophyte formation.[32] Cartilage consists of water (70%) and a type II collagen framework with proteoglycans and glycosaminoglycans produced by chondrocytes. Proteoglycans in turn bind of hyaluronate in order to stabilize its macromolecule.[33] The loss of articular cartilage may start as a focal lesion and progressively extend to involve specific joint compartments, thus inducing alterations in articulating surfaces and leading to progressive loss of cartilage.[34] By using the macroscope, this process results in the cystic degeneration of the bone surrounding the joint, with loss of cartilage and irregular abnormal bone formation at the edges of the joint as well as the narrowed joint space. Additionally, microscopically, there is flaking and fibrillation of the

articular cartilage surface and destruction of the cartilage microarchitecture with formation of holes within it. Conclusively, the pathology of OA involves the whole joint in a disease process that includes focal and progressive articular cartilage loss with concomitant changes in the bone underneath the cartilage, including development of osteophytes.

Even the pathogenesis of OA is well established, the causes of OA are not completely understood and its progression significantly differs from a patient to another.[21, 35] Moreover, it is unclear whether osteoarthritis is a single disease or many disorders with a similar final common pathway. One key point that argues in favor of the idea that OA is several distinct entities is that the osteoarthritis of the knee and hip may be associated with different risk factors, suggesting that they should be regarded as unique disease whereas OA of other joints also remains unclear if they should be considered as separate entities.[36]

Osteoarthritis is usually classified into two groups; primary and secondary OA. Primary OA can be localized or generalized. Secondary OA has underlying cause, such as trauma, obesity, or inflammatory arthritis. But in practice there is sufficient overlap to make this classification impractical or unhelpful.[20] Radiography has been the main method used to define osteoarthritis in both medical practice and epidemiological studies. Community-based radiography studies show that this condition is particularly common in older people.[31, 37] Although the variations among data observed can be seen, partly due to population differences, possibly also because of the use of different cut-off points to define the presence or absence of osteoarthritis, and additionally, the sensitivity of the radiograph itself.[38] The use of MRI (Magnetic Resonance Imaging) and arthroscopy can make it clearer that early osteoarthritic changes are not apparent on the radiograph but this technique is not practical in the large population studies.

Disease progression in osteoarthritis is generally slow, and occurs over years or decades. The rate of progression is variable between individuals. Many patients with clinically diagnosed osteoarthritis may not suffer considerable progression by either symptoms or radiographic changes over long periods.[39, 40] The correlation between the degree of radiological change and symptom is weak. Only 30% of patients with radiographic evidence of OA complain of pain at relevant site.[41] It is common for patients with radiological osteoarthritis to have few or no symptoms, whereas the classical symptoms may occur in the absence of structural changes on

plain radiography. Progression then is somewhat unpredictable over time in the same individual, and joint destruction may occur in episodes.[42] Due to this weak correlation, the distinctions between disease and non-disease, more severe or less severe are actively problematic and complicate most aspects of osteoarthritis study.

1.2 Clinical features and risk factors

Joint damage and joint pain are both common. It is usually painful in character and poorly located.[43] In advance cases, pain may awaken the patient from sleep because of the loss of protective muscular joint splinting, which limits painful motion during the day. OA is sometimes associated with acute or subacute inflammation. Other common complaints from patient suffering OA are short-lasting morning stiffness, crepitus (a cracking sound, as the joint is move), muscle spasm, capsular contracture, and joint enlargement. Articular gelling is particularly universal in elderly patients, especially in the lower extremity joints. Knee and hips are the most common osteoarthritis founded in broad population mainly since these are weight-bearing joints.

Risk factors for osteoarthritis can be mainly categorized into two groups; systemic, and local biomechanical. The first group consists of gender and ethnicity, age, and sex. Risks associated with obesity, joint injury, joint deformity, sports participation, and muscle weakness are counted for being local biomechanical factors. Ethnicity differences in knee and hip osteoarthritis have been reported by which conflicting results, One large national study in US, suggested higher rates of knee OA in African-American women but not men whereas another study from the rural area suggested no difference in disease prevalence among these groups.[44, 45]

Recent meta-analysis showed the presence of sex differences in OA prevalence and incidence, with females generally at a higher risk.[46] The preceding systemic risk factor is ageing. The normal ageing process causes the substantial increased laxity around joints, and reduced chondrocyte function, all leading to a propensity for osteoarthritis. The Framingham Study found that 27% of those aged 63 to 70 had radiographic evidence of knee osteoarthritis, increasing to 44% in the over 80 aged group.[47] Other well established systemic factors are bone density, estrogen replacement therapy (in postmenopausal women), genetics. Nutrition factors associated with vitamin C, vitamin D that are all anti-oxidants have been reported significantly correlated with knee osteoarthritis.[48]

Obesity is the strongest modifiable risk factor. It is also one important local biomechanical factor for osteoarthritis. Three to six times the body weight is transferred across the knee joint during walking. The Chingford Study showed that for every two units increase in body mass index (approximately 5 kg), the odds ratio for developing radiographic knee osteoarthritis increased by 1.36.[49] Also, the increased risk of developing osteoarthritis was found in joint fractures and trauma. The Framingham Study found men with a history of knee injury were at a 5-6 fold increased risk of developing osteoarthritis and this usually occurs in a younger age group resulting in prolonged disability and unemployment.[50]

Additionally, sport participation and occupational factors are proven as the critical biomechanical risk factor. Jobs in which workers do overworking the joints and fatiguing muscles that protect the joints considerably increase the risk for osteoarthritis in those joints. For sport participations, the epidemiologic studies have demonstrated that participation in certain sports increases the risk for osteoarthritis.[51, 52] Sports activities appearing to increase the risk for osteoarthritis include those that demand high-intensity, direct joint impact. Efforts to decrease these risks should be the careful pre-participation evaluation of individual risk factors.

Muscle weakness which is well recognized of its common occurrence is at quadriceps muscle is usually found in patients with knee osteoarthritis. This abnormality was suggested in one longitudinal study that it is not only results from painful knee osteoarthritis but also is itself a risk factor for structural damage to the joint.[53]

From all risks above, the prevention or delaying the onset of osteoarthritis from some modifiable behaviors, involving life style changes may avert the broader clinical problems of musculoskeletal disability that can be found in most advance cases.

1.3 Diagnosis

There is currently no gold standard diagnostic test for osteoarthritis. In an attempt to address this issue, the ACR (American College of Rheumatology) has established classification criteria for knee osteoarthritis based on clinical, laboratory, and radiological items.[54] Knee osteoarthritis should be diagnosed at the early stages of the disease, in order to initiate therapy when the potential for progression of the disease is high and associated treatments appear to be the most effective.[55] Magnetic resonance imaging, while potentially more accurate and precise than conventional X-

rays, still experiences a clear lack of accessibility. Biochemical markers of bone, cartilage and synovium are actually studied and could be potentially useful.[56] To date, the radiographic evidence at relevant painful sites in those patients who complained about their pains has been performed to determine how the disease progresses in terms of the joint narrowing space (JNS). Even the correlation between symptoms and radiographic was low [57, 58], the risk of progression in clinical OA patients with radiographic abnormalities is still substantial.[55, 59]

At a clinical level, these limitations have made the diagnosis and treatment remain difficult to predict which individual patients will deteriorate, experience the most severe functional impairment and eventually require joint replacement therapy.[60] All patients' complains about their pain encompassing the radiograph, which can show the joint narrowing space have been mutually used as the diagnosis method. No blood tests are routinely indicated in the workup of a patient with chronic knee pain unless symptoms and sign suggest rheumatoid arthritis or other forms of inflammatory arthritis. Radiography is indicated in the workup of patient if knee pain is noctural or is not activity-related.[19] If knee pain persists after effective therapy for osteoarthritis, a radiograph may reveal clues to a missed diagnosis. Magnetic resonance imaging (MRI) is likely to reveal changes that indicate the presence of osteoarthritis, but it is not suggested in the workup of older persons with chronic knee pain. MRI findings of osteoarthritis are common in middle-aged and older adult with and without knee pain.[61] Examination of the patient should include testing for various possible causes of knee pain. These include the laboratory testing for gout, joint tumors, meniscal tear, and trochanteric bursitis.

1.4 Treatment approaches

The disease is not curable, but treatments are available aimed to reduce patients' pain and joint inflammation and alter the course of the disease by decreasing the progression of joint damage. The goals of the contemporary management of the patient with OA continue to include control of pain and improvement in function and health-related quality of life, with avoidance, if possible, of toxic effects of therapy.[21] A new additional concept of treatment OA is to delay progression. The status and requirements of patients often change over time, thus making it necessary to review and adjust treatment regularly rather than rigidly continuing a single intervention. Management plan should be individualized and patient centered, agreed on by the patient and doctor in a mutual discussion. Non-pharmacological approaches should be

tried first, and plans may need to be modified as the patient condition changes. Suggested algorithm for the management of knee osteoarthritis and methods used in non-pharmacological approach were illustrated in figure 1 and table 1, respectively. Patient education remains the most effective therapy for OA[22] and drug therapy for pain management is also most effective when combined with non-pharmacologic strategies.[62]

Pharmacological interventions

(1) Analgesics, non-steroidal anti-inflammatory drugs, and cyclo-oxygenase-2 inhibitors

Acetaminophen

The relative role of simple analgesics (acetaminophen or paracetamol) versus NSAIDs in the medical management of OA has been debated in recent years in the medical community.[63] Part of this debate stems from the fact that the pathogenesis of OA is complex and not well understood. Latest systematic review of effectiveness of acetaminophen for osteoarthritis showed superior pain efficacy to placebo with a similar safety profile. In the comparator-controlled RCTs, acetaminophen was less effective overall than NSAIDs in terms of pain reduction and patient global assessment but both drugs had similar efficacy in terms of improvement in functional status.

ACR guideline suggested that the relief of mild-to-moderate joint pain afforded by the simple analgesics, acetaminophen, is comparable with that achievable with NSAIDs.[21] Furthermore, there was no differences in responses to acetaminophen and ibuprofen in knee OA patient with clinical features of joint inflammation.[64] Available evidence supports the recommendation of ACR guideline to use acetaminophen as initial therapy for OA in addition to non-pharmacological interventions (table 2.1).

Figure 2.1 An algorithm for the suggested management of knee osteoarthritis [65]

Management of Osteoarthritis of the Knee

Nonpharmacologic treatment (e.g., patient education and support, exercise, weight loss, joint protection)

plus

Acetaminophen in a dosage of up to 4 g per day to control pain and other symptoms, and before activity

↓

Add topical capsaicin cream applied four times daily, if needed.

↓

If joint effusion is present, consider aspiration and intra-articular injection of a corticosteroid, such as 40 mg of triamcinolone.

↓

If more pain or symptom control is needed, add an NSAID in a low dosage, such as 400 mg of ibuprofen taken four times daily

↓

If more pain or symptom control is needed, use the full dosage of an NSAID, plus misoprostol or a proton pump inhibitor if the patient is at risk for upper gastrointestinal tract bleeding or ulcer disease, or substitute a cyclo-oxygenase-2 inhibitor for the NSAID; some patients may benefit from intra-articular injections of a Hyaluronic acid-like product.

↓

If the response is inadequate, consider referring the patient for joint lavage, arthroscopic debridement, osteotomy or joint replacement.

Table 2.1 Nonpharmacologic therapy for patient with osteoarthritis[18, 21]

Patient education
Self-management program
Personalized social support
Weight loss
Aerobic exercise programs, rang of motion exercise, muscle strengthening excercise
Physicial therapy
Assistive devices for ambulation, daily livings
Patellar taping
Appropriate footwear
Bracing
Occupational therapy
Energy conservation

Non-steroidal anti-inflammatory drugs

As shown in treatment algorithm (Fig.2.1), for patients who do not obtain adequate symptom relief with acetaminophen, use of NSAIDs should be considered. The choice between a non-selective NSAIDs and a COX-2 inhibitor should be made after evaluation of risk factors, particularly for upper gastrointestinal, renal and cardiovascular toxicity.[66]

While nonselective NSAIDs provide effective pain relief, their use is associated with well known gastrointestinal (GI), renal and platelet side effects. Less severe GI complications include dyspepsia, abdominal pain, diarrhea and nausea. Nonselective NSAID therapy may less commonly result in more serious GI complications, including perforation, obstruction and hemorrhage from gastric and duodenal ulceration and other complications, all of which may lead to hospitalization.[67, 68] The incidence of the more serious symptomatic GI ulcers and ulcer complications ranges from 1 to 5% depending on the length of treatment.[69] Multiple risk factors increase the likelihood of GI complications in patient taking NSAIDs. Common risk factors include age, previous ulcer disease, and concomitant oral corticosteroid therapy.

The options for medical management of the patient with osteoarthritis who is at increased risk for a serious adverse upper gastrointestinal event are use a nonselective NSAIDs with gastroprotective therapy or a COX-2 specific inhibitor.Both conventional NSAIDs and COX-2 inhibitors may cause acute deterioration in renal function, fluid retention and hypertension. The newer COX-2 inhibitors are considerably more expensive than the conventional NSAIDs, and uncertainty remains about potential increased risk of cardiovascular risk. Myocardial infarctions and cardiovascular thrombotic events in patient taking COX-2 inhibitors or conventional NSAIDs were reported in many studies. [24, 26, 70-72]

The evidences supporting use of non-steroidal anti-inflammatory drugs in osteoarthritis were recently reviewed.[73] It reported NSAIDs can reduce short tem pain in osteoarthritis of the knee slightly better than placebo, but may be ineffective for long-term use for this condition. As serious adverse effects are associated with oral NSAIDs, only limited use can be recommended. Additionally, several short term studies (under six months) have shown that non-steroidal anti-inflammatory drugs are more effective than placebo in reducing pain and improving function, but there have been few studies that have lasted longer than two years.[18] It should be noted that pain efficacy by taking either conventional NSAIDs is comparable to that achieved with selective COX-2 inhibitors. [21]

Centrally acting analgesic

Tramadol is a synthetic opioid agonist that inhibits reuptake of norepinephrine and serotonin. It can be considered for use in patients in whom acetaminophen therapy has failed and who have contraindications to NSAIDs and COX-2 inhibitor. Although several studies have examined use of Tramadol to treat general pain, few controlled studies have examined its use in osteoarthritis. Pain efficacy of Tramadol was comparable to that of ibuprofen in patient with hip and knee osteoarthritis.[74] It is useful as adjunctive therapy in patients with osteoarthritis whose symptoms were inadequately controlled with NSAIDs.[75] Patients who do not respond to or cannot tolerate Tramadol and NSAIDs and continue to have severe pain may be considered candidates for opioid therapy as well as the intra-articular therapies.

(2) Intra-articular injections

Glucocorticoid injections

Intra-articular glucocorticoid injections are of value in the treatment of acute knee pain in patients with OA, and may be predominantly beneficial in patients who have signs of local inflammation with a joint effusion.[76, 77] Injections can be used as monotherapy in selected patients or as an adjunct to systemic therapy with an analgesic, a non-selective NSAID, or a selective COX-2 inhibitor. Joints should be aspirate and injected by using aseptic technique. Some patients may experience a mild flare of synovitis due to a reaction to the crystalline steroid suspension. The effect of repeated injections is unknown and it is recommended that a single joint not be injected more than three times a year.[78] A recent study of the use of intra-articular steroid concluded that, although frequently repeated injections (four times per annum) were not remarkably effective for reducing pain, they were safe.[79]

Viscosupplementation

Serum hyaluronan (HA) is a marker of osteoarthritis status.[80] HA is a high molecular weight glycosaminoglycan composed of alternating subunits of glucosamine of glucosamine and glucuronic acid. It is a component of synovial fluid, responsible for its viscoelasticity. HA has an important role in maintaining normal joint function by providing support and lubrication and regulating biochemical processes. In OA of the knee, both synovial fluid elastoviscosity and hyaluronan concentration are reduced, which exposes the knee to potential physical damage.[81]

Intra-articular injections of high molecular weight hyaluronates were originally thought to act as fluid replacement.[82] At the present, its biologic activation of multiple protective mechanisms may explain the long-term clinical benefits.[83] There is significant supportive evidence for at least one hyaluronan (sodium hyaluronate) having a positive effect on cartilage matrix.

In recent meta-analysis of intra-articular Hyaluronic acid in treatment of knee osteoarthritis, the authors concluded that it had a small effect when compared with an intra-articular placebo. However, some studies reported supportive results for the hyaluronans.[84, 85] HA might provide effective pain relief after a single course of treatment. Pain can recur in many patients, usually after an interval of several months. Thus, the retreatment in patients who have benefited from a first course is clinically indicated.

(3) Chondroprotective agents

glucosamine

This compound occurs naturally in the body and may be involved in the repair and maintenance of normal cartilage. It is an amino monosaccharide that is formed in the body as glucosamine 6-phosphate. glucosamine is the most fundamental building block required for the biosynthesis of the classes of compounds, such as glycolipids, glycoprotein, glycoaminoglycans, hyaluronate, and proteoglycans. It has been viewed as a preferred substrate for the biosynthesis of glycosaminoglycan chains and, subsequently, for the production of aggrecan and other proteoglycans and cartilage.[86]

There are three forms of glucosamine: glucosamine sulfate, glucosamine hydrochloride, and N-acetyl-glucosamine. These glucosamine compounds are generally derived from chitin, a biopolymer present in the exoskeleton of marine invertebrate animals. glucosamine is usually taken orally and in humans 90% is absorbed. Its biochemical pathways is actively transported from extracellular tissue into cells by glucose transporters; insulin facilitates glucosamine transport into cell.[87] It has been used for many years in veterinary medicine for relief of arthritis symptoms. Recent laboratory studies indicated that both glucosamine and chondroitin are absorbed from the gastrointestinal tract and appear to be capable of increasing proteoglycan synthesis in articular cartilage.[88]

Several clinical trials were performed by using glucosamine sulfate in patient with osteoarthritis. Most of which have demonstrated favorable effects. Two long-term clinical trials were able to show a statistically significant slowing of radiographic progression of OA of the knee over 3 year, in addition to demonstrating a significant improvement in validated symptom scores for OA.[28, 29] These trials are now preliminary evidence that glucosamine may actually be able to slow the radiographic progression of OA of the knee. However, the validity of this conclusion has been disputed, with the main criticism being related to the accuracy of the radiographic methods used to quantify the progression of OA of the knee.

Of note, according to the most recent Cochrane review of glucosamine for treating osteoarthritis, most trials were sponsored by a manufacturer of the product.[27] The authors suggested perhaps the major limitation with extrapolating the generally favorable results from the glucosamine RCTs lies in the fact that most (75%) of the studies in the Cochrane review evaluated exclusively the prescription made by Rotta Pharmaceutical Company.

Because of most RCTs have been of a relatively short duration, information is still needed on more well-designed trials in long-term efficacy and safety of glucosamine in OA. Virtually all of the published RCTs have investigated glucosamine sulfate. It is not known whether the generally favorable results obtained with glucosamine sulfate can be generalized to other glucosamine-containing preparations, including glucosamine hydrochloride.[89] As of these suggestions, the glucosamine HCl/chondroitin Arthritis Intervention Trial (GAIT), a 24 week randomized, double-blind, placebo and Celecoxib controlled, multicentre trial sponsored by the National Institutes of Health US was conducted and just finished recently.[30]

Patients were randomly assigned to receive 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, both glucosamine and chondroitin sulfate, 200 mg of Celecoxib daily, or placebo for 24 weeks. Up to 4000 mg of acetaminophen daily was allowed as rescue analgesia. The primary outcome measure was a 20% decrease in knee pain from baseline to week 24. GAIT provided supportive results for using glucosamine HCl in combination with chondroitin sulfate in patients with moderate-to-severe knee pain. Taking glucosamine and chondroitin sulfate alone did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee.[30] Adverse events reported in this trial were generally mild and evenly distributed among the groups. Additionally, Chan and colleagues expressed concern about the potential adverse effects of long-term glucosamine therapy on glucose homeostasis[90], citing evidence that glucosamine may increase insulin resistance and/or impair insulin secretion.[91]

Conclusively, glucosamine may be effective in pain-relieving in subgroup patient and taking continuously over long period may delay disease progression. In making therapeutic decisions, physicians and patients alike should be aware of these data. Continuing research is needed to establish the potential efficacy and increase understanding of the biology, pharmacology, and pharmacokinetics of this agent.

2. Budget impact analysis

It is now widely recognized among decision-makers that value of money represents a key criterion in deciding which healthcare interventions should be made available in collectively funded healthcare systems. Budget impact analysis can be viewed as an effective tool serving this particular objective. Details in this part

support this statement by explaining what the budget impact analysis (BIA) is and how it can comprehensively integrate to other economic evaluations by focusing on its importance and applications. To better understanding about the budget impact analysis, the comparison of this approach and other similar economic evaluations is needed and then presented in the subsequent section. Finally, the guidelines for budget impact analysis were reviewed.

2.1 What is BIA?

A budget impact analysis for a new pharmaceutical product is an economic analysis aiming to estimate of the likely impact of the new drug on a healthcare decision makers' short- and longer-term annual budget.[4] It is an essential part of a comprehensive economic assessment of a new pharmaceutical product and is increasingly required, along with cost-effectiveness analysis, before national or local formulary approval of reimbursement. Decision makers need the budgetary impact estimates of a new drug on annual drug and total healthcare system expenditures for financial planning. They are also interested in the impact of a new drug on annual healthcare service utilization at the system level since they need to understand for the new drug will affect the system in terms of service provision.

2.2 The need for budget impact analyses

The rapid growth of healthcare expenditures, coupled with slowdown in the growth of the economy, has led to increased interest in health economic and financial evaluation of healthcare programs. The need to demonstrate the value for money of new interventions has become firmly established with a particularly strong focus on pharmaceuticals. Before such pharmaceuticals are reimbursable or listed on formularies, they must be shown to be not only clinically effective, but also cost effective. The cost effectiveness of medicines has been widely labeled as the "fourth hurdle" to market, in addition to the traditional 3 hurdles of safety, efficacy and quality, required for its licensing.[1] Whilst this policy remained isolated to Australia and parts of Canada for much of the 1990s, it has now spread rapidly throughout Europe by which currently apply the policy recommendation to the assessment the potential for economic evaluation.[92]

Besides the cost effectiveness of a new pharmaceutical, decision to adding on formulary will also based on the fifth hurdle: budget impact. Traditional economic guidance on pharmaceuticals mainly focused on cost effectiveness analysis, it somewhat failed to realize that purchasers are operating within constrained budget

and whilst maximizing efficiency is one of their objectives, an equally important objective is staying within their budgets.[1] Additionally, such analyses are claimed to be barely practical because the information presented is not in a format that is useable and/or understandable by non- economists.[2]

Cost-effectiveness analysis has been advocated efficiency maximization as a central objective of resource allocation in the health services. It must be acknowledged that the over-riding objective for many healthcare decision-makers is staying within their budget. Whilst this economic evaluation may assist the prioritization of health interventions, it is not sufficient to predict if an intervention is affordable with given resources. Thus, there is a role for budget impact analyses to complementary inform healthcare decision-making. To reach the decision on the best possible interventions especially pharmaceuticals, the decision makers must recognize in a certain way that the particular intervention under consideration is proven in their cost-effectiveness prior to determine if it is affordable as of the results of budget impact analysis. The result format of these analyses is expected to be more practical and understandable for both health economists and non-health economists comparing to information presented in the traditional economic evaluations.

2.3 Comparison of Budget impact analysis and other economic evaluations

2.3.1 Comparing to Cost-effectiveness analysis[4]

Principles of performing budget impact analysis (BIA), which are generally not considered when carrying out a cost-effective analysis (CEA), are also major differences of these two analyses. During performing budget impact analysis, there are several factors need to be taken into account. The first of these involves the inclusion of impact of new drug on all healthcare costs or just those related to the disease of interest. Typically, the standard method for CEA recommend only on the costs and benefits associated with the condition of interest. On the other hand, since a BIA is designed to support financial planning, it appears reasonable to include the impact of the new drug on all healthcare costs despite it is unrelated to the disease.

Second, a BIA generally considers the mix of treatments and the market diffusion of product over time in the target population. This approach is in contrast to a CEA. Theoretical concern in CEA is the efficiency of using new drug compared with alternative treatments and thus the focus of CEA is only those patients who receive the new drug. Deciding which choice of treatment should be made available based on the results of comparison of cost and benefit of which are major findings

from CEA. Whilst BIA provides more realistic budget and healthcare service impact of treatment under consideration by considering the market shares of the combination of all involving treatment regimens.

The third factor involves the number of people seeking care. CEA only compares the cost effectiveness of alternative treatments only for those seeking care rather than mainly considering the expansion of seeking care patients with a health condition that a new drug could be significantly more effective than the current one. The budget impact from treating the increased number of patients who may seek care can be much larger than the budget impact of switching to the new drug those already in treatment. Finally, the off-label use is another considerable concern to healthcare decision makers. It may occur for patients with the condition of interest but outside of the approved label indication or for patent with different conditions altogether. For CEA, this usage is not relevant, since it is estimating the efficiency of the new drug in its approved use.

2.3.2 Comparing to Cost-benefit analysis

The feature that distinguishes among techniques of economic evaluation is the way in which the consequences of healthcare programs are valued. Cost-benefit analysis requires program consequences to be valued in monetary units, thus enabling the analyst to make a direct comparison of the program's incremental cost with its incremental consequences in corresponding units of measurement.[93] Cost-benefit analysis (CBA) converts all costs and benefits and as of this, it is not restricted to comparing programs within healthcare but can be used to inform resource allocation decision both within and between sectors. Partly, CBA is similar to BIA in terms of consideration of health outcome as monetary value. However, to do CBA is to assigning money values to health outcomes while performing BIA is to estimating the arising cost consequences of health outcomes by which the program potentially generates. Clinical consequences of implementing the program, in BIA, have been viewed as benefits attributable to costs including other possible changes of associated healthcare resource uses.

3. Reviews of country-specific guidelines for budget impact analysis

3.1 Australia

While standard methods for performing and presenting the results of cost-effectiveness analyses are well accepted.[94], the same progress has just been made for budget impact analyses. National bodies responsible for pricing and reimbursement of pharmaceutical products in many countries have developed some guidance on financial impact estimation, which are comparable to BIA concept. Guidelines established by *Australia's PBAC* (Pharmaceutical Benefits Advisory Committee) for economic evaluation from Australia specifies the submissions for reimbursement should "estimate the likely prescription volume of the proposed drug on the PBS (Pharmaceutical Benefit Scheme) for at least each of the first two full years from the date it is listed on the Schedule".[95]

The PBAC calls for an epidemiologic approach in estimating the number of patients eligible for the new drug and its comparators. If a drug is to be used in treating an acute condition, the annual incidence of the disease should be used in approximation the number of eligible patients. In contrast, if the drug is used to treat chronic conditions, estimates of the prevalence of the disease should be used. For each In addition, PBAC suggests that any substitution effects with other reimbursed medications currently in use should be included, as should the impact on any other healthcare resources. For each indication that is proposed, the patient numbers should be estimated separately and then summed and modified based on the likely market share for the new drug as well as the potential growth in the overall market.

In general, the following four steps should be applied after the PBS drug budget calculations:

- Add medical care costs of treating side effects of the new drug
- Subtract savings in medical care costs from treating fewer side effects of competing drugs
- Subtract savings in medical care costs from fewer alternative nondrug treatments
- Subtract savings in medical care costs because the drug reduces the burden of illness for the health condition.

These latter estimates should use constant prices without adjusting for inflation, include an annual discount rate of 5%, and consider the full time horizon for the changes in nondrug costs.

3.2 Poland[5]

Poland is the most recent country to establish guidance for conducting BIA. The Polish guidelines offer detailed and precise recommendations for performing a BIA. It was created separately from the Polish guidance for CEA, unlike other country guidance for economic assessment of new healthcare interventions, and offer detailed guidance for preparing the analysis.

The Polish guidelines adopted the epidemiologic approach, the use of a specified time horizon, and formulas for calculation from the Australian guidelines. The calculations for service impact were adopted from the NICE guidelines. The Polish guidelines underscore that a BIAS should be conducted from the perspective of purchaser. It also should be transparent with respect to all input assumptions and the relationship among variables when calculating outcomes. If a predictive model is used, it should be interactive and accessible in order to allow decision makers to assess the scenarios and perform sensitivity analysis. Epidemiologic data, resource use, unit costs, therapy replaced by the new drug and target population should be country specific. Time horizon for the BIA should be until the drug has reached its peak or stable market share from at least 2 years after the drug has been placed on the reimbursement list.

BIA model should be able to predict how savings are realized in the future. Sensitivity analyses should include the impact of underlying assumptions on final results including the impact of variable market diffusion rates. Data on effectiveness and number of people receiving treatment, and the duration of their treatment are requested to be included in BIA. These data include the estimated number of patients eligible for each indicated therapy, efficacy, safety, dose, and treatment period to include long-term use estimated, and concomitant therapy.

Finally, the Polish guidance requests that the estimates of the budget of a new drug should include the impact of changes in the use of other drugs attributable to placing the new drug on the reimbursement list. This impact of changes in other treatments includes:

- Drugs that are prescribed as part of the treatment with the new drug
- Drugs that will be used less often because of therapeutic indications, side effects of current treatment and interactions

3.3 Canada

The *Canadian Co-ordinating Office for Health Technology* (CCOHTA) guidelines for the economic evaluation of pharmaceuticals in Canada states "in addition to the incremental analysis, it is useful to report total costs and total outcome for each alternative", but provide nothing in the way of guidance on how such analyses should be performed.[7]

3.4 England

In *England and Wales*, guidance from NICE (National Institute for Clinical Excellence) has recognized the potential total National Health Service (NHS) of treating the condition as one of the criteria for selection of intervention for appraisal. Also, NICE have initially suggested that the submission should estimate the number of patients for whom the therapy is likely to be clinically cost effective and derive from this an estimate of the total cost to the NHS of adopting it. More recent NICE guidance recommends consideration of the wider NHS implications that includes the prediction of the proportion of eligible patients who might use the technology and any consequential effects for the service as a whole.[96]

The recently published *Dutch* guidelines also state that there should provide an insight into the total costs and effects of both treatments under investigation.[92] Similarly, there has been a great recognition of BIA, which can be a complementary frame of the economics of a new pharmaceutical product through the CEA. The Academy of Managed Care Pharmacy (AMCP) format for formulary submissions was based on the prior work at Regence Blue Shield, which recognized that there was a need to evaluate the efficacy, safety, effectiveness, cost-effectiveness and budget impact of new chemical entities and thus provided a mechanism to submit this information to health plans.

4. Standards for conducting budget impact analyses[1, 4]

BIA complements CEA in helping to decide how best to allocate scare healthcare resources. Since most guideline for economic assessments request that both CEA and BIA are necessary for a comprehensive economic submission. In general, a CEA has been performed for the new intervention for all the relevant population subgroups using current standard methods. The BIA then builds on the base of a complete CEA.

Methods for performing BIA

All budget impact models should explicitly or implicitly take into account the mix of ages, disease severity, and other population characteristics of those with or at-risk for the condition of interest because the new drug may have different short- and long-term impacts on different population subgroups.

The choice of methods for deriving budget impact estimates depends on the condition(s) for which the new drug is indicated and impact of the new drug on that condition as well as the time horizon of the decision maker. Generally, BIA can be categorized into two types: static and dynamic. Static analyses are usually suitable for acute conditions where the new drug impact occurs over a short-time period or for chronic diseases where the time horizon of interest for the analysis is short. Dynamic analyses are appropriate for chronic disease where the new drug slows disease progression and/or reduce premature death rates, and estimates are needed for both short- and long-time horizons.

For an acute illness, a static analysis can commonly be completed using the data from the cost-effectiveness model with the addition of epidemiologic data on the incidence of the acute condition under study. Decision tree model can be applied to the estimates of financial impacts of new drug.

A dynamic analysis for a chronic illness is also derived using data from a CEA with the addition of epidemiologic data on the incidence, prevalence, and natural history of the disease of interest. It is assumed that the cost-effectiveness model for chronic condition takes a lifetime perspective and tracks the person after treatment with the new drug over their remaining lifetime. Some types of modeling needs to be implemented in order to estimate the impact of the new drug on the number of people needing treatment and their mix of disease severity at any time period after the introduction of the new drug. Both Markov and discrete event simulation model can be used to generate estimates these changes.

As of BIA concept, it is also desirable to estimate the annual changes in healthcare eservice use and health outcomes that will accompany the costs change. Since the budget impact may change over time after the new drug is introduced, both because of gradual market diffusion and long-term impact on the condition under study, the budget impact should be estimated for each year until a steady state is reached.

Important factors to consider in BIA

● Model perspective

BIA perspective should be clearly stated and consistent with the view of decision maker.

● Model comparators

The new therapy should be compared with existing and practice therapy.

● Data sources

Input data for the model should be obtained from the best possible, reliable sources and also should be clearly presented along with any assumptions.

● Relationship between short-term and model end points

Any assumptions on clinical effectiveness of product within the analysis time horizon should be explicitly explained.

● Adoption of new therapies

Rate of uptake of new drug and any substitution for current treatments and/or increased demand for another product that may come about as a result of adopting the new drug is needed to be assumed and stated clearly.

● Population subgroups or indications

BIA must allow for the examination of the appropriate population subgroups as seen in the clinical trials.

● Time horizon

Time horizon needs to be appropriately given corresponding to the therapeutic area and decision-maker perspective.

● Transparency

As in the development of any model, all model inputs, model assumptions, and details of calculations are needed to be clearly presented.

● Reporting results

Both healthcare services and currency units should be both reported in BIA.

● Long-term impacts on events

BIA should be able to predict the long-term impact on events i.e. decreased incidence of disease.

● Redeploying resources

Similarly, all possible impacts on redeploying services of the introduction of new drug should be predictable by BIA.

● Uncertainty and sensitivity analysis

Uncertainty around key inputs and assumptions must be analyzed.

● Usefulness of the model for decision makers

BIA should be made accessible to decision maker through construction of the structure, inputs and assumptions.

To consider each of these important features of BIA, a model can be programmed in a modular approach. Through a series of worksheets or form-based applications, this modular approach enables the requirements of transparency and ease-of-use to be achieved. Manuskopf JA et al. proposed four key modules that may be programmed in a BIA.

Firstly, the model objective, definitions, structure and underlying assumptions can be presented to assist users with understanding of the analysis and its approach. Issues about health condition definition for different levels of severity and treatment pathways can be presented. Consequently, the model is programmed to accept various situation-specific input parameters such as prevalence, drug costs, and healthcare resource use costs and anticipated product mix. Module 3 can be constructed to bring the model input together to generate final costs and outcomes. In this module, the decision-analytic models such as Markov, decision tree and simulation can be used to estimate the BIA. Finally, the results generated in module 3 will be presented in a clear and concise manner. Results are comprised of costs in which include drug and other medical costs, and outcomes.

Conclusively, the budget impact analyses are essential part of a comprehensive economic assessment of a new pharmaceutical product and are increasingly required, along with cost-effectiveness analyses. BIA provides information assisting the decision maker in a concise and understandable format. All possible financial impacts were estimated and this information was expected to be more helpful, practical for decision makers to budget planning.

4. Principle of good practice for budget impact analysis proposed by ISPOR (International Society of Pharmacoeconomic and Outcomes Research)

The ISPOR Task Force on Good Research Practices – Budget Impact Analysis proposed a framework for creating budget impact models, guidance about the acquisition and use of data to make budget projections and a common reporting format that will promote standardization and transparency.

The following details are their recommendation for key elements of the analytic framework for budget impact analysis.

Design

Appropriate design of the analytic framework is an important step in budget impact analysis. The design must take into consideration the current understanding of the nature of health condition and the clinical evidence of the current and new technologies. There are several aspects that have to be considered: acuteness of the health condition, type of intervention. These aspects can affect the degree to which time-dependence is crucial in the design, how the size of population is estimated, the unit of analysis, how the intervention uptake is addressed, and the choice of computation framework.

In general, whether or not a health condition model is needed depends on the type of health condition and intervention of interest. For a chronic health condition where time dependency to be a major issue, a health condition model is likely to be needed. The model should be constructed so that it is consistent both with a natural health condition and with the available evidence. Techniques currently used, such as Markov models, might be appropriate. Also, they suggested that the newer techniques such as discrete event simulation, agent-based simulation and differential equations model may be considered if they are tentatively accepted by the decision makers.

For acute, self-limiting, health conditions where the episode is the unit of analysis, simpler techniques using deterministic calculations may be used.

Perspective

Results of budget impact analysis are primarily intended to inform healthcare decision makers, in particular for those who are responsible for healthcare budgets. Hence, the recommended perspective is that of the budget holder. Thus, unlike a cost-effectiveness analysis, where the recommended perspective is of society, which includes all cost implications, a budget impact analysis needs to be flexible enough to generate the results that include various combinations of healthcare, social service, and other costs.

Scenarios to be Compared

Various scenarios should be compared when performing the budget impact analysis. These scenarios were defined by a set of interventions rather than specific individual technologies. The reference scenario should be the current mix of interventions for the chosen population and subgroups. The current mix may include no intervention as well as interventions that might or might not be replaced by the new intervention. Introduction of a new technology sets in motion various marketplace dynamics, including product substitution and possibly market expansion. These need to be modeled explicitly with realistic and justifiable assumptions before the comparisons among scenarios can be made. Thus, the analysis should consider how the current mix of interventions is likely to change when the new intervention is made available.

Population

All patients who might be given the new technology in the time horizon of interest should be included in the analysis. Specifying who is included in the population is not straightforward. It depends on the approved indication but it also reflects local intended restrictions on use, induce demand, and the extent to which practitioners adopt the technology or change pattern of use of existing ones. The budget impact model must be designed to allow for examination of the effect of alternative assumptions about the nature and size of the treated population as well changes in its nature and size over time. Note that the Task Force did not recommend inclusion of off-label use of the new technology in these scenarios since generally accepted methods for doing this are not yet available.

In general, these populations are open in the sense that individuals enter or leave the population depending on whether they currently meet the analyst's criteria for inclusion (e.g., by developing the indication, meeting the intended restrictions, no longer having symptoms, etc.). This is in contrast with CEA where populations are closed (i.e., a cohort of patients is defined at the start and all remain members throughout the analysis).

Subgroups

The framework of budget impact model should allow for subgroups of the population to be considered so that the result analyses can be made specific to these segments. Such aspects as disease severity, co-morbidities, age, gender, and other characteristics that might affect access to the new technology might be taken into

consideration. This may inform decision regarding use of the new technology as a "first line" intervention or reserving for use in patient failing other alternatives. Also, the choice of subgroup must be founded available on clinical studies and epidemiologic studies.

Time horizon

Budget impact analyses should be presented for the time horizons of most relevance to the budget holder. They should accord with the budgeting process of the health system of interest, which is usually annual. The framework should allow, however, for calculating shorter and longer time horizons to provide more complete information of the budgetary consequences.

Although time horizons that go beyond a few years are subject to considerable assumptions, they may in exceptional cases be required to cover the main implications of the health condition. To make the analysis results most useful, the output should be the period by period level of expenses and savings rather than a net present value.

Costing

All resource uses that may change are needed to identify in the step of costing. They have to be estimated the amount of change and valued. In a BIA, this step must be done according to the perspective and interest of the budget holder. Additionally, the resource use considered should be that which is relevant to the health condition and health technology of interest over the chosen time horizon. The impact on productivity and other items outside the health care system costs should not routinely be included in a budget impact analysis as these are not generally relevant to the budget holder.

Sensitivity Analysis

Since there is substantial uncertainty in a budget impact analysis, therefore, a single best estimate is not a sufficient outcome. Instead, the analyst should compute the range of results that reflects the plausible range of circumstances the budget holder will face. Various forms of sensitivity analysis may be carried out. Their usefulness depends on the amount and quality of available data and the needs of the decision makers.

Discounting

The Task Force suggests that it is not necessary to discount the costs sine the budget impact analysis is aimed to present financial streams over time. The computational framework should be constructed so that the decision maker can readily discount these results according to local practice back to a decision time point if they wish to do so.

CHAPTER III
METHODOLOGY

The methodology to conduct this research relies on the comprehensive integration of two concepts. The first concept is the core structure of the study, Budget Impact Analysis (BIA) model. In BIA, there are two important variables involved: cost and utilization of drug interest. Forecast of number of use and the estimation of possible cost of drug were done and illustrative in this part. The cost-consequence model, the second concept, was applied to estimate the treatment cost of adverse events of using NSAIDs. Details of modeling technique used including how the model was constructed by which type and data inputs, were included in each concept.

1. Development of Budget Impact Model

1.1 Model structure

The budget impact model of glucosamine mainly focuses on the changes in uses of healthcare resources associated with the disease of interest. These changes are directed toward on drugs and health services that will tentatively be used less often because of the clinical benefit of new drug over current treatments. They are shown as a part of model comparators. The following budget impact model then was developed.

$$\textbf{Budget impact model} = (C_p \times Q_p) + \sum [\Delta (C_{ki} \times Q_{ki})]$$

Where

C is the average cost (Baht/patient/year).

Q is the number of drug use (patient/year).

p is the drug proposed for listing.

k are the competitive drugs/services.

$i = 1,2,3,\ldots,n$

Competitive drugs and services in the model are those that are currently used to effectively treat knee OA in the setting under study. Hypothetically, all relevant healthcare resources should be determined in BIA model. Nevertheless, in order to address the importance of BIA and also keep model simplistic, only those regarded as

representatives for each therapeutic indication are purposively included in the analysis. Rationales supporting this decision are clarified in section 1.3: rationale for model comparators.

In details, to consider the possible changes in healthcare resources used resulting from glucosamine, there are six drugs and one relevant healthcare service taken into consideration as shown in the following equation. They will be added up with new drug, glucosamine, after it has been listed:

$$\textbf{Budget Impact Model} = \sum_{i=1}^{8} \mathbf{C}_i\mathbf{Q}_i \textit{ at a year after} - \sum_{i=1}^{7} \mathbf{C}_i\mathbf{Q}_i \textit{ at a year before}$$

Here i =1-7 by which the first six i are competitive drugs and new drug, and the latter one is healthcare service: Diclofenac Sodium tablet (i=1), Diclofenac Sodium and Ranitidine tablet (i=2), Diclofenac Sodium and Omeprazole tablet (i=3), Celecoxib tablet (i=4), Tramadol tablet (i=5), Hyaluronic acid Sodium injection (i=6), Physical therapy (i=7) and glucosamine (i =8).

To make the model structure simpler, each drug/service was grouped according to its indication: *indication-based analysis*, resulting in the following budget impact model.

Budget Impact Model = Δ Cost of delaying progression + Δ Cost of pain-relieving

$$= [(\Delta\mathbf{C}_6\mathbf{Q}_6 + \mathbf{C}_8\mathbf{Q}_8)] + [(\Delta\mathbf{C}_1\mathbf{Q}_1) + (\Delta\mathbf{C}_2\mathbf{Q}_2) + (\Delta\mathbf{C}_3\mathbf{Q}_3) + (\Delta\mathbf{C}_4\mathbf{Q}_4) + (\Delta\mathbf{C}_5\mathbf{Q}_5) + (\Delta\mathbf{C}_7\mathbf{Q}_7)]$$

Δ refers to the differences of value of each variable as a result of a comparison of such at before and after the listing of new drug.

1.2 Budget Impact Model descriptions

Objective	Estimate the impact of new drug on healthcare budget
Disease of interest:	Knee osteoarthritis
Model perspective:	Hospital
Model comparators:	see details in (1.3)
Financial impacts:	Financial expenditures of model comparators and relevant healthcare services calculated from average utilization and number of patients.
Time horizon:	One year
Target population:	Patients with knee osteoarthritis who failed to control pain by acetaminophen
Data sources:	Literature, Hospital database
Analysis method:	Probabilistic Analysis (Monte Carlo simulation)

Budget Impact Model was performed with an aim to estimate the financial impact of new drug on healthcare budget. In this study, the knee osteoarthritis was the disease of interest together with the representative drugs/services to treating this disease. glucosamine was selected to be an illustrative case of budget impact analysis. Target population was patients only those who failed to control their pain by acetaminophen.

Financial impacts in this study were defined as financial expenditures incurred from any healthcare services calculated from costs and utilization units of each drug/service. One year time horizon was applied in each budget impact model and replicated analyses will be done until glucosamine could reach the steady market share in terms of number of users (patients).

Data source mainly used hospital database and literatures. Drug utilization data employed the actual data derived from computerized dispensing data and patient medical history from hospital database while probability figures were obtained from literatures. Budget impacts of glucosamine were examined by using the probabilistic analysis. It was introduced to use in this study with an aim to enhance the ability to determine these impacts precisely by taking all uncertainties into consideration. While analytical models are best suited for forecasting and explaining phenomena that have already occurred, simulation models are tools developed for planning and decision-making under uncertainty, before data on the true phenomena are available.

In simulation, each uncertain variable is modeled by a probability distribution. Monte-Carlo simulation was used by involving random sampling of each variable under the specified probability distribution within the model to produce hundreds or thousands of iterations. Each probability distribution is sampled in a way that reproduces the distribution's shape. Hence, the values calculated reflect the probability of the values that might occur.

1.3 Model comparators

Model comparators included glucosamine, diclofenac sodium alone and combination with raniditine and omeprazole, celecoxib, tramadol, hyaluronic acid Sodium injection; healthcare services: physical therapy. In this study, the drug of interest might be viewed differently from those of other BIAs elsewhere. In brief, the model comparators in BIA should have evidently clinical benefits so they are proven of value to cost-effective evaluation and is theoretically suitable for conducting the budget impact analysis. glucosamine is a challenging case aligned with this decisive certainty due to its conflicting results reported in various clinical studies. Some studies reported the favorable results of glucosamine as it was effective as both symptomatic relief and structural modification whilst a fair amount of studies showed the insignificant differences of its efficacy comparing to placebo. glucosamine is then selected for this study as an illustrative instance representing the uncharacteristic scenario in BIA.

There are other associated features further than this problematic issue which can support glucosamine to be of merit to study. Two ultimate goals of osteoarthritis treatment are controlling pain with avoidance of side effects and delaying progression. Most pharmacological agents used nowadays are aimed to relief pain by using analgesics and NSAIDs.

Amongst therapeutic approaches available in the setting under this study, there is only hyaluronic acid injection potentially achievable for both optimal goals of osteoarthritis treatment: controlling pain and delaying progression. However, it has not been widely used because to inject drug directly into articular is sometime unfavorable for patients and also costly. For this study, glucosamine in oral form became an interested agent as it may provide similar clinical benefits to hyaluronic acid and probably less costly. Moreover, the current treatments available especially NSAIDs for pain relieving indication have several substantial adverse effects to

gastrointestinal, renal, and cardiovascular systems while almost all of clinical trials on glucosamine reported only a few minor adverse effects from using this agent. As these reasons, glucosamine can be of clinical value as one treatment choice thus a model comparator in this study.

Only patients those whose pains cannot achieve controllable pain level by acetaminophen, which is the first line drug recommended, are targeted in this analysis. They are clinically considered to use either non-selective or highly selective COX-2 NSAIDs to control pains and regarded as the decision node in the pain-relieving model. In the more advance cases who failed to control pain by these drugs are recommended to use drugs that are more potent, i.e., tramadol. In a certain group, patients are advised to take glucosamine concurrently instead of hyaluronic acid injection. Decisive factors to classify these patients are detailed in the following part of this chapter.

Other relevant healthcare costs taken into consideration are the physical therapy. Supportive pain treatment by physical therapy is common for knee osteoarthritis (OA). Using glucosamine to control pain that is attributable to the changes in physical therapy uses is defined as one clinical consequence in the analysis. Patients with severe symptomatic OA whose pain has failed to respond to medical therapy resulting in the progressive limitation in activities of daily life should be considered for further treatment, total knee replacement. If patients get successful outcome from using structural modification drug, they would be able to delay the disease progression and not yet be a candidate for the total knee replacement. Therefore, this procedure is an ultimate end point for structural modification drug, which should be accounted for in the model analysis. However, due to poor correlation of clinical and radiological signs of disease, the decision to operate surgery then is very much subjective and relies on the interpersonal decision between the patient, their family, and the orthopedic surgeon. Any changes of number of candidates for this particular surgery are difficult to estimate. Thus, the model did not include knee replacement therapy as a model comparator.

2. Estimation the cost of drugs and service used (C_p and C_{ki})

2.1 Pain-relieving agents: NSAIDs and its combinations (C_{ki})

To quantify the cost of using NSAIDs and its combination to prevent gastrointestinal complication, the decision-analytic model, cost-consequence, was developed. A static decision tree model was chosen according to the state of art of performing the budget impact analysis which is suggested to use a static model when the time-frame analysis is short by which in this case only 1 year. Decision tree is conceptually satisfactory for pain-relieving indication because of two reasons. Firstly, the clinical consequences of pain-relieving drug uses do not occur repeatedly and secondly, the likelihood of event occurring in the model is expected to be insignificantly changing in any patient over the relatively short period of time, 1 year.

According to the guideline to perform budget impact analysis, the dynamic analyses using Markov model is appropriate for chronic illness where the new drug slows disease progression. However, in knee osteoarthritis, its progression has been little understood. It is a complex disease, varying from patient to patient. The surrogacy of joint space narrowing to disease progression is small. Poor correlation between this marker and clinical symptoms has been reported. To develop transition states in Markov modeling is then difficult and probably does not well represent the actual progression. Decision tree model is considered as more appropriate model choice in this analysis.

In developing the decision tree, model comparators were considered as decision nodes with clinical consequences as chance nodes. The consensus of three treating physicians was needed before a clinical consequence could be included in the analysis in order to reflect the most practical experience of knee osteoarthritis treatment. All physicians agreed that the pain efficacy of all pain relieving alternatives was not significantly different. Thus, the cost element driven the treatment cost was the treatment associated with adverse events. Only adverse events would then be included in the analytical model. Two major adverse events of using NSAIDs with high prevalence resulting in high cost of treatment were identified for the model. The gastrointestinal and myocardial infarction adverse events were integrated as the clinical consequence on the chance nodes in the decision analytic model. Their prevalence was determined by the number of actual cases experiencing these 2 adverse events in the period of one year. Details of the decision model (decision tree) are as following.

2.1.1 Population

The baseline population of interest consisted of patients enrolled in clinical trials (age ≥ 18 years). To compromise the differences of risk to developing any adverse event based on the variation of duration of use in each patient, the risk estimation was obtained from the meta-analysis in which included various studies with different duration of use in the review process.

2.1.2 Treatment comparators

Drug therapies and dosages used in the model were:

• NSAID: Diclofenac 50 mg *tid*

• H2RA: Ranitidine 150 mg *bid*

• PPI: Omeprazole 20 mg *od*

• Cox2: Celecoxib 200mg *bid*

2.1.3 Cost inputs

Cost data in decision tree analysis consisted of drug cost and treatment cost of adverse events. For drug cost per patient per year, it should be calculated from the unit cost multiplied by the amount of use. Since this study chose not to determine the utilization rate of drug alternatives, the actual total amount of drug use per patient was applied. This number was not only reflect the real-world compliance of each drug it represented the more accurate estimation of treatment costs as well. To foresee the number of use in the next few years, three treating physicians were asked to provide such estimations and their assumptions through Delphi technique. Similarly, the future acquisition cost of each drug/combination was estimated by two pharmacists who were responsible for the purchasing and inventory control.

For the treatment costs of adverse drug events, in order to make the result of analysis well signify the setting-specific application, the actual treatment costs of adverse drug events were picked out. The treatment costs which incurred at inpatient department were estimated based on the diagnosis-related group (DRG) cost of Petchabun hospital. Likewise, the treatment costs of any adverse event at outpatient department were estimated by Delphi technique involving three orthopedic physicians and one medicinal physician. To validate these costs, the comparison between the estimated value given by physicians and the actual treatment pattern of randomly selected patients were made.

Please note that the charge will be alternatively used as a cost in case of treatment cost. For the drug cost, the acquisition cost will be used.

2.1.4 Probabilities

Probabilities of all complications were obtained from meta-analysis. Specific factors which could have an additive effect on baseline probabilities, i.e. history of bleeding and age, would not be taken into consideration.

2.2 Pain-relieving agents: Tramadol (C_{ki})

Cost of pain treatment using tramadol was calculated by the drug acquisition cost and the average number of use per patient per year. The future average amount of tramadol use was estimated by Delphi technique through 3 orthopedicians provided the historical dispensing pattern. No additional resource consumed for adverse events of using this drug was included. The future acquisition cost of tramadol was predicted by 2 purchasing pharmacists by Delphi technique.

2.3 Pain-relieving services: Physical Therapy (C_{ki})

Similarly to tramadol, the average cost of physical therapy each patient used per year (baht/patient/year) was taken into consideration. Since the types and duration of physical therapy provided for each patient were different resulting from the severity of pain, to specifying any type and duration so as to estimate the costs of physical therapy was not practical. Therefore, the actual data of cost of physical therapy of all patients were averaged and the three treating physician provided their best guess of this value in the budget impact analysis in upcoming years by Delphi technique.

2.4 Delaying progression agents: **glucosamine (C_p) and hyaluronic acid injection (C_{ki})**

Costs of using these two drugs consisted of only drug costs. Again, the future average number of use of each drug was calculated based on the historical data on dispensing pattern and then multiplied with the purchasing price. The past dispensing pattern was provided to all physicians for the future estimations used in the budget impact analysis using Delphi technique. The Delphi technique was also used to reach the future acquisition cost of glucosamine and hyaluronic acid by 2 purchasing pharmacists.

3. Estimation of number of patient using each drug/service (Q_p, Q_{ki})

The estimation of number of patients using each drug/service involved two steps. The disease prevalence or patient cases of knee osteoarthritis of the past few years was calculated by based on the actual number of patients visiting orthopedic department. Then the proportion of each treatment alternatives was estimated.

3.1 Estimation of number of patients with knee osteoarthritis

The prevalence of knee osteoarthritis was calculated by using hospital electronic record. To estimate the number of this patient group in the upcoming years, the simple regression analysis was used. Trend lines of the years before and after the introduction of glucosamine into the hospital formulary were estimated. The induced demand effect was also predicted by comparing the slopes of the growth rate before and after the glucosamine introduction. If there were not many differences, the usual trend line was used. In contrary, if a great magnitude of the difference in number of patients with knee osteoarthritis was detected, the induce demand effect was then added onto the regular growth.

3.2 Estimation of number of patients using each drug/service

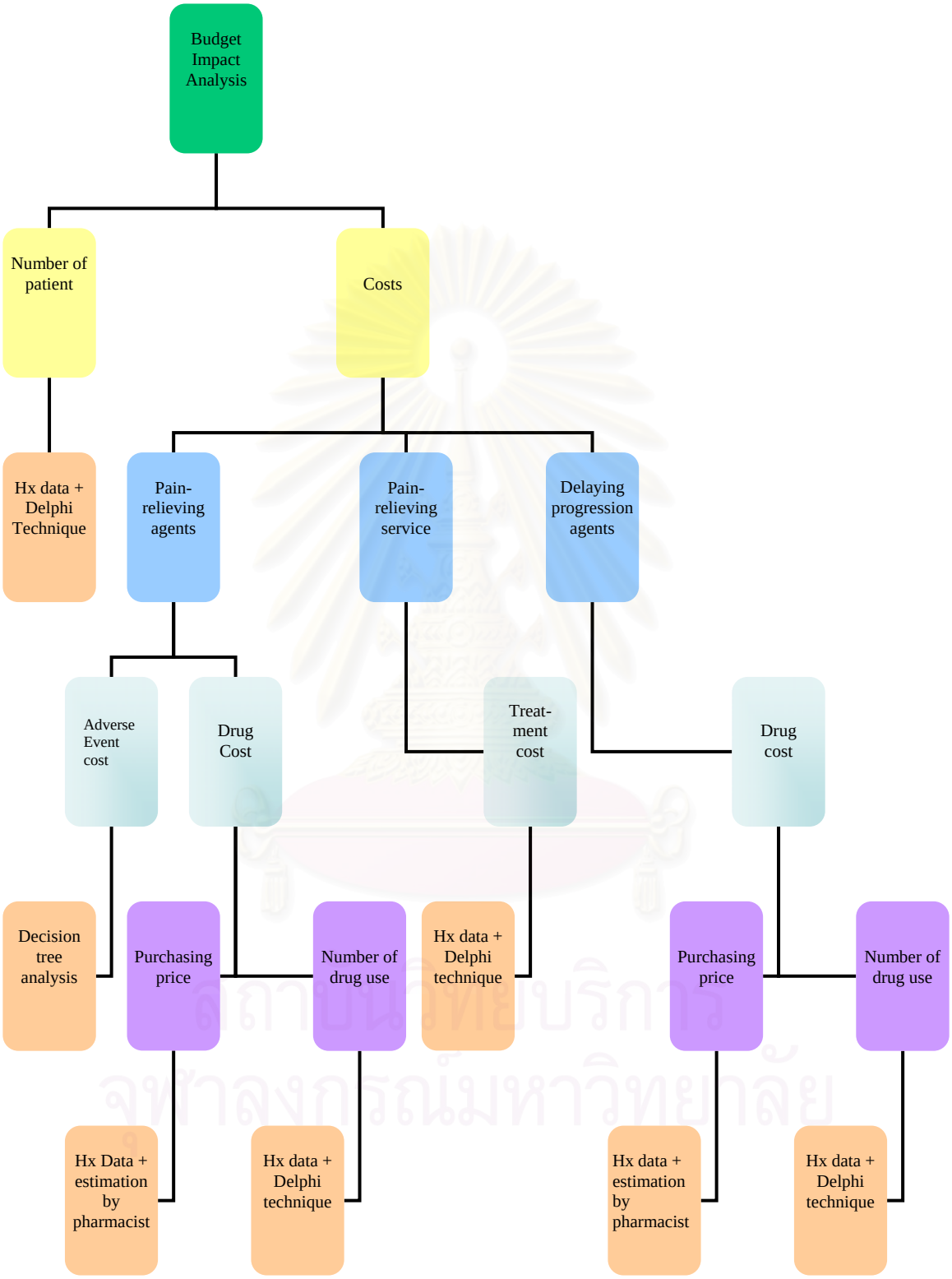
From the same set of dispensing data of knee osteoarthritis patients, the proportion of patients prescribed each drug was extracted. By using the hospital number (HN) of each patient to track back their historical dispensing pattern recorded in the pharmacy database, the movements of patients amid all treatment alternatives were revealed. These data were summarized and presented to three treating orthopedicians as the background data used in estimating the expected number of patients using each drug/service by Delphi technique.

The Delphi technique had been the main method deriving several future estimations used in the budget impact analytical model. Each Delphi comprised maximum of 3 rounds. There were only 3 treating physicians in the orthopedic department at Petchabun hospital, all of them were recruited to participate in the Delphi technique for estimation of variables in this study. Each physician was provided with the background data, e.g., number of users of each drug and data on drug use (tablet/year). They were asked to provide the estimations of such number in the upcoming years. Also, the criteria or assumptions they thought about were also requested. The researcher then collected their responses back and determined if there was any difference in both estimated values and assumptions they made. Summary of their estimations was made and sent back to them in order to reconsider those values

which they viewed differently. Telephone calls might be made by the researcher in order to clarify data estimations and assumptions. The process was replicated until the consensus among them was reached. .

The diagram of how each variable required for budget impact analysis was shown in the following figure.

Figure 3.1 Diagram of data estimation method



CHAPTER IV
RESULTS

To compute the budget impact model of introduction of glucosamine to hospital formulary, the following three key elements are required; size of population, current treatment including treatment-related healthcare service mix without glucosamine and its costs, current treatment mix with glucosamine and its costs. This chapter provides the details of each element in sequence. The two crucial variables for the budget impact analysis- the number of patient using each drug/service (patient/year), the costs of using each drug/service (baht/patient/year) - were estimated based on these three elements. These two variables were plugged in the budget impact model and computed in the last section of this chapter.

I. Size of the Population and number of patients using each treatment alternatives

After glucosamine has been introduced to the hospital in 2005, it was expected to reach the stable market share in 5 years based on the treating physicians' judgments. Therefore his study will examine the budget impact of glucosamine in 2007-2009 by taking the effects from the first two years (2005-2006) of introduction of glucosamine into consideration. The estimated sizes of the population are critical for a determination of the budget impact. This number will be used as the population frame of number of patient using each drug/service of interest in the next three years (2007-2009).

Luckily, there are data on the prevalence of knee osteoarthritis available in 2000-2006. To estimate the size of the population over times, this study then directly used such data to estimate the number of patient with knee osteoarthritis when glucosamine has not been listed in the hospital formulary yet. The prediction of these patients in 2007-2009 was done by integrating the expert's opinions and the actual number in 205-2006. Current and anticipated new treatment pattern were taken into account and aggregating this up to the budget holder's level.

1.1 Projection of number of patient with knee osteoarthritis under hospital formulary without glucosamine

Linear regression technique in SPSS 13.0 was used to predict the number of patient with knee osteoarthritis under the situation that no addition of glucosamine to hospital formulary. Table 4.1 shows the number of patients with knee osteoarthritis in 2000-2006.

Table 4.1 Number of patients with knee osteoarthritis in 2000-2006

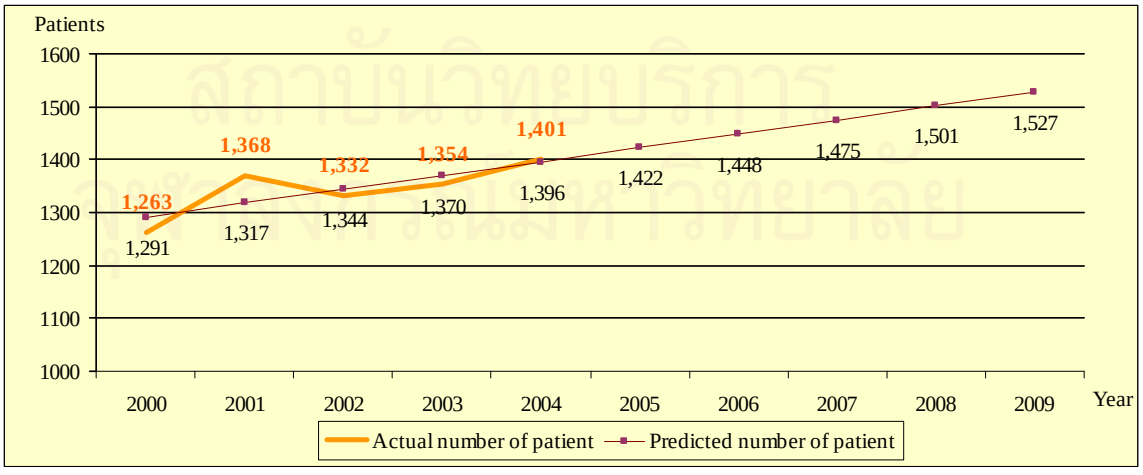
Year	2000	2001	2002	2003	2004	2005	2006
Patients	1,263	1,368	1,332	1,354	1,401	1,437	1,454

There was an upward trend of the number of this patient group. A small reduction was seen in 2002 comparing to 2002 which was 2.63%. The linear regression equation based on data of 2000-2004 which were period that no glucosamine addition to hospital formulary yet, is as following;

Patients with knee osteoarthritis = 26.2(Year) – 51,108.8

This model moderately fits to the data with a R^2= 0.65. Standard error of the estimated variable is 35.43. Figure 4.1 shows the prediction and actual number of patient with knee osteoarthritis.

Figure 4.1 Prediction of number of patient with knee osteoarthritis under no addition of glucosamine to hospital formulary

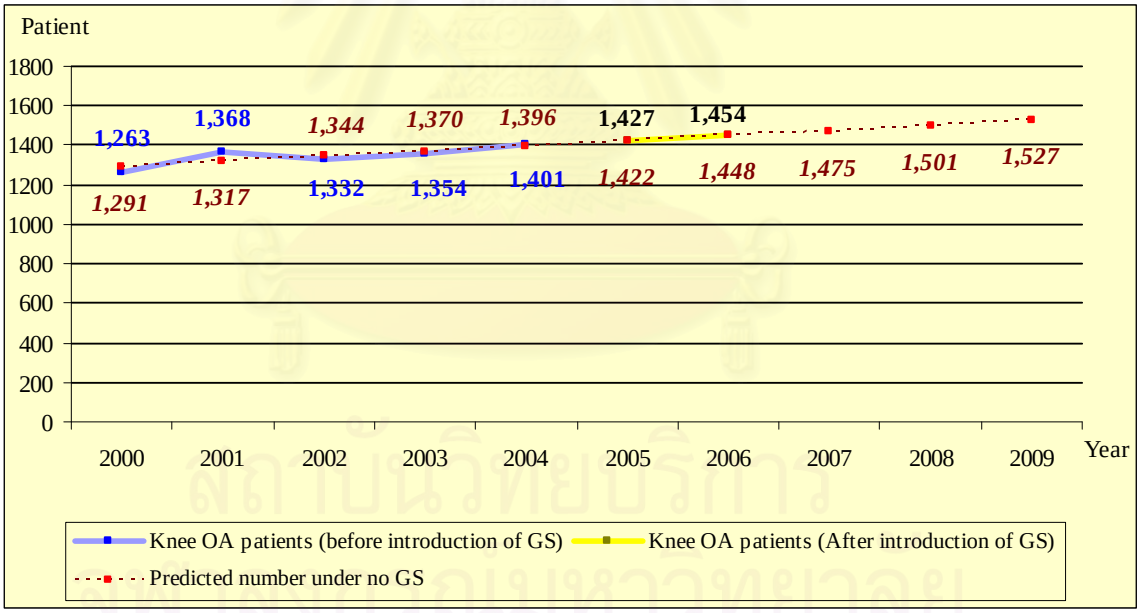


From the regression equation, the number of patient with knee osteoarthritis will be 1,422, 1,448, 1,475, 1,501, and 1,527 patients in 2005-2009 respectively.

1.2 Projection of number of patient with knee osteoarthritis under hospital formulary containing glucosamine

To estimate the number of patient with knee osteoarthritis once glucosamine has already been listed in the hospital formulary, the actual number in 2005-2006 was used. Numbers of patient with knee osteoarthritis in 2005 and 2006 were 1,427 and 1,454 patients. The following figure shows these numbers comparing the predicted numbers of patient with knee osteoarthritis under no addition of glucosamine to formulary based on the linear regression line from the analysis in previous section.

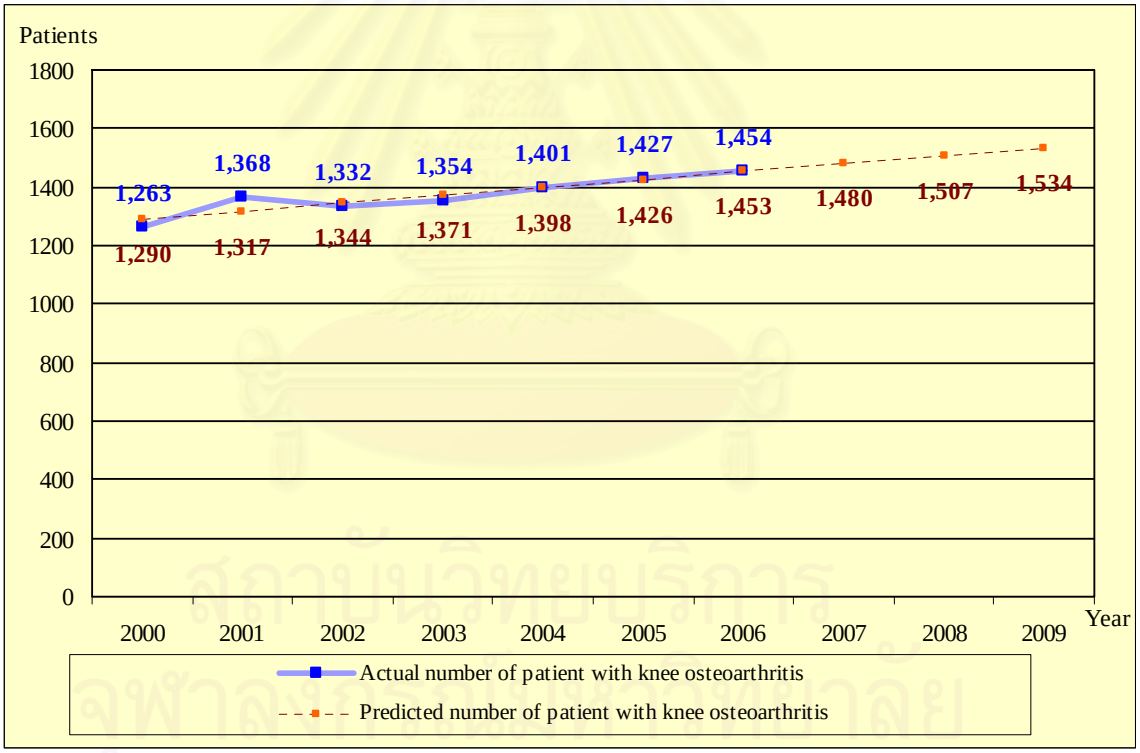
Figure 4.2 Actual and predicted number of patient with knee osteoarthritis before and after the introduction of glucosamine (GS) in the hospital formulary



As shown in figure 4.2, the actual numbers of patient in 2005-2006 are slightly more than the predicted values. Differences between predicted values of number of patient with knee osteoarthritis and actual number were 5 and 6 patients respectively. Since the hospital environment during these years were comparable, then these increases were assumed to be driven by the introduction of glucosamine. Patient's demand can be induced by glucosamine. Efficacy of glucosamine in pain-relieving and delay progression

might be able to create a center of attention in osteoarthritis treatment. Additionally, comparing to a similar drug in terms of efficacy; hyaluronic acid injection, glucosamine is easier and more convenient to use. Those patients who have never been diagnosed and treated before may become the treated patients with glucosamine. However, there was only 4 and 5 patients increasing that their demands were induced by glucosamine. It can be said that there was insignificant effect of induced demand by glucosamine in patients with knee osteoarthritis in this setting. Then the number of patient with knee osteoarthritis will be estimated by establishing the linear regression trend based on all actual numbers of patient in 2000-2006 as shown in figure 4.3.

Figure 4.3 Prediction of number of patients with knee osteoarthritis under the hospital formulary containing glucosamine



The linear regression of the number of patient with knee osteoarthritis as illustrated in figure 4.3 with R^2 of 0.8, is as following;

Patients with knee osteoarthritis = 27.14(Year) – 52,995.86

There will be about 1,480, 1,507, and 1,534 patients in 2007-2009 respectively. Please note these numbers were estimated by taking the likelihood of patients' evolving

over time with and without the new drug. Inflow and outflow rate of patients were estimated to be stable over time. Then these estimated numbers already included those patients which might flow in and flow out.

1.3 Number of patient using each treatment alternatives

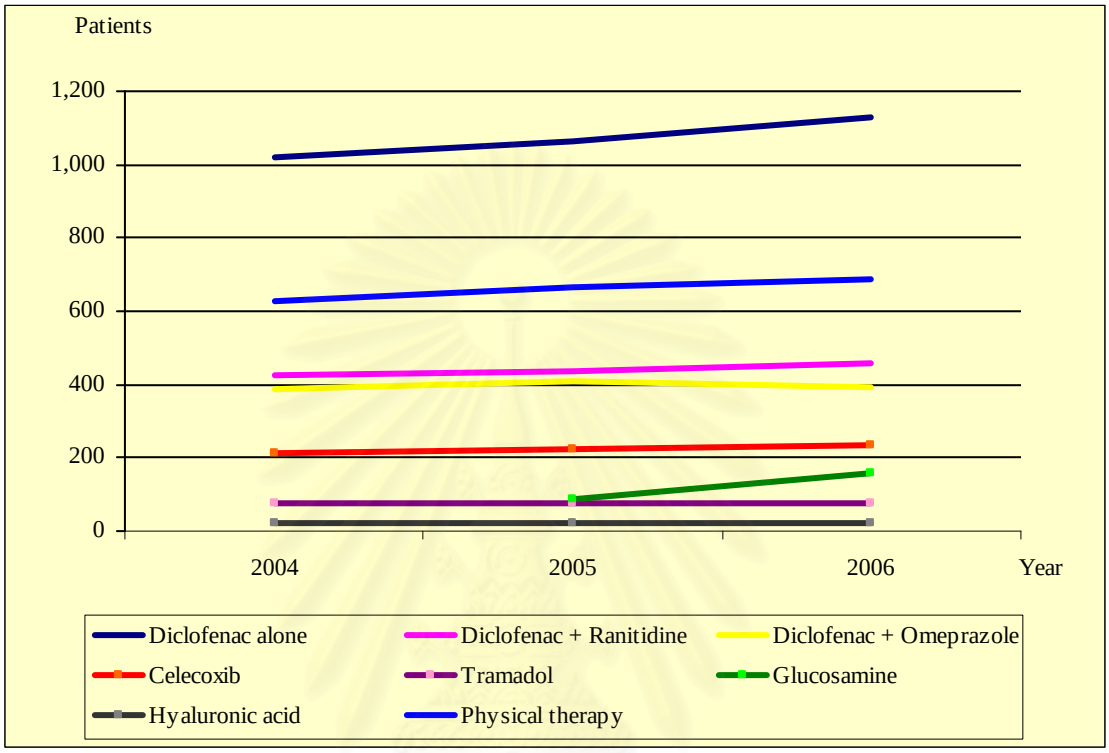
Note that data on utilization of treatment alternatives for knee osteoarthritis in were taken into consideration only three years which were before and after the introduction of glucosamine. This was done with an aim to focus on the changes of utilization pattern affecting from glucosamine. Historical data of number of patient using each treatment alternative; pain-relieving agents, delaying-progression agents, and physical therapy were shown in table 4.2 and figure 4.4. There were minor changes in number of users of pain-relieving agent and physical therapy. Between hyaluronic acid injection and glucosamine, the numbers of patients using these drugs are contradictory. Despite the fact that there was an insignificant difference of Hyluronic acid user during 2004 – 2006, glucosamine users were drastically increasing from 2005 to 2006, about 2 times. It showed that the immediate penetration to the market of glucosamine.

Table 4.2 Total number of patients using treatment alternatives (pain-relieving agents, delaying progression agents, and physical therapy)

Treatment alternatives	Number of patient			
	2003	2004	2005	2006
diclofenac alone	988	1,022	1,065	1,128
diclofenac + ranitidine	368	425	436	457
diclofenac + omeprazole	324	387	410	392
Celecoxib	189	212	225	236
tramadol	67	76	78	75
glucosamine Sulfate	*	*	86	157
hyaluronic acid	20	23	22	21
Physical Therapy	632	625	665	688

***** No glucosamine was available.

Figure 4.4 Graphical illustration of total number of patients using treatment alternatives



Trends of number of patient using each drug were quite similar over 2004-2006 except for glucosamine. Glucosamine has been listed in hospital formulary since 2005. There were only 86 patients using this drug at the first year and it dramatically increased in 2006; 157 patients. Almost two times of number of patients became the glucosamine users. Table 4.3 showed the percentage of market share of each drug and service used for knee osteoarthritis based on patient number using each drug comparing to the total number of patient with knee osteoarthritis (disease prevalence). It showed that diclofenac held the greatest percentage of market share in hospital due to the largest population using this drug. The second major treatment alternative was physical therapy by which about 40% of patients with knee osteoarthritis have been given this service. Two combinations of diclofenac and anti-acid secretion drugs – randitine, omeprazole- were the third ranking of market share, following by celecoxib, tramadol, glucosamine, and hyaluronic acid.

To estimate the number of patient using each drug/service, historical data of utilization pattern was given to three treating physicians before asking them to provide the estimations of such numbers. If there were inconsistency of their estimations, they would be asked to have a group meeting to discuss in particular variables.

According to their estimations of number of patient using each drug in 2007-2009, all of them were comparable to the mean of market share in 2004-2006 but glucosamine, and hyaluronic acid. The intended restricted use was observed in glucosamine pattern. All physicians emphasized that they were likely to prescribe glucosamine in patients with CSMBS (Civil Servant Medical Benefit Scheme) and out-of-pocket. Other patients under different healthcare scheme were prescribed glucosamine when they developed the side effects of NSAIDs and were needed to closely monitor the pattern of drug use. In this patient group, physicians have changed the current prescription drug to more protective combination i.e. diclofenac alone to diclofenac and acid-reduction agent, or to celecoxib, and/or closely monitor the utilization by giving the patients with the minimal amount of drug and more often follow-up visits. Glucosamine also has been prescribed in this patient group with a main aim to relieving the pain rather than delaying progression.

For hyaluronic acid, since it provides the similar pharmacological action comparing to glucosamine, it then was expected to be partially substituted by glucosamine. For those patients who have ever treated by hyaluronic acid, they were likely to continue using this drug.

Table 4.3 Market share of treatment alternatives based on patient number comparing to the number of patient with knee osteoarthritis

Drug/service	% Market share			
	2003	2004	2005	2006
diclofenac	72.97	72.95	74.63	77.58
diclofenac + ranitidine	27.18	30.34	30.55	31.43
diclofenac + omeprazole	23.93	27.62	28.73	26.96
Celecoxib	13.96	15.13	15.77	16.23
tramadol	4.95	5.42	5.47	5.16
glucosamine	-	-	6.03	10.80
hyaluronic acid	1.48	1.64	1.54	1.44
Physical therapy	46.68	44.61	46.60	47.32

Estimation of number of patient using each drug/service in 2007-2009

Assumptions:

1. diclofenac alone: This drug will still hold the largest market share with an approximate 75% every year with a possible range 70-80%.
2. diclofenac and ranitidine: There will be 31% with a possible range 29-32%.
3. diclofenac and omeprazole: There will be around 28% with a possible range 25-30%.
4. celecoxib: celecoxib will share the market about 16% with a possible range 14-18%.
5. tramadol: It was estimated that tramadol will share approximately 5.5%, 6%, 6.5% (4-9%) of patients in 2007-2009 respectively. These numbers reflected the patients with knee osteoarthritis who might develop their pain to more advance stage.
6. glucosamine: There will be 20% (15-30%), 22% (18-35%), and 24% (20%-35%).
7. hyaluronic acid: There will be 1.5% with a possible range 1-2%.
8. Physical therapy: There will be around 46% (38-50%) of patients with knee osteoarthritis going to use this service in 2007-2009 respectively.

From these assumptions, there will be the number of patient using each treatment alternatives as shown in table 4.4.

Table 4.4 Estimated number of patient using treatment alternatives in 2007-2009

Drug/service	2007		2008		2009	
	Most likely value	Range	Most likely value	Range	Most likely value	Range
diclofenac	1,110	1,036-1,184	1,130	1,055-1,206	1,151	1,074-1,227
diclofenac + ranitidine	414	370-444	422	377-452	430	384-460
diclofenac + omeprazole	459	429-474	467	437-482	476	445-491
celecoxib	237	207-266	241	211-271	245	215-276
tramadol	81	59-133	90	60-136	100	61-138
glucosamine	296	222-444	332	271-527	368	301-537
hyaluronic acid	22	15-30	23	15-30	23	15-31
Physical therapy	681	562-740	693	573-754	706	583-767

II. Current treatment mix without and with glucosamine and its costs

As described in the methodology part, there are total six treatment alternatives available before the introduction of glucosamine. These six alternatives were categorized to two groups according to its indication of use; pain-relieving and delaying progression. In the following session, the average cost of treatment of using all alternatives were analyzed and portrayed separately for each indication.

2.1 Average cost of pain-relieving agents/service

There are six treatment alternatives for pain-relieving indications. For NSAIDs and its combination to prevent the gastrointestinal adverse effects, its costs were calculated by taking both drug cost itself and the treatment costs of gastrointestinal events and myocardial infarction. In contrary, for tramadol and physical therapy, the treatment costs consisted of its cost itself. No additional costs were considered.

2.1.1 Average cost of NSAIDs and its combination with anti-acid secretion drugs

Methods used to quantify the drug costs of each NSAIDs and its combination with anti-acid secretion and the treatment costs of adverse events were different. Drug costs per patient per year of each drug for the next three years were forecasted based on the historical utilization pattern whereas the treatment costs of adverse events were obtained from the decision-tree analysis.

2.1.1.1 Treatment costs of adverse events

To quantify the average cost per patient of adverse treatments, the decision-tree model was used. Pain efficacy outcome is assumed to be not significantly across patients. The model considered five treatment options: (i) diclofenac, (ii) diclofenac + ranitidine, (iii) diclofenac + omeprazole, (iv) celecoxib. Two adverse events were considered: gastrointestinal toxicity and myocardial infarction. In order to make budget impact model realistic by allowing these two events can simultaneously occur, two separated decision models were then developed as shown in figure 4.5 and 4.6. The decision tree model was constructed by using decision-analysis software (PrecisionTree® for excel).

Model's perspective was alike as budget impact analysis which was that of hospital and only direct medical costs were considered. Since there are no data on cost available in Petchabun hospital, the charge of treatment and drug price at purchasing were alternatively used.

Adverse event 1: Gastrointestinal adverse events

Model Structure	Decision Tree model
Population	Patient with knee osteoarthritis who failed from acetaminophen
Model outcomes	There are three gastrointestinal adverse events associated with NSAIDs use; serious gastrointestinal complications, symptomatic ulcer, and gastrointestinal discomfort. Gastrointestinal complications included haemorrhage, erosions, perforation. Gastrointestinal discomfort (GI discomfort) included abdominal pain, nausea, dyspepsia.
Perspective	Hospital
Data source	Literatures and hospital database Probabilities used in the decision-tree were obtained from literatures as shown in table 4.5. Healthcare resource (table 4.6) used for each treatment pathway were estimated by three treating physicians. Additionally, for the inpatient care for severe gastrointestinal complications, the average treatment costs were estimated based on the actual charges recorded in DRG (Diagnostic Related Group) database.
Costs considered	Treatment costs in each treatment pathway Drug costs were not included in the model analysis.
Model assumptions	(1) Patients of interest have similar profile of risk factors affecting the probability of gastrointestinal adverse events i.e. age, history of gastrointestinal bleeding. (2) There are non-significant differences between risk of gastrointestinal adverse events among male and female patients.

(3) Patient who developed serious gastrointestinal complications from using NSAIDs alone will shift to NSAIDs + Proton pump inhibitor (PPI) or Coxibs. But this cost consequences of using the new treatment was not included in the analysis. The proportion of this potential users of such drugs will be taken into account during the amount of patient (users) estimation of budget impact analysis.

The model accounted for a physician making a decision to prescribe any option at the initial decision node. Events experienced by the patients after the decision occurred by chance with an estimable probability depicted at chance node. By rolling back each arm, the expected cost of treatment adverse events of each drug can be obtained.

The treatment costs excluded drug cost of each adverse events were obtained. Treatment costs of each treatment pathway as indicated in the decision tree model are highest in diclofenac alone users; 989.677 Baht/patient/year following by Celecoxib (749.625 Baht/patient/year), diclofenac + ranitidine (663.576 Baht/patient/year), and diclofenac + omeprazole (415 Baht/patient/year).

Table 4.5 Probabilities used in the decision tree model of gastrointestinal adverse events of using pain-relieving agents [97]

Variable	Baseline estimate
Probability of GI discomfort	
diclofenac	0.284
diclofenac + ranitidine	0.205
diclofenac + omeprazole	0.122
Celecoxib	0.23
Probability of Symptomatic Ulcer	
diclofenac	0.032
diclofenac + ranitidine	0.018
diclofenac + omeprazole	0.012
Celecoxib	0.008
Probability of Serious GI complications	
diclofenac	0.006
diclofenac + ranitidine	0.002
diclofenac + omeprazole	0.003
Celecoxib	0.003
Probability of inpatient care for GI discomfort	
diclofenac	0.24
diclofenac + ranitidine	0.39
diclofenac + omeprazole	0.39
Celecoxib	0.39
Probability of Outpatient care for GI discomfort	
diclofenac	0.76
diclofenac + ranitidine	0.61
diclofenac + omeprazole	0.61
Celecoxib	0.61
Probability of Endoscopy for GI discomfort	
diclofenac	0.35
diclofenac + ranitidine	0.15
diclofenac + omeprazole	0.15
Celecoxib	0.15
Probability of no endoscopy for GI discomfort	
diclofenac	0.65
diclofenac + ranitidine	0.85
diclofenac + omeprazole	0.85
Celecoxib	0.85

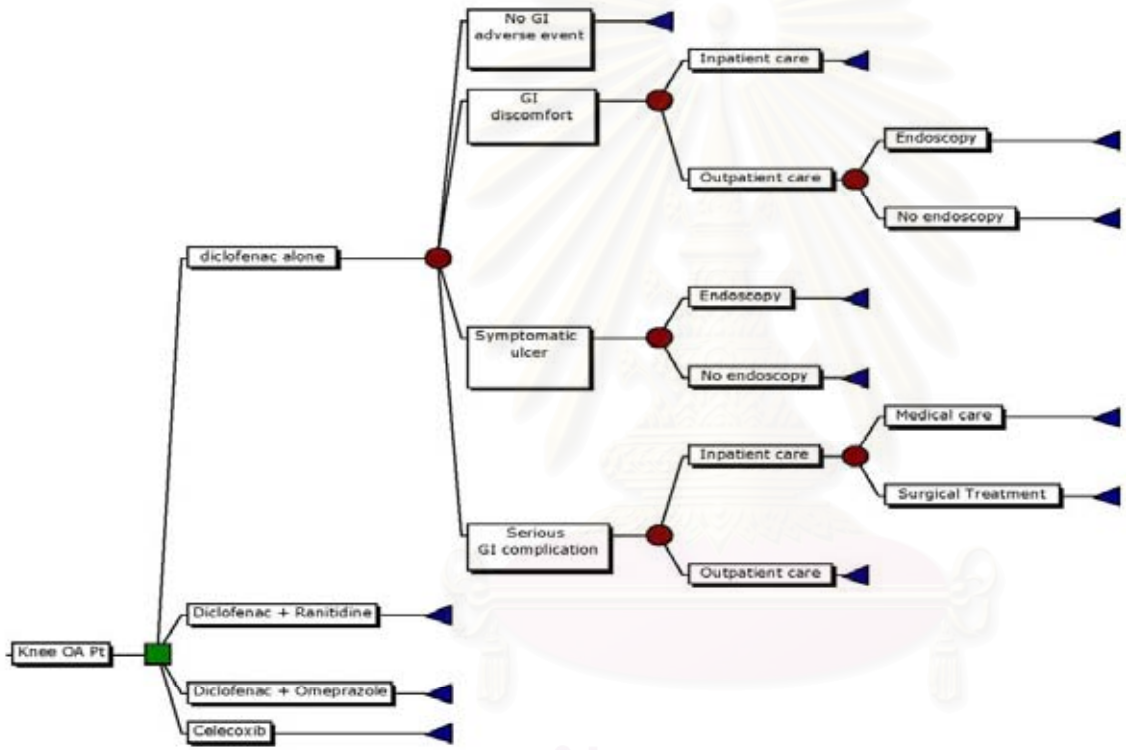
Table 4.5(Continued)

Variable	Baseline estimate
Probability of Endoscopy for symptomatic ulcer	
diclofenac	0.032
diclofenac + ranitidine	0.018
diclofenac + omeprazole	0.012
celecoxib	0.008
Probability of no endoscopy for symptomatic ulcer	
diclofenac	0.968
diclofenac + ranitidine	0.982
diclofenac + omeprazole	0.988
celecoxib	0.992
Probability of inpatient care for Serious GI complication	
diclofenac	0.67
diclofenac + ranitidine	0.56
diclofenac + omeprazole	0.56
celecoxib	0.56
Probability of outpatient care for Serious GI complication	
diclofenac	0.33
diclofenac + ranitidine	0.44
diclofenac + omeprazole	0.44
celecoxib	0.44
Probability of medical care for Serious GI complication	
diclofenac	0.61
diclofenac + ranitidine	0.71
diclofenac + omeprazole	0.71
celecoxib	0.71
Probability of surgery for serious GI complications	
diclofenac	0.39
diclofenac + ranitidine	0.29
diclofenac + omeprazole	0.29
celecoxib	0.29

Table 4.6 Healthcare resources used of gastrointestinal adverse events

Cost variable	Value (Baht/patient/year)
Cost of inpatient care for GI discomfort inpatient Endoscope +1 month ranitidine bid	6521
Cost of outpatient care with endoscopy for GI discomfort outpatient Endoscope +1 month ranitidine bid	6021
Cost of outpatient care without endoscopy for GI discomfort 1 month ranitidine bid	21
Cost of patient care with endoscopy for Symptomatic ulcer outpatient Endoscope + 1 month omeprazole od	6542
Cost of patient care without endoscopy for Symptomatic ulcer 1 month omeprazole bid followed by 1 month omeprazole od	86.8
Cost of inpatient medical management for Serious GI complication	846.1
Cost of outpatient care for serious GI complication 1 month omeprazole bid followed by 2 months omeprazole od	126
Cost of medical care at inpatient department for serious GI complication	17,673.90
Cost of surgical care at inpatient department for serious GI complication	21,237.04

Figure 4.5 Decision tree model of gastrointestinal adverse events of using pain-relieving agents



Adverse event 2: Cardiovascular event (Myocardial infarction)

Myocardial infarction was included as one of major healthcare-resource consumed adverse events of using NSAIDs. Again, decision tree model was developed in order to quantify the average myocardial infarction treatment costs, as shown in figure 4.6. The treatment cost of myocardial infarction computed from the decision tree analysis will be sum up with the drug cost itself.

Model Structure	Decision Tree model
Population	Patient with knee osteoarthritis who failed from acetaminophen
Model outcomes	Acute myocardial infarction (non-fatal)
Perspective	Hospital
Data source	Literatures and hospital database Probabilities used in the decision-tree were obtained from literatures as shown in table 4.7. Healthcare resources for each treatment pathway were illustrated in table 4.8. Note that the cost of outpatient care was estimated by two medical physicians whereas the cost of inpatient care was obtained from the DRG data.
Costs considered	Treatment costs in each treatment pathway Drug costs were not included in the model analysis.
Model assumptions	(4) Patients of interest have similar profile of risk factors affecting the probability of myocardial infarction events i.e. age, history of heart disease. (5) There are non-significant differences between risk of myocardial infarction among male and female patients. (6) Patient who developed myocardial infarction from any treatment options, the patient will stop using that drug but continuing receiving physical therapy. Other possible analgesic drug was not included in the analysis.

(7) Combination of anti-acid secretion drug with NSAIDs does not affect the probability of developing myocardial infarction. Hence, the probability of myocardial infarction among NSAIDs user regardless their varied anti-acid secretion are similar.

Table 4.7 Probabilities used in the decision tree model of non-fatal acute myocardial infarction events of using pain-relieving agents [98-100]

Variable	Probability
Probability of myocardial infarction	
diclofenac	0.0966
diclofenac + ranitidine	0.0966
diclofenac + omeprazole	0.0966
celecoxib	0.1092
Probability of inpatient care for myocardial infarction	
diclofenac	0.118
diclofenac + ranitidine	0.118
diclofenac + omeprazole	0.118
celecoxib	0.0875
Probability of outpatient care for myocardial infarction	
diclofenac	0.882
diclofenac + ranitidine	0.882
diclofenac + omeprazole	0.882
celecoxib	0.9125

Figure 4.6 Decision tree model of non-fatal myocardial infarction of using pain-relieving agents

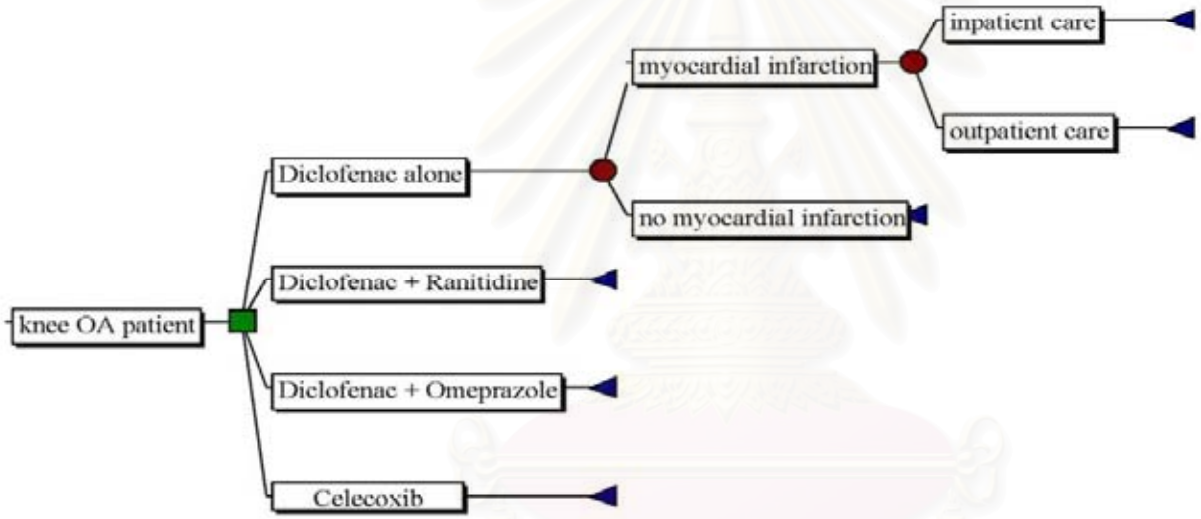


Table 4.8 Healthcare resources used for non-fatal acute myocardial infarction

Cost variable	Value
Cost of inpatient care for an acute MI (Baht/patient/year) Assumed to occur 1 time/year	37,006.13
Annual costs of follow-up at outpatient department following the acute MI	6,828
Enalapril 5 mg BID	1440
Atenolol 50 mg OD	900
Aspirin Gr V OD	270
Nitrate 10 mg TID	648
Nitrate sublingual 5mg prn (10 tab/month)	96
Furosemide 20 mg OD	90
Simvastatin 10 mg HS (90%) and Atorvastatin 10 mg HS (10%)	2880
Folic acid OD	144
Lorazepam 1mg HS	360
Warfarin 3 mg HS	1080

The average treatment costs for myocardial infarction of diclofenac and its combination with anti-acid secretion drug were 4,385.65 Baht/patient/year. For Celecoxib, since its risk of myocardial infarction is higher than NSAIDs then the treatment cost is more expensive; 4,957.69 Baht/pt/year.

These average treatment costs of gastrointestinal adverse events and myocardial infarction were assumed to be steady in each patient who can develop both adverse events every year. Then these numbers were simply used to calculate the total treatment costs of using NSAIDs and its combination by summing up with its drug costs.

In conclusion, the treatment costs (baht/patient/year) of adverse events – gastrointestinal events and myocardial infarction of each drug or combination are as following; diclofenac alone: 5,375.32, diclofenac and ranitidine: 5,049.23, diclofenac and omeprazole: 4,800.65, and Celecoxib: 5,707.32.

2.1.1.2 Drug Costs

The historical utilization pattern of each drugs were examined in order to use this data to forecast the possible amount of use in the next three years. Table 4.10 shows the average cost of drug used per patient per year in 2003-2006. These numbers were obtained from the average use of drug (Table 4.9) multiplied with the average purchasing costs. Note that the purchasing price is the average price that Petchabun hospital paid for the particular drug based on total sale transactions over a year.

To predict the drug costs, the following two variables were taken into consideration. They are the purchasing price each year and the average number of use per patient per year.

Table 4.9 Amount of use of each treatment alternatives

Drug/Service	Amount of use per patient per year			
	2003	2004	2005	2006
diclofenac	145.80	141.10	140.12	141.27
diclofenac combination (1)				
diclofenac	150.80	142.26	146.04	147.24
ranitidine	85.30	75.29	79.68	77.67
diclofenac combination (2)				
diclofenac	135.30	119.03	120.32	110.80
omeprazole	78.30	66.68	70.25	70.61
celecoxib	197.40	206.75	207.04	198.00
tramadol	55.90	50.12	55.83	54.11
glucosamine	0	0	93.92	119.08
hyaluronic acid	4.20	3.83	4.00	4.19
physical therapy (baht)	421.70	382.30	390.35	400.39

Table 4.10 Average drug cost of pain-relieving agents in 2003-2006

Pain-relieving agent and daily dose	Purchasing price (Baht/tab)		Drug Cost (Baht/per patient /year) Oct 02- Sep 03			Drug Cost (Baht/per patient /year) Oct 03- Sep 04		
			Mean	Min	Max	Mean	Min	Max
diclofenac 25 mg TID	0.20		29.16	18	108	28.22	18.00	104.00
diclofenac 25 mg TID + ranitidine 150 mg BID	0.20	1.4	79.95	33	250.5	57.09	39.00	253.00
diclofenac 25 mg TID + omeprazole 20 mg OD	0.20	0.35	136.68	102	472	122.42	102.00	462.00
Celecoxib 200 mg BID	23.07		4,554.02	3,109.84	7,382.40	4,769.61	2,307.00	9,228.00
tramadol 50 mg BID	0.96		53.66	28.8	105.6	48.11	43.20	115.20

Table 4.10 Average drug cost of pain-relieving agents in 2003-2006 (continued)

Pain-relieving agent and daily dose	Purchasing price (Baht/tab)		Drug Cost (Baht/per patient /year) Oct 04- Sep 05			Drug Cost (Baht/per patient /year) Oct 05- Sep 06		
			Mean	Min	Max	Mean	Min	Max
diclofenac 25 mg TID	0.20		28.17	18.00	104.00	28.24	18.00	102.00
diclofenac 25 mg TID + ranitidine 150 mg BID	0.20	0.35	57.09	39.00	253.00	56.63	39.00	251.00
diclofenac 25 mg TID + omeprazole 20 mg OD	0.20	1.40	122.42	102.00	462.00	121.01	102.00	476.00
Celecoxib 200 mg BID	23.07		4,776.52	2,307.00	9,228.00	4,567.76	2,076.30	9,112.65
tramadol 50 mg BID	0.96		53.60	43.20	115.20	51.94	28.80	115.20

Estimation of purchasing price for 2007-2009

Assumptions:

In this study, the purchasing prices of all pharmaceutical agents were assumed to be insignificantly different across three years. Based on the historical data on purchasing price of diclofenac, ranitidine, omeprazole, tramadol, and Celecoxib, the current purchasing prices were similar to price at two previous years.

Estimation of amount of use per patient per year

Assumptions:

1. Amounts of all drugs excluding Celecoxib and glucosamine were assumed to be comparable to data in 2006, with a possible range 5-10% variation each year.
2. Celecoxib use in patient groups who concurrently take glucosamine was expected to 20% decrease because of the successfulness of pain-relieving by glucosamine. This study assumed that in each patient who was given glucosamine had an average 60% chance to achieve the pain-relieving efficacy of glucosamine. Hence, the amounts of Celecoxib use will 12% decrease each year.
3. Tramadol will be used in only patient who can not control their pain by using other analgesic drugs. Amount of use was assumed to be comparable to weighted average mean of it uses in 2005-2006.

From these assumptions, the amounts of use of each drug in 2007-2009 are estimated as following;

diclofenac alone: 141 with a possible range 134-155 tablets/patient/year

diclofenac + ranitidine: 147 (140-161) tablets/patient/year of diclofenac and 80 (76-88) tablets/patient/year of ranitidine

diclofenac + omeprazole: 120 (114-132) tablets/patient/year of diclofenac and 70 (66-77) tablets/patient/year

celecoxib: 174 (165-191), 153 (145-168), and 135 (128-148) tablets/patient/year in 2007-2009 respectively.

tramadol: 53 (29-115) each year.

Estimation of drug cost of pharmaceutical pain-relieving agent

The estimated drug cost of all pharmaceutical pain-relieving agents for 2007-2009 were as following;

2.1.2 Average costs of non-pharmaceutical services for pain-relieving pain in patients with knee osteoarthritis

Physical therapy was the only non-pharmaceutical services included in the analysis. Physicians always prescribe patients to receive physical therapies i.e. ultrasound, heat in order to relieving pain and sometime, inflammation. Though the physicians indicated that they did not much change the proportion of prescribing physical therapy to patients after the inclusion of glucosamine, to comprehensively analyze the financial implication of glucosamine to healthcare budget, the physical therapy is still of value to consider.

Cost of physical therapy as mentioned earlier in methodology, the charge will be alternatively used. Charges of physical therapy specific to knee osteoarthritis are varied across patients. It depends on type of physical therapy, duration of physical therapy, day of service used (after working hour/ in working hour). To compromise these variations in charges, only type of physical therapy and duration of therapy were taken into consideration. It will be multiplied with the reference charges of each type. Any extra charges from after working hour including both after working hour in weekdays and holidays were removed from the costs.

Results showed that the average cost of physical therapy in fiscal year 2005 and 2006 were similar. For fiscal year 2005, the average cost of physical therapy was 390.35 Baht/patient/year. In 2006, it was 400.39 Baht/patient/year which was slightly higher than 2005.

Estimation of average cost of physical therapy per patient per year for 2007-2009

Amount of physical therapy use will not be significantly changed much since it will be simultaneously prescribed by the treating physicians to all patients with moderate to severe pain. Patients with knee osteoarthritis receive the physical therapy regardless what analgesic agents and/or delaying progression agents used.

The average cost of physical therapy per patient per year for 2007-2009 will be 400 baht/patient/year with a possible range 250-2000 baht/patient/year.

2.1.3 Average cost of delaying-progression agents

There are two drugs used in delaying-progression indication; hyaluronic acid injection and glucosamine sulfate. The first drug has been available almost 4 years before the inclusion of glucosamine. Both drugs not only provide the delay-progression efficacy by stimulating the cartilage formation but also pain-relieving efficacy. After glucosamine was available in hospital, it has been more widely used than hyaluronic acid. Table 6 showed the average uses of glucosamine and hyaluronic acid injection.

2.1.3.1 Hyaluronic acid injection

Estimation of purchasing price for hyaluronic acid

Assumptions:

It was assumed to be comparable to an average of Hyalgan® price during 2004-2006. Then the purchasing price for hyaluronic acid for 2007-2009 will be 2,260 baht/amp with a possible range 2%; 2,214-2,305 baht/amp.

Estimation of amount of use of hyaluronic acid

Assumptions:

The dosage regimen for hyaluronic acid is 5 amps/course, and 1-2 times/year. Although the average amount of use of hyaluronic acid in 2004-2006 was 4.01 amps /patient/year and it was not as much of dosage recommendation, the physicians assumed that in 2007-2009, they will prescribe hyaluronic acid at the recommended dose by at least 1 time/year. Then the average amount of use of hyaluronic acid will be 5 amps with a possible range based on the actual prescribing pattern; (3.8-10)

Estimated total cost of using hyaluronic acid per patient per year for 2007-2009

The costs of using hyaluronic acid per patient per year will be 11,300 baht/patient/year, with a possible range 8,413-23,050 baht/patient/year.

2.1.3.2 Glucosamine Sulfate

Estimation of purchasing price for glucosamine

The price for glucosamine sulfate was estimated based on the Viatril-S® which is the available brand in current hospital formulary. Since the amount of use of glucosamine was expected to be more than the current purchasing record, the price per unit (sachet)

then was likely to be cheaper due to the volume discount. After discussed with the pharmacists who are responsible for purchasing and inventory control, it was estimated that the 2% reduction on current price with a possible range; 0.5-3%, would be took place if the total amount of use increases at least 0.5 times of current use. According to the estimation of number of patient using this drug, it can be said that it will increase almost 1 times in 2007 and continue increasing in 2008-2009. So this additional volume discount is highly possible.

Then the purchasing price for glucosamine will be decreased from 36.15 to 35.427 (35.07-35.97) baht/sachet.

Estimation of amount of use of glucosamine

Assumptions:

1. Dosage regimen of glucosamine is 1884 mg once a day, every two day which is equal to 1 sachet.
2. Considering the compliance rate, the mean of using glucosamine in 2006 was expected to reflect the precise compliance rate since it has been more widely used in population (see table 4.11).
3. To achieve the pain-relieving efficacy and also the delaying-progression, it was assumed that the possible range of amount of glucosamine use would have to be used continuously in those patients who well response with glucosamine.
4. To see whether glucosamine works well in which patient, the physicians will prescribe it to patients at least for 4 months at the first period. It will be continued prescribing to those who well response to glucosamine in terms of pain-relieving. In contrary, for those patients who might not be able to get benefit from glucosamine as still having pain in the similar degree before using glucosamine, they will not be given glucosamine after that.

Table 4.11 Average cost of delaying-progression agents

Delaying-progression agents and dose	Cost (Baht/unit)	Average cost (Baht/patient/year) Oct 04- Sep 05)			Average cost (Baht/patient/year) Oct 05- Sep 06		
		Mean	Min	Max	Mean	Min	Max
glucosamine Sulfate (VIARTRIL-S® 1884 MG SACHET) EOD 1yr	36.15	3,395.37	1,084.50	8,676.00	4,304.58	2,169.00	13,014.00
hyaluronic acid injection* (Hyalgan® 5 amps/year)	2,260	9,040.00	2,260.00	15,820.00	9,470.48	2,260.00	22,600.00

In 2006, there were modest differences of average cost of hyaluronic acid injection (9,040 and 9,470.48) but the maximum cost was much higher comparing to 2005. In contrary, the average use of glucosamine was greatly higher in year 2 (2006) after it has been included in the formulary. There were about 1,000 Baht/patient/year of glucosamine use was increased in 2006.

From the above assumptions, the amount of use of glucosamine was estimated to be average 120 sachets/patient/year, with a possible range 60-183 sachets/patient/year.

Estimated total cost of using glucosamine per patient per year for 2007-2009

The estimated costs of using glucosamine were 4,521.24 baht/patient/year with a possible range 2,104.20-6,582.51 baht/patient/year.

III. Budget impact analysis of glucosamine to treating knee osteoarthritis

Budget impact model applied to quantify the financial implications of glucosamine to treating knee osteoarthritis was as followed:

Budget Impact Model at any year

= Cost of delaying progression + Cost of pain-relieving

$$= [(\mathbf{C}_6\mathbf{Q}_6 + \mathbf{C}_8\mathbf{Q}_8)] + [(\mathbf{C}_1\mathbf{Q}_1) + (\mathbf{C}_2\mathbf{Q}_2) + (\mathbf{C}_3\mathbf{Q}_3) + (\mathbf{C}_4\mathbf{Q}_4) + (\mathbf{C}_5\mathbf{Q}_5) + (\mathbf{C}_7\mathbf{Q}_7)]$$

Here, i =1-7 by which the first six i are competitive drugs and new drug, and the non-pharmaceutical healthcare service: diclofenac sodium tablet (i=1), diclofenac sodium and ranitidine tablet (i=2), diclofenac sodium and omeprazole tablet (i=3), Celecoxib tablet (i=4), tramadol tablet (i=5), hyaluronic acid sodium injection (i=6), physical therapy (i=7) and glucosamine (i =8).

Two key variables considered in the budget impact analysis are cost and number of patient. The values of these two inputs of each drug/service were estimated in previous two sections. Table 4.12-4.14 showed the cost inputs and number of patient using each treatment alternative.

Table 4.12 Number of patient and cost inputs in 2007 for budget impact model

Drug/service	Number of patient per year		Costs (baht/patient/year)		
	Most likely value	Range	Drug cost	ADR Treatment cost	Total
diclofenac	1110	1036-1184	28.2	5,375.32	5,403.52
diclofenac & ranitidine	414	370-444	57.4	5,049.23	5,106.63
diclofenac & omeprazole	459	429-474	70	4,800.65	4,870.65
celecoxib	237	207-266	4,014.18	5,707.32	9,721.50
tramadol	81	59-133	50.88	0	50.88
glucosamine	296	222-444	4,521.24	0	4,521.24
hyaluronic acid	22	15-30	11,300	0	11,300.00
physical therapy	681	562-740	400	0	400

Table 4.13 Number of patient and cost inputs in 2008 for budget impact model

Drug/service	Number of patient per year		Costs (baht/patient/year)		
	Most likely value	Range	Drug cost	ADR Treatment cost	Total
diclofenac	1130	1055-1206	28.20	5,816.63	5,403.52
diclofenac & ranitidine	422	377-452	57.40	5,489.97	5,106.63
diclofenac & omeprazole	467	437-482	70.00	5,241.69	4,870.65
celecoxib	241	211-271	3,199.5	6,254.47	8,906.82
tramadol	90	60-136	50.88	0	50.88
glucosamine	332	271-527	4,521.24	0	4,521.24
hyaluronic acid	23	15-30	11,300	0	11,300.00
physical therapy	693	573-754	400.00	0	400.00

Table 4.14 Number of patient and cost inputs in 2009 for budget impact model

Drug/service	Number of patient per year		Costs (baht/patient/year)		
	Most likely value	Range	Drug cost	ADR Treatment cost	Total
diclofenac	1151	1074-1227	28.2	5,816.63	5,403.52
diclofenac & ranitidine	430	384-460	57.4	5,489.97	5,106.63
diclofenac & omeprazole	476	445-491	70	5,241.69	4,870.65
Celecoxib	245	215-276	3,529.71	6,254.47	9,237.03
tramadol	100	61-138	50.88	0	50.88
glucosamine	368	301-537	4,521.24	0	4,521.24
hyaluronic acid	23	15-31	11,300	0	11,300.00
Physical therapy	706	583-767	400	0	400.00

3.1 Budget Impact Analysis

3.1.1 Budget analysis of 2003-2004

= Cost of delaying progression + Cost of pain-relieving

$= [(\mathbf{C}_6\mathbf{Q}_6 + \mathbf{C}_8\mathbf{Q}_8)] + [(\mathbf{C}_1\mathbf{Q}_1) + (\mathbf{C}_2\mathbf{Q}_2) + (\mathbf{C}_3\mathbf{Q}_3) + (\mathbf{C}_4\mathbf{Q}_4) + (\mathbf{C}_5\mathbf{Q}_5) + (\mathbf{C}_7\mathbf{Q}_7)]$

Data inputs for budget impact analysis in 2003-2004 was deterministically calculated based on the actual number of patient using each treatment alternatives and average cost per patient per year in the reference year. This data and budget impact result were shown in the following table. Budget impact analyses of 2003-2004 were shown in table 4.15-4.16 respectively.

Table 4.15 Budget analysis of 2003

Drug/Service	Data inputs for budget impact analysis		
	Number of patient	Average cost per patient	Total cost
diclofenac	988	5,404.48	5,339,626.24
diclofenac + ranitidine	368	5,129.18	1,887,538.24
diclofenac + omeprazole	324	4,937.33	1,599,694.92
celecoxib	189	10,261.34	1,135,064.36
tramadol	67	53.66	3,595.22
hyaluronic acid	20	9,040.00	180,800.00
physical therapy	632	421.70	266,514.40
Drug budget			***10,950,647.88***
Total budget			***11,217,162.28***

The drug budget for knee osteoarthritis in 2003 was 10,950,647.88 baht. Total budget was 11,217,162.28 baht.

Table 4.16 Budget analysis of 2004

Drug/Service	Data inputs for budget impact analysis		
	Number of patient	Average cost per patient	Total cost
diclofenac	1,022.00	5,403.54	5,522,417.88
diclofenac & ranitidine	425.00	5,106.32	2,170,186.00
diclofenac & omeprazole	387.00	4,923.07	1,905,228.09
celecoxib	212.00	10,476.93	2,221,109.16
tramadol	76.00	48.11	3,656.64
hyaluronic acid	23.00	8,646.96	198,880.00
Physical therapy	625.00	382.30	238,938.00
Drug budget			***12,021,477.77***
Total budget			***12,260,415.77***

In 2004, the drug budget for knee osteoarthritis was 12,021,477.77 baht and the total budget impact which included physical therapy was 12,260,415.77 baht.

3.1.2 Budget analysis of 2005-2006

Table 4.17 Budget analysis of 2005

Drug/Service	Data inputs for budget impact analysis		
	Number of patient	Average cost per patient	Total cost
diclofenac	1,065.00	5,403.49	5,754,716.85
diclofenac & ranitidine	436.00	5,106.32	2,226,355.52
diclofenac & omeprazole	410.00	4,923.07	2,018,458.70
Celecoxib	225.00	10,483.84	2,358,864.00
tramadol	78.00	53.60	4,180.80
glucosamine	86.00	3,395.37	292,001.97
hyaluronic acid	22.00	9,040.00	198,880.00
Physical therapy	665.00	390.35	259,580.00
Drug budget			***12,853,457.84***
Total budget			***13,113,037.84***

Table 4.18 Budget analysis of 2006

Drug/Service	Data inputs for budget impact analysis		
	Number of patient	Average cost per patient	Total cost
diclofenac	1,128.00	5,403.56	6,095,215.68
diclofenac & ranitidine	457.00	5,105.86	2,333,378.02
diclofenac & omeprazole	392.00	4,921.66	1,929,290.72
Celecoxib	236.00	10,275.08	2,424,918.88
tramadol	75.00	51.94	3,895.68
glucosamine	157.00	4,304.58	675,819.69
hyaluronic acid	21.00	9,470.48	198,880.00
Physical therapy	688.00	400.39	275,470.00
Drug budget			***13,661,398.67***
Total budget			***13,936,868.67***

In 2005, the drug budget and total budget of knee osteoarthritis treatment were about 12,853,457.84 and 13,113,037.84 baht respectively. Slightly increases in both budgets were found in 2006. Drug budget of 2006 was 13,661,398.67 baht while the total budget was 13,936,868.67 baht.

3.1.3 Budget analysis 2007-2009

3.1.3.1 Budget analysis of 2007

Data inputs for budget impact analysis of 2007-2009 were plugged in the budget impact model and probabilistic analyzed. Monte-carlo simulation (Crystal Ball®) was used to compute the probable budget impact of knee osteoarthritis treatment in 2007. In a Monte Carlo simulation, a random value is selected for each of the tasks, based on the range of estimates. The model is calculated based on this random value. The result of the model is recorded, and the process is repeated. A typical Monte-Carlo simulation calculates the model hundreds or thousands of times, each time using different randomly-selected values.

When the simulation is complete, a large number of results from the model were obtained, each based on random input values. These results are used to describe the likelihood of reaching various results in the model. Probability distribution which

is the likelihood of specific values occurring out of a range or set of values to characterize the data is needed to do Monte-Carlo simulation.

For cost input, since its range of value contains an infinite set of possible value, the distribution then is said to be continuous. Lognormal distribution was applied to characterize the cost of drug/services since most of the values occur near the minimum value; positively skewed. This cost cannot fall below the lower limit of zero but may increase to any point without limit. Note that there are two parameters needed in lognormal distribution; mean and standard deviation. Mean cost at year of interest was estimated in previous section. Using historical data in 2006, the standard deviation of drug cost can be determined.

For number of patient using each drug which was estimated by expert's judgments, to reflect the highest possibility of mean value to occur, the triangular distribution was used. The triangular distribution shows the number of successes when the minimum, maximum, and most likely values are known. The parameters for the triangular distribution are minimum, maximum, and likeliest. There are three conditions underlying a triangular distribution: the minimum and maximum numbers of items are fixed and the most likely number of items falls between the minimum and maximum values, forming a triangular shaped distribution, which shows that values near the minimum and maximum are less likely to occur than those near the most likely value. The following tables showed the result analysis of budget impact in 2007.

Table 4.19 Budget analysis of 2007

Variable	Mean	SD	Range	Distribution
Cost of diclofenac	5,844.83	15.66		Lognormal
diclofenac user	1,110		1,036-1,184	Triangular
Cost of diclofenac & ranitidine	5,547.37	1.44		Lognormal

Table 4.19 Budget analysis of 2007

Variable	Mean	SD	Range	Distribution
Cost of diclofenac	5,844.83	15.66		Lognormal
diclofenac user	1,110		1,036-1,184	Triangular
Cost of diclofenac & ranitidine	5,547.37	1.44		Lognormal
diclofenac & ranitidine user	414		370-444	Triangular
Cost of diclofenac & omeprazole	5,311.69	98.5		Lognormal
diclofenac & omeprazole user	459		429-474	Triangular
Cost of celecoxib	10,268.65	2,469.08		Lognormal
celecoxib user	237		207-266	Triangular
Cost of tramadol	50.88	22.1		Lognormal
tramadol user	81		59-133	Triangular
Cost of glucosamine	4,521.24	1,823.40		Lognormal
glucosamine user	296		222-444	Triangular
Cost of hyaluronic acid	11,300.00	2,637.44		Lognormal
hyaluronic acid user	22		15-30	Triangular
Cost of physical therapy	400.00	335.25		Lognormal
physical therapy user	681		562-740	Triangular
Drug budget	***14,242,684.19***			
Total budget	***14,577,846.02***			

After 100,000 trials, the means of drug budget and total budget in 2007 were 14,242,684.19 baht (10,796,126.45 – 23,111,903.73) and 14,577,846.02 baht (10,908,186.38 -25,965,810.34) respectively. Drug budget was 97.70% of total budget of knee osteoarthritis treatment. Figure 4.7 and 4.8 showed the forecast chart of drug and total budget impact analysis. These figures displayed the results of the simulations by using distribution to show the number (frequency) of values occurring in a given interval. Probability in this chart can be interpreted as a chance existing of attaining a value in a given interval.

From figure 4.7, the maximum chance which was 5.164 % (probability = 0.05164) was seen at 13,825,000 baht where as the maximum chance (5.929%) of the total budget of was observed at 14,287,500 baht (figure 4.8). Figure 4.9 and 4.10 show the sensitivity charts. They provide data with the ability to quickly and easily judge the influence each cell has on a particular forecast cell based on their contrition to variance of forecast value. The cost of diclofenac and omeprazole has the highest sensitivity ranking

following by cost of celecoxib and cost of glucosamine in both of drug budget and total budget. glucosamine user and diclofenac user rank the third and fourth sensitive variables. With a 93.2% and 90.9% of variance of forecast variable contributed by cost of diclofenac and omeprazole, cost of celecoxib, and cost of glcosamine in drug budget and total budget, these three variables can be considered the most important variable in the model. The assumption with the lowest sensitivity ranking is the least important one in the model which is number of tramadol user. The effect of this assumption on the target forecast is not as great as the others.

Figure 4.7 Forecast chart of drug budget 2007

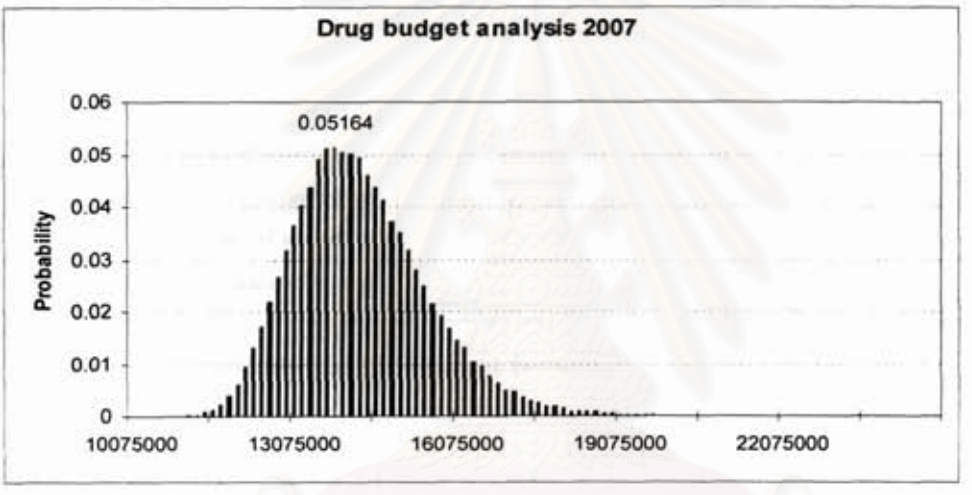


Figure 4.8 Forecast chart of total budget 2007

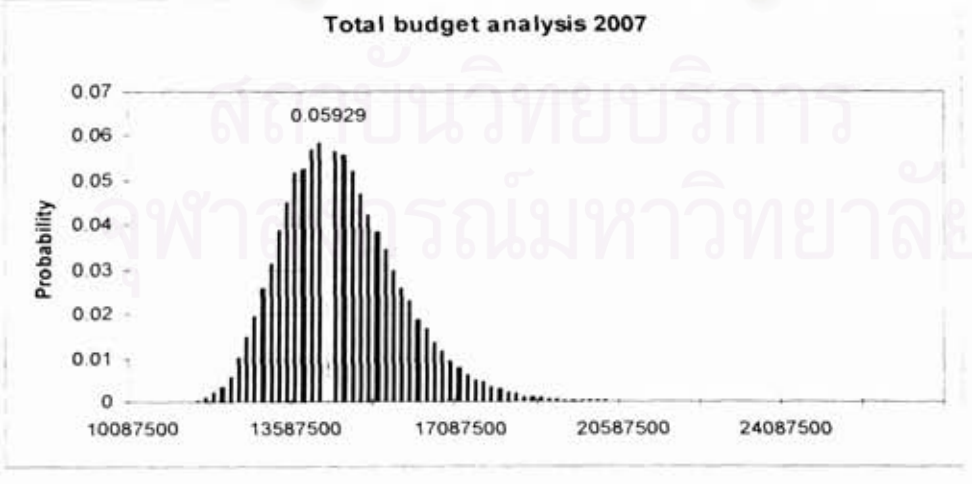


Figure 4.9 Sensitivity chart of target forecast: drug budget 2007

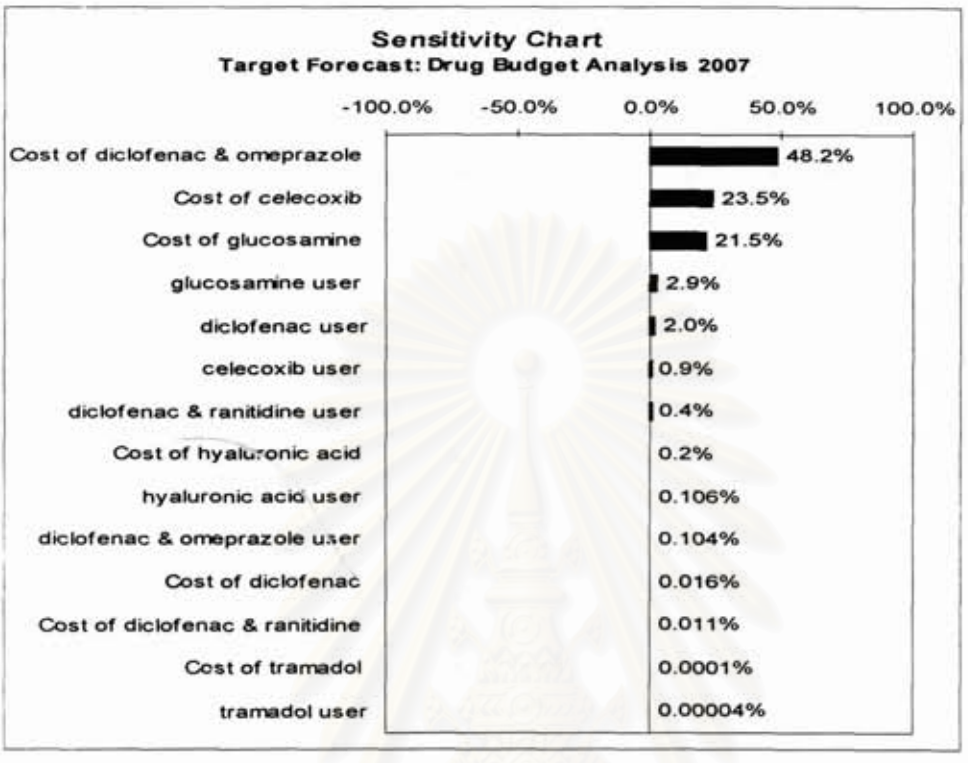
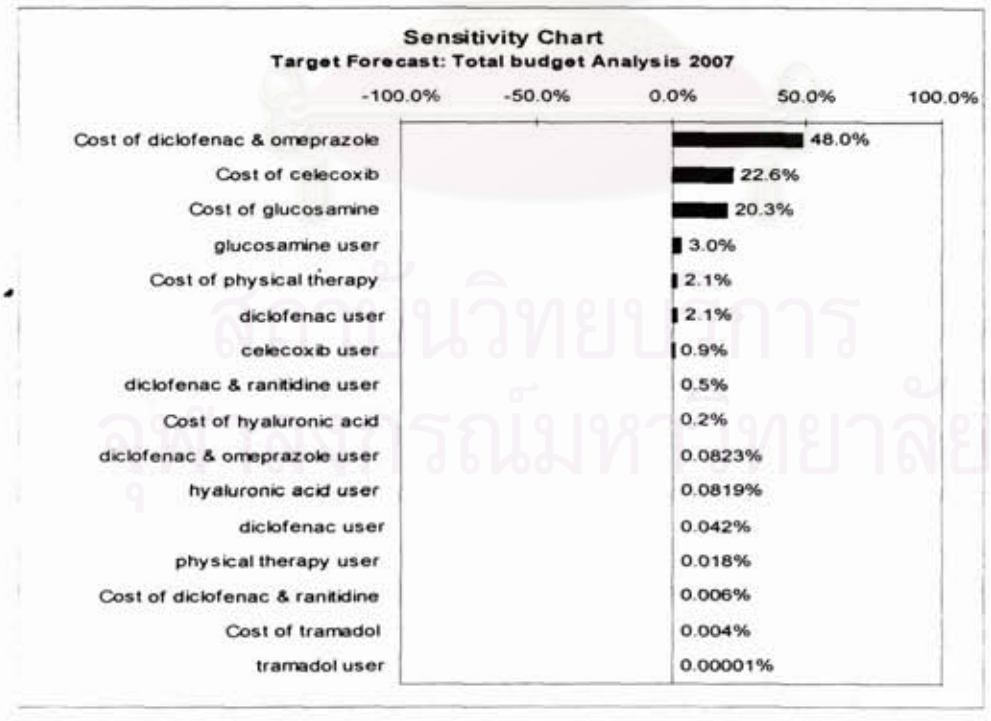


Figure 4.10 Sensitivity chart of target forecast: total budget 2007



3.1.3.2 Budget analysis of 2008

Data inputs from table 4.13 were plugged in to the budget impact model. Note that the standard deviations used in lognormal distribution were obtained from data of 2006. By using the same distribution type as described in the previous section, the budget impact result of 2008 was calculated and shown in the following table.

Table 4.20 Budget analysis of 2008

Variable	Mean	SD	Range	Distribution
Cost of diclofenac	5,403.52	15.66		Lognormal
diclofenac user	1130		1,055-1,206	Triangular
Cost of diclofenac & ranitidine	5,106.63	1.44		Lognormal
diclofenac & ranitidine user	422		377-452	Triangular
Cost of diclofenac & omeprazole	4,870.65	98.5		Lognormal
diclofenac & omeprazole user	467		437-482	Triangular
Cost of Celecoxib	9,237.03	2,469.08		Lognormal
Celecoxib user	241		211-271	Triangular
Cost of tramadol	50.88	22.1		Lognormal
tramadol user	90		60-136	Triangular
Cost of glucosamine	4,521.24	1,823.40		Lognormal
glucosamine user	332		271-527	Triangular
Cost of hyaluronic acid	11,300	2,637.44		Lognormal
hyaluronic acid user	23		15-30	Triangular
Cost of physical therapy	400	335.25		Lognormal
Physical therapy user	693		573-754	Triangular
Drug budget	***14,676,740.42***			
Total budget	***14,941,326.94***			

After 100,000 trials, the mean of drug budget in 2008 was 14,676,740.42 (11,882,252.70 -21,730,632.39) baht whereas of the total budget was 14,941,326.94 (12,072,658.56 -22,781,379.12) baht. Probability of each value was shown in figure 4.11-4.12. The maximum probabilities of drug budget (0.03384) and total budget (0.04836) were seen at 14,336,666.67 and 14,695,000 baht respectively. Similar to 2007, the drug budget was about 98.23% of total budget.

The cost of glucosamine became the most important variable of the model analysis of drug budget and total budget due to its highest level of variance contribution to the forecast value as shown in figure 4.13-4.14. Costs of celecoxib and glucosamine user were the further sensitive variables. The cost of diclofenac and ranitidine was the least sensitive variable in both of total budget model while the cost of tramadol was at this position of drug budget analysis.

Figure 4.11 Forecast chart of drug budget 2008

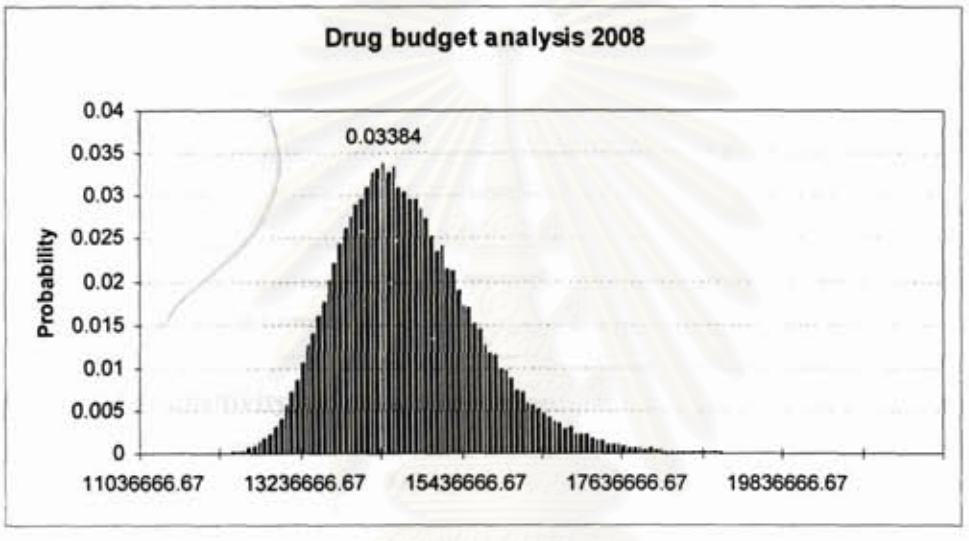


Figure 4.12 Forecast chart of total budget 2008

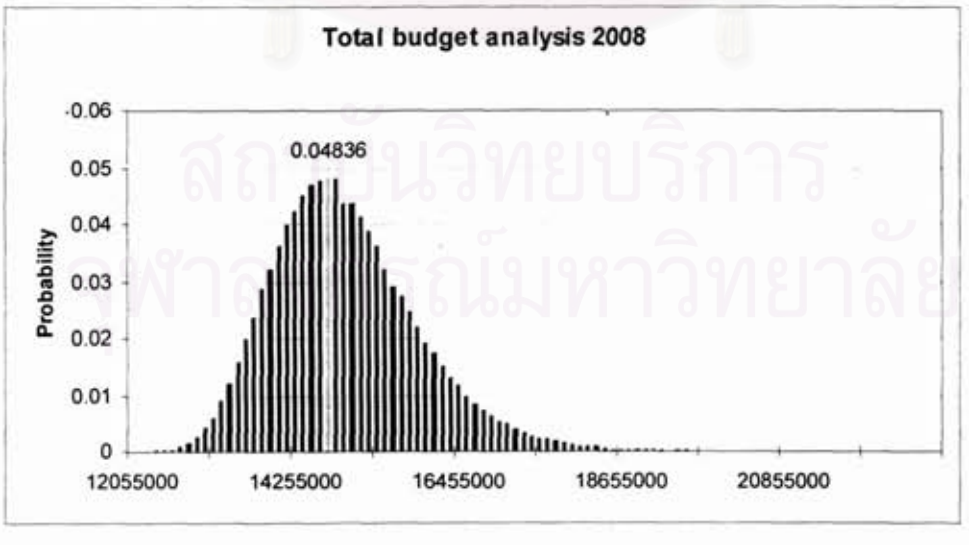


Figure 4.13 Sensitivity chart of target forecast: drug budget 2008

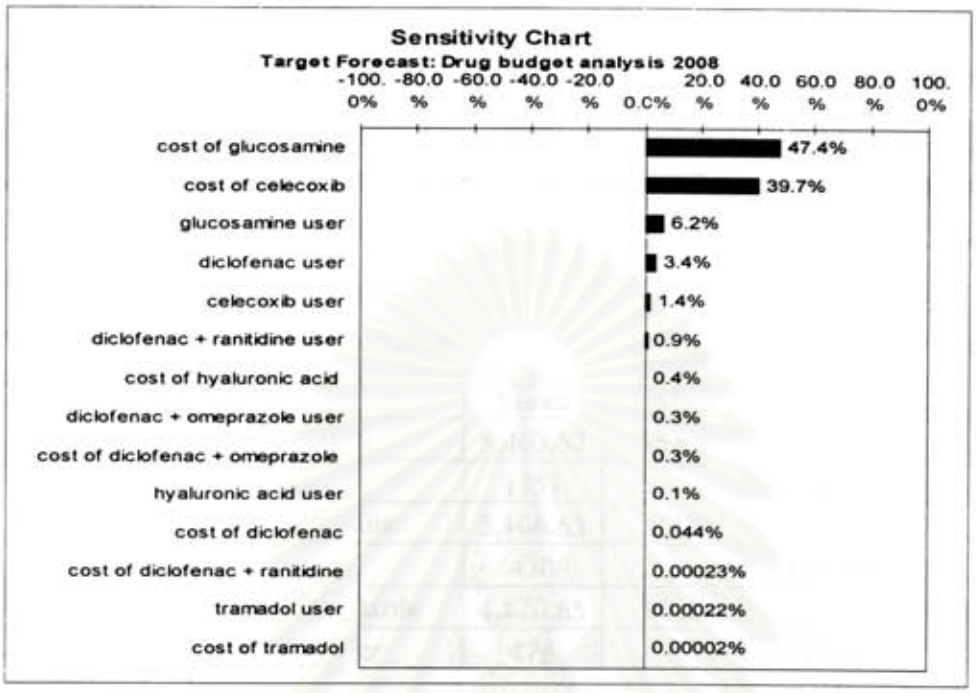
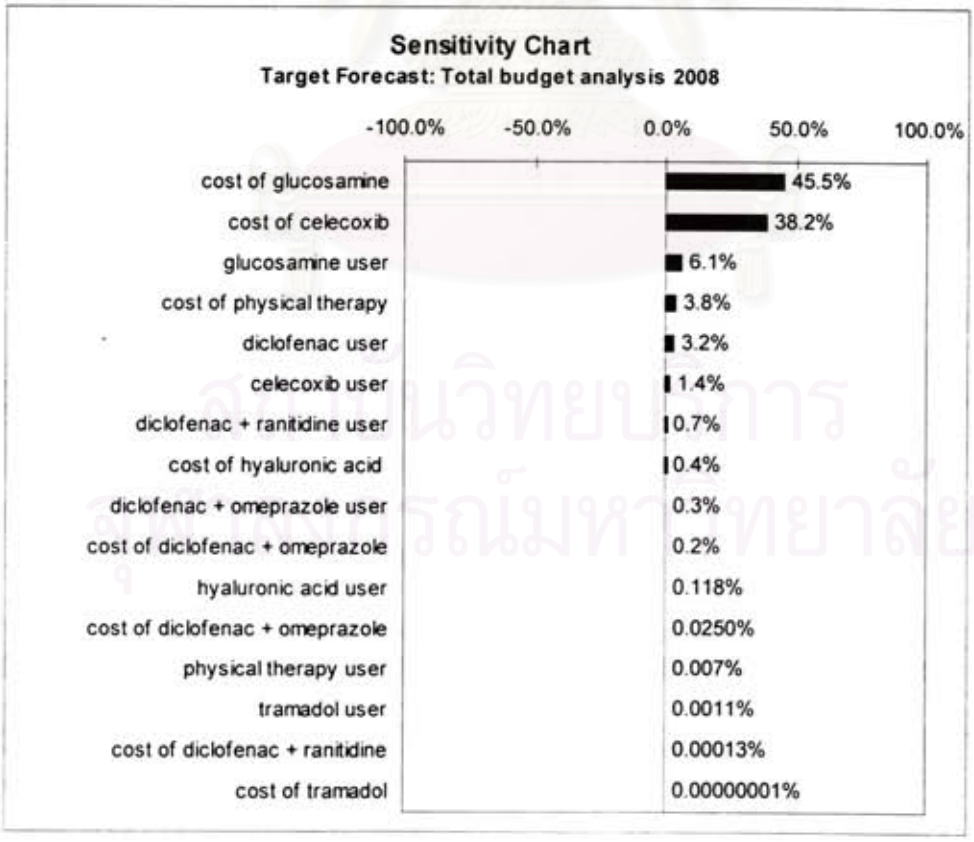


Figure 4.14 Sensitivity chart of target forecast: total budget 2008



3.1.3.3 Budget analysis of 2009

In 2009, it was expected that glucosamine will reach the steady market share by which there will not be significantly increases of number of patient using this drug in the future years. Data in table 4.14 was applied in the budget impact model. Results were shown in table 4.21. After 100,000 trials, the mean of drug and total budget impact were 14,938,052.79 (12,079,125.14-23,400,389.92) and. 15,216,784.23 (12,259,380.26 - 25,768,398.12) baht respectively.

Table 4.21 Budget analysis of 2009

Variable	Mean	SD	Range	Distribution
Cost of diclofenac	5,403.52	15.66		Lognormal
diclofenac user	1151		1,074-1,227	Triangular
Cost of diclofenac & ranitidine	5,106.63	1.44		Lognormal
diclofenac & ranitidine user	430		384-460	Triangular
Cost of diclofenac & omeprazole	4,870.65	98.5		Lognormal
diclofenac & omeprazole user	476		445-491	Triangular
Cost of Celecoxib	8,906.82	2,469.08		Lognormal
Celecoxib user	245		215-276	Triangular
Cost of tramadol	50.88	22.1		Lognormal
tramadol user	100		61-138	Triangular
Cost of glucosamine	4,521.24	1,823.40		Lognormal
glucosamine user	368		301-537	Triangular
Cost of hyaluronic acid	11,300	2,637.44		Lognormal
hyaluronic acid user	23		15-31	Triangular
Cost of physical therapy	5,403.52	335.25		Lognormal
Physical therapy user	1,151		583-767	Triangular
Drug budget	***14,938,052.79***			
Total budget	***15,216,784.23***			

According to figure 4.15 and 4.16, the maximum probabilities of drug budget and total budget; 0.041 and 0.04899, were seen at 14,526,666.67 baht and 14,841,666.67 baht respectively. Similar to 2007-2008 data, the cost of glucosamine was the most sensitive variable to both of drug and total budget following by the cost of diclofenac (see figure 4.17-4.18). Only these two variables, they contributed about 80% to the variance of forecast value. Next to these two variables, the number of patients using glucosamine and diclofenac user were the further variables with the third and fourth ranking of variance

contribution to drug and total budget model. The cost of tramadol was the least sensitive variable for drug budget and the total budget model.

Figure 4.15 Forecast chart of drug budget 2009

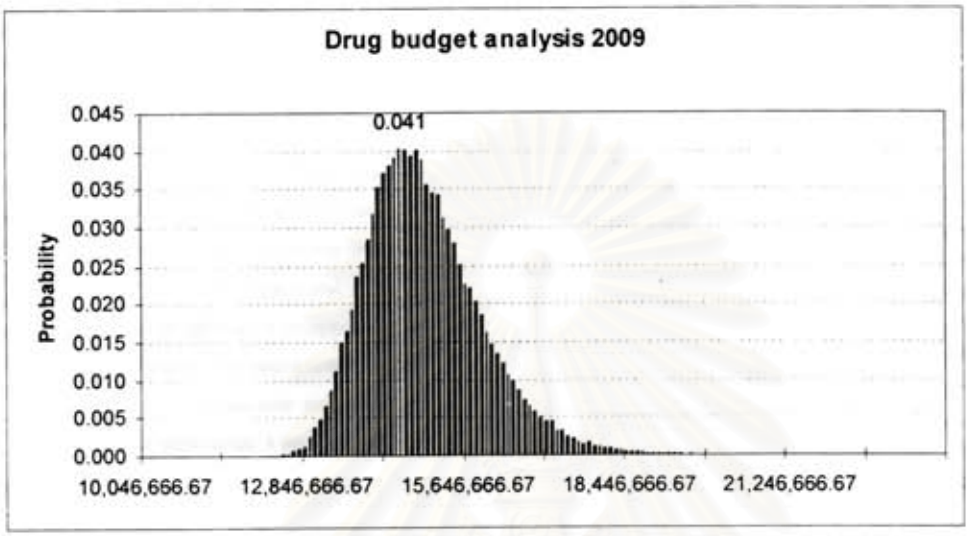


Figure 4.16 Forecast chart of total budget 2009

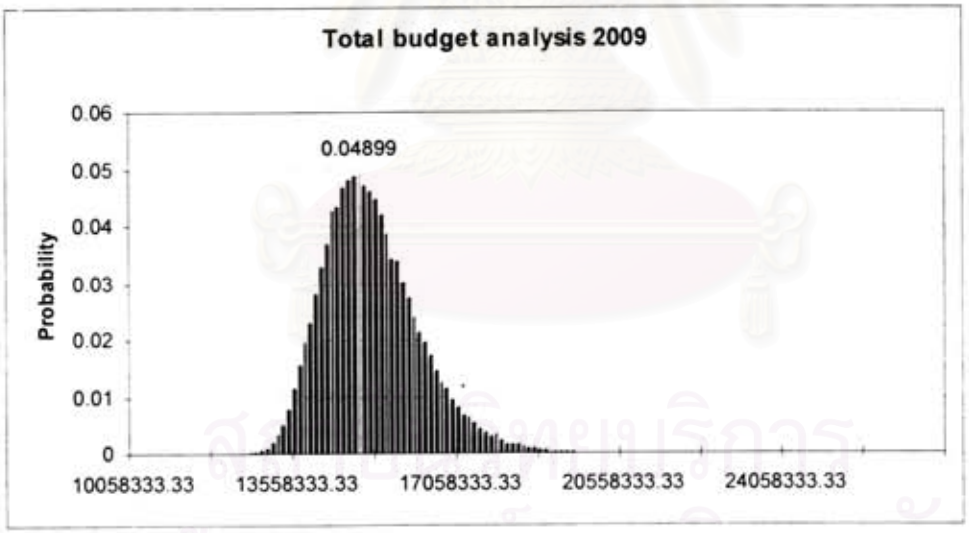


Figure 4.17 Sensitivity chart of target forecast: drug budget 2009

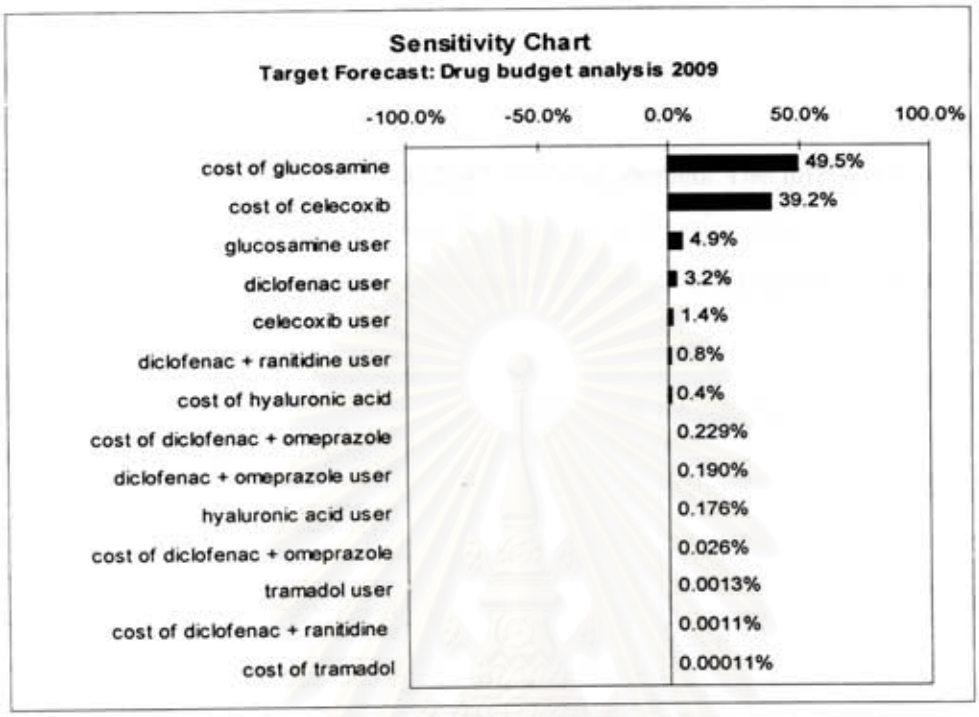
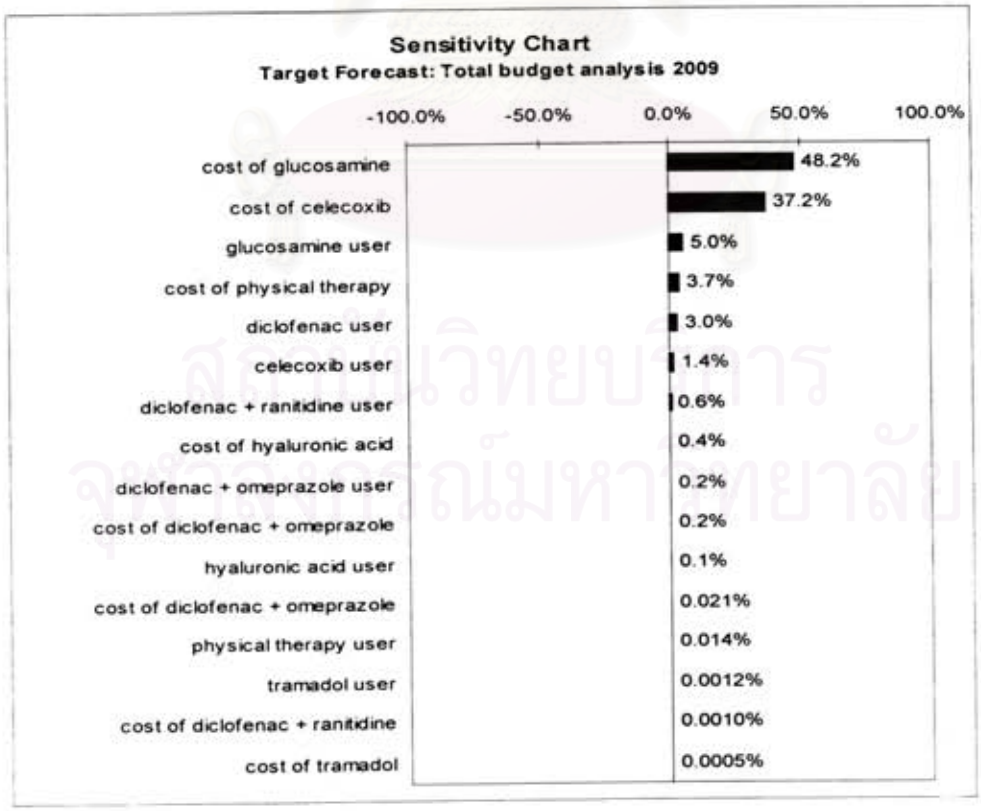


Figure 4.18 Sensitivity chart of target forecast: total budget 2009



3.2 Budget impact analysis of introduction glucosamine to formulary in 2005-2009

In order to know how much glucosamine affected the total budget of knee osteoarthritis treatment in terms, the differences of actual budget spent in 2004 which is year before the introduction of glucosamine to formulary and the actual budget in 2005-2006 and the forecasted budget in 2007-2009 are needed. The following table showed the drug and total budget of knee osteoarthritis in all respective years.

Table 4.22 Drug and total budget of knee osteoarthritis treatment in 2004-2009

Year	Drug budget of knee OA (million baht)	Differences (million baht)	% Growth rate	Total budget of knee OA (million baht)	Differences	% Growth rate
2003	11.0			11.2		
2004	12.0	1.0	9.1	12.3	1.1	9.8
2005	12.8	0.8	6.7	13.1	0.8	6.5
2006	13.6	0.8	6.2	13.9	0.8	6.1
2007	14.2	0.6	4.4	14.6	0.7	5.0
2008	14.7	0.5	3.5	14.9	0.3	2.1
2009	14.9	0.2	1.4	15.2	0.3	2.0

The growth rate of drug budget in 2003-2004 was the highest rate at 9.1% comparing to of 2005-2009. In 2005, the first year of availability of glucosamine, the growth rate of drug budget decreased to be 6.7% which was similar to of total budget in the respective years. Diminished growth rate was seen again in both of drug budget and total budget in 2006. There were 6.2% and 6.1% growth rate of drug budget and total budget in 2006 respectively.

The forecasted drug budgets in 2007-2009 were about 14.2, 14.7, and 14.9 million respectively. There were not much significantly increases of drug budget and total budget in these three years. Only approximately 0.43 million baht per year of drug budget and total budget were increased, in which the average growth rate of drug budget was 3.1%, and of total budget was 3.0%.

3.3 Sensitivity analysis

In this present study, there is little point to an extensive probabilistic sensitivity analysis since the degree of variability and the extent of correlation among parameters were examined all together during the analysis already. The ranges of variables were estimated based on realistic scenarios and with the best knowledge and included in the model. By using the probabilistic analysis method, the limited knowledge of degree of variability and correlation among parameters were taken into consideration. Valid and reliable data sources for the cost calculation and the estimation of future values of number of use and patients were used. Having said this, the usefulness of sensitivity analysis might be not much as expected.

CHAPTER V
DISCUSSION AND CONCLUSION

I. Budget Impact Analysis Results

Results of total budget impact including both drug budget and non-pharmaceutical budget were increased from 11.0 million baht in 2003 to 14.9 million baht in 2009. From this figure, there were only 3.9 million baht increased during the third year to fifth year after glucosamine has been listed in the hospital formulary.

The drug expenditures of Petchabun hospital in the past three years (2004-2006) were 65, 83, and 97 million baht. The growth rates of this expenditure were 27.69%, and 16.87%. Comparing the growth rates of hospital drug expenditure to those of drug budget of knee osteoarthritis, there were great differences. Inclusion of glucosamine partially contributed the increase of budget spent for knee osteoarthritis treatment about 6.2% and 6.7% (2005-2006). Note that the drug budget of knee osteoarthritis also included cost of adverse event treatment of non-steroidal anti-inflammatory drugs based on DRG cost. Then there are some costs which are non-drug i.e. surgery, hospitalization. If these costs can be excluded, there will be the smaller growth rates of drug budget of knee osteoarthritis treatment comparing to drug expenditure. Also, with this reason, the proportions of drug budget of knee osteoarthritis to total drug expenditure in hospital (18.46%, 15.42%, and 14.02% in 2004-2006) were overestimated.

In 2007, there are about 120 million baht allocated for drug expenditure. Using this figure comparing to the drug budget of knee osteoarthritis treatment, it showed that drug budget for knee osteoarthritis was 11.83% of total drug expenditure. The growth rate of total drug expenditure was also much higher than of drug budget for knee osteoarthritis; 12.74% and 4.4%.

By average, there were 430,000 baht increasing each year after the introduction of glucosamine to hospital formulary. There were only 86 patients from total 1,437 patients with knee osteoarthritis (6%) becoming glucosamine user in the 2005 which is the first year of glucosamine listing in hospital formulary. In a year after, there were almost two times of number of patient using glucosamine (157 patients). The proportion of

glucosamine users to total patients with knee osteoarthritis in 2006 was 10.8%. Based on the forecasted number of glucosamine user in 2009; 368 patients, there will be 368 patients from the estimated 1,534 patients with knee osteoarthritis (24%).

Market penetration of glucosamine in 2005-2006 was not an immediate type. It was increased from 6% coverage of patients to 10%. However, based on the treating physicians' opinions, it was expected to expand its market size with a double penetration rate in 2007; 20% patient coverage. The gradual penetration rates were expected to happen in 2008-2009; 2% increase each year. However, even the number of patients using glucosamine in 2007 was expected to be two times of 2006, the drug and total budget did not much increase. There were 600,000 baht of drug budget increased this year which was less than of 2005-2006; 800,000 baht. Moreover, the expected additional drug budget in 2008 was only 500,000 baht which was the probable effect from the reduction use of Celecoxib (174 to 153 tablets per patient per year) in addition to a comparable of number of Celecoxib users (238 to 241 patients) included in the model. The estimated drug budget in 2009 was approximately 14.9 million baht and build up to total budget of 15.2 million baht.

The introduction of glucosamine brought the dynamic changes in terms of number of patient using each drug (market share) and the quantity of analgesic use. Physical therapy was not highly affected by glucosamine uses. Most of effects were observed in the changes of pain-relieving agents. Interestingly, there also was small effect of glucosamine use in the utilization of hyaluronic acid which can be considered as the targeted competitive drug. As mentioned earlier, there were average 430,000 baht increasing each year after glucosaming has been listed. This amount of money equate to about the cost of knee replacement of about 5 patients. Therefore, considering only this figure and if the long-term use of glucosamine can really delay progression i.e. patients can stay in comparable disease stage (mild-to-moderate pain), by given the incremental costs of 430,000 baht to nearly 400 patients, it might be worthy of note to including glucosamine in hospital formulary.

Additionally, the increases of drug budget and total budget in 2007-2009 occurred with a slower rate than the likely pattern. It can be said that somehow the introduction of glucosamine to formulary did contribute a modest effect to both of drug budget and total

budget of knee osteoarthritis treatment. However, before jumping into making conclusion without any specification, to considering the study limitation which might bring a drawback to the study conclusion is crucial.

II. Study Limitations

The first limitation is related to type of model used in the budget impact model. Knee osteoarthritis is a chronic disease which theoretically should be modeled by using the more complex model i.e. Markov model. Additionally, the indication of glucosamine which could be altered the disease progression has supported the use of Markov model. However, to develop the disease transition stage in Markov model is not practical in knee osteoarthritis. Pain symptom that is main clinical manifestation in knee osteoarthritis should be used to define the disease stage in relation to how the disease has progressed. Unfortunately, there is no clinical indicator has a strong correlation with pain and disease progression. Joint narrow space which is very good indicator to examine the delay progression in patients who might be candidate for knee replacement has a weak correlation with pain. Then, to develop the Markov model and analyze the budget impact of using glucosamine directly in the model itself was viewed as unpractical method.

More simple decision model was used in this study. Decision tree analysis together with Probabilistic analysis was alternatively applied. The present study did not compute the budget impact directly from the decision-tree model (multiplying the average cost of using each comparator yielded from decision-tree with the expected number of use). By thinking another way, to well dealing with uncertainty in the model since key parameters in budget impact are estimated sometime with limited knowledge, the probabilistic analysis then was used. There were some studies using the deterministic analysis to estimate the formulary impact of new product.(101-104) All of them estimated the possible utilization of new drug based and impacts of use of other competitive drugs in the same indication. Framework of the present study was different from them since there are not only drugs in the same indication were included in the analysis but also other drugs/services used in disease treatment were taken into consideration. Budget impact model for knee osteoarthritis then was developed by using the “disease-based framework” and constructed each variable based on “indication-based analysis”. This can

be viewed as the cost variables were built in the situation that allows them to have interconnection to each other. Glucosamine became an interesting choice to study by applying this concept due to its benefits in delaying progression and pain-relieving. It can be well built in the model by having the interconnection with other pain-relieving agents, health services, and delaying-progression drug.

Moreover, there were drug costs and other additional costs of using drug i.e. treatment of adverse events included in the analysis. Hospital data can not show the number of patient who developed adverse events from using non-steroidal anti-inflammatory drugs and their costs. Therefore, the decision-tree model analysis was incorporated in the analysis in the process of determining such costs. Monte-Carlo simulation was used to yield the probable budget impact of knee osteoarthritis treatment without and with glucosamine. Since this method is suitable for analysis with uncertain data by generating value under a prior specified distribution, it then provided more realistic results than deterministic analysis.

By doing such method, the ultimate outcome of using glucosamine in long-term could not be incorporated in the decision-tree model which is suitable for modeling the short-term period. Then the budget impact analysis in this study refers to the probable budget will be spent by only obtaining the pain efficacy outcome as a benefit return of investment, not the delaying progression which is a desirable outcome.

The second limitation is related to the estimation of costs and number of patient in the model regarding the method used and factor affecting the prescribing pattern. These variables were estimated based on the historical dispensing pattern together with the physicians' opinions. The mean and range including all actual utilization were used to do the further 3-year forecasts. Many assumptions were made based on physicians' opinion brought together with the likely trend. Similarly to number of patient, the trend of patients with knee osteoarthritis was determined and used to forecast the future values. In particularly, for glucosamine, the amount of use (sachet) and number of patient, based on the sensitivity chart, they were the most sensitive variable. Cost of glucosamine which is related to amount of use contributed the most variance to the drug budget and total budget. In brief, these two variables of each drug/service are uncertain. There is little was known about how glucosamine penetrates in the market even it has been listed for 2

years. Only thing was observed during this two years is that it has rapidly growing in terms of the number of patients using this drug.

It can be said that even the estimation of cost variable especially the cost of glucosamine and Celecoxib in this study were used the most possibly practical, reliable method, they still are the most uncertain variable in the model. The range of budget impact was quite large. It means that these variables have significant impact on the forecast both through its uncertainty and its model uncertainty. They are needed to be further investigated in the hopes of reducing its uncertainty, and therefore its effects on the target forecast.

For the factors affecting the prescribing pattern, it seems to be a major source of variable's uncertainty. All of the treating physicians (3 physicians) agreed that glucosamine will be used in wider patient groups. The characteristics of potential glucosamine users can be categorized into two groups; clinical-related and setting-specific policy-related.

In the clinical-related group, there are two subgroups. The first subgroup is patients who developed any adverse event from non-steroidal anti-inflammatory drugs i.e. diclofenac alone, diclofenac and its combinations, Celecoxib. As needed-basis regimen of analgesic then will be used with this patient group in order to minimize or avoid the recurrent of adverse events. glucosamine will be additionally given to them with an aim to decrease the amount of use of analgesics and delay progression. The second subgroup is those patients with mild-to-moderate pain. Regarding the clinical evidence of using glucosamine up to date, glucosamine appears to be beneficial the most in this patient group more than patients with more sever pain.

The setting-specific policy-related group refers to those patients with selected healthcare scheme which fits to the local intended restricted use. Despite the fact that what level of pain the patients have, whether they pay out-of-pocket for the drug/service, and whether they can reimburse the medical expense from their insurance/healthcare scheme, are another key issue of using glucosamine. glucosamine has not been listed in both of the essential drug list and non-essential drug list. Even though there is no official restriction of using glucosamine, based on the historical dispensing pattern and personal communication with physicians, glucosamine is tentatively used in patients with CSMBS

(Civil Servant Medical Benefit Scheme) and out-of-pocket rather than those with universal coverage, social security scheme. Note that the patients who became to be glucosamine users can meet either clinical-related criterion or setting-specific policy-related group. These potential glucosamine users were expected to be about 368 patients in 2009 which are likely to be primarily composed of patients with CSMBS and out-of-pocket scheme.

These two criteria brought a lot of uncertainty to the number of glucosamine user and amount of glucosamine used as indicated in the sensitivity chart of drug budget. To reduce the uncertainty of these estimations, the actual data are needed. Closely follow-up the changes of utilization in glucosamine is a good method to obtain the more reliable and valid data. Also, the re-calculation of budget impact when any unexpected change was occurred is recommended.

III. Conclusion and concept application

In conclusion, the result analysis of budget impact in this present study gave the impression to support the inclusion of glucosamine to formulary because of its minor incremental budget (430,000 baht per year) which falls under the regular annual growth of drug budget and total budget of knee osteoarthritis in years before the introduction of glucosamine into the hospital formulary. However, due to the study limitations described earlier, the further investigation of data inputs (value, distribution) is recommended in order to minimize uncertainty to achieve the anticipated budget.

The budget impact concept to the decision making can be applied in both of hospital level and upper level i.e. national essential drug list. It is an essential part of a comprehensive economic assessment of a health care technology and is increasingly required, along with cost-effectiveness analysis, prior to formulary approval or reimbursement. In hospital level, it can be used to aid the decision making whether new drug should be listed, which patient group benefit the most, what restriction it should be done in relation to new drug. It provides a prediction of how a change in mix of drugs and other therapies used to treat a particular health condition will impact the budget.

The drawing of budget boundaries is a highly local exercise. In particular, some budgets may have a narrow focus. For example, in one location the pharmacy budget

holder will only be concerned with the expenses for drugs but in another, this may be subsumed within a total hospital budget. Thus, the perspective of a given budget holder may cover very different elements according to location. Whereas it is mandatory for the analyst to address the needs of the selected budget holders, it is also desirable for the analytic framework to be able to encompass broader or narrower the budgetary boundaries. In this way, the analysis will not only be able to show the hospital managers what they need to see, but also can extend beyond that to provide a more comprehensive view of the fuller economic implications of the intervention in the hospital.

In the upper level i.e. national essential drug list, the budget impact analysis should be integrated to the decision-making process. Budget Impact Analysis (BIA) should be viewed as complementary to cost-effectiveness analysis (CEA), not as a variant or replacement. Whereas, CEA evaluates the costs and outcomes of alternative technologies over a specified time horizon to estimate their economic efficiency, BIA addresses the financial stream of consequences related to the uptake and diffusion of technologies to assess their affordability. Obviously, both CEA and BIA share many of the same data elements and methodological requirements, but there are important differences in how these data and methods are incorporated into the models because of their different intended use. There may be circumstances where the CEA indicates an efficient technology while the BIA results indicate that it may not be affordable. Then the action plan could be further developed in consistent with the result analysis and the policy recommendation from both CEA and BIA.

Additionally, in both level of application of BIA, using the scenarios that consist of a set of specific assumptions and data inputs of interest to the decision maker in the analysis are likely to provide the more realistic outcomes of budget impact analysis rather than just using a scientifically chosen base or reference case.

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