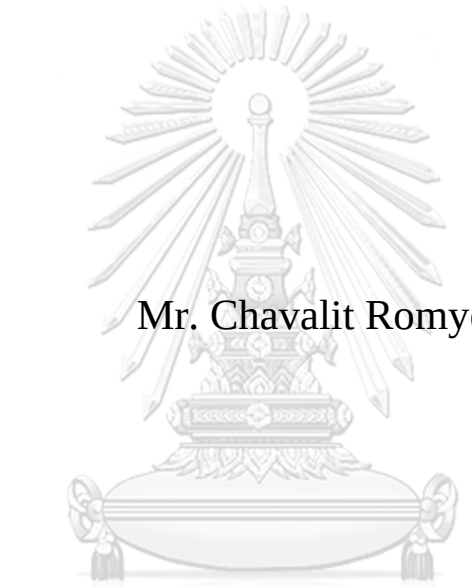
PROSTATE CANCER SCREENING IN THAILAND: COST-EFFECTIVENESS ANALYSIS AND BUDGET IMPACT EVALUATION

Mr. Chavalit Romyen



A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Social and Administrative Pharmacy

Department of Social and Administrative Pharmacy
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การตรวจคัดกรองมะเร็งต่อมลูกหมากในประเทศไทย: การวิเคราะห์ต้นทุนประสิทธิผลและการประเมินผลกระทบด้านงบประมาณ

นายชวลิต ร่มเย็น

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
สาขาวิชาเภสัชศาสตร์สังคมและบริหาร ภาควิชาเภสัชศาสตร์สังคมและบริหาร
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Thesis Title	PROSTATE CANCER SCREENING IN THAILAND: COST-EFFECTIVENESS ANALYSIS AND BUDGET IMPACT EVALUATION
By	Mr. Chavalit Romyen
Field of Study	Social and Administrative Pharmacy
Thesis Advisor	Associate Professor Police Lieutenant PUREE ANANTACHOTI, Ph.D.

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ชวลิต ร่มเย็น : การตรวจคัดกรองมะเร็งต่อมลูกหมากในประเทศไทย: การวิเคราะห์ต้นทุนประสิทธิผลและการประเมินผลกระทบด้านงบประมาณ. (PROSTATE CANCER SCREENING IN THAILAND: COST-EFFECTIVENESS ANALYSIS AND BUDGET IMPACT EVALUATION) อ.ที่ปรึกษาหลัก : รศ. ภญ. ร.ต.ท.หญิง ดร. ภูรี อนันตโชติ

วัตถุประสงค์ : เนื่องจากยังไม่มีนโยบายบรรจุการตรวจคัดกรองมะเร็งต่อมลูกหมากในชุดสิทธิประโยชน์ของระบบประกันสุขภาพภาคบังคับของประเทศไทย การศึกษานี้จึงทำการรวบรวม ผลการศึกษาที่เกี่ยวข้องและ ทำการประเมินความคุ้มค่ารวมถึงผลกระทบด้านงบประมาณ ของการตรวจคัดกรองมะเร็งต่อมลูกหมากในประเทศไทย

ระเบียบวิธีวิจัย : รวบรวมผลการศึกษาอย่างเป็นระบบ วิเคราะห์อภิมาน จากนั้น ทำการศึกษา ต้นทุนประสิทธิผลโดยใช้แบบจำลองเพื่อเปรียบเทียบแนวทางการตรวจคัดกรองมะเร็งต่อมลูกหมากในรูปแบบต่างๆ เทียบกับการไม่ตรวจคัดกรอง และทำการประเมินผลกระทบด้านงบประมาณหากดำเนินการตรวจคัดกรองมะเร็งต่อมลูกหมากในประเทศไทย

ผลการศึกษา :จากผล การรวบรวมข้อมูลอย่างเป็นระบบ พบว่า การตรวจคัดกรองมะเร็งต่อมลูกหมาก มีความแตกต่างกัน ในการตรวจคัดกรองแต่ละรูปแบบ โดยการตรวจด้วยวิธี ของ ESRPC จะมีอัตราการตรวจพบมะเร็งต่อมลูกหมากในอัตราที่สูงที่สุด (OR 1.65; 95%CI 1.60-1.71) ในขณะที่วิธีของ Goteborg จะลดการเสียชีวิตจากมะเร็งต่อมลูกหมากได้มากที่สุด (OR 0.41; CI 0.31-0.56) จากการวิเคราะห์เภสัชศาสตร์ด้วยแบบจำลอง การใช้แนวทางการคัดกรองแบบยุโรป (ESRPC) และ แนวทาง ของประเทศ นอร์ดิก (Goteborg) ให้ค่า ICUR อยู่ที่ 97,350 THB and 95,554 THB ซึ่งถือว่าเป็นทางเลือกที่คุ้มค่า เมื่อ เทียบกับเกณฑ์การยอมรับได้ หากทำการปรับใช้ การตรวจคัดกรองมะเร็งต่อมลูกหมาก โดยใช้แนวทางแบบยุโรป จะให้ผลวิเคราะห์ผลกระทบด้านงบประมาณต่อผู้ป่วยในระยะเวลา 5 ปี ได้ 302.58, 601.92, 901.45, 1200.95 and 1500.64 บาท ตามลำดับ

สรุป : เปรียบเทียบกับการไม่ตรวจคัดกรองโรค การตรวจคัดกรองมะเร็งต่อมลูกหมากตามแนวทางของยุโรป เป็นแนวทางที่มีความคุ้มค่า หากมีการปรับใช้การตรวจคัดกรองในประเทศจะมีผลกระทบด้านงบประมาณที่เพิ่มขึ้น ซึ่งต้องนำไปพิจารณาร่วมกับผลประโยชน์ทางคลินิกที่ได้ ในแง่ของ การรอดชีวิตและจำนวนปีสุขภาวะที่เพิ่มขึ้น

สาขาวิชา เภสัชศาสตร์สังคมและบริหาร ลายมือชื่อนิสิต .....

ปีการศึกษา 2562 ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

5876552833 : MAJOR SOCIAL AND ADMINISTRATIVE PHARMACY
KEYWORD: Prostate Cancer, Screening, Meta-Analysis, Cost-Effectiveness Analysis, Budget impact analysis

Chavalit Romyen : PROSTATE CANCER SCREENING IN THAILAND: COST-EFFECTIVENESS ANALYSIS AND BUDGET IMPACT EVALUATION. Advisor: Assoc. Prof. Pol.Lt. PUREE ANANTACHOTI, Ph.D.

Objectives: As public health insurance schemes in Thailand did not included prostate cancer screening in their benefits package, this study aimed to systematically gather the effectiveness and explore the cost effectiveness of difference prostate cancer screening programs for the Thai population and find the financial impact for adapting prostate cancer strategy.

Method: We perform systematic and network meta-analysis, health economic evaluation using Markov's model to compare four prostate cancer screening strategies with no screening options. And we perform budget impact analysis to assess the potential burden for adopting selected strategy.

Result: The result from systematic review and network meta-analysis suggest the difference of outcome between each prostate cancer screening strategies, ESRPC Scheme yield the most efficacy in term of prostate cancer diagnosis rate (OR 1.65; 95%CI 1.60-1.71) and Goteborg scheme yield the most efficacy in term of prostate cancer related death(OR 0.41; CI 0.31-0.56). Based on the pharmacoeconomic result simulated by Markov's model, ESRPC and Goteborg schemes compared to no screening strategy yield ICUR at 97,350 THB and 95,554 THB respectively while CAP Scheme and PLCO Schemes are dominated option. For applying prostate cancer screening strategy (ESRPC Scheme), total budget impact per patients estimated for 5 years were 302.58, 601.92, 901.45, 1200.95 and 1500.64 THB respectively

Conclusion: Comparing to No Screening option, ESRPC scheme and Goteborg scheme is Cost Effectiveness strategy options. (ICUR Within threshold of 1XGDP (Around 150,000-200,000 THB). Applying ESRPC screening scheme will affect budget impact in Thailand which needed to weight with clinical benefit as screening will improve life year gained and QALY.

Field of Study:	Social and Administrative Pharmacy	Student's Signature .....
Academic Year:	2019	Advisor's Signature .....

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Chavalit Romyen

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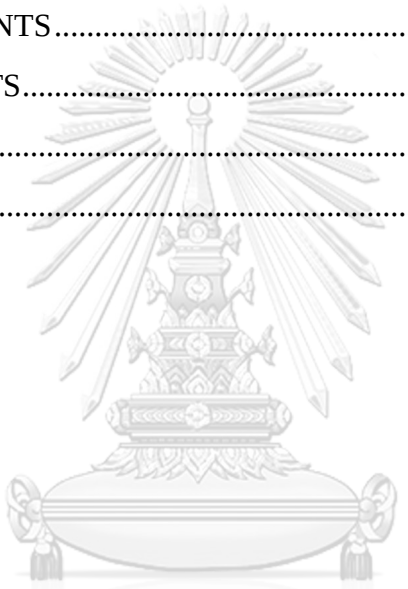

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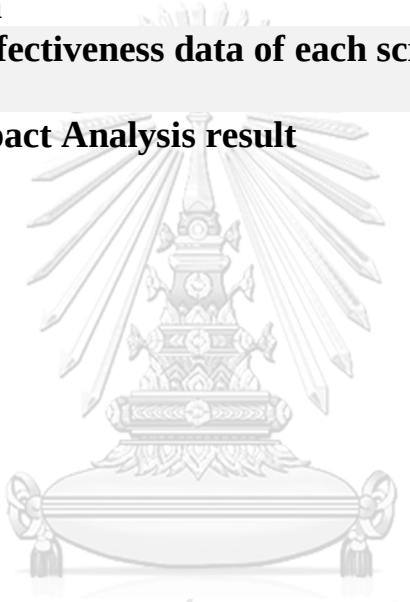

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Chapter 1: Introduction

Prostate cancer is one of burden disease worldwide. As its incidence is found in one of the highest ranks among cancer in men from year by year and it also has the strong increasing trend during the last decade. Prostate cancer may cause many subsequence problems such as mortality, morbidity and many costs due to the treatment especially in later stage of disease. Ratio between mortality and incidence seem to be varied among each country which favor ratio in developed country with high rate of prostate cancer diagnosis at early stage. (1)

In Thailand, prostate cancer is one of the most important tumors in men. Prostate cancer incidence rate from Thailand were reported as around 6,647 new cases per year and death is found around 2,886 cases per year. (2) Furthermore, high proportion of advance stage prostate cancer known to be high in Thailand which lead to poor prognosis. The issue of prostate cancer under-diagnosis is highly debated among Thai physicians.

Screening is one of the important steps for the management of specific diseases. An appropriate screening program will help the healthcare provider to diagnose the disease at early stage which generally related to better prognosis of disease. There are many important screening tools that emerged recently such as prostate specific antigen (PSA) screening and digital rectum examination (DRE) screening for prostate cancer, mammography for breast cancer or chest x-ray for lung cancer. (3)

Despite many randomized controlled studies attempted to evaluate the outcome of screening in prostate cancer detection and survival benefits. (4) There are still many clinical gaps of the previous randomized controlled study results that challenging to solve.

The recommendation to adapt prostate cancer screening program is varying around the worlds , many countries recommended screening program but there is some country recommend against this strategy. (5) This result was based on the high concern of harm regarding to PSA screening such as psychological burden, risk of overtreatment or economic burden that may outweighed the benefit that shown to be very small. However, many recommendations and guidelines believe that appropriate screening program may have the value for prostate cancer treatment but need to be adjusted to the specific population only. And the

result from various health economic evaluation around the world are still conflicting ad suggest that it should be done in local context to match with each country's situation.

In our study, we conducted the systematic review, network meta-analysis to summarize the evidence of risk and benefit from prostate cancer screening. We performed economic evaluation to explore the cost effectiveness of difference scenario of prostate cancer screening program to find the best decision scenario for using appropriate screening program in the target population. Finally, we conducted the budget impact analysis comparing adopting prostate cancer screening with no screening among targeted population. This evidence would support the decision maker to apply the most appropriate screening program for managing prostate cancer's burden in Thailand.

Chapter 2: Literature Review

a) Overview of cancer

Cancer is one of the most burdening disease for both incidence and severity contexts. [6]As the report from WHO statistic, cancer was found at a second leading cause of death behind cardiovascular disease. [7]

Global burden of disease study report incidence of 17.5 million cases of cancer per years and 8.7 million cases per years died with cancer in 2015. Prostate cancer is found at 4th rank of incidence among all of cancer cases and found at 2nd place among men cancer follow lung cancer. The incidence of cancer is varying among the country which have the trend to improve especially for developing country including Thailand. In figure 1, it shows the relative change in incidence of cancer and Thailand shown 10-20% increase in relative change of cancer from 2005-2015. Figure 2 shows the relative change of cancer's mortality and Thailand also shown 0-10% increase in mortality rate. [8]

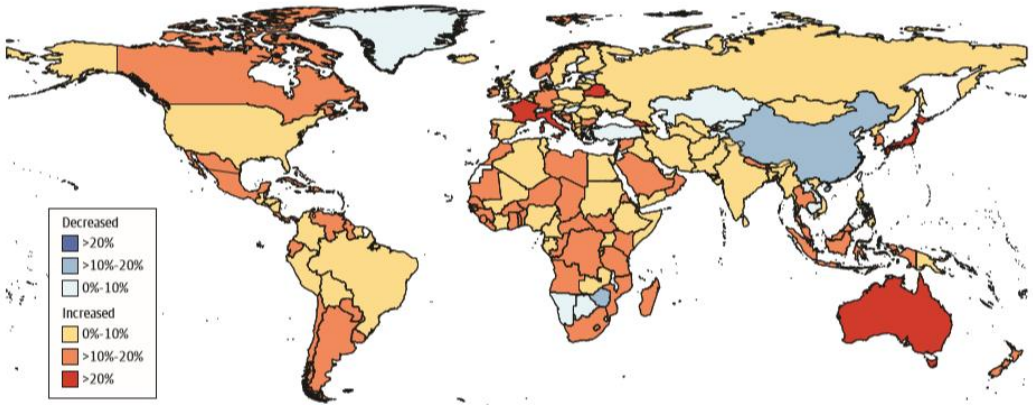


Figure 1: **Relative change in cancer's incidence rate from 2005-2015**

Source : Fitzmaurice C, JAMA Onco, 2017 [8]

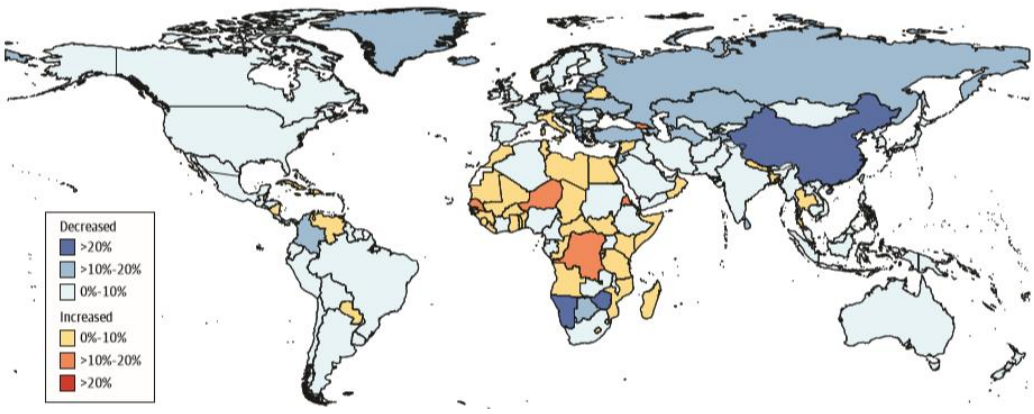


Figure 2: **Relative change in cancer's mortality rate from 2005-2015**

Source : Fitzmaurice C, JAMA Onco, 2017 [8]

The incidence and severity of disease make prostate cancer become the global public health problem**.** The complexity of the disease and treatment lead to many consequences, and cause several impacts including economic impact, clinical impact, and humanistic impact**.**

b) Prostate cancer overview

Prostate cancer is one of burden disease worldwide. As its incidence is found in one of the highest ranks among cancer in men from year by year and it also has the strong increasing trend during the last decade. Prostate cancer may cause many subsequence problems such as mortality, morbidity, and many costs due to the treatment especially in later stage of disease. Ratio between mortality and incidence seem to be varied among each country which favor ratio in developed country with high rate of prostate cancer diagnosis at early stage. [9]

Incidence of prostate gland is in the highest rank of cancer in men globally. As cancer statistic report published in 2018, [2] Prostate cancer is diagnosed at around 1.28 million population which are in 4th rank of all cancer and 2nd rank of cancer in men and estimated death around 0.36 million population annually worldwide. This result is consistent with the report by global burden of disease study in 2015 [8]as the new case was

found around 1.6 million cases per years and death per years was 366,000.

Moreover, as categorized by country, prostate cancer have highest incidence in men in 103 countries and reported to be the leading cause of cancer death in 29 countries. As compare among each region, Asia seem to have lowest incident of prostate cancer, but rising incidence trend was observed for 10 years period . [(1)]

According to Globocan's statistic data, there is the difference shown between developing country and developed country in the incidence and mortality ratio of prostate cancer. While in developed country, the incidence of prostate cancer is found at around 758,700 cases per year and the mortality rate is at 142,000. However, in developing country, the incidence of prostate cancer is found at 353,000 but the mortality rate is found at 165,500. And the incidence and mortality ratio were found to be more favorable in the country that have good recommendation of prostate cancer screening program including Australia, North America, and Europe. Figure 3 shows the comparison between developing and developed country in term of incidence and mortality of prostate cancer. [(1)]

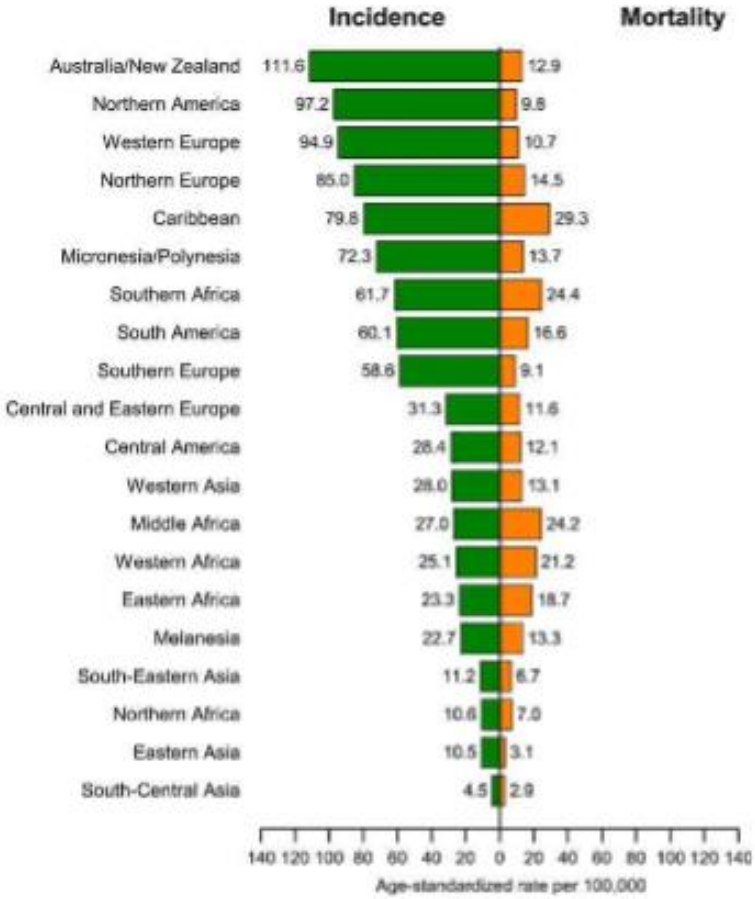


Figure 3: Incidence and mortality of prostate cancer among various country

Source : Center MM, EUR UROL, 2012. [1]

Prostate gland is the solid, round, heart shaped organ located in pericapsular space between bladder and urogenital diaphragm**.** Function of prostate gland is to produce the fluid, which help transportation of sperm during ejaculation process**.** Basic fluid produced by prostate gland will archive at seminal vesicle and secreted during ejaculation to make the balance environment for sperm mobility [9]

Definitive etiology of prostate cancer is still under-study**.** The most important regulation process of prostate gland growth is related to hormonal control via testosterone pathway**.** [10] Testosterone level is regulated by many steps of hormone starting with hypothalamus gland secretion of luteinizing hormone releasing hormone **(**LHRH**).** LHRH

stimulates pituitary gland to secrete the important hormone called luteinizing hormone **(**LH**)** and follicular stimulating hormone **(**FSH**).** LH and FSH will stimulate the testis, which is the major source of testosterone secretion, to product the testosterone hormone**.** Testosterone hormone will bind with androgen receptor to stimulate DNA signaling and induce the growth of prostate gland**.** And, testosterone may be converted to Dihydrotestosterone, which have more potency than testosterone and can stimulate DNA signaling like testosterone action**.** Another source of androgen production especially adrenal gland can produce androgen hormone, which can act via receptor activation**.** This hormonal activity had found to be related with prostate cancer and is the major target for prostate cancer treatment**.**

Clinical presentations of prostate cancer usually asymptomatic in patients with mildly or localized disease. Ureteral dysfunction symptom such as urinary frequency, hesitancy or dribbling can be found mostly in locally invasive disease, which the tumor spreading into the urogenital pattern. In addition, impotence can be found as the result of abnormal function of prostate gland. At the late stage, the diseases can spread to other area by three patterns: local extension to nearby area, lymphatic drainage to lymph node and the last is metastasis via hematogenous dissemination. The most common metastasis site of prostate cancer is bone that can cause many related symptoms such as back pain, cord compression, and pathologic fractures. However, prostate is a rare site for metastatic involvement from other solid tumors. [11]

As many literatures attempt to find the risk factors of prostate cancer development and found many factors [12]such as age, ethnicity (black have found more incidence of prostate cancer than white), family history, Food with high content of fats, occupation that exposed with chemical especially cadmium, some genetic polymorphism (CAG, CYP17, SRD5A2, GSTT1). [13]

Many subsequence problems have been found relating to prostate cancer including morbidity due to symptom of prostate cancer especially for advance disease and metastasis disease, prostate cancer specific mortality which is significantly high especially for patients who have the disease in later stage. In addition, prostate cancer required intervention which might cause significantly financial burden to the patients. [14]

In Thailand, prostate cancer is the one of the most important tumors in men. Prostate cancer incidence rate from Thailand were reported as around 6,647 new cases per year and death is found around 2,886 cases per year. [2] The incidence of prostate cancer in Thailand is estimated at around 7.1 per 100,000 persons according to data from Thailand national cancer institute during 2010-2012 and found as the most common cancer in Thai men [15]. Furthermore, many proportions of advance stage prostate cancer known to be high in Thailand which may be led to poor prognosis. And the issue of under-diagnosis of prostate cancer especially is highly debated among Thai physicians.

c) Prostate cancer Management Paradigm

Prostate cancer natural history is starting with slow growth tumor located in small area of prostate gland. This stage may be called "Preclinical stage" as it usually has no symptom either than signal to detect the abnormality. The uses of screening tool may help to detect prostate cancer 11-12 year before clinical symptom has been occurred and this will be the important tool to detect the cancer at early stage. Localize disease that occurred early which tumor is generally confined only in prostate gland may require localized treatment such as surgery or radiation. However, if the tumor spread into nearby area, which call "advance disease", systematic treatment base on hormonal therapy will be required. However, the disease can progress and metastasis after hormonal controlled which may require more aggressive treatment such as chemotherapy or other new agent with novel mechanism of action. [16]

There are many prognostic factors that may relate with prostate cancer treatment outcomes. Race difference had been found to have the great impacts for prostate cancer survival outcome. As the result from the systematic review and meta-analysis, black men shown poorer prognosis compared with white which still cannot be explained by adjusting other confounding factors (such as age, PSA screening or another comorbidity). [17] This is the great example which shown the value of prognosis factors for describe the key outcome difference among each prostate cancer patients.

Important prognosis factor of prostate cancer is tumor grading evaluated by histological biopsy. The most popular scoring system use in prostate cancer is Gleason score, which grade the tumor differentiation pattern form 0-10. As lower score indicated the good differentiation of cell and higher score indicate the tumor with poorly differentiation pattern. [18]

Staging of prostate cancer is the most important tool to predict the prognosis of the disease. The most popular staging system is AUA system (American Urology Association) which divided the staging of disease as A (Non-palpable disease), B (Prostate gland confined), C (pericapsular area involvement) and D (Metastatic disease). [19] Another staging system is TNM system that mainly used by oncologist and health care provider that assess the tumor in three dimensions including tumor size, nodal involvement, and metastasis pattern. [20] Staging of disease was strongly associated with prostate cancer survival. Staging by AUA system and survival outcome was shown in table 1.

Table 1: Staging by AUA system and survival outcome.

Staging	Survival
A_1	95%
$A_2 – B_2$	80%
C	60% (Median Survival ≈5 y)
D_1	40%
D_2	10% (Median Survival ≈2 y)

Moreover, prostate cancer staging is also related with patients' quality of life. [21]As many studies has collected quality of life for each stage of prostate cancer by various method such as standard gamble, time trade off or EQ-5D questionnaires. More advance stage of prostate cancer is related with lower utility score as shown in Figure 4 below

Study	Starting state utility	Treatment for localized	Advanced	End of Life
Heijnsdijk et al	0.99	0.67	0.6	0.4
Keller et al	1.0	0.95	0.9	0.6
Pataky et al	1.0	0.88	0.85	0.5
Roth et al	1.0	0.75	0.75	0.33

Figure 4: Utility data assign to health state from various study

Adapted from Source: Sanghera et al. 2018. BMC Cancer. [21]

d) Rationale of cancer Screening

Screening in one of the key recommendations for manage cancer problem and it is the important step for disease management**.** [22] As cancer have difference prognosis features and early detection of cancer is associated with better prognosis**.** There are many key screening methods for various cancer and many guidelines discuss on it**.**

The primary focus for early detection of cancer is target on cancer with high incidence including breast cancer, colorectal cancer, lung cancer, cervical cancer, endometrial cancer, and prostate cancer**.** Many guidelines have long history of developing for prostate cancer, American cancer society has established full guideline since 2010, however, it need to be updated based on current existing evidence. [23]

Screening is one of the important steps for the management of specific diseases. As appropriate screening program will help the healthcare provider to diagnose the disease at early stage which generally related to better prognosis of disease which related to reducing mortality, morbidity and reflect the overall cost of disease management. There are many important screening tools that emerged recently such as prostate specific antigen (PSA) screening and digital rectum examination (DRE) screening for prostate cancer, mammography for breast cancer or chest x-ray for lung cancer.

e) Prostate cancer screening tool

Prostate cancer screening tool including symptomatic assessment, digital rectal examination, and serum prostate specific antigen testing. Symptomatic assessment has some limitation because of the disease usually asymptomatic at early stage of disease and may cause under-

detection or late detect the disease at advance stage. Digital rectal examination is the method with high specificity, cheap, safe, and conveniently to perform. However, the expertise of physician is particularly important to perform this screening and early disease will have non-palpable prostate gland, which cannot be detected by digital rectal examination. [24]

Prostate specific antigen (PSA) testing is the most popular tool for prostate cancer screening. PSA referred to the glycoprotein secreted by epithelial cell of prostate gland, which might increase its value in abnormal situation such as malignancy clone or abnormal condition of prostate gland such as prostatitis or benign prostatic hypertrophy. Prostate specific antigen is secreted to the serum. Generally, there is no standard cut-point for appropriate PSA value but generally use the cut point at 3-4.0 ng/ml. However, there are many confounding that can make the PSA increasing such as some condition (benign prostatic hypertrophy, prostatitis) and some of the medication can lower PSA value. Increasing age and some ethnicity (black) may found the higher PSA level that general population. These confounding maybe lead the result to be false positive or false negative. PSA testing accuracy was reviewed in many studies and shown about 60-70% specificity and 67-75% sensitivity. [25]

Digital Rectal Examination is the screening tool that need to be performed by skilled physician and might be use concomitantly with PSA test to increase the sensitivity of screening. Tumor of prostate gland become palpable and can be detected by this invasive procedure. However, in early stage of tumor, this test maybe lack sensitivity.

Meta-analysis of prostate specific antigen and digital rectal examination as screening test was conducted to summarize the accuracy of each screening tool. [25] As this study found PSA+DRE sensitivity is at around 72.1%, specificity 93.2% and positive predictive value 25.1% respectively.

Key benefit of cancer screening is including the improvement in cancer diagnosis rate and many studies has shown survival benefit. However, the risk of cancer screening is including anxiety of the result, have the chance for false positive test and false negative test, additional

requirement of hospital resource including biopsy needed, hospitalization needed and overtreatment.

f) Prostate cancer screening evidence

Raise of concern of PSA screening benefit is increasing recently, as the benefit of PSA screening on survival cannot be proved through many of the study and recent systematic reviews. Another concern is regarding to the high false positive rate following the screening, which may cause psychological burden and lead to over-diagnosis and/or over-treatment that cause many problems of unnecessary adverse events. [26]

As PSA screening benefit has been studied in many of randomized controlled trials and the result was inconsistency among each study. In figure 5 showed the result from key randomized controlled study in prostate cancer screening and mortality rate with the focus on two largest randomized controlled trials were conducted in Europe (ESRPC trial) and America (PLCO trial). In ESRPC trial the significantly reduction of prostate cancer related mortality was found favoring PSA screening arm (relative risk 0.8; CI 0.7-0.9). However, this outcome was shown not significantly benefit in PLCO trial (relative risk 1.0; CI 0.9-1.2). Meanwhile, both of evidence found the increase in prostate cancer detection rate concurrently. [27]

Trial	Size of Study population (Screening +Control)	Target Age group (years)	Follow-up (years)	Number of prostate cancer deaths (Screening +Control)	RR for prostate cancer mortality
Norkoping	1,494+7,532	50-69	20	30+130	1.2 (0.8-1.7)
Stockholm	2,400+24,772	55-70	13	53+506	1.1 (0.8-1.5)
Quebec	31,133+15,353	45-80	11	153+75	1.0 (0.8-1.3)
PLCO	38,340+38,343	55-74	15	255+244	1.0 (0.9-1.2)
ESRPC	72,891+89,352	55-69	13	355+545	0.8 (0.7-0.9)

Figure 5: Prostate cancer mortality from prostate cancer screening trial

Adapted from Source: Auvinen A, Transl Androl Urol. 2018. [27]

Djulbekovic and Cochrane review[4] conducted two systematic reviews in 2010 and pooled the result to show the neutral effect of PSA screening on survival benefit. [28] However, there are remains a room for another meta-analysis because latest update study with longer follow-up has been published which has not incorporated in the recent systematic reviews. Also, there still have many advance methods like Bayesian analysis, cumulative analysis or meta-regression that may make the analysis better and may have significant value in answer remaining question especially the key difference between each evidence.

Updated analysis from ESRPC trial from 13 years follow-up, rate ratio of prostate cancer mortality in men screened was 0·73 (95% CI 0·61–0·88) compared with the men without screening program. [29] Another latest evidence on prostate cancer screening is from Goteborg study that report the latest result from 18 years follow-up, the result show rate ratio for prostate cancer death at 0.65 (CI 0.49-0.87) and also suggest the greater benefit of PSA screening is show at men age 55-59 years. [30]

On the other side, updated analysis from PLCO trial from 15 years follow-up, prostate cancer screening show rate ratio (RR) at 1.03 (95% confidence interval [CI], 0.87-1.23). However, it was estimated that 86% of the men in the control arm and 99% of the men in the intervention arm received any PSA testing during the trial. [31] And also, the data from CAP trial perform in United Kingdom report the result from 10 years follow-up, rate ratio [RR] was reported at 0.96((95%CI,0.85to 1.08); p=.50). [32] However, Screening was found to increase prostate cancer detection rate, increase prostate cancer detection in early stage.

Conflicting result from multiple randomized controlled trials might be related to the difference among studies. The factor that different between each study is including age range in inclusion criteria, follow-up Time, combination with DRE, screening frequency and PSA Level at cut-off for Biopsy. [4]

Despite many randomized controlled studies attempted to evaluate the outcome of screening in prostate cancer detection and survival benefits. There are still many clinical gaps of the previous randomized controlled study results that challenging to solve. First, result from vary study seem to be different among each other with may be contributed to each study characteristic such as PSA screening procedure use in each

study, patients selected in each study and the et al which leading to inconsistency of benefit that shown from difference randomized controlled trial which might need appropriate strategy to analyze the result. Second, PSA screening may have the great benefit in some defined subgroup and the little effect in another subgroup. This result was described previously in ESRPC trial that shown the modest effect of PSA screening in age group 55-69 years more than younger or older age group. From this concept, there still may be another risk factor that associated with the outcome of PSA screening populations and the decision-analysis might needed to be considered for most appropriate scenario. Third, there are another dimension beyond the context of benefit of screening such as risk and harm of screening or not screening, psychological and quality of life dimension, Health economic consideration should be raised to considered through decision analysis. The decision analysis base on the appropriate scenario of each situation should be conducted and may assist to find the best decision of applying screening program in prostate cancer patients.

g) Prostate cancer pharmacoeconomic evaluation

There are several countries that conduct the study to estimate the burden of prostate cancer in economic perspective**.** In Canada, economic model of prostate cancer management from diagnosis from death was conducted using Markov simulation model**.** Estimation cost from the model is around 9,000 million dollars including diagnosis and staging cost, treatment cost and caring cost of life care [33]**.** Cost burden of prostate cancer was generally high but varies among each country**.** [34] Cost analysis in local country context is still warrants**.**

Studies on economic evaluation in assessment of PSA screening value are still insufficient**.** As reviewed by Imamura on 2008 [35], cost effectiveness analysis and cost utility analysis are mainly conducted by using model approach and the results is varying among each study**.** In example, Monte-Carlo simulation using Markov model was studied by Ross and colleagues**.** [36] to identify the best approaches for PSA screening and found the best strategy is starting PSA screening from age 40-45 and screening as biennial instead of annually screening and start after age 50 years old**.** And the micro-simulation study from ESRPC data also suggest cost effectiveness of prostate cancer screening but the result

is limited to only short-term screening. [37] Therefore, health technology assessment in the context of specific country is still warrant.

Several cost-utility analyses have been reported from various studies, favorable cost utility results are reported by Carvalho et al[38] and Kobayashi et al. [39] However, the result is contrast with the study conducted by Krahn et al. [40] The inconsistency of the result might come from the difference in context of each evaluation and the assumption of their models.

There is one systematic review combine cost-effectiveness study from various country. [21] The cost effectiveness of prostate cancer screening is still unclear depend on scenario and each countries' context. Therefore, specific data for each country is required.

In Thailand, mass screening for prostate cancer is not quite popular. The value of PSA and DRE are reserved for diagnosis purpose and for treatment follow up indicator only. However, insurance package and private hospital still include PSA screening as the one of check-up package in men over 45 years old or as discussed with the patients. Price for one-time PSA screening was varying among each hospital around 300-1,500 Thai Baht. As weighing between risk and benefit of PSA screening, this screening method is suggested to use in individual patients who preferred screening or have some risk factor that tended to have more risk of prostate cancer or tended to have worst outcome. Therefore, the best decision scenario should be defined.

h) Budget Impact Analysis

Budget impact analysis is the essential part of complete economic assessment that use concomitant with pharmacoeconomic evaluation. The key aim of budget impact analysis is to provide the financial information and forecasts the financial effect for adopting intervention before decision making. [41]

In budget impact analysis, several components need to be defined including key population, chosen intervention and alternative, perspective, time horizon, model description, data element, data collection, source of the data and analysis method.

As the result from the review, there is still no evidence of budget impact analysis for prostate cancer screening program in Thai setting and evidence is limited in global setting**.**

i) Prostate cancer screening recommendation and guideline

Various recommendation and debate were made for PSA screening role in prostate cancer , US FDA had approved to use PSA screening as e one of the prostate cancer screening tools since 1994 and Medicare **(**the global health insurance in Europe**)** decided to apply PSA screening annually in population with age more than 50 years old**.** However, some of the physician may design to apply the screening program earlier at patients age 40 or 45 years old especially for patients that have some of the risk factors **(**Black, Have family history etc..**).** [(42)]

American Urology Association has summarized latest recommendation to start screening program with DRE and PSA in men with age over 55-69 years old or men over 40 years old with risk factor such as family history or African American racial**.** [(43)]

In contrast, American cancer society guideline recommends prostate specific antigen test with or without digital rectal examination test in men over than 50 years old with the informed decision-making process about benefit and risk of prostate cancer screening**.** Figure 6 show screening guideline variation in United states**.** **[(44)]**

Organization	Screening Approach	Cut point Age	Biopsy Criteria
American Cancer Society	Shared Decision Making	50	PSA ≥ 4 ng/ml
American College of Physician	Shared Decision Making	45	PSA ≥ 4 ng/ml
American Urological Association	Shared Decision Making	55	PSA ≥ 4 ng/ml
US Prevention Service Taskforce	Recommend Against (As of 2012)	N/A	N/A

Figure 6: **Prostate cancer screening guideline in US**

Adapted from Source: Smith AR.CA Cancer J Clin .2017. **[(44)]**

Moreover, age to inform decision making process for prostate cancer screening is vary among guidelines as shown in figure 7**.** As some

guideline may suggest for early age screening at 40-45 years such as NCCN and Melbourne consensus**.** However, some guideline suggested for later age at 55-60 years such as American urology association.

Guideline	Age (years)
NCCN, Melbourne Consensus	40-45
MSKCC	45
EAU-ESTRO-SIOG	50; 45 if family history or African-American
ASCO, ACS,ACP	50
AUA, USPSTF (draft)	55-69

Figure 7: **Age to start decision making process in various guideline Adapted from Source: Kohestani K**. **Transl Androl Urol**.**2018**. [5]

Prostate cancer screening in Asia PSA-based screening is not widespread in many Asian countries**.** However, the results from one study conducted in Japan shown screening is sufficiently contributed to detecting prostate cancer at an early stage, in which the decreased mortality rate following optimal treatments was expected**.** And the Japanese Urological Association **(**JUA**)** . [45]

The recommendation to adapt prostate cancer screening program is varying around the worlds, many countries recommended screening program but there is some country recommend against this strategy. This result was based on the high concern of harm regarding to PSA screening such as psychological burden, risk of overtreatment or economic burden that may outweighed the benefit that shown to be small. However, many recommendations and guidelines believe that appropriate screening program may have the value for prostate cancer treatment but need to be adjusted to the specific population only. [46] And the result from various health economic evaluation around the world are still conflicting ad suggest that it should be done in local context to match with each country's situation.

In Thailand, there is no standard recommendation for screening tools use in prostate cancer**.** Generally, Thai physician usually follow the recommendation of AUA and/or NCCN guideline**.** One study conducted in Siriraj hospital use the PSA and/or PSA screening in 982 elderly men

and followed by transrectal ultrasound guided biopsy in case of abnormal PSA and/or DRE**.** Other cohorts that reported in 200 Thai healthy men seeking for medical check-up during the anniversary celebration of Siriraj hospital found prostate cancer detection rate around 4**.**5**%.** [47] Studies for long-term survival benefit, cost effectiveness and concern of humanistic outcome are currently still warranting in Thailand**.**

As the process of health technology assessment to support the decision making for including the new technology/treatment strategy to reimbursement scheme, five filter decision model is currently used. This is mean the problem needed to be prioritized, health technology should have benefit and risk ratio. Moreover, the health technology should be assessed about value of money whether it was cost effectiveness within the acceptability threshold. Affordability is also the important feature and final consideration as the policy recommendation should be made.

Chapter 3: Methodology

A. Overview of study design

The flow of this study was divided into three phases including, first, we performed the systematic review for gather evidence regarding to prostate cancer screening benefit and risk assessment, recommendation guideline and insurance coverage scheme among each country. Second, we combined the data together and performed the health economic evaluation to explore the cost effectiveness of various prostate cancer screening programs compared with no screening option and compared with each other. Finally, we evaluated the budget impact of performing population based prostate cancer screening.

We thought that our study would provide information of benefit/risk, cost-effectiveness analysis and budget impact evaluation of screening program for health care provider and health care decision maker. This evidence might assist decision-maker to apply or not apply prostate cancer screening program in Thailand and to find the most appropriate scenario for apply prostate cancer screening in Thailand.

B. Systematic review, meta-analysis, and network meta-analysis for key outcome parameters

Systematic review and meta-analysis are the methods that applied to delivered two important goals**.** Systematic review is a critical assessment method of existing evidence to make the summarization and try to solve specific focus question**.** Meta-analysis uses the statistical model to quantitatively derive a summary estimation of effect and meanwhile meta-analysis have another important aim to explore and describe the difference between each study which related to the different result**.**

Network meta-analysis (NMA) and multiple treatment comparisons (MTC) of randomized controlled trials (RCT) has been introduced as an extension of pairwise meta-analysis, with the advantage to facilitates indirect comparisons of multiple interventions that have not been studied in head-to-head studies. Key features of network meta-analysis compare with standard meta-analysis is including visualization

of larger amount of evidence, estimation the relative effectiveness of all intervention and can rank order for the intervention in the field. [48]

Key step in conducting systematic review and meta-analysis are including the formulate of study question and establish protocol, literature search and retrieval based on pre-setting specify database. Next, the paper selection would base on selection criteria as specify in the protocol and the data extraction plus quality assessment step and finally the analysis step using proper method.

The study questions that we set for systematic review were the comparison between the use of PSA screening program compare with no PSA screening program in population the come to has PSA screening in randomized controlled trial. The interested outcomes were prostate cancer detection rate and prostate cancer specific survival.

Key electronic database used in our searching method including PubMed, Embases and Cochrane Central**.** Moreover, we performed additional search by using manual search of local dissertation, discussion with the key expert, expanding paper from the reference and searching of latest abstract from major meeting from latest annual meeting in Urology and Oncology**.** Keywords used for performing the searching included "Prostate Specific Antigen", “Screening Program", “Prostate Cancer".

Key selection criteria of our review were i**.** Randomized controlled study comparing screening method with no screening, ii**.** Reported specific outcome interested including prostate cancer detection rate and prostate cancer specific survival, and iii. have appropriate follow-up time with is specified as more than 10 years**.** The exclusion criteria are including I. Study was published in languages other than English, ii. Cannot obtain the full publication, and iii. By judgement of investigator as considered for the quality of the study.

Two independent reviewers performed identification, selection and data extraction of each study**.** Data extraction form was used to extract the key components including key outcome of each study, key characteristic of each study**.** Inconsistency of two reviewers was solved during the consensus**.**

Quality assessment of each study was performed for each study using the Jadad score and adapted criteria from Grade and Consort.

Quality assessment was performed by two researchers and inconsistent assessment was observed and reported.

In the step of pooled data synthesis, Meta-analysis is performed by using random effect model**.** We assessed the heterogeneity between each study by using I2 and X2 testing method**.** Publication bias is tested by using Egger and Begg's test**.** After performing classical meta-analysis and if the result from classical meta-analysis defined high heterogeneity, we considered the use of network meta-analysis using Bayesian method to pool effect size of outcome among each comparison and provide the estimation interval. Moreover, Bayesian method can also provide treatment ranking probabilities that refers to the probabilities estimated for each treatment in a network for achieving a placement in an ordering of treatment effects from best to worst.

C. Pharmacoeconomic evaluation

Health economic analysis is the important tool to assist decision maker to perform the technology assessment. As limited resource, the decision should be based on cost and benefit weighing for each technology.

The study is conducted using modeling to estimate the multiple scenarios for each decision option. Pharmacoeconomic evaluation performed in our study is based on Thai health intervention technology assessment guidance.

Pharmacoeconomic evaluation has been categorized into 4 major types base on cost and type of outcomes selected for evaluation including cost-minimization analysis (CMA), cost benefit analysis (CBA), cost effectiveness analysis (CEA) and cost utility analysis (CUA). For our study, we selected cost utility analysis because prostate cancer is the disease that have burden in term of clinical impact, economic impact, and humanistic impact.

D. Perspective and Time Horizon

We used the societal perspective that included the perspective of health care provider, patients, and the entire stakeholder of technology assessment**.** We assumed the time horizon around 40 years because

prostate cancer has slow prognosis and we focus for the final- outcome assessment**.** Cycle length is set at 1 year**.**

E. Target population and source of data

The target population of our study is designed for men aged within the range of 50-70 years old based on available published evidence that might have the risk for developing prostate cancer in Thailand setting and intended to have prostate cancer screening based on many recommendations from various guideline.

As the lack of country-specific data, source of the data mainly used in our analysis is based on data from literature review, we will select the data from explicit and transparent systematic review approach. Quality assessment of the selected data source will be assessed and reported in appropriate format.

F. Selected intervention and key comparators

The alternative selected for our analysis is the strategies to apply the prostate cancer screening program which based on four large randomized controlled trials including

1. Apply PSA screening for population start at 50 years old until 65, Use PSA cut points as 3 ng/ml to perform guided biopsy, Screening interval is set at every 4 years. (ESRPC Scheme).

2. Apply PSA screening combined with DRE for population start at 50 years old until 65, Use PSA cut-points as 2.5 ng/ml to perform guided biopsy, Screening interval is set at every 2 years (Goteborg Scheme).

3. Apply PSA screening for population older than 50 years old, Screening is set at only one time, PSA cut points as 3 ng/ml to perform guided biopsy. (Cap Scheme).

4. Apply PSA screening combined with DRE for population start at 55 years old until 70, Use PSA cut-points as 4 ng/ml. Screening interval is set at annually for 3-5 years (3 years for DRE and 5 years for PSA). (PLCO Scheme)

5. No Prostate Cancer Screening program.

G. Cost identification, collection, and valuation strategy

Cost included in the study is mainly count on direct cost in term of both medical and non-medical related cost. Direct costs that use for input to the model including cost of intervention perform **(**PSA screening, DRE Screening**)** based on selected strategy, cost of concomitant laboratory procedure for diagnosis **(**TRUS guided Biopsy**)**, cost of treatment of various staging of disease **(**including surgery and radiation therapy for localized treatment, hormonal therapy for advanced treatment, chemotherapy for metastasis treatment and novel agent for post-chemotherapy treatment**).** The valuation of the cost is based on standard of treatment that given following national guideline depending on the stage of prostate cancer.

Discounting method are applied for all cost by using 3**%** discount rate**.** All cost needs to be adjusted to 2020 value**.** Cost measurement is based on macro-costing method with mainly collected from structured literature review**.** Evidence collected from literature review will be assessed for quality of evidence and generalizability issue**.** Cost data which have the better evidence quality and within the same context is selected first**.** Prioritized reference is based on local study**.** Study which difference context is used if no local study available**.**

H. Outcome parameters and outcome collection strategy

Outcome that used in this study is divided into short-term outcome and long-term outcome. Short-term outcomes are including sensitivity, specificity of the screening strategy, prostate cancer detection rate and probability of prostate cancer stage distribution. Long-term outcomes are including prostate cancer specific survival, survival probability of each stage, transitional probability between each stage and utility data for each stage.

The primary source of information is from the literature review gathering by systematic review approach**.** Meta-analysis and network meta-analysis will be used if the data from multiple study needed to be pooled together.

I. Modelling methodology, construction, and validation

Modeling is the simulation mathematical tool that helpful for answer the specific question rather than conduct the real-world study which may require long follow up, high amounts of expense and

workload and impossible to conduct at difference possible scenario**.** The population use in the model is the population intended to have PSA screening including Men that have age more than fifty years old and they should not have diagnosis with prostate cancer or prostate related disease at the time of screening**.** Source of data for cost and outcome parameter will mainly derive from literature search using systematic review method**.**

This study used decision tree and Markov's model show in figure 8 and figure 9 that applied based on MISCAN microsimulation model that was developed by cancer intervention and surveillance modelling network (CISNET) for prostate cancer screening evaluation**.** Discount rate is set at 3**%.** All cost and utility will be adjusted to 2020**.**

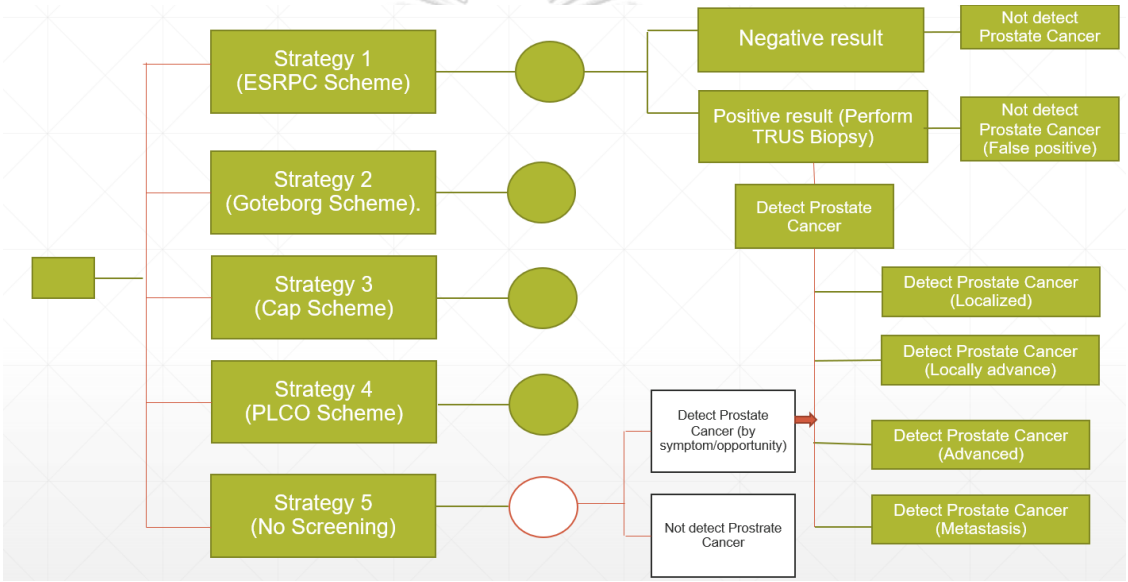


Figure 8: Decision Tree model

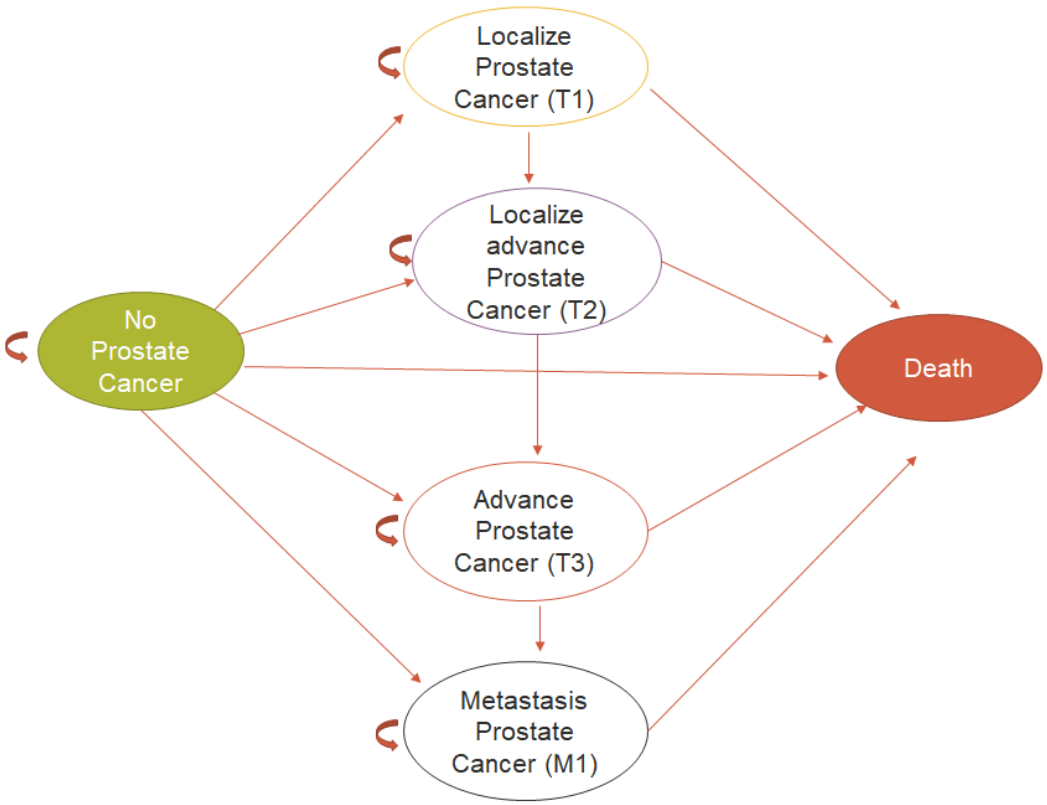


Figure 9: **Applied markov's model**

Validation process of the model is performed by consulting experts in the field of prostate cancer management including urologist and oncologist in Thailand.

J. Model Assumption

Key assumptions of the model are including first, we compared four prostate cancer screening strategies and no screening strategies. The key differences of each alternative are including cost of implementing each strategy, difference in prostate cancer diagnosis rate, difference in stage distribution and difference in prostate specific mortality. Second, we set the treatment assumption for each health state for use to calculate the cost. No prostate cancer staging will require the active surveillance in the arm that applied continuously prostate cancer screening program until set-point age. Localize prostate cancer (T1) will require the local prostatectomy that is gold standard surgical therapy for disease at this

stage. For locally advance disease (T2) will require the use of surgical therapy with combination of radiation therapy. Advance prostate cancer (T3) will require hormonal therapy including orchidectomy or hormonal medication. Metastasis prostate cancer (M1) will require chemotherapy and novel-agents such as abiraterone or enzalutamide. The probability of treatment choice for each state will also be take consideration in the model. Third, we combined the use of decision analysis model for step of screening consideration and Markov model for estimation the long-term effect of screening program.

K. Uncertainty Analysis

Uncertainty analysis included deterministic and probabilistic sensitivity analysis**.** Deterministic approaches are performed to check the robustness of the model by vary the cost of PSA screening, vary the cost of prostate cancer treatment, vary the incidence of prostate cancer and vary the mortality rate due to prostate cancer**.** Probabilistic sensitivity analysis is also performed to include range of multiple outcome range into the model**.** Simulation of value using Monte Carlo approach will be performed**.** This process was set to repeat around 10,000 times to gives us all the range and test the robustness of the model**.**

L. Budget impact analysis

Key population for the budget impact analysis is Men with age within the range of 50 to 70 years. Intervention uses is mass screening program of prostate cancer using PSA alone**.** Time horizon is set at around 5 years**.** Data source that use for the budget impact analysis model is come from explicit literature review including epidemiology data**.** The results of the scenarios **(**sets of assumptions and inputs and outcomes**)** analyzed will be described**.** These scenarios may consist of optimistic, pessimistic, and most likely input values determined from the uncertainty analysis of the key variables from the perspective of the decision maker**.** The results of all uncertainty analyses will be presented as a Tornado diagram**.**

The model used a Markov's framework with a 1-year cycle time. Patients may transition between six health states: No PC, PC stage 1, PC stage 2, PC stage 3, PC stage 4 (Metastasis) and death. Patients have a chance of progressing to death from any health state.

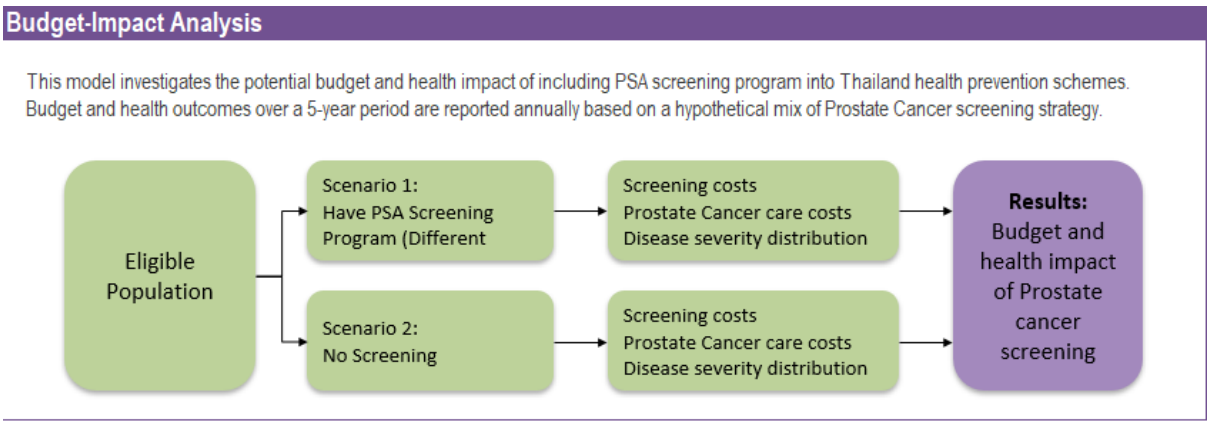


Fig 10: Budget Impact Model

Adapted from: Sullivan. Value in Health.2014. [41]

M. Population used in budget impact analysis

Table 2 below shown the population that will be used in the budget impact model. We considered the person for simulate the data starting from 100,000 populations. The incidence of individual diagnosed with prostate cancer among the population age 50-70 year is 7 people per 100,000 populations (15), the use of screening scheme will increase the incidence of prostate cancer diagnosis to 19 people per 100,000 populations (According to risk ratio for ESRPC scheme from network meta-analysis).

Table 2: Population Model

Parameters	Value
Total number of persons in the population of the health plan (Population Age over than 50 -70 Years)	100,000
Number of individuals diagnosed with prostate cancer	0.0072 * 100,000 = 7
Number of individuals diagnosed with prostate cancer (With Screening Scheme)	0.0188 * 100,000 = 19

Figure 11 below shown the distribution of prostate cancer staging. In the scenario of no screening people, large number of populations will be confined in advance and metastasis stage (67.7% and 23.7%

respectively, data from Thai Prostate cancer registry [15]). In contrast with the scenario with screening program, more patients will be found out in localized and localized advance stage (50% and 37% respectively, data from ESRPC study). [29]

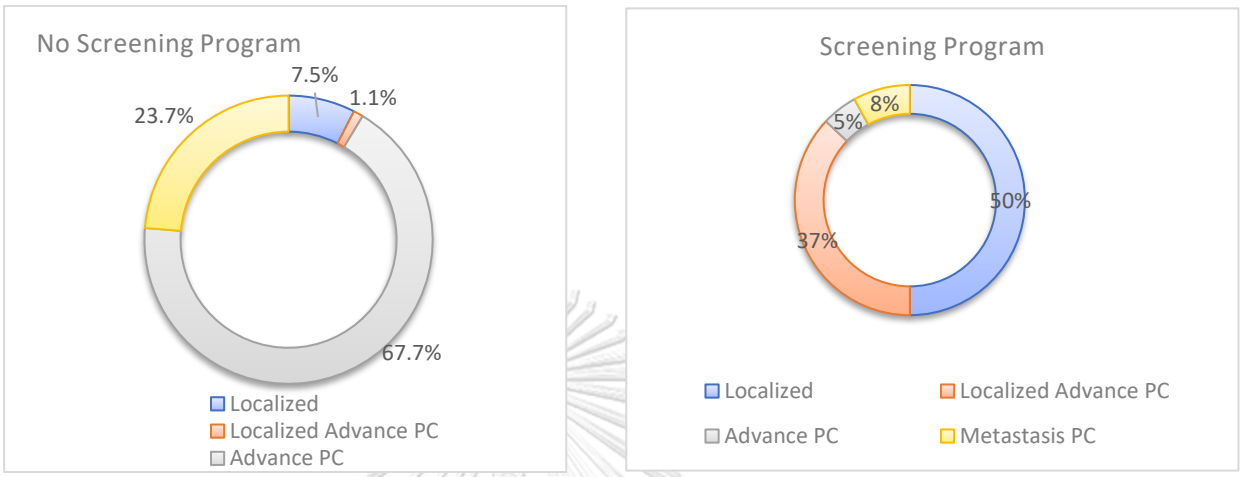
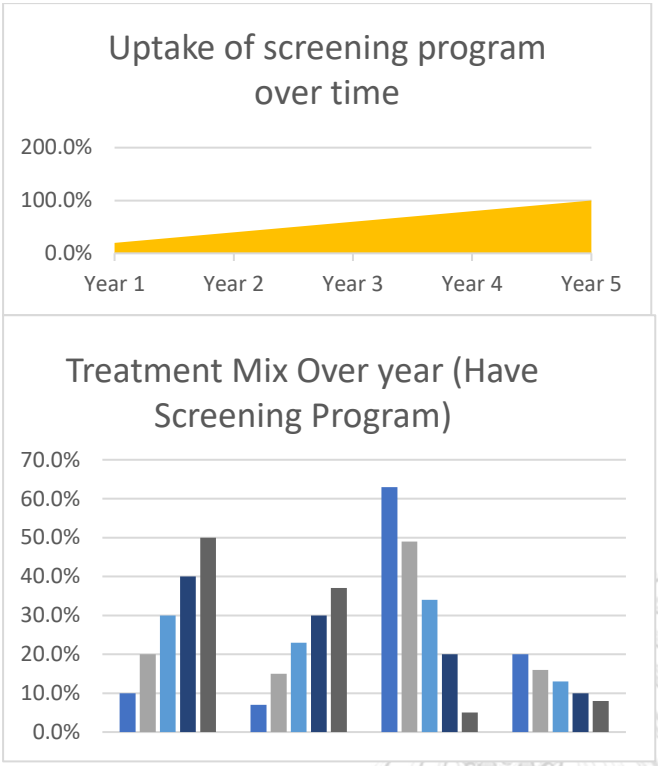


Figure 11: Distribution by each stage

As the result of the uptake of screening program for 5 year as shown in figure 12, we use the uptake rate as absolutely addition of 20% per year assumed by hypothesis (As the uptake rate from various country from published literature are varied from 10-50%) [49] , once the improving of screening program uptake, the treatment mixed will change from majority in advance and metastasis disease to localize and localize advance disease.



Figures 12: Treatment Mix

N. Data Analysis Plan

After performing systematic review, meta-analysis and network meta-analysis, result presentation in term of pooled comparison of effectiveness among each alternative will be reported. Other component of the model including cost, probability, effectiveness data and utility data are shown and transferred to use in pharmacoeconomic model.

After performing pharmacoeconomic evaluation, result presentation is shown in the term of Incremental cost effectiveness ratio including cost per additional case of prostate cancer diagnosis, cost per LYG, cost per QALY**.** We used the threshold at 150,000 THB /QALY to consider the cost-effectiveness of screening strategy and calculated the net monetary benefit for applying the screening program**.**

Chapter 4: Result

A. Systematic Review and Meta-Analysis

a. Study Search result

After we searched the databases using the prespecify keywords, we found 714 records identified from database searching after applying the selection criteria, we primarily identify 7 records that have been qualified for full eligibility check. The flowchart of searching strategy is shown in figure 13, four large randomized controlled trial were selected for data extraction after full eligibility check. Brief characteristic of selected study is shown in table 3.

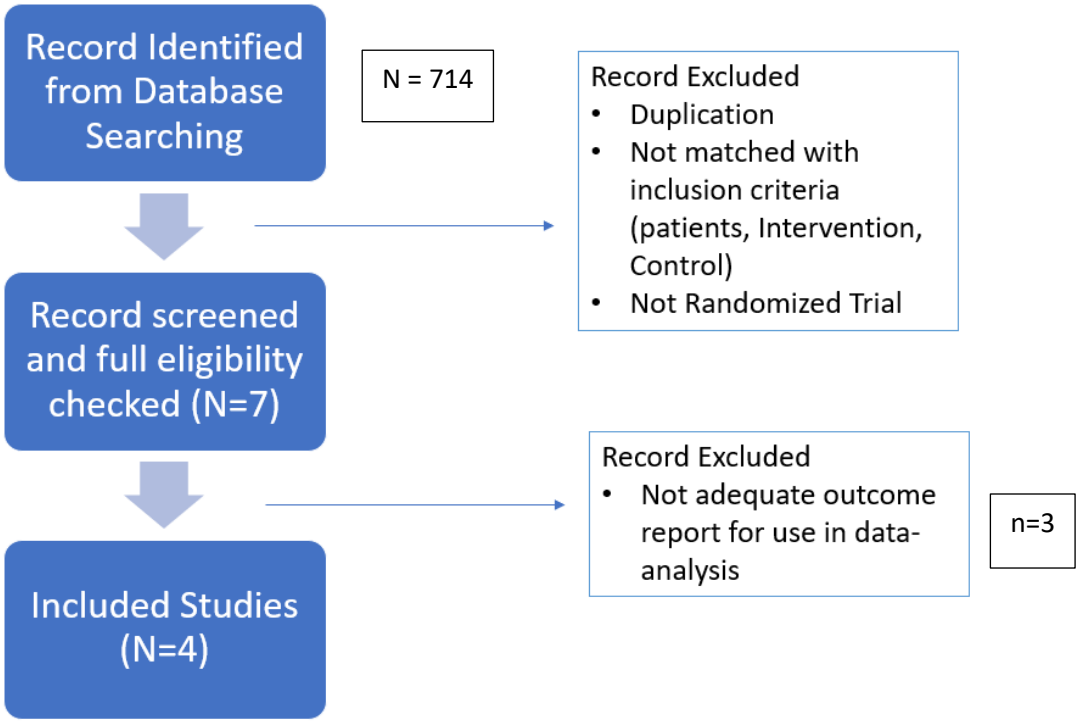


Figure 13: Study search flowchart according to PRISMA Diagram

Table 3: Included studies for meta-analysis.

Enroll ID	Study name	Author	Year	Quality Assessment (Risk of Bias)
1	Mortality Results from a Randomized Prostate-Cancer Screening Trial (PLCO)	Gerald L.Andriole, Pinsky	2017	Low
2	Screening and Prostate-Cancer Mortality in a Randomized European Study (ESRPC)	Fritz H.Schroder	2014	Low
3	Mortality results from the Göteberg randomised population-based prostate-cancer screening trial (Goteborg)	Jonas Hugosson	2017	Low
4	Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial (CAP Study)	Richard Martin	2018	Low

b. Key Difference between each study

Each selected study used different prostate cancer screening strategy, population characteristic and outcome as shown in table 4. The result from classical meta-analysis suggest that prostate cancer screening strategy increase the rate of prostate cancer diagnosis, reduce prostate cancer related death but not shown the significant effect on non-specific death reduction. Classical meta-analysis shown high level of heterogeneity in all outcomes.

Table 4: Key difference in each study

Study Title	Age range (Years)	Number of populations	Frequency of PSA Screening	RR for PC Diagnosis (95%CI)	RR for PC related death (95%CI)
1.PLCO Study (US)	55-74	76,683	PSA Annually for 5 Years	1.22 (1.16-1.29)	1.04 (0.87-1.24)
2. ESRPC Study (Europe)	50-74	162,388	PSA screening for every 4 Years	1.57 (1.51-1.62)	0.83 (0.73-0.94)
3. Goteborg Study (Nordic country)	50-64	20,000	PSA screening for every 2 Years	1.51 (1.39-1.63)	0.65 (0.48-0.87)
4. CAP Study (UK)	50-69	419,582	One Time Screening	1.19 (1.14-1.25)	0.96 (0.85-1.08)

c. Result from Classical Meta-analysis

The result of classical meta-analysis that pooled the result from 4 clinical studies as shown in figure 14 and 15 suggested that prostate cancer screening significantly improve the prostate cancer diagnosis rate (RR 1.33: CI 1.17-1.51) and significantly reduce prostate cancer related death (RR 0.67: CI 0.51-0.86). However, the result of meta-analysis for both outcomes shown high number of heterogeneities as I^2 equal to 97.3% and 91.6%, respectively). This result suggest that we might not be able to use the pooled result of the outcome as the different pattern and outcome identified from each study and suggest the use of network meta-analysis.

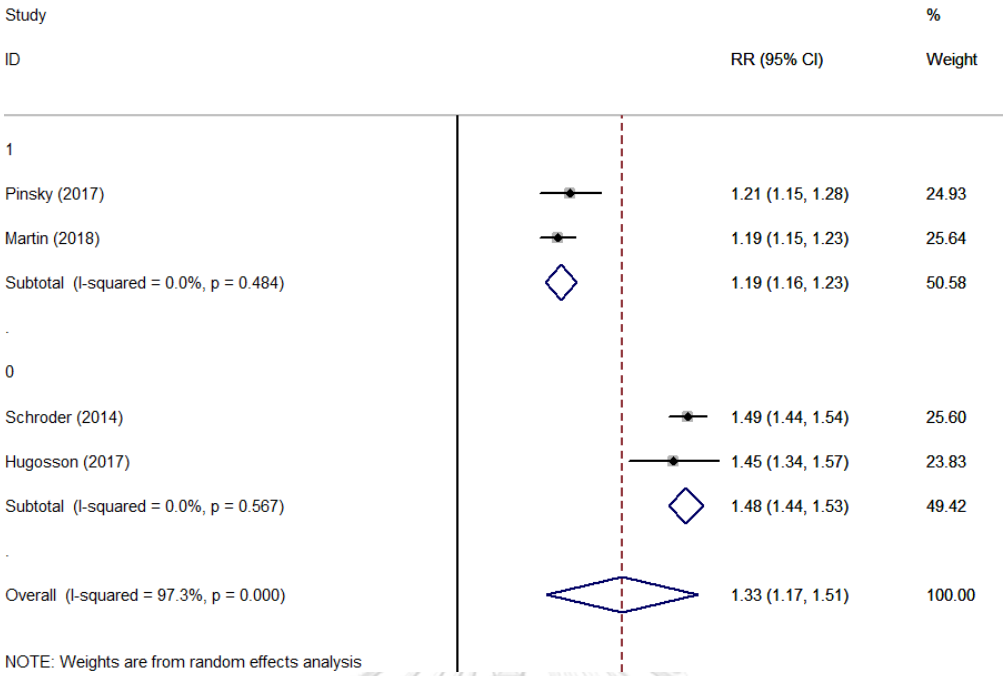


Figure 14: Forest plot shown the result of classical meta-analysis (Prostate cancer Diagnosis)

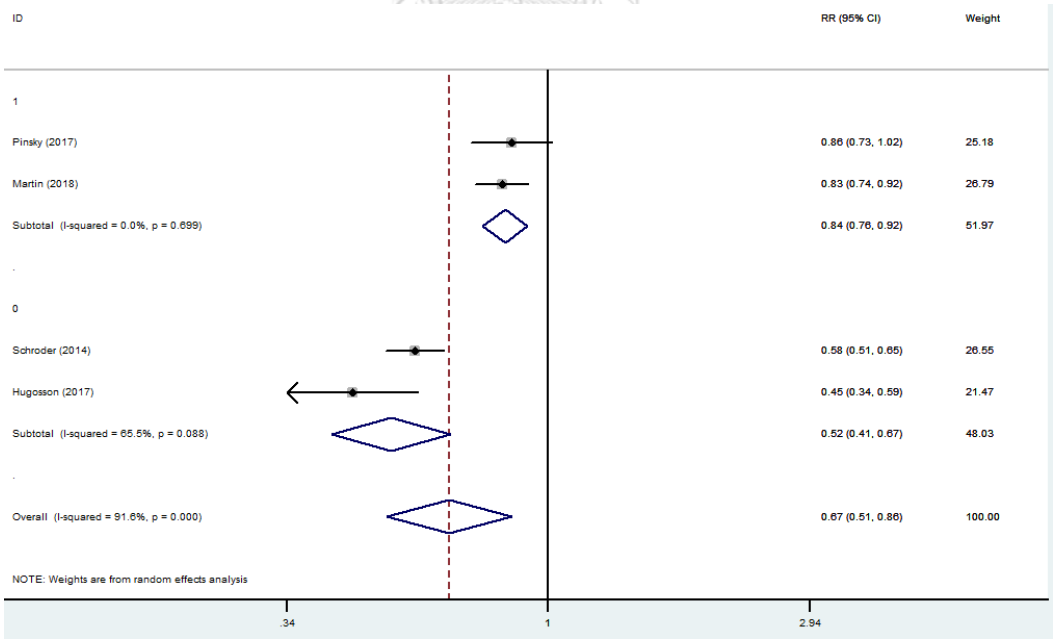


Figure 15: Forest plot shown the result of classical meta-analysis (Prostate cancer related death)

d. Result from Network Meta-Analysis

Prostate Cancer Diagnosis capability

From the result of network meta-analysis, As shown in figure 16, for prostate cancer diagnosis rate, all prostate cancer screening schemes are statistically increase prostate cancer diagnosis rate compared with no-screening. ESRPC scheme shown the highest odd ratio (OR 1.65; 95%CI 1.60-1.71) followed by Goteborg scheme (OR 1.52; 95%CI 1.40-1.66), PLCO scheme (OR 1.23; 95%CI 1.16-1.30) and CAP scheme (OR 1.20; 95%CI 1.16-1.24).

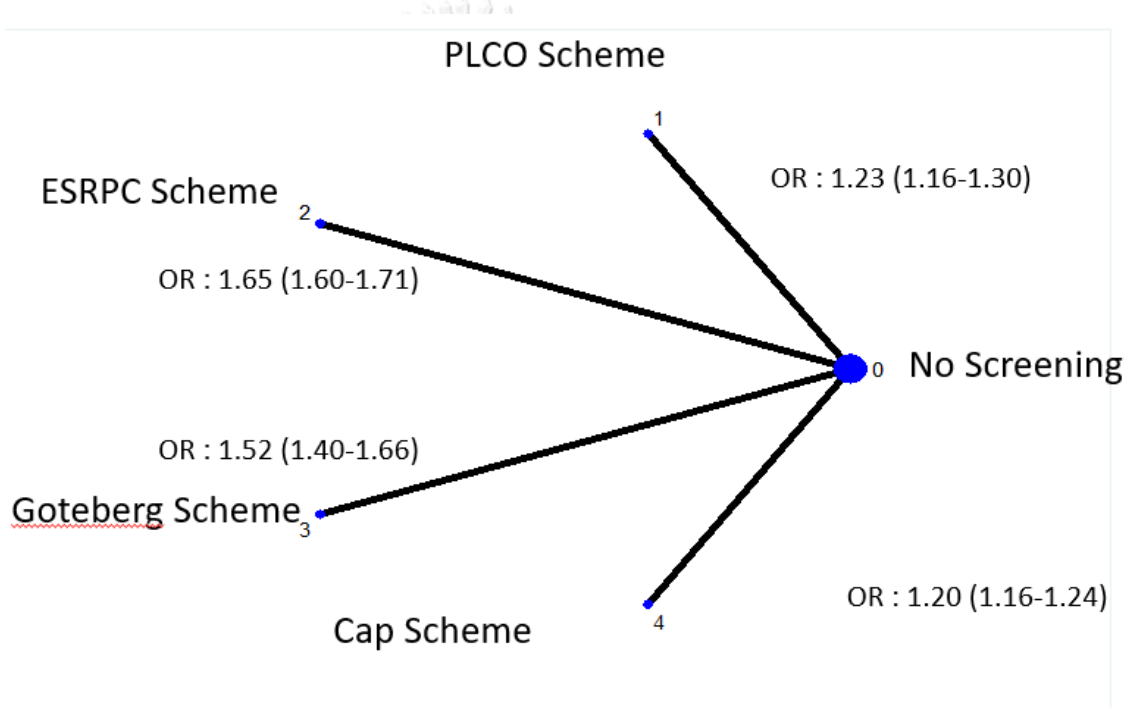


Figure 16: Network meta-analysis: Prostate cancer diagnosis

Prostate Cancer Related Death

For Prostate-Cancer related death, three schemes including Goteborg scheme, ESRPC scheme and Cap scheme show significantly reduce of prostate cancer related death compared with no screening. With the highest ratio show in Goteborg scheme (OR 0.41; CI 0.31-0.56) and ESRPC scheme (OR 0.55; CI 0.48-0.63). The result of this analysis is shown in figure 17.

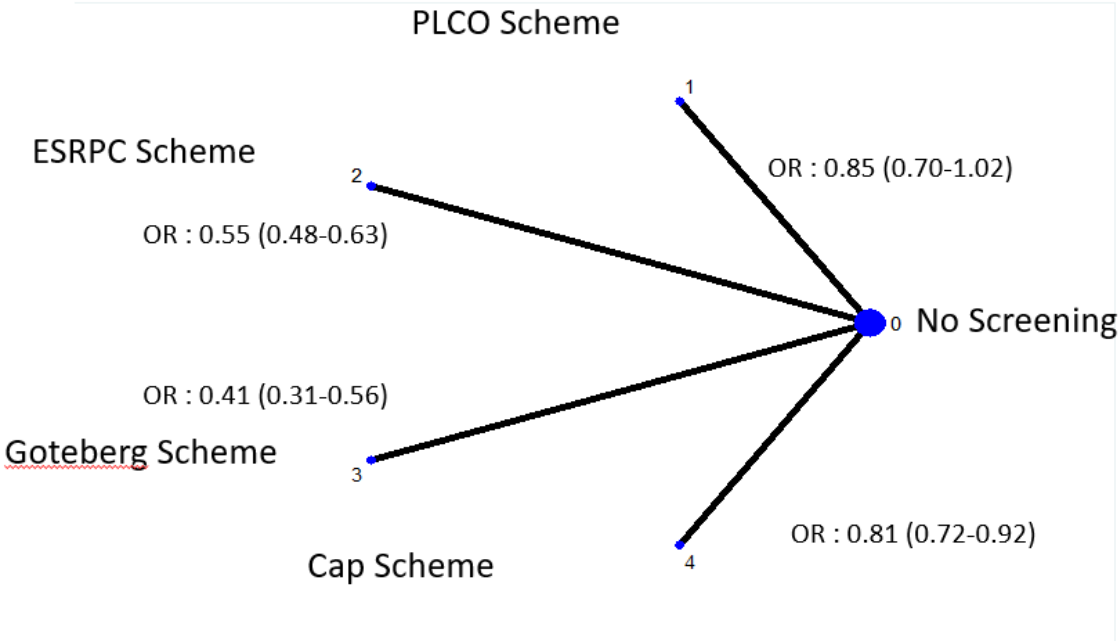


Figure 17: Network meta-analysis: Prostate cancer related death

B. Pharmacoeconomic Results

a. Cost and Outcome Data

The cost of the screening program and treatment is showed in Table 5, by using the value for each cost by the reference price of DMSC, we calculated the cost of each screening strategy and cost of each stage by calculating the annual cost regarding to assume treatment use in each stage. The result of cost calculation was shown in table 6.

Table 5: Cost

No	Description	Value	Reference
1	Cost for PC screening (PSA Screening)	300	Reference Price DMSC
2	Cost for PC diagnosis (TRUS guide biopsy)	1,000	Reference Price DMSC
3	Cost of surgical therapy	2,400	Reference Price DMSC
4	Cost of radiation therapy	12,000	Reference Price DMSC
5	Cost of hormonal therapy	5,000	Reference Price DMSC

6	Cost of surgical castration (Orchidectomy)	500	Reference Price DMSC
7	Cost of chemotherapy	60,000	Reference Price DMSC
8	Cost for Novel agent	100,000	Reference Price DMSC

Table 6:Screening Cost of each strategy and stage cost

Cost	Value	Detail
Stage Cost for Localized Disease	2,400	Cost for prostatectomy
Stage cost for Localized Advance Disease	12,000	Cost of radiation therapy
Stage Cost for Advance Disease	5,000	Cost of Hormone Therapy per
Stage Cost for Metastasis Disease	100,000	Cost of Novel/Chemo
Cost of Screening ESRPC	1,500	4 Years screening interval
Cost of Screening Goteborg	3,000	Every 2 years
Cost of Screening CAP	300	One Time Only
Cost of Screening PLCO	1,500	PSA Annually for 5 Years (± DRE Annually for 3 Years)

The key effectiveness data that will be used in the model synthesized from network meta-analysis for prostate cancer diagnosis rate and prostate specific death compared within each scheme is shown in Table 7. For prostate cancer related diagnosis, ESRPC scheme yield the most effectiveness (RR 1.65: 95% CI 1.60-1.71). For Prostate cancer specific death, Goteborg scheme yield the most effectiveness (HR 0.41: 95% CI 0.31-0.56).

Table 7: Effectiveness Data

Outcome Description	RR	95% CI	Sources
RR for PC Diagnosis (PLCO Scheme)	1.23	1.16-1.30	Network Meta-Analysis

RR for PC Diagnosis (ESRPC Scheme)	1.65	1.60-1.71	Network Meta-Analysis
RR for PC Diagnosis (Goteborg Scheme)	1.52	1.40-1.66	Network Meta-Analysis
RR for PC Diagnosis (CAP Scheme)	1.20	1.16-1.24	Network Meta-Analysis
HR for Prostate specific death (PLCO Schemes)	0.85	0.70-1.02	Network Meta-Analysis
HR for Prostate specific death (ESRPC Schemes)	0.55	0.48-0.63	Network Meta-Analysis
HR for Prostate specific death (Goteborg Schemes)	0.41	0.31-0.56	Network Meta-Analysis
HR for Prostate specific death (CAP Schemes)	0.81	0.72-0.92	Network Meta-Analysis

The utility data obtained from the publication for each prostate cancer staging is shown in Table 8. As the local data is unavailable, we used the data from the study of De Carvalho instead. In this study, utility is obtained from utility estimation technique and used in several cost-effectiveness model.

Table 8: Utility Data

No	Parameters	Base case value	Data Source
1	Utility for normal population (Without Prostate Cancer)	0.99	De Carvalho 2017
2	Utility after screening	0.95	De Carvalho 2017
3	Utility for False positive test	0.9	De Carvalho 2017
4	Utility for localized prostate cancer	0.8	De Carvalho 2017
5	Utility for locally advanced prostate cancer	0.75	De Carvalho 2017

6	Utility for advance prostate cancer	0.6	De Carvalho 2017
7	Utility for metastasis prostate cancer	0.4	De Carvalho 2017
8	Utility for Death	0	De Carvalho 2017

b. Pharmacoeconomic Evaluation

Cost effectiveness data of each strategy show in table 9 and figure 18 and 19, By using the threshold of 1X GDP of Thailand (around 150,000 THB), Only ESRPC and Goteborg scheme yield the cost-effectiveness result with ICUR equal to 97,349.42 THB and 95,553.49 THB, respectively.

Table 9: Cost and Effectiveness data of each screening strategies

Strategy	Discounted Total cost	Discounted Life years	Discounted QALYs
No Screening	94,201.28	12.74	11.00
PLCO	111,947.84	13.22	10.98
ESRPC	166,718.80	14.55	11.74
Goteborg	213,611.32	15.47	12.25
CAP	116,003.03	13.36	11.06

PLCO Strategy VS No Screening

ICER 1 (PLCO VS No Screening)	35946.44271
ICUR 1	243451.4985
ICER (Discounted) 1	**37562.84555**
ICUR (Discounted) 1	**-921730.647**

ESRPC Strategy VS No Screening

ICER 2 (ESRPC VS No Screening)	40083.18241
ICUR 2	86582.84152
ICER (Discounted) 2	**40138.10653**
ICUR (Discounted) 2	**97349.41966**

Goteborg Strategy VS No Screening

ICER 3 (Goteburg VS No Screening)	43910.43488
ICUR 3	89528.21644
ICER (Discounted) 3	**43716.08103**
ICUR (Discounted) 3	**95553.49205**

CAP Strategy VS No Screening

ICER 4 (CAP VS No Screening)	35076.6127
ICUR 4	139702.9978
ICER (Discounted) 4	**35403.00251**
ICUR (Discounted) 4	**334968.674**

Figure 18: Incremental data of 4 treatment strategies

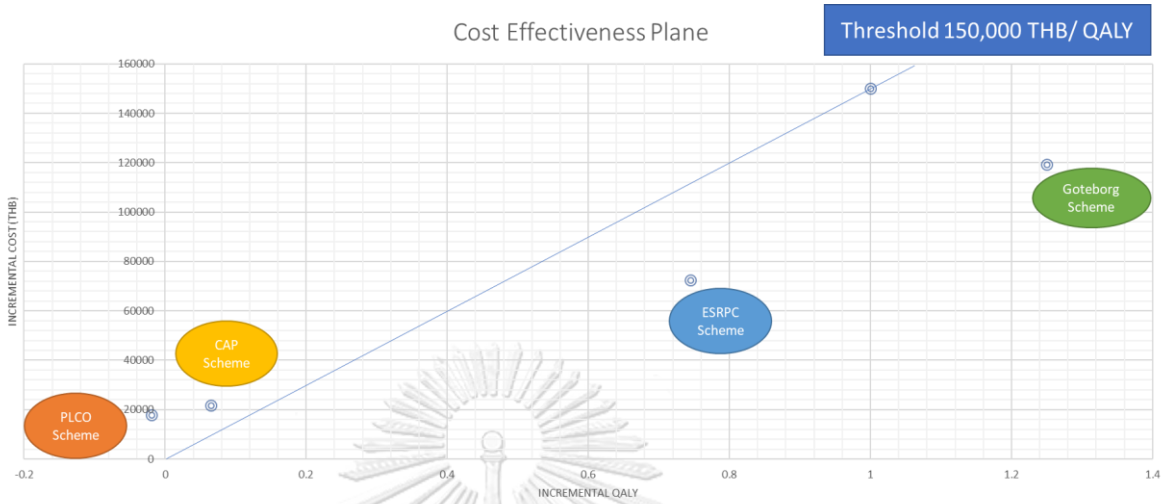


Figure 19: Cost Effectiveness Plane

c. **Sensitivity Analysis**

The result from sensitivity analysis suggested the robustness of the result of the model as shown in figure 20. Factors that have strongest effect on the result is the stage cost of the metastasis stage, Tornado diagram is shown in figure 21.

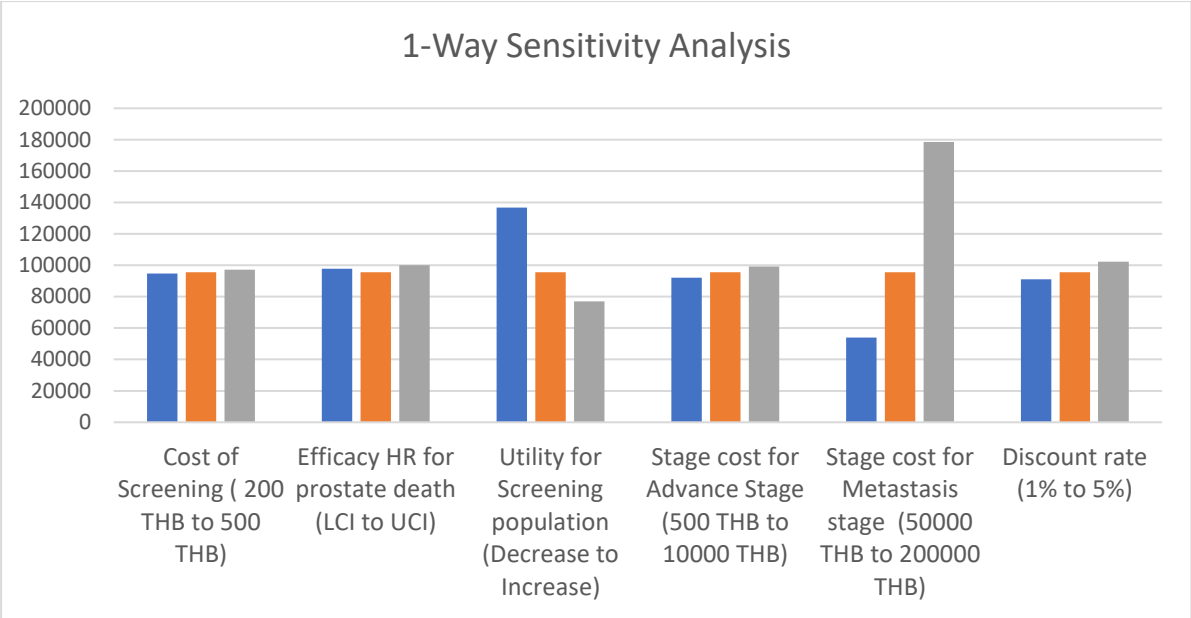


Figure 20: 1 Way Sensitivity Analysis

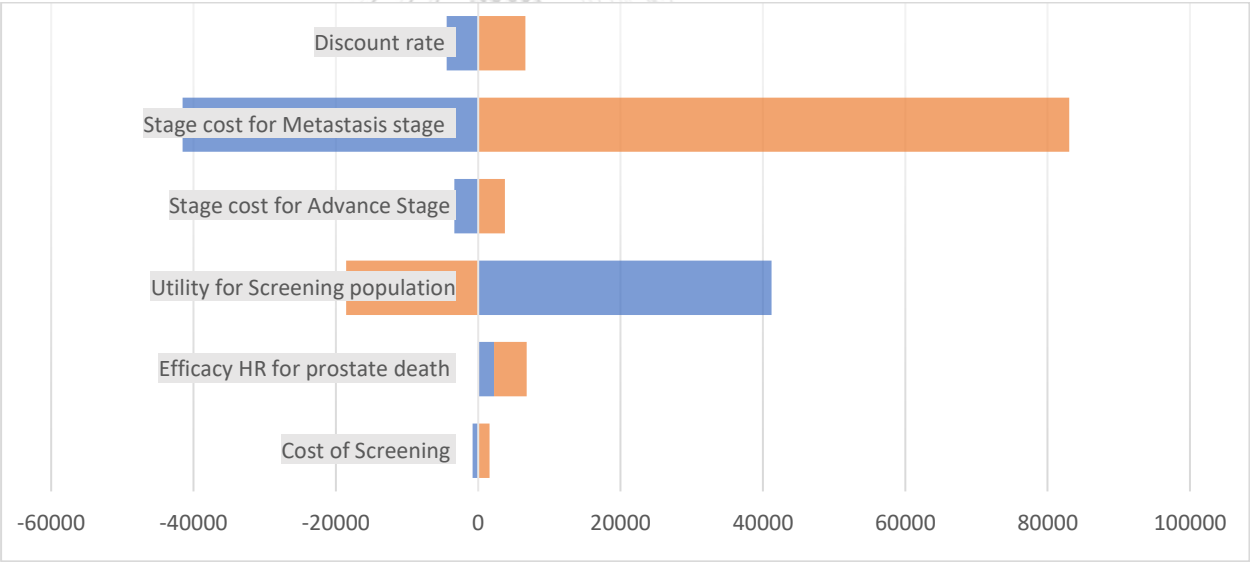


Figure 21: Tornado Diagram

C. Budget Impact Analysis

According to the result from cost-effectiveness analysis, we selected ESRPC scheme for assessing budget impact. As the ESRPC and Goteborg is proved to be cost effectiveness, however, the data from

ESRPC came from larger evidence compared with Goteborg schemes therefore considered as more credible data.

The budget impact result for five years is presented in figure 22 below. For applying prostate cancer screening strategy, total budget impact for policy maker are 30 million, 60 million, 90 million, 120 million and 150 million THB and total budget impact per patient estimated for 5 years are 303, 602, 902, 1,201 and 1,501 THB, respectively. (Please see detail in Table 10)

Scenario 1: Screening Strategy	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Screening Cost	15M	30M	60M	90M	120 M	150 M
Treatment Cost : PC Stage 1	3,384.00	4,512.00	9,024.00	13,536.00	18,048.00	22,560.00
Treatment Cost : PC Stage 2	2,481.60	15,792.00	33,840.00	51,888.00	67,680.00	83,472.00
Treatment Cost : PC Stage 3	63,638.00	59,220.00	46,060.00	31,960.00	18,800.00	4,700.00
Treatment Cost : PC Stage 4	445,560.00	376,000.00	300,800.00	244,400.00	188,000.00	150,400.00
Total costs	**15.515 M**	**30.455 M**	**60.390 M**	**90.342 M**	**120.292 M**	**150.261 M**
	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario 2: No screening Strategy						
Screening Cost	-	-	-	-	-	-
Treatment Cost : PC Stage 1	1,296.00	1,296.00	1,296.00	1,296.00	1,296.00	1,296.00
Treatment Cost : PC Stage 2	950.40	950.40	950.40	950.40	950.40	950.40
Treatment Cost : PC Stage 3	24,372.00	24,372.00	24,372.00	24,372.00	24,372.00	24,372.00
Treatment Cost : PC Stage 4	170,640.00	170,640.00	170,640.00	170,640.00	170,640.00	170,640.00
Total costs	**197,258.4**	**197,258.4**	**197,258.4**	**197,258.40**	**197,258.4**	**197,258.4**

Budget impact	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	15 M	30 M	60 M	90 M	120 M	150 M
PC care budget impact	317,805.2	258,265.6	192,465.6	144,525.60	95,269.60	63,873.60
Total budget impact	**15.318 M**	**30.258 M**	**60. 192 M**	**90.144 M**	**120.095 M**	**150.064 M**

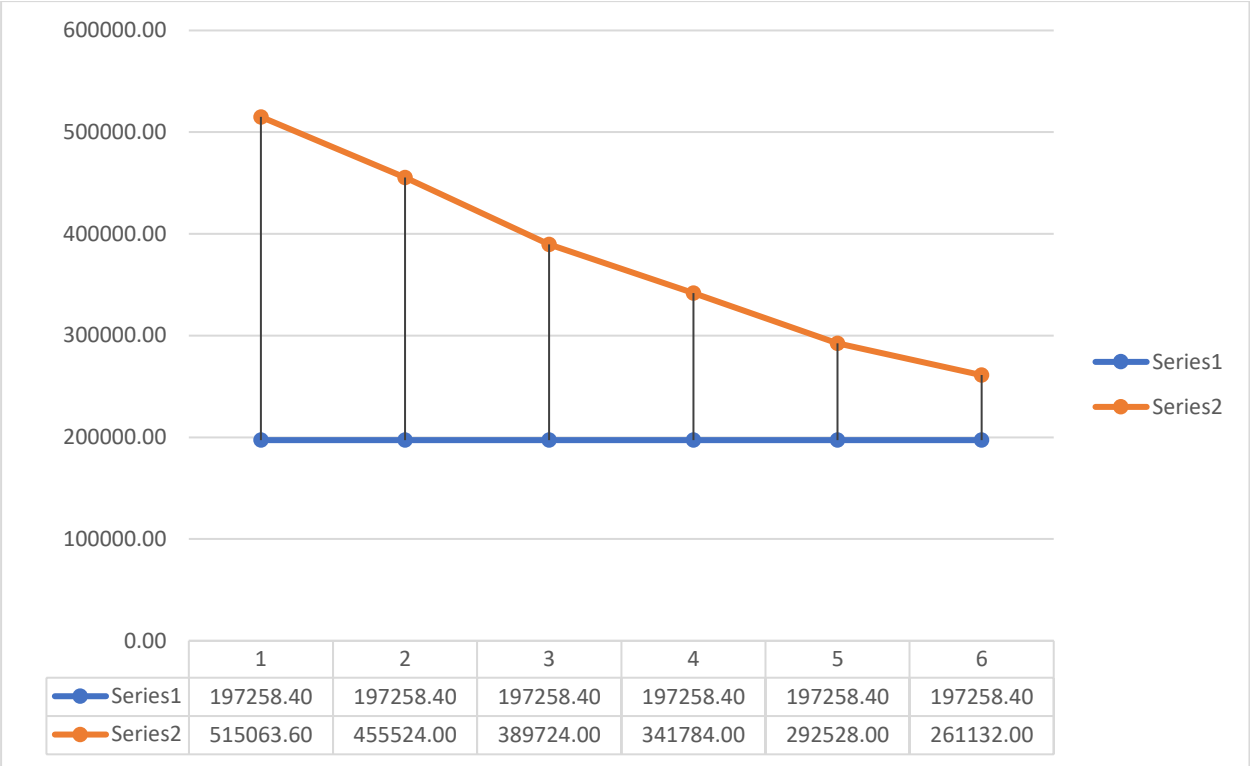
*M for Million, Unit is Thai Baht

Figure 22: Budget Impact Result

Table 10: Budget Impact

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5
Pharmacy budget impact per patients	300.00	600.00	900.00	1,200.00	1,500.00
PC care budget impact per patients	2.58	1.92	1.45	0.95	0.64
Total budget impact per patients	302.58	601.92	901.45	1,200.95	1,500.64

From the figure 23 below, the cost of prostate cancer screening will be higher in the early year due to the cost of screening. However, the cost of prostate cancer care can be decreased by the change of cancer treatment staging distribution followed by the effect of screening strategy.



	1	2	3	4	5	6
Series1	197258.40	197258.40	197258.40	197258.40	197258.40	197258.40
Series2	515063.60	455524.00	389724.00	341784.00	292528.00	261132.00

Figure 23: Comparison of treatment cost for screening strategies

Chapter 5: Discussion and Conclusion

A. Key Findings

Prostate cancer screening strategy can increase the rate of cancer diagnosis and three schemes show the benefit for reduction of prostate cancer related death. For the implementation perspective based on the best outcome, ESRPC and Goteborg schemes seem to be the best screening strategy.

Difference schemes of prostate cancer screening shown difference outcome. The factors that might show most important for treatment outcome is the frequency of the screening method. While ESRPC and Goteborg scheme which shown better outcome of screening utilized screening strategies every 2-4 years until cut-off age. In contrast, PLCO scheme which only do screening for five-year duration and CAP scheme which only do screening as one-time only shown inferior outcome compared with ESRPC and Goteborg scheme.

The result from pharmacoeconomic analysis suggest that the used of ESRPC scheme and Goteborg scheme with the most intensive frequency of screening program improve quality adjusted life years and resulted as cost-effectiveness options compared with the Thailand's Threshold.

The implementation of prostate cancer screening program will affect the total budget impact. Calculating for five-year time frame, total budget impact for policy maker are 30 million, 60 million, 90 million, 120 million and 150 million THB and total budget impact per patient are 302.58, 601.92, 901.45,1200.95 and 1500.64 THB respectively. The addition of the budget is mainly contributed by the screening cost and percentage of program uptake. However, the total cost budget cancer care can be decreased from the benefit of prostate cancer staging redistribution due to prostate cancer screening program.

As the prostate cancer screening program will change the stage distribution of prostate cancer. With the implementation of prostate cancer screening program, more percentage of patients will be diagnosis as early stage including localized disease or locally advance disease. In contrast with to no screening strategy, more percentage of patients will be diagnosis mainly at advance stage or metastasis stage which require

different treatment strategy and will affect higher cost of management. This should be weighted between the increasing of budget impact due to implementation of screening program with the reduction of budget impact due to the management of disease in later stage.

Our health economic result and budget impact analysis is consistent with the previous analysis in multiple countries including England, Canada, United State. Key consideration factor is the difference in effectiveness of each strategy, as the scheme with low intensity of cancer screening show the low effectiveness data and result in dominated cost-effectiveness profile.

B. **Conclusion and Implementation**

The strength of our study is we use the local data in term of cost and for the effectiveness data, we use the result from network meta-analysis which considering the comparison of difference prostate cancer screening scheme. The limitation of our study including the lack of some local study including the utility data and local effectiveness of screening program which might affect the generalizability issue of the result. Key limitation of our study is including the nature of difference of the outcome from conflicting evidence of the published study. Other limitation that we have are only limited options to do the analysis and lacking head to head study between each screening strategy to use as the direct evidence.

The Model that we use in this study is the simplify model and the calculation of cost is base on top-grossing method. The recent evidence might include more complex model of prostate cancer management and the local data generation will be very crucial to make the model have more validity and generalizability. The trend of using budget impact analysis as the key essential part of health technology assessment is uprising. As budget impact will let the decision maker to know whether what is cost if we implement the program compare with the outcome that can be yielded.

According to the systematic review and network meta-analysis, our result suggests that ESRPC Schemes shown best result for increase prostate cancer diagnosis rate (increase chance of prostate cancer diagnosis by 65%) and Goteborg schemes shown most favorable result in

reduce prostate cancer related death (reduce risk of prostate cancer death by 59%).

In conclusion, our result suggesting that when comparing with no screening option, the implementation of ESRPC Scheme and Goteborg scheme is Cost Effectiveness strategy options as ICUR is Within threshold of Thai acceptance threshold (as 1X-GDP:Around 150,000-200,000 THB).In addition, our study suggests the implementation of prostate cancer screening in Thailand. As it might result in little increase the budget impact in early phase of implementation, However, in the longer phase of implementation, it will improve the effectiveness of prostate cancer management in Thailand and may reduce the overall budget impact of the treatment in long-term consideration.

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