PHARMACEUTICAL CARE FOR PULMONARY TUBERCULOSIS TREATMENT IN THAILAND

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ABSTRACT

OBJECTIVES

Three objectives were to compare: 1) treatment success; 2) healthcare resource uses; and 3) out-of-pocket (OOP) expenditures, indirect costs, and health-related quality of life (HRQoL) associated with pharmaceutical care, home visit, and modified DOT in three referral hospitals in Songkhla province, Thailand.

METHODS

Project 1&2 were retrospective cohort study collecting data from 1,398 pulmonary TB patients who started treatment between October 2010 and September 2013. Project 3 was a prospective study collecting data from 104 pulmonary TB patients who started treatment between January and May 2014. The propensity score matching and generalized linear models (GLMs) were used to compare the outcomes associated with three supervision approaches by adjusting for baseline characteristics.

RESULTS

Project1: The differences in treatment success rate were not statistically significant when comparing pharmaceutical care with either home visit (success rate: 92.76% versus 94.74%) or modified DOT (success rate 93.37% for both).

Project2: The mean direct healthcare costs to public payer were $519.96 (95% confidence interval (CI): $437.31 to $625.58) for pharmaceutical care,

$1,020.39 (CI:$911.13 to $1,154.11) for home visit, and $887.79 (CI:$824.28 to $955.91) for modified DOT.

Project3: Mean OOP expenditures were $907.56 (CI:$603.80 to $1,269.41), $148.47 (CI:$109.49 to $194.89), and $95.35 (CI:$69.11 to $129.63), while the indirect costs were $1,925.68 (CI:$922.06 to $3,284.94), $2,393.66 (CI:$1,435.01 to $3,501.98), and $833.33 (CI:$453.87 to $1,263.45), for those receiving pharmaceutical care, home visit, and SAT, respectively. Mean health utility scores at the baseline and the end of treatment were 0.679 and 0.830, 0.713 and 0.905, and 0.708 and 0.913 for the patients receiving pharmaceutical care, home visit, and SAT, respectively.

CONCLUSION

Pharmaceutical care is clinically and economically effective compared with the other strategies studied. A large-scale prospective study is warranted to strengthen evidence to support policy making in TB management in Thailand.

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LIST OF ABBREVIATIONS

ADRs	adverse drug reactions
CSMBS	the civil servant medical benefits scheme
DOT	directly observed therapy
DS-TB	drug susceptible TB
E	ethambutol
EPTB	extra-pulmonary tuberculosis
EQ-5D-3L	EuroQol five-dimensional three-level questionnaire
EQA	external quality assurance
GLMs	generalized linear models
H	isoniazid
HRQoL	health-related quality of life
HIV	human immunodeficiency virus
LCU	local currency unit
MDR-TB	multidrug-resistance tuberculosis
NEDs	non-essential drugs
OOP	out-of-pockets
PPP	purchasing power parity
PTB	pulmonary tuberculosis
QALYs	quality-adjusted life years
R	rifampin
S	streptomycin

SAT	self-administered therapy
SSS	the social security scheme
TB	tuberculosis
UC	the universal coverage
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis
Z	pyrazinamide

PREFACE

This thesis combines three consecutive works that have been prepared for publication in peer-reviewed journals. Two of the papers have been accepted for publication while the other has been submitted for publication and currently under revision. The contributions of Pimwara Tanvejsilp to all three papers within this thesis include: developing the research questions, conception and design of study, performing the data collection, analyses, interpreting the results, writing the manuscripts, submitting the manuscripts for publication and responding to reviewer comments.

CHAPTER 1:

PULMONARY TUBERCULOSIS AND SUPERVISION STRATEGIES FOR ENHANCING ADHERENCE TO PULMONARY TUBERCULOSIS TREATMENT IN THAILAND

1.1 TUBERCULOSIS BURDEN

Tuberculosis (TB) is an infectious disease caused by bacteria called *Mycobacterium tuberculosis*. Although this disease may affect many sites in the body, the lung is the most common site of infection. Pulmonary TB is an airborne transmitted disease. A cough or sneeze from an active pulmonary TB patient releases the bacteria into the air to be inhaled by non-infected persons [(1)]. Although TB deaths rate has reduced by 47% between 1990 and 2015 [(1)], TB is still one of the top ten causes of death worldwide [(2)]. In 2015, there were approximately 10.4 million new cases of TB and 1.4 million TB related deaths [(2)]. TB causes pain and psychological suffering, and consequently results in a reduction in physical activities and health-related quality of life (HRQoL) of patients [(3,4)]. Furthermore, in some societies, TB patients may suffer from discrimination, loss employment, or depression [(5)].

1.2 TREATMENT AND DISEASE CONTROL

The most appropriate control strategy is to provide effective treatment especially for

pulmonary TB which is airborne transmitted. According to WHO treatment guideline [6], first-line anti-TB medications include isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), and streptomycin (S). The standard treatment regimen for drug-susceptible pulmonary TB is a daily of four first-line antibiotics for at least *six* months (2HRZE/4HR) divided into two treatment phases: intensive phase (2-month) and a continuous phase (4-month). Re-treatment patients are treated with an 8-month regimen (2HRZES/1HRZE/5HRE).

Poor adherence to TB treatment is common due to long treatment duration, a large number of medications prescribed, and the risk of adverse drug reactions (ADRs) [7]. Poor adherence could increase the risk of treatment failure, relapse, mortality, chance of TB transmission, and drug resistance, and also result in increased health resource utilization and prolonged treatment duration [8-10]. The resistant strains of *Mycobacterium tuberculosis* contributed to multidrug-resistance TB (MDR-TB) where the TB is resistant to at least both isoniazid and rifampicin [11]. Patients with MDR-TB are more complicated because they require longer treatment period (at least 20-month) with complex combinations of second-line agents, including injectable medications [12]. In addition, these regimens are more expensive and may be associated with higher risk of ADRs compared with the first-line agents [13]. As a result, patients' adherence to TB treatment regimen is necessary for effective TB treatment, the prevention of drug resistance, and the protection of the TB transmission to the public [6].

1.3 ADHERENCE AND TB TREATMENT SUCCESS

According to a model developed by Karumbi et al [14], strategies designed to enhance patients' adherence and result in TB treatment success could be implemented in two different approaches. First is to deal with individual barriers (e.g. family encouragement, social support, patient education, physical accessibility support, treatment supervision, reminders). Second is to provide supportive health care system (e.g. sufficient health care staff, convenient location, well organized system). In addition to those strategies, several factors are associated with adherence and affect TB treatment outcome. These factors were divided into four categories:

1. **Individual demographics.** Personal factors such as age[15] , gender[16] , socioeconomic[23-16] , residence[15] , distance to healthcare facilities [24,25], could influence patients' adherence to TB treatment. These factors are risk factors for poor treatment outcomes as well. Older age is a significant factor associated with unsuccessful treatment [26,27]. A number of studies found that females are associated with better treatment success [27-33]. Difficulty in access to TB center also resulted in higher default rate [15].
2. **Co-existing conditions:** Patients with co-morbidities use multiple medications. This factor contributed to lower adherence [34]. Diabetes status is a risk factor for poor treatment outcomes and relapse [35,36]. TB treatment outcome in HIV-positive patients was poorer than those with HIV-negative [37].
3. **Proxy for TB severity:** Disease severity at baseline determines patients' adherence to TB treatment [15,21]. Clinical characteristics such as chest radiography

[38-40], history of previous TB treatment [26,38-40], and drug- resistance [26,35,38-40] are risk factors for poor treatment outcomes. The default rate was higher in patients who were re-treatment, and in those with abnormal chest radiography [21].

4. **Complications in TB treatment:** Medication adverse effects are associated with non-adherence in TB patients. Undesirable adverse events resulted in stopped medication use [41,42] and unsuccessful treatment [15,43]. Hospitalization was also related to poor treatment outcomes [44,45]. In 2011, the proportion of treatment success in MDR-TB patients was 48% worldwide [37].

Conceptual framework described factors influencing adherence and TB treatment success is shown in Figure 1

1.5 STRATEGIES FOR ENHANCING ADHERENCE FOR PULMONARY TB TREATMENT

According to the WHO TB treatment guideline [6], supervised treatment is the process for helping patients adhere to their TB medications, completing their TB treatments, ensuring that the patients receive proper care, and detecting treatment interruption. Directly observed therapy (DOT) is a WHO recommended strategy of supervision. This strategy requires an observer to observe and record when patients take the medications. In addition to the supervision of medications intake service, the continuous communication between the patient and the observer also enhances compliance to TB treatment by improving patient education, resolving any obstacles to treatment, and allowing for early detection and management of ADRs [6].

The method of supervision should be implemented as a patient-centered approach [6]. Although DOT has been a WHO recommended strategy to promote adherence for pulmonary TB patients, there are barriers to the implementation of DOT in resource-constrained countries. In Thailand, these barriers included limited health care personnel, resource constraints, and cost of transportation borne by patients [46]. A study in Pakistan showed that DOT costs twice as much as self-administered therapy (SAT) [47]. A recent systematic review compared treatment outcomes between DOT and SAT [14]. According to the six RCTs identified, the review concluded that supervision of drug intake alone may not improve adherence to TB treatment. Other supportive strategies tailored to each specific context should be considered for supplementing a DOT program [14,48,49]. A systematic review evaluating the effectiveness of strategies to promote adherence to pulmonary TB treatment found that a few modified DOT (the combination of DOT and other interventions) may improve adherence to TB treatment [50]. An example of these strategies was one study demonstrated that a case management strategy of patient education, DOT for the first two months, and weekly home visit increased treatment success in new TB patients [51]. Pharmaceutical care, where clinical pharmacists provide patient education to improve patient's knowledge associated with the disease and medication use and address patient's drug-related problems, is another potential supervision approach to enhance adherence to TB treatment [34,52].

1.6 TB FINANCING

Sources of funding for TB control in resource-constrained countries are divided into two

major types: domestic funding and international donor funding. Domestic funding refers to the funding from national and local governments and is the main source of funding for national TB control. International donor funding is mainly from the global fund. The external funding is often supplementary and rarely covers main TB control activities [1,53]. According to the self-reporting of 123 countries globally, the funding available in 2015 for TB prevention, diagnosis and treatment was US$ 6.6 billion. Eighty-seven percent (US$ 5.8 billions) of this fund was from domestic sources, while international donor funding was US$ 0.8 billion [12]. In most WHO high burden TB countries, the estimated cost per patient ranged from US$100 − US$500 for drug-susceptible TB and to US$5,000 − US$10,000 for those with MDR-TB [12].

Direct health care costs to public healthcare payers start before TB diagnosis. People with TB related symptoms undertake the initial clinical consultation, non-TB specific medications and other diagnostic tests [54,55]. In the TB diagnostic process, patients may require multiple visits to complete the diagnostic tests and meet health care professionals [56,57]. There are also other relevant costs such as treatment of ADRs, hospitalization, nutrition and others incurred before and during TB treatment.

Other than the burden on the public healthcare system, TB also imposes a significant impact on patients and their families [5]. Before TB is diagnosed by a public healthcare provider, people with TB related symptoms may pay to seek care in a private healthcare unit. During TB diagnosis and treatment, patients also pay out-of-pockets (OOP)

expenses, especially for food, transportation, and accommodation when receiving care at the hospital [5].

The productivity loss due to the disease (i.e., on average three to four months work time loss) has become the main driver of indirect costs [5]. Furthermore, the premature death related to TB illness results in approximately 15 years of additional income loss [5]. A systematic literature review on the financial burden of TB, borne by patients and their families in low- and middle-income countries indicated that the total costs were composed of three parts: 20% direct medical costs, 20% direct non-medical costs, and 60% indirect costs. They also reported that, on average, 50% of the total cost incurred during illness onset to TB diagnosis [58]. The total costs associated with TB borne by the patients accounted for 39% of annual household income [58]. One of the financial risk protection plans in WHO TB strategy (2016 - 2035) is to push forward the provision of TB diagnosis and treatment, free of charge, through universal health coverage [12,58,59].

1.7 TB IN THAILAND

Thailand is one of the 30 WHO high burden countries for TB, TB/HIV and MDR-TB with nearly 117,000 new TB patients, and 13,800 TB related deaths in 2015 (8,400 deaths were HIV negative TB cases and 5,400 cases were deaths among HIV positive TB cases) [2]. In 2015, the domestic funding for the Thai National TB program exceeded the

contributions from international donors, with only 10% of the budget funded internationally [2].

Thai nationals are covered under one of the three public insurance schemes: the universal coverage (UC) which was established in 2002, the civil servant medical benefits scheme (CSMBS), and the social security scheme (SSS), all funded through general tax revenues [60]. The CSMBS covers government employees, pensioners and their dependents in which insured persons can access, free of charge, to medical services at all government hospitals. The SSS is for private employees who can freely access medical services at a contracted hospital. Every Thai citizen not covered under the CSMBS or the SSS is covered by the UC but need to pay all medical costs out of pocket if they seek health care services outside their primary resident area. As of 2015, 75% of the Thai population are covered under the UC [2]. The national TB program adopts the daily dose regimen whereby most drug-susceptible patients take the TB medications themselves at home and visit a health center or a district hospital at least once a month for medication refill. Patients with MDR-TB visit the nearest health center every day for treatment.

In Thailand, resources for DOT, including the availability of healthcare personnel, are limited. Furthermore, OOP costs for receiving DOT (e.g. transportation) impose a burden on patients [46]. Therefore, it is not feasible to implement DOT nationwide. Several different strategies are currently adopted for enhancing adherence to TB treatment in referral

hospitals in southern Thailand. The description of each of these TB treatment adherence enhancement strategies is shown in Table 1.

1. **Pharmaceutical care:** A university hospital enhances adherence to TB treatment through providing timely clinical pharmacist-led patient education, monitoring and management of ADRs, identifying other drug-related problems, and an evaluation of treatment adherence. At the first visit, the clinical pharmacist provides a mobile phone number and encourages patients to contact them anytime if they need any consultation on the TB treatment. Patients receive pharmaceutical care at every outpatient visit and take medications by themselves at home. The clinical pharmacist will contact patients who miss their TB clinic visit.
2. **Home visit:** At each outpatient visit, nurse provides patient education, monitor and manage ADRs, and evaluate treatment adherence. Patients take medications by themselves and have a weekly home visit by non-medical staff (e.g. case manager) for the first two months followed by a monthly home visit after two months until the treatment completed. During the home visit, the non-medical staff observes whether patients take their medication properly, and addresses any problem with their treatments. The non-medical staff will contact patients who miss their TB clinic visit.
3. **Modified DOT**: At each outpatient visit, nurse or pharmacist provide patient education, monitor and manage adverse drug reactions (ADRs), and evaluating treatment adherence. Patients take daily medications under the direct supervision of a non-medical staff at home for the first 2 weeks of treatment. Then patients

take the medications by themselves at home with regular home visit by non-medical staff (e.g. twice a week for the first month, once a week in the second month, and twice a month until the treatment completed). The aim of home visits is to observe whether patients have any problem with taking their medication. Nurse will contact patients who miss their TB clinic visit.

1.8 OUTLINE OF THE THESIS

This thesis consists of three consecutive parts that assesses three different supervision approaches which are currently adopted for enhancing adherence to pulmonary TB treatment in referral hospitals in southern Thailand: pharmaceutical care, home visit, and modified DOT. These approaches are tailored to local contexts of each study hospital, since DOT, a WHO recommended strategy to promote adherence for pulmonary TB patients, is not feasible to implement nationwide due to resource constraints. Pharmaceutical care is a more recent and relatively simple approach. However, our knowledge of pharmaceutical care for enhancing adherence in pulmonary TB patients is very limited. The aim of this thesis is consequently to broaden current knowledge of effectiveness of pharmaceutical care compared with the other two supervision approaches that have been used under the usual health care practice in referral hospital in the vicinity. In addition, since health care resource uses and costs have been recognized as an important piece of information to inform health policy making, this research also aimed at supporting policy-makers by estimating economic impacts

associated with these three approaches.

For properly assessing these strategies, several specific aspects were investigated. The first project compared the clinical effectiveness (e.g. treatment success rate) among three different strategies (Chapter 2). The second project estimated and compared direct health care resource uses and costs associated with each approach (Chapter 3). The last project compared the costs associated with TB borne by patients and the society (e.g. OOP expenditures and indirect costs) and HRQoL (Chapter 4). The final chapter (Chapter 5) discusses the key findings based on the research evidence presented in this thesis, implications, limitations, and directions for future research.

Chapter 2 reports a retrospective cohort study using clinical data collected from patient medical records and TB registration records comparing the treatment success rate among three supervision approaches. A total of 1,398 adult pulmonary TB patients were included in the analysis. Propensity score matching was used to account for differences in patient baseline characteristics. We found evidence that treatment success rates were similar when comparing pharmaceutical care with either home visit or modified DOT. All three strategies were associated with high success rate for pulmonary TB treatment in Thailand, and all exceeded the WHO treatment success target of 85% for new smear positive patients. This work provides needed evidence for the effectiveness of pharmaceutical care for enhancing adherence to pulmonary TB treatment. Our findings have provided

evidence for the potential role of the clinical pharmacists to improve adherence in TB patients who took medications by themselves at home.

Given the evidence found in Chapter 2, Chapter 3 addresses a further question which touches upon the topic of economic impact of these approaches. This work was a retrospective cohort study conducted on the 1,398 patients analyzed in the Chapter 2. We estimated direct health care resource uses and costs associated with each approach. Generalized linear models (GLMs) was used to compare the costs while accounting for differences in patient baseline characteristics. Pharmaceutical care was associated with lower direct health care costs, because the intervention had no supervision activities (e.g. providing home visits or DOT at patient's home), while these posed substantial costs for the home visit and modified DOT groups. However, this study included only direct health care costs incurred in hospital.

Chapter 4 therefore investigated the costs to patients and the society. This was a prospective cohort study using data collected in 104 adult pulmonary TB patients. Because of a change in treatment policy in one of the study hospitals, we explored the financial burden incurred to patients receiving SAT (an approach when patients take medications by themselves at home without any additional supervision approach) instead of modified DOT in this Chapter. The analyses compared the OOP expenditures, indirect costs, and HRQoL among patients who received pharmaceutical care, home visit, and SAT. This work was aimed at understanding the financial burden and improving the

strategies for financial risk protection in pulmonary TB patients. Moreover, given an advantage of a prospective cohort study, we could explore the effects of TB on patients' employment status and the differences in socioeconomic characteristics (e.g. income levels, educational attainment) through patient interviews, which were not feasible in our previous retrospective work. We found that the financial burden varied markedly across different treatment strategies due to the influence of several factors such as public insurance coverage, socioeconomic status, disease severity, distance to TB services. The patients receiving pharmaceutical care experienced the highest OOP expenditures, compared with those receiving home visit and SAT. Patients receiving home visits had the highest indirect costs as well as the highest improvement in utility scores. Reducing the direct and indirect costs incurred during seeking care, TB diagnosis, and treatment initiation is necessary for controlling the financial burden imposed by TB on patients and the society. However, only a small number of pulmonary TB patients, particularly MDR-TB cases, were recruited in this study. Future larger-scale study would be useful to confirm our findings and to inform health policy.

Finally, Chapter 5 presents a summary of the key findings, implications, limitations of this thesis, and directions for future research. This thesis is the first step towards enhancing our knowledge of pharmaceutical care for improving adherence in pulmonary TB treatment. Pharmaceutical care is a promising option for providing cost-effective care for a portion of TB patients in Thailand, but it should be systematically compared with other options in a large-scale prospective study in order to strengthen evidence to support policy making about the most efficient use of limited resources to TB management.

The markedly differences in characteristics of patients receiving different treatment strategies, particularly the public insurance coverage, socioeconomic status, disease severity, distance to TB services and willingness to pay, may be atypical in other settings. Caution should be exercised when generalizing the research findings to other populations. However, the evidence also indicated that the most important periods for controlling the financial burden imposed by TB on patients and the society are during seeking care, early TB diagnosis, and treatment initiation.

This thesis also provides additional evidence for the longitudinal changes in TB patients' HRQoL over at least six months which has been rarely reported. The utility of EuroQol five dimensions and three level questionnaire (EQ-5D-3L) facilitates the calculation of quality-adjusted life years (QALYs) which could support economic evaluations of different supportive approaches in the future work.

Further studies need to be carried out focusing on MDR-TB management. Large-scale longitudinal studies would be useful to assess the costs and HRQoL associated with three different approaches in MDR-TB patients, in order to assess the budgetary impact of the ongoing changes in MDR-TB treatment and to support economic evaluations of new approaches for MDR-TB management.

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Figure 1: Factors influencing adherence and TB treatment success

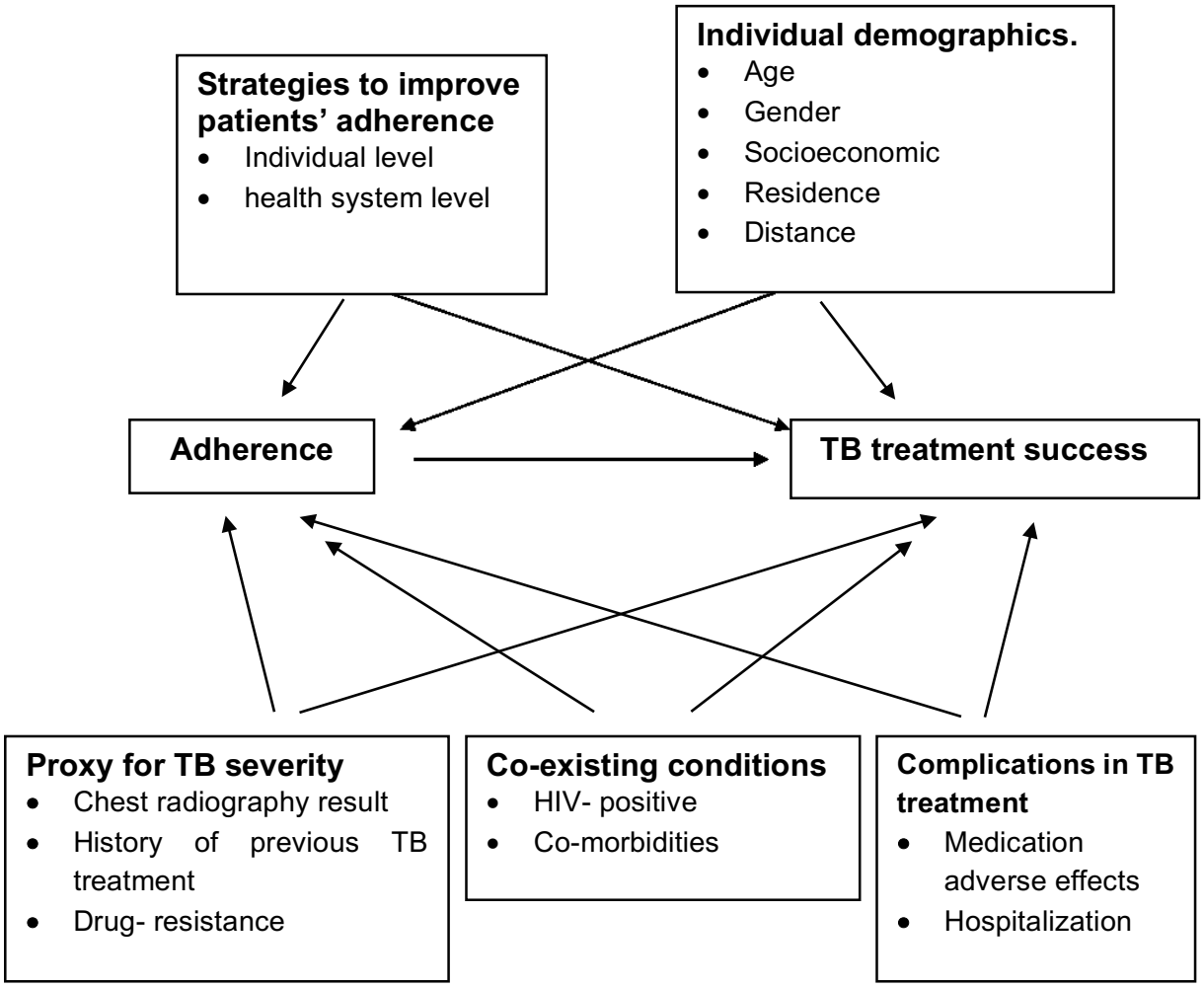

Table 1: Characteristics of each treatment strategies

Services		Pharmaceutical care	Home visit	Modified DOT
Outpatient visits	Who provides the services?	clinical pharmacist	nurse	nurse or pharmacist
	Activities	• pharmacist-led patient education • monitoring and management of ADRs • identifying other drug-related problems • evaluation of treatment adherence • providing pharmacist's telephone consultation	• nurse-led patient education • monitoring and management of ADRs • evaluation treatment adherence	• nurse- or pharmacist-led patient education • monitoring and management of ADRs • evaluation of treatment adherence
Supervision activities	Who provides the services?	none	non-medical staff	non-medical staff

	Activities	none	• Home visits
			  ○ Patients take medications by themselves at home with regular home visit
				• DOT
				  ○ Patients take medications under the direct supervision
				• Home visits
				  ○ Patients take the medications by themselves at home with regular home visit

	Visit schedule	none	• Home visits
			  ○ Once a week in the first two months
			  ○ Once a month until treatment completion
				• Daily DOT
				  ○ First two weeks of treatment
				• Home visits

				○ Twice a week for the first month ○ Once a week in the second month ○ Twice a month until treatment completion

APPENDIX 1.I: Disease classification [6]

Case definitions:

- Tuberculosis suspect. Any person who presents with symptoms or signs suggestive of TB. The most common symptom of pulmonary TB is a productive cough for more than 2 weeks, which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, hemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).
- Case of tuberculosis. A definite case of TB (defined below) or one in which a health worker (clinician or other medical practitioner) has diagnosed TB and has decided to treat the patient with a full course of TB treatment.
- Definite case of tuberculosis. A patient with *Mycobacterium tuberculosis* complex identified from a clinical specimen, either by culture or by a newer method such as molecular line probe assay. In countries that lack the laboratory capacity to routinely identify *M. tuberculosis*, a pulmonary case with one or more initial sputum smear examinations positive for acid-fast bacilli (AFB) is also considered to be a "definite" case, provided that there is a functional external quality assurance (EQA) system with blind rechecking.

Cases of TB are also classified according to the key features discussed below:

1. Classification based on anatomical site of disease

- Pulmonary tuberculosis (PTB) refers to a case of TB (defined above) involving the lung parenchyma. Military tuberculosis is classified as pulmonary TB because there are lesions in the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra-pulmonary TB (EPTB). A patient with both pulmonary and EPTB should be classified as a case of pulmonary TB.
- EPTB refers to a case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on at least one specimen with confirmed *M. tuberculosis* or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy. The case definition of an EPTB case with several sites affected depends on the site representing the most severe form of disease. Unless a case of EPTB is confirmed by culture as caused by *M. tuberculosis*, it cannot meet the “definite case” definition given above.

2. Classification based on bacteriological results

Bacteriology refers to the smear status of pulmonary cases and the identification of *M. tuberculosis* for any case by culture or newer methods.

All patients suspected of having pulmonary TB should submit at least two sputum specimens for microscopic examination in a quality-assured laboratory. When possible, at least one early-morning specimen should be obtained, as sputum collected at this time has the highest yield. All persons with chest radiographic findings suggestive of TB should submit sputum specimens for microbiological examination.

Smear-positive pulmonary case

A case of pulmonary TB is considered to be *smear-positive* if one or more sputum smear specimens at the start of treatment are positive for AFB (provided that there is a functional EQA system with blind rechecking).

In countries without functional EQA, the definition from the third edition of these guidelines applies: a smear-positive pulmonary TB case was defined as one with:

- two or more initial sputum smear examinations positive for AFB, or
- one sputum smear examination positive for AFB plus radiographic abnormalities consistent with active PTB as determined by a clinician, or
- one sputum smear positive for AFB plus sputum culture-positive for *M. tuberculosis*.

The definition of a new sputum smear-positive pulmonary TB case is based on the presence of at least one acid fast bacillus (AFB+) in at least one sputum sample in countries with a well functioning EQA system.

Smear-negative pulmonary case

Smear-negative PTB cases should either:

- have sputum that is smear-negative but culture-positive for *M. tuberculosis*:
    - a case of pulmonary TB is considered to be *smear-negative* if at least two sputum specimens at the start of treatment are negative for AFB in countries with a functional EQA system, where the workload is very high and human resources are limited;
    - in all settings with an HIV prevalence of >1% in pregnant women or ≥5% in TB patients, sputum culture for *M. tuberculosis* should be performed in patients who are sputum smear-negative to confirm the diagnosis of TB.

OR

- meet the following diagnostic criteria:
    - decision by a clinician to treat with a full course of anti-TB therapy; and
    - radiographic abnormalities consistent with active pulmonary TB and *either*:
        - laboratory or strong clinical evidence of HIV infection *or*:
        - if HIV-negative (or unknown HIV status living in an area of low HIV prevalence), no improvement in response to a course of

broad-spectrum antibiotics (excluding anti-TB drugs and fluoroquinolones and aminoglycosides).

Pulmonary TB cases without smear results are no longer classified as smear-negative; instead, they are recorded as “smear not done” on the TB register and on the annual WHO survey of countries.

For patients suspected of having EPTB, specimens should be obtained from the suspected sites of involvement. Where available, culture and histopathological examination should also be carried out. Additionally, a chest X-ray and examination of sputum may be useful, especially in persons with HIV infection.

3. Classification based on history of previous treatment: patient registration group

- New case is a patient who has never had treatment for tuberculosis or who has taken anti-tuberculosis drugs for less than one month. New patients may have positive or negative bacteriology and may have disease at any anatomical site.
- Previously treated patients have received one month or more of anti-TB drugs in the past, may have positive or negative bacteriology and may have disease at any anatomical site. They are further classified by the outcome of their most recent course of treatment as shown below.

Categories of disease: registration types

Categories		Description
New case of TB		A patient who has never been treated for TB or has taken anti-TB drugs for less than one month.
Previously treated case of TB		A patient who has been treated for one month or more with anti-TB drugs in the past. Re-treatment cases are further classified by the outcome of their most recent course of treatment into four categories.
	Relapse	patients have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
	Treatment after failure	Patients have previously been treated for TB and their most recent course of treatment failed i.e. they had a positive sputum smear or culture result at month 5 or later during treatment.
	Treatment after loss to follow-up	Patients have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as treatment after default patients which are patients who interrupted treatment for two consecutive months [3])

	Other	Patients who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

4. Classification based on HIV status [11]

HIV-positive TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-ART register or in the ART register once ART has been started.

HIV-negative TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly.

HIV status unknown TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

APPENDIX 1.II: Treatment outcome definitions [6,11]:

Cured: A patient who was initially smear-positive and who was smear-negative in the last month of treatment and on at least one previous occasion.

Completed treatment: A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable. This definition applies to pulmonary smear-positive and smear-negative patients and to patients with extra-pulmonary disease.

Died: A patient who died from any cause during treatment.

Failed: A patient who was initially smear-positive and who remained smear-positive at month 5 or later during treatment.

Defaulted (Lost to follow-up): A patient whose treatment was interrupted for 2 consecutive months or more.

Not evaluated: A TB patient for whom no treatment outcome is assigned. This includes cases 'transferred out' to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

Transferred out: A patient who transferred to another reporting unit and for whom the treatment outcome is not known.

Successfully treated: A patient who was cured or who completed treatment.

APPENDIX 1.III: The pharmaceutical care for TB management at Songklanagarind Hospital, Thailand

The pharmaceutical care provided in the study hospital is operated by a team of four well-trained clinical pharmacists with the aim to provide pharmaceutical care for patients who use medications that require special monitoring (e.g. the use of warfarin in patients with mechanical heart valve, venous thromboembolism (VTE), and atrial fibrillation), close supervision (e.g. patients with pulmonary TB, Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), complicated administration technique (e.g. inhalers, injectable insulin). All pharmacists in the team can provide effective care based on the standard procedures for each of those medications.

The pharmaceutical care for pulmonary TB management is provided for monitoring patients from the beginning until the end of pulmonary TB treatment. The unique component of pharmaceutical care is that, at each outpatient TB clinic visit, the team delegates one clinical pharmacist standing by for providing timely patient education. In addition, at the first visit, the clinical pharmacist provides a mobile phone number and encourages patients to contact them anytime if they need any consultation on the TB treatment. Patients receive pharmaceutical care at every outpatient visit and take medications by themselves at home.

The standard protocol for pharmaceutical care included:

1. Pharmaceutical care at the first visit
    1.1 Provide timely patient education related to:
        1.1.1 Disease, medications, and life style modifications.
        1.1.2 What to do, when patients forgot to take their medications.
        1.1.3 Appropriate storage conditions for their medications.
        1.1.4 Possible ADRs and advising on their management.
        1.1.5 Recommendation to take persons who have close contact with TB patient (e.g. a friend or family members) to receive tuberculin skin test.
    1.2 Promote adherence:
        1.2.1 Emphasizing patients' awareness of the importance to return for the next visit.
        1.2.2 Providing the reason why they must comply with medication regimen.
    1.3 Offer pharmacist telephone consultation and encourage patient to contact them anytime if they need any consultation on the TB treatment
    1.4 Pharmacist note:
        1.4.1 The pharmacist's recommendations and future plan were noted.
        1.4.2 Patient's special need for supervision was noted.
2. Pharmaceutical care at the follow-up visits
    2.1 Review the future plan and patient's special need that were noted in the previous visit.
    2.2 Assess patients' adherence to treatment and identify any factors which may predispose patients to non-adherence using indirect methods included patient

interviews, pill counts, observing self-administered DOT card, and measurement of health outcomes (e.g. sputum smear, sputum culture).

2.3 Monitor ADRs and advise on their management.

2.4 Identify other drug related problems (DRPs) e.g. potential drug interaction

2.5 Encourage patient to contact them anytime if they need any consultation on the TB treatment.

2.6 Contact patients who were lost to follow up as soon as possible.

CHAPTER 2:

EFFECTIVENESS OF PHARMACEUTICAL CARE IN ENHANCING ADHERENCE TO SELF-ADMINISTERED PULMONARY TUBERCULOSIS TREATMENT IN THAILAND

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SUMMARY

What is known and objective: With resource constraints in Thailand, directly observed therapy (DOT) for treating tuberculosis (TB) may not be feasible to implement. To improve patients' adherence, hospitals either modify DOT or adopt different approaches: pharmaceutical care or home visit. Our objective was to assess pulmonary TB treatment success rate of pharmaceutical care compared to home visit and modified DOT in Thailand.

Methods: We conducted a retrospective cohort study using data collected in adult pulmonary TB patients starting treatment between October 2010 and September 2013 in three hospitals in Thailand. This study was approved from the Research Ethics Board at each of the participating hospitals. We built the propensity score matching to account for differences in patient baseline characteristics.

Results: Analysis included 1,398 patients. Before matching, treatment success rate for patients receiving pharmaceutical care was 94.9%, home visit 93.6%, and modified DOT 90.1%. The propensity score matched cohorts indicated that differences in treatment success rate were not statistically significant when comparing pharmaceutical care with either home visit (success rate: 92.76 % versus 94.74%, risk difference: 1.97%, 95% CI -3.64% to 7.59%) or modified DOT (success rate 93.37% for both, risk difference: 0%, 95% CI -5.30% to 5.30%).

What is new and conclusion: Pharmaceutical care, home visit, and modified DOT are all associated with high success rate for pulmonary TB treatment and exceeded the WHO target.

Keywords: pharmaceutical care; adherence; pulmonary tuberculosis; self-administered therapy; patient education

2.1 WHAT IS KNOWN AND OBJECTIVE

Directly observed therapy (DOT) has been a World Health Organization (WHO) recommended strategy to promote adherence for pulmonary tuberculosis (TB) patients [1]. However, there are barriers to the implementation of DOT in resource-constrained countries. A recent systematic review compared treatment outcomes between DOT and self-administered therapy (SAT) [2]. According to the six RCTs identified, the review concluded that DOT alone may not improve adherence to TB treatment. Moreover, it has been reported that DOT may cost twice as much as SAT [3]. It is therefore of public health importance to consider other supportive strategies that are tailored to a country-specific context [2,4,5]. In fact, a systematic review evaluating the effectiveness of strategies to promote adherence to TB treatment found that modified DOT (the combination of DOT and other interventions) may improve adherence [6]. An example of these strategies was one study demonstrated that a case management strategy of patient education, DOT for the first two months, and weekly home visit increased treatment success in new TB patients [7]. Pharmaceutical care, where clinical pharmacists provide patient education to improve patient's knowledge on the disease and medication use and address patient's drug-related problems, is yet another approach to enhance TB treatment compliance [8,9]. However, data demonstrating the effectiveness of this approach is limited.

In Thailand, resources for DOT, including the availability of healthcare personnel, are limited. Furthermore, out of pocket costs for receiving DOT (e.g. transportation) impose a burden on patients [10]. Therefore, it is not feasible to widely implement DOT in Thailand. Several different strategies are currently adopted for enhancing adherence to TB treatment in referral hospitals in southern Thailand. One is modified DOT, where at each outpatient visit, nurses or pharmacists provide patient education, monitor and manage adverse drug reactions (ADRs), and evaluate treatment adherence. Patients take medications under the direct supervision of a non-medical staff at home for the first two weeks of treatment. Then patients take the medications by themselves at home with regular home visit by non-medical staff (e.g. twice a week for the first month, once a week in the second month, and twice a month until the treatment completed). Another is home visit, where at each out-patient visit, a nurse provides patient education, monitor and manage ADRs, and evaluate treatment adherence. Patients take medications by themselves and have a weekly home visit by a non-medical staff for the first two months followed by a monthly home visit after two months until the treatment completed. A more recent strategy is pharmaceutical care, where a university hospital provides timely patient education, monitoring and management of ADRs management, identifying other drug-related problems, and an evaluation of treatment adherence by clinical pharmacist. At the first visit, the clinical pharmacist provides a mobile phone number and encourages patients to contact them anytime if they need any consultation on the TB treatment. Patients receive pharmaceutical care at every outpatient visit and take medications by themselves at home. The clinical pharmacist will contact patients who miss their TB clinic visit.

Given that there is no evidence on performance of pharmaceutical care compared with the home visit and the modified DOT, the objective of this study was to assess the comparative effectiveness of pharmaceutical care versus to the home visit and the modified DOT strategies in pulmonary TB patients in Thailand.

2.2 METHOD

2.2.1 Data source and target population

We conducted a retrospective cohort study based on *patient* medical *records* and TB registration records. The study was conducted in three hospitals in Songkhla province, southern Thailand, Songklanagarind Hospital, Hatyai hospital, and Songkhla hospital where pharmaceutical care, home visit, and modified DOT was adopted, respectively. Songklanagarind hospital is an 850-bed teaching hospital affiliated to the Prince of Songkla University (PSU). Hatyai hospital (700-bed, tertiary care) and Songkhla hospital (480-bed, secondary care) are the main provincial referral hospitals under the Ministry of Public Health. This study was approved from the Research Ethics Board at each of the participating hospitals.

Our eligibility criteria included the following: patients ≥ 18 years of age, pulmonary TB confirmed by a physician and classified bacteriologically as smear-positive or smear-negative, TB treatment started between October 2010 and September 2013, and a treatment period of ≥ 2 months in one of the study hospitals. The patients were

categorized into two groups: new cases were patients who never had TB treatment or who has just started taking anti-TB drugs for < 1 month prior to the study period, and re-treatment cases were patients who were registered as “relapse”, “treatment after failure”, or “treatment after default” (Table 1).

The standard treatment regimen is a daily *combination* of four first-line antibiotics for at least *six* months (2HRZE/4HR) divided into two treatment phases: intensive phase (2-month) and continuous phase (4-month). Re-treatment cases were treated with an 8-month re-treatment regimen with first-line drugs (2HRZES/1HRZE/5HRE). While, patients with multidrug-resistance TB (MDR-TB) require at least 20-month treatment period with second-line agents [11].

2.2.2 Outcome measures

TB treatment outcome definitions are defined in Table 1 [1,12]. The primary outcome was TB treatment success [1], i.e. a patient who was either cured or completed treatment. WHO sets the treatment success target for new smear positive pulmonary TB patients as 85% [13]. Patients who experienced treatment failure, died, or defaulted were categorized as unsuccessful treatment. Transferred out patients were not included in the treatment success measurement.

2.3 STATISTICAL ANALYSIS

Descriptive analyses were conducted to explore the distributions and categorize the variables. Categorical variables were analyzed using Chi-squared test, unless expected cell counts were low, in which case Fisher's Exact test was used instead. Significance was set at $p < 0.05$. Data was entered through the SPSS software [14].

Propensity score matching was performed to adjust the differences in baseline characteristics among the patients treated with different strategies. Propensity scores use logistic regression to predict the probability that patients will receive a treatment based on their measured covariates at baseline [15]. Patients from different groups are then matched on their propensity scores, which generally brings about the balance in baseline covariates. Propensity score analysis was conducted separately for two comparisons: 1) pharmaceutical care versus home visit and 2) pharmaceutical care versus modified DOT. In each comparison, propensity scores were generated using the baseline covariates of age, sex, health insurance, HIV status, other co-morbidities, sputum smear result, chest X-ray result, registration type, and initial treatment regimen. Patients receiving pharmaceutical care or the other treatment were matched by one-to-one matching without replacement. The matching was conducted manually with a caliper (a maximum allowable difference in propensity score between groups) of width equal to 0.2 of the standard deviation (SD) of the estimated propensity score [16]. Balance in baseline covariates was investigated by standardized differences between two treatment groups that should be close to zero ($|d| < 0.1$) [17,18]. The risk difference was calculated. McNemar's test was used to test the statistical significance

of the difference in proportion for TB treatment success between matched groups. Confidence intervals of the risk difference were estimated using a method for matched-pairs data recommended by Agresti and Min [19]. The relative risk in the probabilities of treatment success with pharmaceutical care versus the other treatment was calculated. Confidence intervals of the relative risk were estimated the methods introduced by Agresti and Min [19].

2.4 RESULTS

Between October 2010 and September 2013, 2,444 adult cases started pulmonary TB treatment in the three study hospitals. A total of 1,398 patients met our eligibility criteria and were included in the analysis (Figure1). There were 315, 559, and 524 patients that received pharmaceutical care, home visit, and modified DOT, respectively. Baseline characteristics and complications in TB treatment of included patients are described in Table 2. Nine of 11 baseline characteristics differed significantly between the hospitals (Chi-squared test, $p < 0.05$). Forty-one percent of patients in the pharmaceutical care group were > 55 years of age, compared to 26.3% and 28.1% in the home visit and the modified DOT group. Most study patients were smear positive (86.0%, 79.6%, and 66.4% in patients receiving pharmaceutical care, home visit, and modified DOT, respectively). Seventeen percent and 19% of patients receiving home visit and modified DOT respectively were HIV positive, compared to 3.2% in the pharmaceutical care group. Durations of the intensive phase were 2.5, 2.7, and 2.5

months while the continuous phase took 4.6, 5.2, 4.0 months on average in the patients receiving pharmaceutical care, home visit, and modified DOT, respectively.

2.4.1 Treatment success rate

For the whole cohort before matching, the treatment success in patients receiving pharmaceutical care was 94.9% (95% confidence interval (CI) 92.47 to 97.33), home visit 93.6% (95% CI 91.57 to 95.63), and modified DOT 90.1% (95% CI 87.54 to 92.66). When focusing only on the 903 new smear positive patients, the success rates were 95.1% (95% CI 92.41 to 97.79), 93.2% (95% CI 90.81 to 95.59), and 90.3% (95% CI 86.95 to 93.65) for patients receiving pharmaceutical care, home visit, and modified DOT, respectively.

2.4.2 Propensity score matching

Pharmaceutical care versus home visit: a total of 304 patients were matched. Baseline characteristics of the patients in the propensity score matched cohort are shown in Table 3. In the propensity score matched cohort, total 152 matched pairs were balanced with standardized differences of prevalence ranged from zero to 0.080.

Out of 152 patients in each group, 141 in the pharmaceutical care group and 144 in home visit group had treatment success, with a corresponding success rate of 92.76 % and 94.74%, respectively. The risk difference in the success rate was 1.97% (95%

CI -3.64% to 7.59%). A McNemar's test showed that there was no significant difference in the treatment success rate between two groups (p=0.648). The relative risk of experiencing treatment success in the cases treated with pharmaceutical care compared to those with home visit was 0.98 (95% CI 0.92 to 1.04).

Pharmaceutical care versus modified DOT: A total of 362 patients were matched. Baseline characteristics of the patients in the propensity score matched cohort are shown in Table 3. In propensity score matched cohort, the 181 matched pairs were balance with standardized differences of prevalence ranged from zero to 0.046. Out of 181 patients in each group, both the pharmaceutical care group and the modified DOT group had 169 patients with treatment success (success rate 93.37%). The risk difference in the success rate was 0% (95% CI -5.30% to 5.30%). The relative risk of experiencing treatment success in the cases treated with pharmaceutical care compared to those with modified DOT was 1 (95% CI 0.94 to 1.06).

2.5 Discussions

We found that all three TB treatment strategies were associated with a high success rate and exceeded the WHO target. The propensity score matched cohorts indicated no statistically significant difference in the treatment success rate when comparing pharmaceutical care with either home visit or modified DOT. This is consistent with the conclusion from a logistic regression (home visit: OR 1.42; 95% CI 0.67 to 3.04, and

modified DOT: OR 0.83; 95% CI 0.39 to 1.76: see Appendix 2.II), when pharmaceutical care was set as the reference.

Pharmaceutical care, a relatively simpler strategy, was shown to have similar effectiveness in achieving treatment success compared with home visit and the modified DOT. Our findings provide evidence to policy-makers to support a strategy that is feasible to implement with fewer resources needed than the other strategies studied. Moreover, pharmaceutical care may receive better cooperation from patients, compared to modified DOT or home visits which are frequently associated with stigma [20,21].

There is a lack of evidence for the effectiveness of pharmaceutical care coupled with SAT compared directly with DOT, different forms of DOT, or SAT in TB treatment. Only one available RCT found that clinical pharmacist-directed patient education could improve adherence to treatment in new TB patients compared with routine medical and nursing care [8]. However, in this study, direct observation of patients occurred at an inpatient clinic during the intensive phase (the first two months). Pharmaceutical care provision was administered randomly only in the continuous phase (before discharge and at each outpatient clinic visits) where patients took medications by themselves at home. The clinical pharmacist was mainly responsible for educating patient, and identifying treatment related drug interactions and adverse events. Nevertheless, these problems appeared prominently in the intensive phase [22,23]. As a result, one of our study hospitals implemented pharmaceutical care at the beginning

of TB treatment to support patients who took medications by themselves at home; the strategy of applying care in the intensive phase has strengthened the role of pharmacists to improve TB patients' adherence compared with Clark et al.

Compared with the other two treatment strategies, the unique component of pharmaceutical care is that the clinical pharmacist provides timely services on patient education and also supports patient-centered communication by providing pharmacist consultation service at anytime through mobile phone. This is in contrast to modified DOT model where care must be sought in a TB clinic where availability may be restricted (e.g. such as once weekly clinic in our study hospital).

Home visits are an alternative to the modified DOT strategy to enhance TB treatment. In addition to in-hospital services, regular home visits are used to reinforce the supervision, and address problems that arise. Home visits have been used as a supportive strategy to promote adherence to pulmonary TB treatment in a number of studies [7,24]. One study demonstrated that daily DOT in the first two months followed by weekly home visit was associated with significant higher treatment success in new TB patients, compared to SAT coupled with monthly home visit throughout the treatment period [7]. They also found significant correlation between patients' adherence in the first two months and treatment success rate. This is consistent with one of the WHO's DOTS strategy which proposed the importance of direct supervision in the initial two months of treatment [25]. These are in agreement with our findings.

Since the daily DOT was not feasible to provide throughout the first two months, the modified DOT and home visit model at our study hospitals provided close supervision by offering weekly home visit until the initial two months were completed instead.

Our study had a number of limitations. The data used in the analysis came from a retrospective patient chart review. Some information such as patients' comorbidities, ADRs, and hepatotoxicity was recorded differently across the hospitals. The differences in each hospital's standard procedures and the format of hospital database (some paper based medical documents were not converted to the computer based yet) resulted in incomplete data for some variables e.g. HIV status, baseline chest radiography. Given the nature of an observational study design, we also noticed differences in baseline patient characteristics. The three hospitals also differed in the service provided, hospital policy, and the numbers of healthcare personnel assigned in TB clinic. The propensity score method provided adjustment for some but not all variations in these factors. Differences in health literacy and socioeconomic characteristics (e.g. income levels, educational attainment) could have influenced adherence to therapy, but were not examined due to limitations of the retrospective review. Further research in the costs associated with each strategy was conducted for evaluating the costs incurred to health care provider, costs incurred by patients and family members, and health-related quality of life. These costs would also help in properly assessing these strategies.

2.6 WHAT IS NEW AND CONCLUSION

Pharmaceutical care, home visit, and modified DOT were all associated with high success rate for pulmonary TB treatment in Thailand and exceeded the WHO treatment success target.

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AUTHOR CONTRIBUTIONS

All authors developed conception and design of study; P.T. performed the data collection, analyzed the data, and prepared the manuscript; F.X., E.P., M.L., and J.D. performed critical revision of the manuscript

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DECLARATION OF CONFLICTING INTERESTS

The authors do not have a commercial or other association that might pose a conflict of interest.

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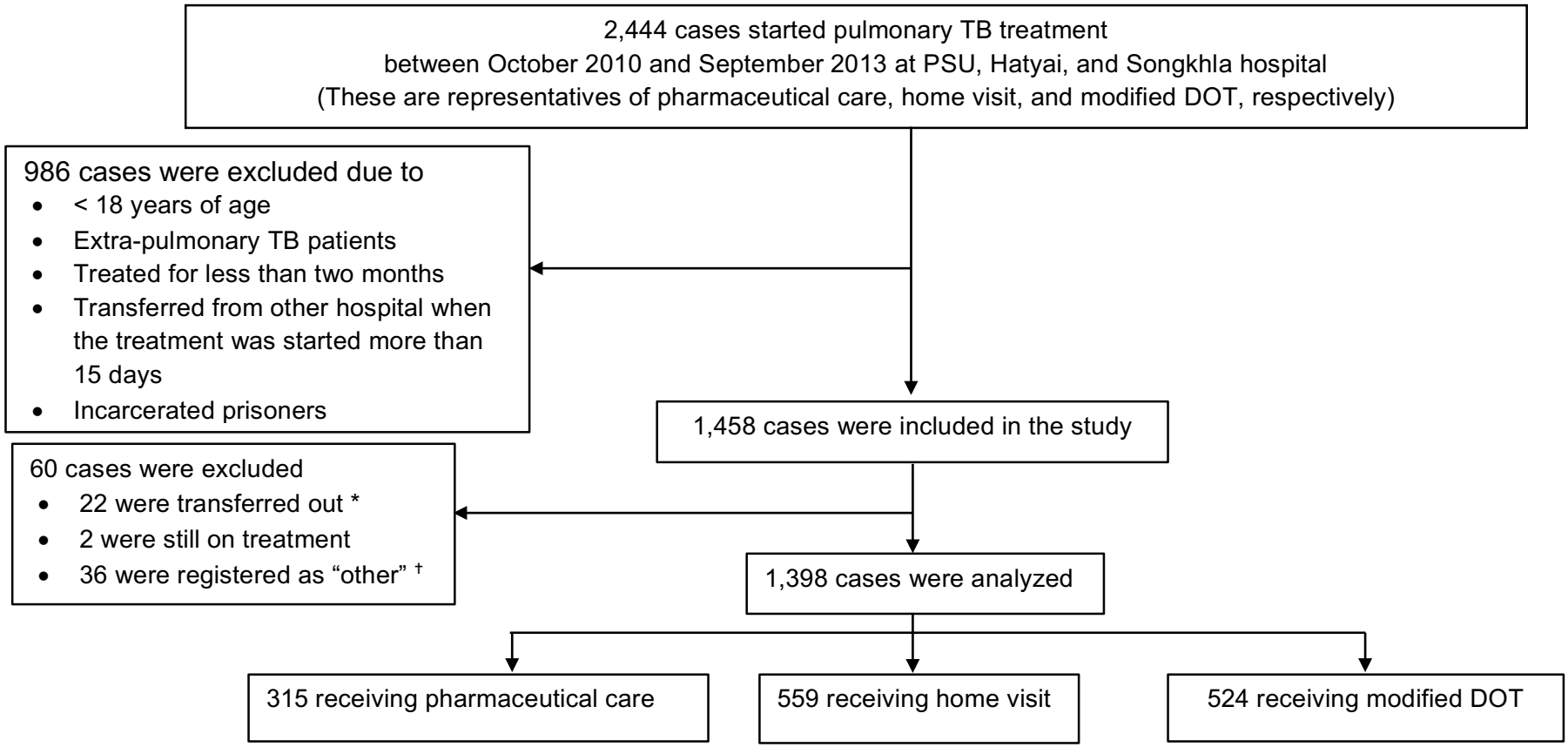
Figure 1: Flowchart of study participants



NOTE: * "Transferred out" occurred when patients have started the TB treatment for a certain amount of time, then they have to relocate to other district for their personal reasons. Therefore, these patients transferred to another reporting unit located in their new address. Transferred patients who the treatment outcome was available were included in the analysis, while those the treatment outcome was unknown were excluded. † Patients were categorized as "other cases" by using their available medical record and/or their provided information. The definition for "other cases" was defined in Table 1.

Table 1: Definitions of the registration group and the treatment outcomes for TB patients [1,12]

<table>
<tr><td colspan="2">Registration group (any site of disease)</td><td>Bacteriology</td><td>Outcome of most recent prior treatment</td></tr>
<tr><td colspan="2">New case of TB</td><td>+ or -</td><td>-</td></tr>
<tr><td rowspan="4">Previously treated</td><td rowspan="2">Relapse</td><td rowspan="2">+</td><td>Cured</td></tr>
<tr><td>Treatment completed</td></tr>
<tr><td>Treatment after failure</td><td>+</td><td>Treatment failed</td></tr>
<tr><td>Treatment after default</td><td>+</td><td>Defaulted</td></tr>
<tr><td colspan="2">Transfer in</td><td>+ or -</td><td>Still on treatment</td></tr>
<tr><td colspan="2">Other</td><td>+ or -</td><td>All cases that do not fit the above definitions, such as patients:
For whom it is not known whether they have been previously treated;
Who were previously treated but with unknown treatment outcome (whether the treatment completed or not);
Who have returned to treatment with smear-negative pulmonary TB or bacteriologically negative extrapulmonary TB</td></tr>
<tr><td colspan="2">Treatment outcome</td><td colspan="2">Definition</td></tr>
<tr><td colspan="2">Cured</td><td colspan="2">A patient who was initially smear-positive, then was smear-negative in the last month of treatment and on at least one previous occasion (e.g. at the end of the fifth and sixth month for 6-month standard treatment regimen)</td></tr>
<tr><td colspan="2">Treatment completed</td><td colspan="2">A smear-negative patient who finished the treatment, or a smear -positive who completed treatment without bacteriology results in the last month of treatment</td></tr>
</table>

Failed	A patient who was initially smear-positive and who remained smear-positive at month 5 or later during treatment
Defaulted	A patient whose treatment was interrupted for 2 consecutive months or more
Transferred out	A patient who transferred to another reporting unit and for whom the treatment outcome is not known
Died	A patient who died from any cause during treatment

Table 2: Baseline characteristics and complications in TB treatment of 1,398 participants categorized by supervision strategy

Note:

- *Fisher's Exact test, † Oneway-ANOVA
- Thai population have been covered under one of the three public insurance schemes, namely the civil servant medical benefits scheme (CSMBS), the social security scheme (SSS), and the universal coverage (UC).
- Category1 is the standard treatment regimen with first-line drugs (2HRZE/4HR); Category 2 is the 8-month re-treatment regimen with first-line drugs (2HRZES/1HRZE/5HRE); Category 4 is the treatment regimen for patients with MDR-TB which required at least 20-month treatment period with second-line agents [11].

Variable		1,398 cases			p-value
		Pharm care (n=315)	Home visit (n=559)	Modified DOT (n=524)	
		n (%)	n (%)	n (%)	
Baseline characteristics					
Sex	Male	192 (61.0)	388 (69.4)	342 (65.3)	0.037
	Female	123 (39.0)	171 (30.6)	182 (34.7)	
Mean age (SD), years		49.90 (18.42)	44.85 (15.83)	45.38 (16.56)	<0.001†
Age group, years	18-24	34 (10.8)	52 (9.3)	44 (8.4)	<0.001
	25-34	46 (14.6)	114 (20.4)	110 (21.0)	
	35-44	39 (12.4)	129 (23.1)	127 (24.2)	
	45-54	66 (21.0)	117 (20.9)	96 (18.3)	
	>55	130 (41.3)	147 (26.3)	147 (28.1)	

Variable		1,398 cases			p-value
		Pharm care (n=315)	Home visit (n=559)	Modified DOT (n=524)	
		n (%)	n (%)	n (%)	
Live in Songkhla	Yes	178 (56.5)	559 (100)	524 (100)	<0.001
	No	137 (43.5)	0	0	
Health Insurance	Universal Coverage	95 (30.2)	375 (67.1)	352 (67.2)	<0.001
	CSMBS	132 (41.9)	32 (5.7)	61 (11.6)	
	Social Security Scheme	12 (3.8)	113 (20.2)	92 (17.6)	
	Not covered by public health insurance	76 (24.1)	39 (7.0)	19 (3.6)	
Pre-existing liver disease	Yes	3 (1.0)	4 (0.7)	2 (0.4)	0.523*
	No	312 (99.0)	555 (99.3)	522 (99.6)	
HIV	Yes	10 (3.2)	99 (17.7)	100 (19.0)	<0.001
	No	256 (81.3)	445 (79.6)	420 (80.2)	
	Unknown	49 (15.6)	15 (2.7)	4 (0.8)	
Co-morbidity	Yes	157 (49.8)	154 (27.5)	140 (26.7)	<0.001
	No	158 (50.2)	405 (72.5)	384 (73.3)	
Sputum smear	Positive	271 (86.0)	455 (79.6)	348 (66.4)	<0.001
	Negative	44 (14.0)	114 (20.4)	176 (33.6)	
Chest X-ray	Normal	14 (4.4)	4 (0.7)	20 (3.8)	0.001
	Abnormal	299 (94.9)	541 (96.8)	495 (94.5)	
	No baseline available	2 (0.6)	14 (2.5)	9 (1.7)	

Variable		1,398 cases			p-value
		Pharm care (n=315)	Home visit (n=559)	Modified DOT (n=524)	
		n (%)	n (%)	n (%)	
Registration	New	288 (91.4)	539 (96.4)	473 (90.3)	<0.001
	Re-treatment	27 (8.6)	20 (3.6)	51 (9.7)	
Initial treatment regimen	Category 1	309 (98.1)	546 (97.7)	517 (98.7)	0.164*
	Category 2	4 (1.3)	13 (2.3)	6 (1.1)	
	Category 4	2 (0.6)	0	1 (0.2)	
Complications in TB treatment					
Develop to MDR-TB	Yes	5 (1.6)	2 (0.4)	1 (0.2)	0.019*
	No	308 (97.8)	557 (99.6)	522 (99.6)	
	MDR-TB at baseline	2 (0.6)	0	1 (0.02)	
Re-Challenge anti-TB drug use	Yes	27 (8.6)	63 (11.3)	43 (8.2)	0.186
	No	288 (91.4)	496 (88.7)	481 (91.8)	
Hepatotoxicity with anti-TB drugs	Yes	19 (6.0)	40 (7.2)	26 (5.0)	0.320
	No	396 (94.0)	519 (92.8)	498 (95.0)	
Adverse events	No adverse events	146 (46.3)	389 (69.6)	429 (81.9)	<0.001
	Severe	28 (8.9)	63 (11.3)	45 (8.6)	
	Mild	141 (44.8)	107 (19.1)	50 (9.5)	
Hospitalization for TB	Yes	7 (2.2)	127 (22.7)	145 (27.7)	<0.001
	No	308 (97.8)	432 (77.3)	379 (72.3)	
Treatment duration					

Variable	1,398 cases			p-value
	Pharm care (n=315)	Home visit (n=559)	Modified DOT (n=524)	
	n (%)	n (%)	n (%)	
Duration of intensive phase, months; Mean (SD)	2.5 (1.4)	2.7 (1.1)	2.5 (0.99)	0.001†
Duration of continuation phase, months; Mean (SD)	4.6 (2.2)	5.2 (3.1)	4.0 (1.4)	<0.001†

Table 3: Baseline characteristics of participants in the propensity score matched cohort

Note:

- Thai population have been covered under one of the three public insurance schemes, namely the civil servant medical benefits scheme (CSMBS), the social security scheme (SSS), and the universal coverage (UC).
- Category1 is the standard treatment regimen with first-line drugs (2HRZE/4HR)

Variable		Pharmaceutical care VS Home visit (n = 304)			Pharmaceutical care VS Modified DOT (n = 362)		
		Pharm care (n=152)	Home visit (n=152)	Standardized Difference of prevalence	Pharm care (n=181)	Modified DOT (n=181)	Standardized Difference of prevalence
		n (%)	n (%)		n (%)	n (%)	
Sex	Male	86 (56.6)	86 (56.6)	0	113 (62.4)	113 (62.4)	0
Age group, years	18-24	21 (13.8)	20 (13.2)	0.018	22 (12.2)	23 (12.7)	0.015
	25-34	19 (12.5)	16 (10.5)	0.063	23 (12.7)	22 (12.2)	0.015
	35-44	25 (16.4)	24 (15.8)	0.016	21 (11.6)	21(11.6)	0
	45-54	30 (19.7)	29 (19.1)	0.015	36 (19.9)	38 (21.0)	0.027
	=>55	57 (37.5)	63 (41.4)	0.080	79 (43.6)	77 (42.5)	0.022
Health Insurance	UC	75 (49.3)	78 (51.3)	0.040	91 (50.3)	94 (51.9)	0.032
	CSMBS	34 (22.4)	32 (21.1)	0.032	60 (33.1)	57 (31.5)	0.034
	SSS	10 (6.6)	10 (6.6)	0	11 (6.1)	11 (6.1)	0
	Not covered by public health insurance	33 (21.7)	32 (21.1)	0.015	19 (10.5)	19 (10.5)	0

Variable		Pharmaceutical care VS Home visit (n = 304)			Pharmaceutical care VS Modified DOT (n = 362)		
		Pharm care (n=152)	Home visit (n=152)	Standardized Difference of prevalence	Pharm care (n=181)	Modified DOT (n=181)	Standardized Difference of prevalence
		n (%)	n (%)		n (%)	n (%)	
HIV	Yes	8 (5.3)	7 (4.6)	0.028	7 (3.9)	8 (4.4)	0.025
Other comorbiditie s	Yes	68 (44.7)	71 (46.7)	0.040	88 (48.6)	92 (50.8)	0.044
Sputum smear	Positive	128 (84.2)	127 (83.6)	0.016	146 (80.7)	146 (80.7)	0
Baseline chest X-ray	Abnormal	148 (97.4)	147 (96.7)	0.041	173 (95.6)	174 (96.1)	0.025
Registration	New	148 (97.4)	147 (96.7)	0.041	169 (93.4)	171 (94.5)	0.046
Initial treatment regimen	Category 1	151 (99.3)	151 (99.3)	0	181 (100)	181 (100)	0

APPENDIX 2.I: Sample size calculation

In this study, the significant level (α) was set at 0.05 (two-tailed), while the power was set at 0.80. The sample size was calculated according to the following formula.

$$n = [\frac{Z_{1-\frac{\alpha}{2}}\sqrt{2\bar{p}(1-\bar{p}} + Z_{1-\beta}\sqrt{p_1\,(1-p_1) + \,p_2(1-p_2)}}{p_1 - p_2}]^2$$

$$\bar{p} = \frac{p1 + p2}{2}$$

In 2011, the treatment success rate was 91.4% (p1) in new smear positive patients who received pharmaceutical care, while the success rate was 84% (p2) in those who received home visit. Thus, the required sample size for new smear positive patients from each supervision approach was 310 cases or around 930 new smear positive patients for the three supervision approaches. Therefore, the retrospective review was conducted in pulmonary TB patients who started new treatment course at one of the three hospitals between October 2010 and September 2013.

APPENDIX 2.II: Multivariate analyses for predictors of successful treatment compared with unsuccessful treatment in pulmonary tuberculosis patients

Note:
- Multivariate model included all significant factors from the univariate model.
- References used in each category were supervision strategy (pharmaceutical care), sex (female), age group (18-24), health Insurance (UC), HIV status (No), re-challenge anti-TB drug use (No), hepatotoxicity with anti-TB Drug (No), adverse events (No), and hospitalization for TB (No)
- Thai population have been covered under one of the three public insurance schemes, namely the civil servant medical benefits scheme (CSMBS), the social security scheme (SSS), and the universal coverage (UC).
- are significant difference ($p < 0.05$)

Variable		Treatment success (n = 1,398)		Multivariate	
		Yes	No	Adjusted OR	95% CI
Supervision strategy	Home visit	523	36	1.42	0.67 – 3.04
	Modified DOT	472	52	0.83	0.39 – 1.76
Sex	Male	839	83	0.43*	0.26 – 0.73
Age group, years	25-34	240	30	0.39	0.14 – 1.08
	35-44	272	23	0.81	0.29 – 2.29
	45-54	268	11	1.12	0.37 – 3.39
	>55	389	35	0.44	0.16 – 1.23
Health Insurance	CSMBS	214	11	1.93	0.90 – 4.11

Variable		Treatment success (n = 1,398)		Multivariate	
		Yes	No	Adjusted OR	95% CI
	Social Security Scheme	204	13	1.58	0.81 – 3.09
	Not covered by public health insurance	128	6	1.78	0.70 – 4.58
HIV status	Yes	168	41	0.29*	0.17 - 0.50
	Unknown	63	5	0.56	0.20 – 1.56
Re-challenge anti-TB drug use	Yes	109	24	0.70	0.10 – 5.05
Hepatotoxicity with anti-TB Drug	Yes	70	15	0.93	0.36 – 2.41
Adverse events	Severe	111	25	0.59	0.09 – 4.12
	Mild	275	23	0.69	0.39 – 1.20
Hospitalization for TB	Yes	234	45	0.48*	0.29 – 0.77

CHAPTER 3:

HEALTH CARE RESOURCE USES AND OUT OF POCKET EXPENSES ASSOCIATED WITH PULMONARY TUBERCULOSIS TREATMENT IN THAILAND

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ABSTRACT

Background. In Thailand, pharmaceutical care has been recently introduced to tertiary hospital as an alternative supervision approach to improve adherence to tuberculosis (TB) treatment in addition to home visits and modified directly observed therapy (DOT). Our previous study has shown that TB treatment success rates with pharmaceutical care are very similar to those obtained with home visit or modified DOT. However, the economic impact of pharmaceutical care in managing TB patients is not known.

Objective. To estimate and compare health care resource uses and costs associated with pharmaceutical care compared to home visit and modified DOT in patients with pulmonary TB in Thailand from a societal perspective.

Methods. We conducted a retrospective study using data collected from adult pulmonary TB patients who started treatments between October 2010 and September 2013 in three hospitals in Thailand. Resource uses and costs were abstracted from the hospital billing database. We used generalized linear models (GLMs) to compare the costs associated with different supervision approaches by accounting for patient baseline characteristics.

Results. The mean direct health care costs per patient to the public payer were $519.96 (95% confidence interval (CI): $437.31 to $625.58) associated with pharmaceutical care, $1,020.39 (95%CI: $911.13 to $1,154.11) for home visit, and $887.79 (95%CI: $824.28 to $955.91) for modified DOT. The mean costs to patients were $175.45 (95%CI: $130.26 to $230.48) for those receiving pharmaceutical care, $53.77 (95%CI: $33.25 to $79.44) for home visit, and $49.33 (95%CI: $34.03 to $69.30) for modified DOT. After adjustment for baseline characteristics, pharmaceutical care was associated with statistically significant lower direct costs compared with home visit (-$354.95, 95%CI: -$285.67 to -$424.23) and modified DOT (-$264.61, 95%CI: -$198.76 to -$330.46).

Conclusion. Compared with home visit and modified DOT, pharmaceutical care was associated with lower direct health care costs. Pharmaceutical care is a promising option for providing cost-effective care for TB patients in Thailand.

Key Points for Decision Makers

1. In Thailand, pharmaceutical care is a more recent and relatively simple approach to improve adherence to pulmonary tuberculosis (TB) treatment compared with home visits and modified directly observed therapy (DOT).

2. Our findings shed the light on the potential role of the clinical pharmacist in pulmonary TB outpatient service. Timely pharmacist-led patient education for every outpatient visit and pharmacist-provided telephone consultation were clinically effective and required less health care resources.

3. Pharmaceutical care is a promising option for providing cost-effective care for TB patients in Thailand.

3.1 INTRODUCTION

According to World Health Organization (WHO), Thailand is one of the 22 high-burden countries for TB with nearly 160,000 TB patients, and 11,900 TB-related deaths in 2014 [1]. In 2014, the domestic funding for the Thai National TB program exceeded the contributions from international donors, with only 11% of the budget funded internationally [1]. Most TB patients seek health care in public hospitals where TB diagnosis and treatment are covered by Thai public insurance schemes. Health care for people with TB-related symptoms usually starts with initial clinical consultation, diagnostic tests, and non-TB specific medications [2,3]. TB diagnostic process may require multiple visits to complete the tests and meet health care professionals for medical diagnosis [4,5]. Before TB diagnosis and during TB treatment, health care may include hospitalization, treatment of adverse drug reactions (ADRs), and augmenting nutrition.

Although WHO recommends directly observed therapy (DOT) to promote adherence for pulmonary TB patients [6], it is not feasible to widely implement DOT for TB control in Thailand, especially in the large hospitals due to health care resource constraints. Therefore, national TB program adopts the daily dose regimen whereby patients take the TB medications themselves at home and visit a health center or a district hospital at least once a month to refill their prescriptions. Hospitals adopt different supervision approaches, including home visit and modified DOT (see below for details). Recently, pharmaceutical care, a pharmacist-led patient education, was adopted in a tertiary

hospital to improve adherence to TB treatment.

According to our previous retrospective cohort study [7], all three TB treatment adherence enhancement strategies that are currently adopted in Thai referral hospitals were associated with high rates of success and exceeded the WHO treatment success target of 85%. However, there is little evidence on the economic implications associated with these strategies. Health care resource uses and costs have been recognized as an important piece of information to inform health policy making, especially in allocating public funds in resource constrained contexts. Therefore, this study is to, from the societal perspective, estimate and compare direct costs associated with pharmaceutical care compared to home visit and modified DOT in pulmonary TB patients in Thailand.

3.2 METHODS

3.2.1 Data sources

This was a retrospective study based on patient medical records, TB registration records, and the billing database at three public referral hospitals in Songkhla province, southern Thailand: Songklanagarind hospital, Hatyai hospital, and Songkhla hospital where pharmaceutical care, home visit, and modified DOT, respectively, have been adopted. Songklanagarind hospital is an 850-bed teaching hospital affiliated to the Prince of Songkla University (PSU). Hatyai hospital (700-bed, tertiary care) and Songkhla hospital (480-bed, secondary care) are the main provincial referral hospitals

under the Ministry of Public Health. This study was approved by the Research Ethics Board at each of the participating hospitals.

Pharmaceutical care provides pharmacist-led patient education at every outpatient visit regarding disease, medications, possible adverse drug reactions (ADRs), and life style modifications. The home visit approach provides regular home visit until treatment completion. The modified DOT provides direct observation, but only for the first two weeks when TB treatments start, then followed by regular home visits. The description of each of these TB treatment adherence enhancement strategies is shown in Table 1.

3.2.2 Patient eligibility criteria

The eligibility criteria for this cost analysis included: age ≥ 18 years, pulmonary TB confirmed by a physician and classified bacteriologically as smear-positive or smear-negative, TB treatment started between October 2010 and September 2013, and a treatment period of ≥ 2 months in the study hospitals.

3.2.3 Recommended TB treatment in Thailand

First-line anti-TB medications include isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), and streptomycin (S). The standard treatment regimen for drug-susceptible pulmonary TB is a daily combination of four first-line antibiotics (2HRZE/4HR) for at least six months divided into two treatment phases: an intensive phase (first two months) and a continuous phase (the remaining four months). Re-

treatment patients are treated with an 8-month re-treatment regimen (2HRZES/1HRZE/5HRE) while patients with MDR-TB require second-line agents (at least 20 months) as recommended by the WHO [1].

3.2.4 Health care resource uses and costs

The cost analysis was conducted from a societal perspective, which included direct health care costs to the public payer and to the patients. Costs were estimated separately for the pre-TB treatment period (from illness onset to TB diagnosis) and the TB treatment period (from the start to the completion of TB treatment). These costs were considered as costs associated with TB diagnosis and treatment if patients were diagnosed with at least one of the two ICD-10 codes, respiratory TB (A15 or A16). There are a few other relevant health care resource uses (e.g. treatment of ADRs, hospitalization, nutrition and others). Therefore, costs incurred with some ICD-10 codes needed to be investigated concurrently with other information (e.g. type of outpatient service, laboratory investigation, patient medical record, and TB registration record) before they were determined to be associated with TB diagnosis and treatment (See Appendix 3.I).

The Thai population has been covered under one of the three public insurance schemes: the civil servant medical benefits scheme (CSMBS), the social security scheme (SSS), and the universal coverage scheme (UC), all funded through general

tax revenues [8]. The CSMBS covers government employees, pensioners and their dependents in which insured persons can access, free of charge, to medical services at all government hospitals. The SSS is for private employees who can freely access medical services at a contracted hospital. Every Thai citizen not covered under the CSMBS or the SSS is covered by the UC but need to pay all medical costs out of pocket if they seek health care services outside their primary resident area. As of 2015, 75% of the Thai population are covered under the UC [9].

Following the Thai Comptroller General's Department's health care service classification, we categorized direct costs into seven categories: medications, laboratory investigation and pathology, diagnostic radiology, medical services, supervision activities, hospitalization, and miscellaneous costs. Except medications costs which were calculated using a mark-up method, unit costs of services in all remaining categories were set by factoring the costs related to labor, material, capital, overhead, and future development costs. Direct costs for each health care service in the hospitals were calculated by multiplying the natural units for the services with the corresponding unit costs. Costs associated with implementing supervision activities (i.e., the home visit at Hatyai hospital and the modified DOT at Songkhla hospital) were estimated separately as non-medical staff must be hired for providing these services. In addition to the salary paid from hospital, the global fund paid these staff 600 baht for each smear positive drug-susceptible patient who successfully completed treatment and 300 baht monthly for supervising each MDR-TB patient.

Methods for handling missing information varied depended on the type of data. Missing resource use items for laboratory investigation and diagnostic radiology were replaced manually by using each hospital's standard procedures for pulmonary TB care. For example, if the procedure indicates the requirement of two chest X-ray examinations at the beginning and the end of treatment, but only the cost of performing the first chest X-ray is available. One unit of chest X-ray examination was added and multiplied with the corresponding unit costs (e.g. 220 Thai baht per one chest x-ray examination). Missing quantities of medication used were estimated from patients' drug regimen. For example, if drug regimen indicated the use of HRZE for one month, the quantity of each medication used for one month were counted and multiplied with its corresponding unit price.

Costs not covered by patients' health insurance (i.e. out of pocket expenditures) were also retrieved from hospital billing databases. These costs included copayment, non-essential drugs (NEDs), food nutrition, and non-covered medical costs (e.g., cost incurred to patients when accessed to the services provided outside their district).

All costs were calculated in Thai currency (Thai baht), adjusted with the cumulative inflation rate from the year of data collection to 2015 [10], and then converted to international dollars using the 2015 purchasing power parity (PPP) conversion factor of private consumption (local currency unit (LCU) per international $) [11].

3.3 STATISTICAL ANALYSIS

Descriptive analyses of demographic data were conducted to describe the patient population included in the cost analyses. Categorical variables were analyzed using Chi-squared test, unless expected cell counts were low, in which case Fisher's exact test was used. Mean and standard deviation (SD) was calculated for continuous variables and differences were evaluated using analysis of variance (ANOVA).

For the cost data, measures other than the arithmetic mean (e.g. median costs, log transformed costs) do not provide information about the costs of treating all patients, which is more informative for health care policy decisions [12]. Therefore, we reported as arithmetic mean costs with SD. Since the Shapiro-Wilk test indicated that all costs data were positively skewed, nonparametric bootstrap technique was used to compare arithmetic mean costs and to derive the 95% confidence intervals (CI) [13].

Differences in the total costs between treatment strategies adjusted for baseline demographic were investigated by generalized linear models (GLMs) [14, 15]. The performance of GLMs with the inverse gaussian and gamma distribution were investigated. Two different link functions (e.g. the identity and log link) were compared. Covariates act additively in the identity-link model, and multiplicatively in the log-link model [14]. Thus, GLMs using an identity link estimate the difference in costs, while those using a log link estimate a ratio. The model included six baseline covariates of

treatment strategy, sex, age, habitat, health Insurance, and HIV status. Model performance was assessed by using normal probability plots (P-P plots), normal quantile plots (Q- Q plots) of deviance residuals [14, 16], and Akaike information criterion (AIC) [14, 17]. Smaller AIC values indicate better-fitting models; differences of ten or more in AIC indicate that the better-fitting model should be strongly preferred [14]. Normal plots were assessed visually. When points fall close to the reference line this indicates that model assumptions are suitable [14, 16, 18]. Data analyses were performed using SPSS software [19].

3.4 RESULTS

Between October 2010 and September 2013, 2,444 adult cases started pulmonary TB treatment in the three study hospitals and 1,398 patients met our eligibility criteria and were included in the analysis. There were 315 patients on pharmaceutical care, 559 on home visit, and 524 on modified DOT (Figure 1). Baseline characteristics and complications in TB treatment of the included patients are described in Table 2.

Forty-three percent of patients in the pharmaceutical care group traveled from neighboring province to seek TB care at the study hospital, while all patients in the home visit and the modified DOT groups lived in Songkhla province. Sixty-seven percent of patients each in the home visit and the modified DOT groups were covered by the UC, compared to only 30.2% in the pharmaceutical care group. The pharmaceutical care group had more patients who accessed health care that was not

covered by their public insurance (24.1%, 7.0%, and 3.6% for patients receiving pharmaceutical care, home visit, and modified DOT, respectively). Only two percent of patients in the pharmaceutical care groups were hospitalized, while 22.7% and 27.7% were hospitalized in home visit and modified DOT groups, respectively. Durations of the intensive phase were 2.5, 2.7, and 2.5 months while the continuous phase took 4.6, 5.2, 4.0 months on average in the patients receiving pharmaceutical care, home visit, and modified DOT, respectively (Table 3).

3.1 Health care resource uses and direct costs incurred before and during TB treatments

In the pre-TB treatment period, the primary health care resource use in the patients receiving pharmaceutical care was laboratory investigation $100.55 (95%CI: $94.82 to $106.46); while for those receiving home visit and modified DOT, the main resource use was hospitalization ($137.64, 95%CI: $100.92 to $180.73 and $137.77, 95%CI: $111.45 to $164.91, respectively).

During TB treatment period, the main resource use for the patients receiving pharmaceutical care was medications ($269.33, 95%CI: $227.40 to $324.52). For patients receiving home visit and modified DOT, the main health resource uses included medications, supervision activities, and hospitalization (Table 4).

The mean direct costs per patient to the public health care payer were $519.96 (95%CI: $437.31 to $625.58), $1,020.39 (95%CI: $911.13 to $1,154.11), and $887.79 (95%CI: $824.28 to $955.91) for those receiving pharmaceutical care, home visit, and modified DOT, respectively (Table 4). The mean costs to patient were $175.45 (95%CI: $130.26 to $230.48), $53.77 (95%CI: $33.25 to $79.44), and $49.33 (95%CI: $34.03 to $69.30) for those receiving pharmaceutical care, home visit, and modified DOT, respectively (Table 4). The mean total direct costs per patient were $695.41 (95%CI: $609.34 to $813.10), $1,074.16 (95%CI: $964.49 to $1,211.83), and $937.12 (95%CI: $872.79 to $1,009.90) for those receiving pharmaceutical care, home visit, and modified DOT, respectively (Table 4). There was significant difference in mean total costs when comparing pharmaceutical care with either home visit or modified DOT.

The main expenses for pharmaceutical care were medications and laboratory investigation (39.0% and 36.7% of total costs, respectively). On the other hand, the three largest contributors to total costs in home visit and modified DOT were hospitalizations, medications, and supervision activities (33.4%, 26.2%, and 20.3% in home visit; 28.9%, 22.9%, and 23.2% in modified DOT) (Figure 2).

The differences in mean total costs between treatment strategies when adjusted for baseline characteristics were investigated by the GLMs. The P-P and Q-Q plots were similar for models with the same distribution regardless of the link function (Figure 3).

The model performance assessment using the AICs (Table 5) and graphical analyses indicated that the GLMs with the inverse gaussian distribution and identity link were the best model. After adjustment for baseline characteristics, pharmaceutical care was associated with statistically significant lower direct costs compared with home visit (-$354.95, 95%CI: -$285.67 to -$424.23) and modified DOT (-$264.61, 95%CI: -$198.76 to -$330.46) (Table 6).

3.5 Discussion

Our previous study has shown that TB treatment success rates for pharmaceutical care are very similar to those for home visit or modified DOT [7]. This cost analysis shows that the pharmaceutical care approach was associated with lower costs compared with the other two approaches. Pharmaceutical care is a relatively simple strategy and requires less health care resources. The main health resource uses in the pharmaceutical care group were medications and laboratory investigation. In contrast, the supervision activities were one of the three main resource uses for both home visit and modified DOT groups.

Differences in patient characteristics across treatment strategies may have explained the difference in some health care resource uses. The pharmaceutical care group had lower hospitalization costs because almost half (43.5%) of patients traveled from a neighboring province seeking TB care at the study hospital. This implies that their illness might not be severe. If these patients had any severe respiratory condition or

required emergency admission, access to local hospitals would have happened. In contrast, the home visit and the modified DOT groups had higher hospitalization costs because these two hospitals are the main provincial referral hospitals under the Ministry of Public Health that generally have higher numbers of TB patients as well as more severe cases. These hospitals are the first choice for local patients who need free and urgent TB care.

The large variation in costs observed in our study is consistent with a systematic review by Laurence et al [20]. They reported that the costs to health care providers varied widely across different and within country income level groups. Hospitalization accounted for 74% of all provider-incurred costs for treating drug-susceptible TB in all country income groups, but only 12 % in upper middle-income countries. They also reported that the mean outpatient costs were 12 times less than hospitalization costs. However, direct costs have reduced over time (between 1990 to 2015) due to the lower admission rates and more ambulatory care in many countries. These trends are supported by previous studies indicating that ambulatory care was clinically effective and cheaper, compared to inpatient hospital care during the first two months (intensive phase) [21, 22]. The ambulatory model, therefore, has become the standard of TB care in high-burden countries [23], including Thailand.

Obviously, patients in the pharmaceutical care group paid three–fold higher out-of-pocket costs for the TB treatments compared to those receiving home visit and

modified DOT. Most of these expenses were direct health care costs incurred when patients accessed to services outside their district. Apart from the issue of hospital's location, the insurance policy is founded on the referral system. Patients in need of specialized treatment would be referred directly to the hospitals under the Ministry of Public Health. Since the study hospital is an academic tertiary hospital, a possible explanation for these patients' willingness to pay out-of-pocket may be that they had more confidence in the quality of care provided in this hospital.

In Thailand, the provision for home visits and modified DOT is funded by the Ministry of Public Health, in alignment with the WHO's recommended strategy and the global fund's incentives for patient supervision. Advantages of these supervisory activities are to provide close observation at patients' homes, to check if patients have had any difficulty taking TB medications, and to ensure TB screening of the index patients' family members. In contrast, pharmaceutical care is more recent and differs from the WHO's recommended strategy, which emphasizes the importance of direct supervision in the initial two months of treatment [24]. Our findings shed the light on the potential role of the clinical pharmacist in TB outpatient service. Timely pharmacist-led patient education for every outpatient visit and pharmacist-provided telephone consultation were clinically effective and required less health care resources. A larger scale, prospective study is warranted to generate more robust evidence to support Thai policy making about the most efficient use of limited resources to fight TB in this developing country.

Our study has limitations. The data used in the analysis came from a retrospective hospital database review. A number of patients had missing information and the approach to handle missing information depended on the type of data. Since this study abstracted costs from hospital database, only direct health care costs were included. In addition, a large proportion of the patients in the pharmaceutical care group came from other regions, the direct non-medical costs and indirect costs incurred by them would be expected to be higher than those in the other two hospitals. Future study should consider including indirect costs as well.

3.6 CONCLUSION

Compared with home visit and modified DOT, pharmaceutical care was associated with lower direct health care costs. Pharmaceutical care is a promising option for providing cost-effective care for TB patients in Thailand.

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Transparency declaration: This research was a part of a retrospective cohort study in which the result on the comparative effectiveness of pharmaceutical care versus to home visit and modified DOT was previously publish in the Journal of Clinical Pharmacy and Therapeutics [7], whereas this study focused on health care resource uses and costs associated to those three different strategies. The material regarding study participants was reproduced with permission from the copyright owner.

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Conflict of interest: All authors declare that they have no conflict of interest.

Author contributions: All authors developed conception and design of study; P.T. performed the data collection, analyzed the data, and prepared the manuscript; F.X., M.L., and J.D. performed critical revision of the manuscript

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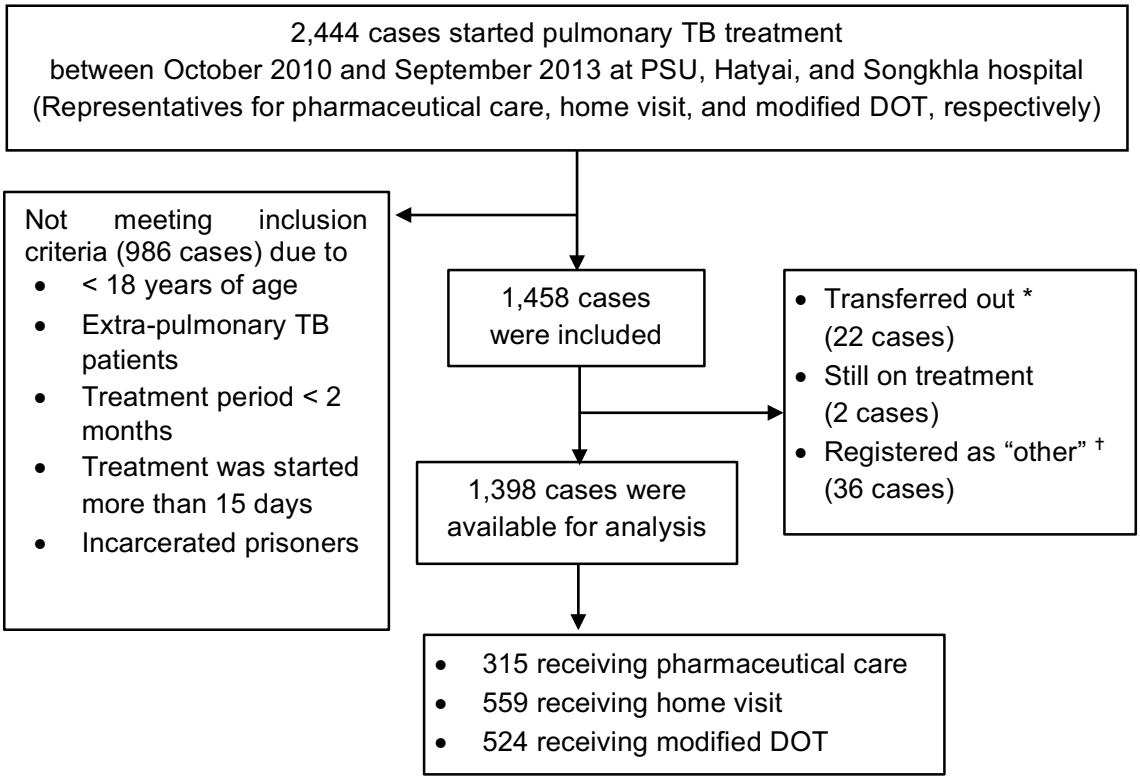
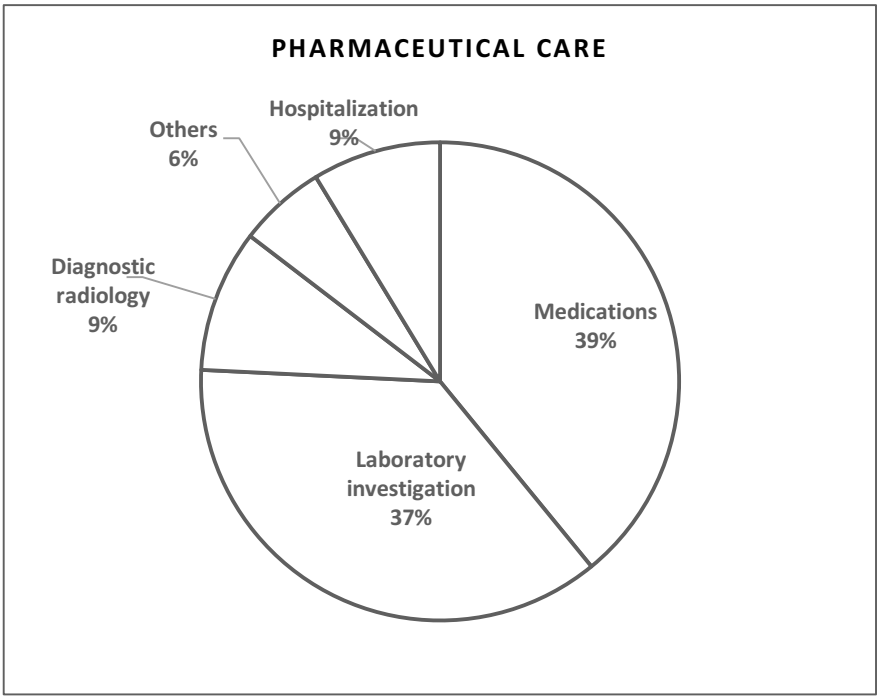
Figure 1: Flowchart of study participants



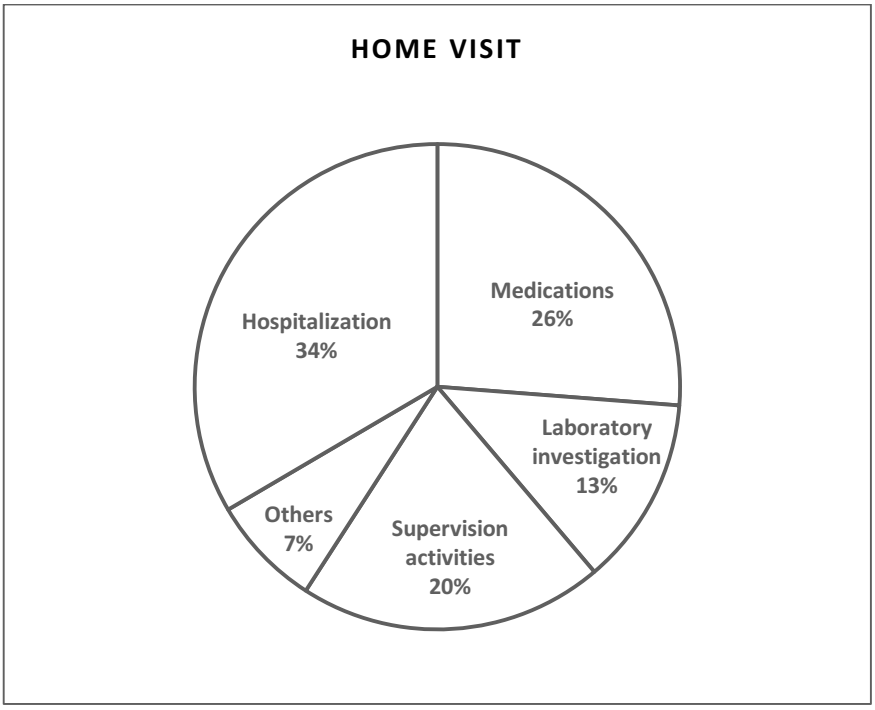
NOTE:
* "Transferred out" cases are patients who have already started the TB treatment, then relocated to new address and were transferred to another reporting unit in their new district. Transferred patients who the treatment outcome was unknown were excluded.
† Patients were categorized as "other" by using their available medical record and/or their provided information. The definition for "other cases" was all cases that do not fit the definitions of "new", "previously treated" (e.g. relapse, treatment after failure, treatment after default), and "transfer in", such as patients: for whom it is not known whether they have been previously treated; who were previously treated but with unknown treatment outcome (whether the treatment completed or not); who have returned to treatment with smear-negative pulmonary TB or bacteriologically negative extra-pulmonary TB.

Figure 2: Breakdown of total costs incurred for each treatment strategy: a.) Pharmaceutical care, b.) Home visit, and c.) Modified DOT. Percentages are proportion of respective sub-component cost out of the total costs.

a.)



b.)



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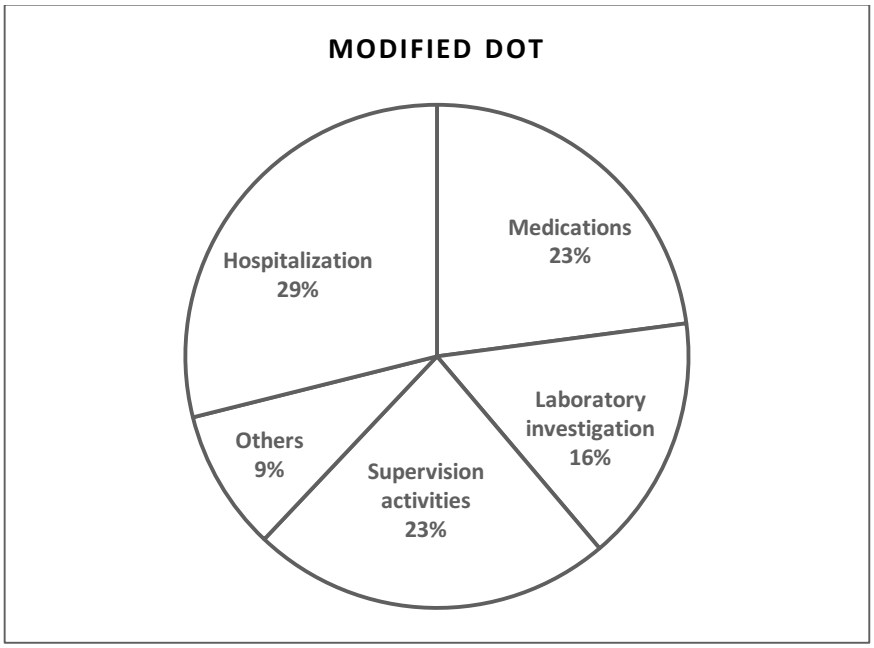
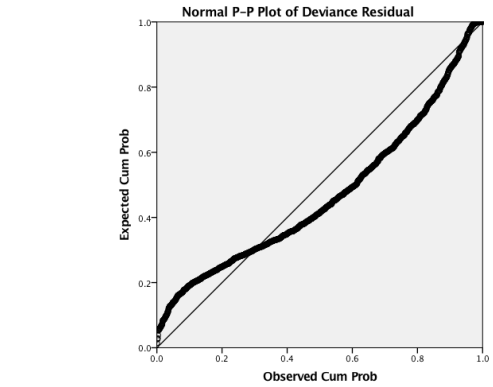
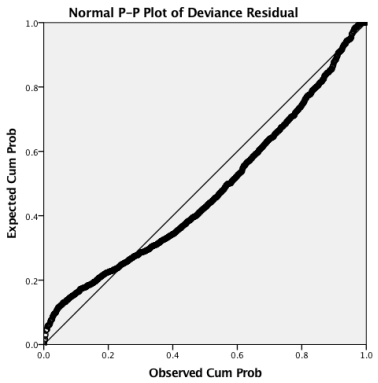

MODIFIED DOT
Medications
23%
Laboratory
investigation
16%
Supervision
activities
23%
Others
9%
Hospitalization
29%

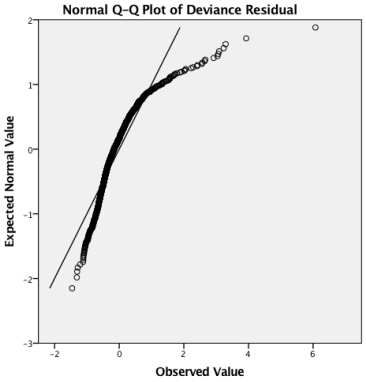
Figure 3: Normal probability plots (P-P plots) of deviance residuals for the GLMs: (a) gamma family and identity link; (b) inverse gaussian family and identity link. Normal quantile plots (Q- Q plots) of deviance residuals for the GLMs: (c) gamma family and identity link; (d) inverse gaussian family and identity link. Similar plots are obtained with a log link.



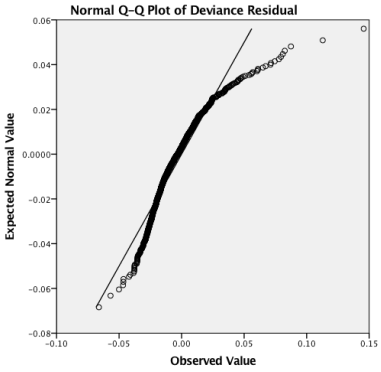
(a)



(b)



(c)



(d)

Table1: Characteristics of each treatment strategies

Services		Pharmaceutical care	Home visit	Modified DOT
Outpatient visits	Who provides the services?	clinical pharmacist	nurse	nurse or pharmacist
	Activities	• pharmacist-led patient education • monitoring and management of ADRs • identifying other drug-related problems • evaluation of treatment adherence • providing pharmacist's telephone consultation	• nurse-led patient education • monitoring and management of ADRs • evaluation treatment adherence	• nurse- or pharmacist-led patient education • monitoring and management of ADRs • evaluation of treatment adherence
Supervision activities	Who provides the services?	none	non-medical staff	non-medical staff

	Activities	none	• Home visits
			  ○ Patients take medications by themselves at home with regular home visit
				• DOT
				  ○ Patients take medications under the direct supervision
				• Home visits
				  ○ Patients take the medications by themselves at home with regular home visit

	Visit schedule	none	• Home visits
			  ○ Once a week in the first two months
			  ○ Once a month until treatment completion
				• Daily DOT
				  ○ First two weeks of treatment
				• Home visits
				  ○ Twice a week for the first month

				○ Once a week in the second month ○ Twice a month until treatment completion

Table 2: Baseline characteristics and complications in TB treatment of 1,398 participants categorized by treatment strategy

Note:
*Fisher's Exact test, † One-way ANOVA
Thai population have been covered under one of the three public insurance schemes, namely the civil servant medical benefits scheme (CSMBS), the social security scheme (SSS), and the universal coverage (UC).

Variable		1,398 cases			p-value
		Pharm care (n=315)	Home visit (n=559)	Modified DOT (n=524)	
		n (%)	n (%)	n (%)	
Baseline characteristics					
Sex	Male	192 (61.0)	388 (69.4)	342 (65.3)	0.037
	Female	123 (39.0)	171 (30.6)	182 (34.7)	
Mean age (SD), years		49.90 (18.42)	44.85 (15.83)	45.38 (16.56)	<0.001†
Age group, years	18-24	34 (10.8)	52 (9.3)	44 (8.4)	<0.001
	25-34	46 (14.6)	114 (20.4)	110 (21.0)	
	35-44	39 (12.4)	129 (23.1)	127 (24.2)	
	45-54	66 (21.0)	117 (20.9)	96 (18.3)	
	≥55	130 (41.3)	147 (26.3)	147 (28.1)	
Live in Songkhla	Yes	178 (56.5)	559 (100)	524 (100)	<0.001
	No	137 (43.5)	0	0	
Health Insurance	Universal Coverage	95 (30.2)	375 (67.1)	352 (67.2)	<0.001
	CSMBS	132 (41.9)	32 (5.7)	61 (11.6)	
	Social Security Scheme	12 (3.8)	113 (20.2)	92 (17.6)	
	Not covered by public health insurance	76 (24.1)	39 (7.0)	19 (3.6)	
HIV status	Yes	10 (3.2)	99 (17.7)	100 (19.0)	<0.001
	No	256 (81.3)	445 (79.6)	420 (80.2)	
	Unknown	49 (15.6)	15 (2.7)	4 (0.8)	

Variable		1,398 cases			p-value
		Pharm care (n=315)	Home visit (n=559)	Modified DOT (n=524)	
		n (%)	n (%)	n (%)	
Co-morbidity	Yes	157 (49.8)	154 (27.5)	140(26.7)	<0.001
	No	158(50.2)	405 (72.5)	384 (73.3)	
Sputum smear	Positive	271 (86.0)	455 (79.6)	348 (66.4)	<0.001
	Negative	44 (14.0)	114 (20.4)	176 (33.6)	
Registration	New	288 (91.4)	539 (96.4)	473 (90.3)	<0.001
	Re-treatment	27 (8.6)	20 (3.6)	51 (9.7)	
Complications in TB treatment					
Develop to MDR-TB	Yes	5 (1.6)	2 (0.04)	1 (0.2)	0.019*
	No	308 (97.8)	557 (99.6)	522 (99.6)	
	MDR-TB at baseline	2 (0.6)	0	1 (0.02)	
Re-Challenge anti-TB drug use	Yes	27 (8.6)	63 (11.3)	43 (8.2)	0.186
	No	288 (91.4)	496 (88.7)	481 (91.8)	
Hepatotoxicity with anti-TB drugs	Yes	19 (6.0)	40 (7.2)	26 (5.0)	0.320
	No	396 (94.0)	519 (92.8)	498 (95.0)	
Adverse events	No adverse events	146 (46.3)	389 (69.6)	429 (81.9)	<0.001
	Severe	28 (8.9)	63 (11.3)	45 (8.6)	
	Mild	141 (44.8)	107 (19.1)	50 (9.5)	
Hospitalization for TB	Yes	7 (2.2)	127 (22.7)	145 (27.7)	<0.001
	No	308 (97.8)	432 (77.3)	379 (72.3)	

Table 3: Drug regimen and treatment duration of 1,398 included patients categorized by treatment strategy

Note:
*Fisher's Exact test, † One-way ANOVA
H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, and S = streptomycin

Variable		1,398 cases			p-value
		Pharm care (n=315)	Home visit (n=559)	Modified DOT (n=524)	
		n (%)	n (%)	n (%)	
Drug regimen					
Initial treatment regimen	2HRZE/4HR	309 (98.1)	546 (97.7)	517 (98.7)	0.164*
	2HRZES/1HRZE/ 5HRE	4 (1.3)	13 (2.3)	6 (1.1)	
	Others	2 (0.6)	0	1 (0.2)	
Treatment duration		Mean (SD)	Mean (SD)	Mean (SD)	
Duration of intensive phase, months		2.5 (1.4)	2.7 (1.1)	2.5 (0.99)	0.001†
Duration of continuation phase, months		4.6 (2.2)	5.2 (3.1)	4.0 (1.4)	<0.001†

Table 4: Mean direct costs per patient by cost category (in 2015 international dollars) incurred to health services and to 1,398 patients before and during TB treatment categorized by treatment strategy.

Note:
Medical services included medical supplies, special diagnostics, medical equipment, operations services, outpatient services, and physical therapy
Miscellaneous costs included food solution, ambulatory care, copayments, other non-medical services, and special physician fees

Services		Pharm care (N=315)		Home visit (N=559)		Modified DOT (N=524)	
		Arithmetic mean (SD)	95%CI	Arithmetic mean (SD)	95%CI	Arithmetic mean (SD)	95% CI
Pre-TB treatment	Medications	2.51 (8.97)	1.62 - 3.61	0.16 (1.39)	0.06 – 0.28	1.96 (9.59)	1.30 – 2.75
	Laboratory investigation	100.55 (52.57)	94.82 – 106.46	27.50 (25.21)	25.55 – 29.66	21.33 (27.86)	18.75 – 23.79
	Diagnostic radiology	28.50 (62.65)	22.51 – 35.51	18.90 (41.47)	15.71 – 22.73	14.90 (40.21)	12.19 – 18.31
	Medical services	10.47 (26.78)	7.80 – 13.19	3.32 (2.28)	3.14 – 3.52	5.26 (4.38)	4.91 – 5.66
	Miscellaneous costs	0.46 (3.10)	0.18 – 0.83	0.55 (1.12)	0.46 – 0.65	0.04 (0.29)	0.02 – 0.06
	Hospitalization	18.02 (218.66)	2.53 – 43.98	137.64 (502.38)	100.92 – 180.73	137.77 (348.95)	111.45 – 164.91
	Total costs	160.51 (239.07)	141.26 – 185.59	188.08 (492.02)	151.99 – 228.63	181.27 (345.40)	150.99 – 210.55
	Costs to public payer	108.23 (128.51)	94.11 – 122.86	180.30 (491.39)	144.04 – 220.70	160.16 (311.25)	134.71 – 187.11
	Costs to patients	52.28 (227.35)	34.73 -77.77	7.79 (57.64)	4.01 – 12.76	21.11 (165.22)	9.53 – 37.15
TB treatment	Medications	269.33 (431.09)	227.40 – 324.52	281.57 (213.33)	266.33 – 297.36	212.66 (158.38)	202.55 – 225.86
	Laboratory investigation	154.53 (133.98)	140.97 – 171.08	107.58 (70.64)	102.12 – 113.33	127.81 (104.53)	119.40 – 137.27
	Diagnostic radiology	38.47 (43.85)	34.46 – 43.28	22.46 (15.39)	21.28 – 23.80	26.66 (30.21)	24.38 – 29.30
	Medical services	27.55 (31.48)	24.45 – 31.21	30.50 (40.51)	27.72 – 33.98	36.11 (38.74)	33.23 – 39.64
	Supervision activities	0	-	218.23 (178.05)	205.47 – 232.03	217.67 (182.09)	201.83 – **233.64**
	Miscellaneous costs	2.60(16.38)	1.22 – 4.57	4.08 (8.38)	3.48 – 4.70	1.93 (4.26)	1.60 – 2.29

Services		Pharm care (N=315)		Home visit (N=559)		Modified DOT (N=524)	
		Arithmetic mean (SD)	95%CI	Arithmetic mean (SD)	95%CI	Arithmetic mean (SD)	95% CI
	Hospitalization	42.42 (624.54)	0 – 113.08	221.65 (1,237.85)	135.60 – 326-58	133.03 (557.95)	90.32 – 181.95
	Total costs	534.91 (879.99)	451.33 – 650.14	886.07 (1,286.99)	789.66 – 995.53	755.86 (656.35)	700.76 – 817.97
	Costs to public payer	411.73 (863.56)	330.99 – 521.12	840.09 (1,270.06)	745.59 – 948.39	727.63 (644.72)	675.15 - 789.90
	Costs to patients	123.18 (327.19)	88.56 – 165.54	45.98 (275.80)	27.58 – 70.07	28.22 (112.17)	19.13 – 38.91
Total	Total costs	695.41 (904.88)	609.34 – 813.10	1,074.16 (1,465.81)	964.49 – 1,211.83	937.12 (768.00)	872.79 – 1,009.90
	Total costs to public payer	519.96 (883.05)	437.31 – 625.58	1,020.39 (1,455.52)	911.13 – 1,154.11	887.79 (747.26)	824.28 – 955.91
	Total costs to patients	175.45(432.88)	130.26 – 230.48	53.77 (298.17)	33.25 – 79.44	49.33 (219.93)	34.03 – 69.30

Table 5: Comparison of GLMs with two different types of distributions and either identity or log link for models including six baseline covariates.

Distributions	Link functions	AIC
Gamma	Identity	21,220.19
	Log	21,223.12
Inverse Gaussian	Identity	20,720.10
	Log	20,724.58

Table 6: Difference in mean total direct costs between the specified group compared with reference group when impact of differences in baseline characteristics was adjusted by GLMs with inverse gaussian distribution and the identity link.

Note:
References used in each category were supervision strategy (pharmaceutical care), gender (female), age group (18-24), habitat (non-local), health Insurance (UC), HIV status (No); Significance for all statistical analysis was at $p < 0.05$.

Variable		Difference in mean costs	95% CI	p-value
Supervision strategy	Home visit	354.95	285.67 to 424.23	<0.001
	SAT	264.61	198.76 to 330.46	<0.001
Gender	Male	-5.39	-54.73 to 43.94	0.830
Age group, years	25-34	123.52	44.88 to 202.16	0.002
	35-44	121.94	42.06 to 201.83	0.003
	45-54	206.00	124.45 to 287.56	<0.001
	>55	216.28	136.55 to 296.02	<0.001
Habitat	Local	-148.43	-232.50 to -64.35	0.001
Health Insurance	CSMBS	18.58	-55.37 to 92.53	0.622
	Social Security Scheme	-98.71	-168.63 to 28.79	0.006
	Not covered by public health insurance	40.14	-40.19 to 120.46	0.327
HIV status	Yes	780.04	605.67 to 954.41	<0.001
	Unknown	41.30	-63.77 to 146.36	0.441

APPENDIX 3.I: ICD-10 codes that needed to be investigated concurrently with other information (e.g. type of outpatient service, laboratory investigation, patient medical record, and TB registration record) before considering as costs associated with TB diagnosis and treatment.

Categories	ICD-10 Codes	Diseases, health conditions or services
Symptoms before TB diagnosis or cause of hospitalization	• J0-9 • R05 • R042 • R91 • Z000 • Z030 • Z201	• Diseases of the respiratory system • Cough • Hemoptysis • Abnormal findings on diagnostic imaging of lung • Encounter for general adult medical examination • Encounter for medical observation for suspected diseases and conditions ruled out • Contact with and (suspected) exposure to TB
TB and TB related diseases	• A17-19 • A310 • B200 • B22-24 • B90	• Other type of TB • Pulmonary mycobacterial infection • Human immunodeficiency virus (HIV) disease resulting in mycobacterial infection • HIV disease resulting in other specified diseases or other conditions • Sequelae of tuberculosis
Treatment of ADRs	• K75 • L270-1 • T50, T78	• Other inflammatory liver diseases • Skin eruption due to drugs & medicaments taken internally • Adverse effects

CHAPTER 4:

OUT OF POCKET EXPENDITURES, INDIRECT COST AND HEALTH-RELATED QUALITY OF LIFE OF PATIENTS WITH PULMONARY TUBERCULOSIS IN THAILAND

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ABSTRACT

Background. In Thailand, referral hospitals may adopt different supervision approaches, including pharmaceutical care and home visits, to improve adherence to tuberculosis (TB) treatment.

Objective. To compare out-of-pocket (OOP) expenditures, indirect costs, and health-related quality of life (HRQoL) among TB patients who received pharmaceutical care compared to home visit and self-administered therapy (SAT) in Thailand.

Methods. We conduct a prospective study to collect OOP expenditures, indirect costs, and HRQoL from a subsample of 104 adult pulmonary TB patients who started treatment between January and May 2014 in the three hospitals. Patient interviews, patient medical records, and hospital billing database were the three sources of the data. Differences in the mean of OOP expenditures and indirect costs among treatment strategies adjusted for baseline characteristics were investigated by generalized linear models (GLMs).

Results. Out of 255 patients who started pulmonary TB treatment during the specified period, 104 patients were interviewed and included in the analysis (29, 38, and 37 patients receiving pharmaceutical care, home visit, and SAT, respectively). The mean total OOP expenditures per patient were $907.56 (CI: $603.80 to $1,269.41), $148.47 (CI: $109.49 to $194.89), and $95.35 (CI: $69.11 to $129.63) for those receiving pharmaceutical care, home visit, and SAT, respectively. The GLM indicated statistically significant lower OOP expenditures for patients receiving either home visit

or SAT (ratio of mean costs: 0.247, CI: 0.142 to 0.427, and 0.318, CI: 0.187 to 0.540, respectively), when compared to those receiving pharmaceutical care. The indirect costs incurred by the patients receiving pharmaceutical care, home visit, and SAT were $1,925.68 (CI: $922.06 to $3,284.94), $2,393.66 (CI: $1,435.01 to $3,501.98), and $833.33 (CI: $453.87 to $1,263.45), respectively. The GLM found no statistically significant difference in indirect costs in the home visit and SAT group (ratio of mean costs: 1.904, CI: 0.754 to 4.802, and 0.792, CI: 0.289 to 2.175, respectively), when pharmaceutical care was set as a reference. The mean health utility scores (using the 3-level EuroQol five dimensions questionnaire (EQ-5D-3L)) at the baseline and at the end of treatment were 0.679 and 0.830, 0.713 and 0.905, and 0.708 and 0.913 for the patients receiving pharmaceutical care, home visit, and SAT, respectively.

Conclusion. The patients receiving pharmaceutical care experienced the highest OOP expenditures, compared with those receiving home visit and SAT. Patients receiving home visit had the highest indirect costs as well as the highest improvement in utility scores. Differences in patient characteristics among patients receiving different strategies had a high impact on a large variation in financial burden. Reducing the financial burden incurred during seeking care, TB diagnosis, and treatment initiation is necessary.

4.1 INTRODUCTION

Tuberculosis (TB) imposes a significant impact not just on the public healthcare system but also on patients and their families. Patients have to pay out of their own pockets for costs of health care, food, and transportation when seeking care and receiving TB diagnosis and treatment at the health center or the hospital [(1)].

Many TB patients are economically productive adults [(2)], and productivity loss due to the disease is the main driver of indirect costs [(1)]. A systematic literature review reported that the financial burden of TB borne by patients was composed of three parts: 20% direct medical costs, 20% direct non-medical costs, and 60% indirect costs [(3)]. In addition to the economic impact, TB causes pain and psychological suffering and also consequently results in a reduction in health-related quality of life (HRQoL) of patients [(4,5)].

The economic burden of TB has a significant, multifaceted impact on low and middle-income countries [(6)]. Patients may have poor compliance to medications due to financial burden, resulting in worsening health, potential spread of the disease, and/or death [(6)]. One of the World Health Organization (WHO) global target for reducing economic impact is to push forward the provision of TB diagnosis and treatment, free of charge, through the national universal health coverage [(3,7,8)].

Thailand established national universal coverage in 2002 [9]. All citizens of Thai nationality are covered under one of the three public insurance schemes, namely, the civil servant medical benefits scheme (CSMBS), the social security scheme (SSS), and the universal coverage scheme (UC). Access to public TB diagnostic services and treatment is free of charge in Thailand. The national TB program adopts the daily dose regimen whereby most drug-susceptible patients take TB medication themselves at home and visit a health center or a district hospital at least once a month for medication refill. Patients with multidrug-resistance TB (MDR-TB) have to visit the nearest health center every day for treatment.

There are barriers to the implementation of directly observed therapy (DOT), a WHO recommended strategy to promote adherence for pulmonary TB patients [10], in resource-constrained countries [11,12]. Other supportive strategies are therefore tailored to a country-specific context [13-15]. In Thailand, three alternative supervision approaches, pharmaceutical care (pharmacist-led health education), home visits, and self-administered therapy (SAT), are adopted by referral hospitals to improve adherence to TB treatment. However, evidence on the economic impact associated with these approaches is limited. The objective of this study was to compare the out-of-pocket (OOP) expenditures, indirect costs, and HRQoL for TB patients who received pharmaceutical care compared to home visit and SAT in Thailand.

4.2 METHODS

4.2.1 Data source and target population

This was a prospective cohort study that followed patients for at least six months or until the treatment course was complete. The OOP expenditures such as copayment and health care costs not covered by public health insurances (i.e. non-essential drugs (NEDs), seeking care outside their service area) were retrieved from the hospital's database, while other OOP expenditures, productivity loss, and HRQoL were obtained through patient interviews. Patients' clinical data were retrieved from patient medical records and TB registration records. Costs were separately estimated in two main phases: pre-TB treatment period (from illness onset to TB diagnosis) and TB treatment period (from the start to the completion of TB treatment). All costs were calculated in Thai currency, adjusted with the cumulative inflation rate from the year of data collection to 2015 [16], and then converted to international dollars using the 2015 purchasing power parity (PPP) conversion factor of private consumption (local currency unit (LCU) per international $) [17].

The study was conducted in three hospitals in Songkhla province, southern Thailand: Songklanagarind hospital, Hatyai hospital, and Songkhla hospital where pharmaceutical care, home visit, and SAT, respectively, have been adopted. Songklanagarind hospital is an 850-bed teaching hospital affiliated to the Prince of Songkla University (PSU). Hatyai hospital (700-bed, tertiary care) and Songkhla

hospital (480-bed, secondary care) are the main provincial referral hospitals under the Ministry of Public Health. This study was approved by the Research Ethics Board at each of the participating hospitals.

The patient eligibility criteria included the following: patients ≥ 18 years of age, confirmed pulmonary TB by a physician and classified bacteriologically as smear-positive or smear-negative, TB treatment started between January and May 2014, and a treatment period of ≥ 2 months in one of the study hospitals. A convenience sample was recruited in each of the study hospitals. Eligible patients were informed of the purpose of the study and assured that refusal to participate would not affect their TB care.

4.2.2 TB supervision strategies

Pharmaceutical care provides pharmacist-led patient education at every outpatient visit, while home visit provides regular home visits until treatment completion and SAT is an approach when patients take medications by themselves at home without any additional supportive approach. The treatment regimen and descriptions of these strategies were described in our previous retrospective cohort study [18,19].

Patients were interviewed three times during clinic visits in the intensive phase (day 0, day 14 or 30, and day 60 of TB treatment). Then, they were interviewed once every two months during the continuous phase of treatment (the remaining four months). Most patients were interviewed while waiting in the clinic. The eligible patients who

missed the interview at the clinic visit were contacted and interviewed by telephone within 14 days after the clinic visit. If patients could not be reached through the telephone, they were interviewed at their next clinic visit. Patients were interviewed using a questionnaire consisting of three parts: 1) socio-demographic information (first visit only); 2) OOP expenditures and productivity loss (the value of paid and unpaid production loss due to illness, time spent seeking treatment, disability [20]); and 3.) HRQoL measured using the EuroQol five-dimensional three-level (EQ-5D-3L) Thai version [21,22].

The EQ-5D-3L is the most preferred utility-based questionnaire in Thailand, because it is short and easy to understand [23]. The EQ-5D-3L includes five attributes: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression [24]. Each attribute has three response levels representing no, some, and severe problems. Patients were asked to select the level that best described their current health status for each of these five attributes, and then assess their global health status by using the visual analog scale (VAS). The EQ-5D-3L health utility score was calculated by using the Thai value set [25], in which the utility score can range between -0.45 and 1. The score "1" and "0" represents perfect health and death, respectively, while negative values indicate states worse than death. For the VAS, patients were asked to mark the point on a vertical scale that best described their current health status where "100" and "0" represent "best imaginable health" and "worst imaginable health", respectively.

Relevant OOP expenditures collected during the interviews included: 1) health care costs and other medications costs (e.g. vitamins, antibiotics, anti-cough) occurred in the private healthcare units; 2) costs of transportation, food, and accommodation. Productivity loss was measured including time unable to work due to TB, travel time to and from hospital, time spent at the hospital (waiting time, consultation time, and hospitalizations), and time spent by accompanying family members on outpatient visits or during hospitalizations. If patients were hospitalized, we assumed one accompanying family member per patient and eight hours of working time loss per day. To estimate the indirect costs due to productivity loss, the amount of time lost due to TB illness was multiplied by patient or the family member's hourly wage rate. If the wage was not available, we used daily minimum wage in Songkhla province (300 baht per day, in 2015) [(26)].

4.3 STATISTICAL ANALYSIS

Descriptive analyses were conducted to explore the distributions and categorize the variables under study. Categorical variables were analyzed using Chi-squared test, unless expected cell counts were low, in which case Fisher's Exact test was used. Means and standard deviations (SD) were calculated for continuous variables. Differences in means were evaluated using analysis of variance (ANOVA). The EQ-5D-3L utility scores between the start of intensive phase and the end of continuous phase were compared using paired t-test.

We reported the cost data as arithmetic mean costs with SD, since other measures (e.g. median costs, log transformed costs) do not provide sufficient information to estimate total costs at the population level, which is informative for healthcare policy decisions [27]. The Shapiro-Wilk test indicated that all cost data were positively skewed ($p<0.001$), nonparametric bootstrap technique was thus used to compare arithmetic mean costs and to derive the 95% confidence intervals (CI) [28].

Differences in the mean costs (e.g. OOP expenditures and indirect costs) among treatment strategies adjusted for baseline characteristics were investigated by generalized linear models (GLMs) [29,30]. The model included seven baseline covariates, namely, treatment strategy, sex, age, habitat, education, income, and health Insurance.

The performance of GLMs was assessed by comparing two different distributions (e.g. inverse gaussian and gamma distribution) and two different link functions (e.g. identity and log link). Because the covariates act additively on the mean, the models with identity link present the results as the difference in mean costs. On the contrary, those with log link present the ratio of means due to the fact that the covariates act multiplicatively [29]. Model performance was assessed by using Akaike Information Criterion (AIC) [29,31] and graphical analyses: 1) scatter plots of deviance residuals versus fitted values; 2) normal probability plots (P-P plots) of the deviance residuals;

and 3) normal quantile plots (Q- Q plots) of the deviance residuals [29,32]. Smaller AIC values indicate more appropriate model. Differences of ten or more in AIC indicate the better-fitting model [29]. The more suitable models provided normally distributed deviance residuals (indicated by a random scatter of points from the scatter plots and the straight line on the normal plots) [29,32,33]. Data analyses were performed using SPSS software [34]. Significance for all statistical analysis was set at $p < 0.05$ whenever applicable.

4.4 RESULTS

Between January and May 2014, 205 adult patients started pulmonary TB treatment in these three hospitals. A total of 104 patients from the three hospitals met our inclusion criteria and were included in the analysis (29, 38, and 37 patients receiving pharmaceutical care, home visit, and SAT, respectively, see Figure1). Baseline characteristics and complications of TB treatment are described in Table 1. Thirty-eight percent of the patients in the pharmaceutical care group came from neighboring provinces to seek TB care at the study hospital, while all patients in the home visit and SAT groups were from Songkhla province. There were 41.4%, 78.9%, and 67.6% of patients with education level less than high school in pharmaceutical care, home visit, and SAT groups, respectively. Pharmaceutical care had the lowest percentage of patients (6.9%) who were unable to work due to TB compared with home visit (23.7%) and SAT groups (18.9%). Mean monthly income before TB and current income were $1,381.97 and $1,184.59 in pharmaceutical care group, $738.67 and $421.76 in home

visit group, and $569.48 and $417.79 in SAT group. Pharmaceutical care group had the highest percentage of patients who accessed healthcare not covered by their public insurance (37.9%, 7.9%, and 0% for patients receiving pharmaceutical care, home visit, and SAT, respectively).

The treatment success in 104 patients receiving pharmaceutical care, home visit and SAT were 100%, 97.37%, and 83.78%, respectively (Table 2). WHO sets the treatment success target for new smear positive pulmonary TB patients as 85% [(35)]. When focusing only on the 72 new smear positive patients, the success rates were 100%, 95.80%, and 80.95% for patients receiving pharmaceutical care, home visit, and SAT, respectively. One patient (2.6%) in home visit group died. In the SAT group, there were two patients (5.4%) who died, and four (10.8%) who defaulted treatment. The average durations of the intensive phase were 2.5, 2.7, and 2.2 months while the continuous phase were 4.3, 5.5, 4.6 months in the patients receiving pharmaceutical care, home visit, and SAT, respectively.

4.4.1 OOP expenditures

The mean total OOP expenditures per patient were $907.56 (CI: $603.80 to $1,269.41), $148.47 (CI: $109.49 to $194.89), and $95.35 (CI: $69.11 to $129.63) for those receiving pharmaceutical care, home visit, and SAT, respectively (Table 3). The main expense across all treatment strategies was transportation costs (Figure 2). The differences in mean total OOP expenditures between the treatment strategies when

adjusted for baseline characteristics were investigated by the GLMs. The model performance assessment using the AICs (Table 4) and the graphical analyses (Figure 3) indicated a strong preference for the gamma model and the log link. After adjustment for baseline characteristics (Table 5), there were statistically significant lower OOP expenditures for patients receiving either home visit or SAT (ratio of mean costs: 0.247, CI: 0.142 to 0.427, and 0.318, CI: 0.187 to 0.540, respectively), when compared to the patients receiving pharmaceutical care.

In the pre-TB treatment period, pharmaceutical care group incurred higher OOP expenditures ($169.48, CI: $120.04 to $233.31), when compared with those receiving either home visit ($42.09, CI: $19.81 to $72.17) or SAT ($19.11, CI: $13.52 to $26.71). The OOP expenditures were driven mostly by outpatient visits that were not covered by the patients' health insurance (40.94%) and transportation costs (28.51%). Patients receiving home visit had the main expenses from hospitalizations that were not covered by the health insurance (32.36%) and food supplement (30.94%). The largest expenses in patients receiving SAT were transportation (44.22%) and health care costs occurred in the private healthcare units (23.13%).

During TB treatment period, the main OOP cost driver across all treatment strategies was also transportation costs ($278.53, CI: $173.94 to $400.67, $57.15, CI: $43.81 to $72.55, and $47.19, CI: $36.75 to $60.48 for those receiving pharmaceutical care, home visit, and SAT, respectively). In addition, patients in pharmaceutical care group also had high expenses due to outpatient visits (24.63%) and hospitalizations

(20.43%) that occurred outside the service area and were not covered by public health insurance. Patients in pharmaceutical care group paid higher OOP expenditures ($738.07, CI: $458.96 to $1,095.58), compared with those in either the home visit or SAT group ($106.38, CI: $79.24 to $136.36, and $76.24, CI: $50.90 to $109.50, respectively).

4.4.2 Indirect costs incurred by patients

In the pre-TB treatment period, on average, ten patients in home visit group had lost a total of 37 work days, while five patients each in the SAT and pharmaceutical care groups reported a loss of 24 and 12 work days, respectively. In the TB treatment period, patients had lost a total 107, 76, and 54 work days among 18, 10 and 12 patients who received home visit, SAT, and pharmaceutical care, respectively (Table 6).

The indirect costs were $1,925.68 (CI: $922.06 to $3,284.94), $2,393.66 (CI: $1,435.01 to $3,501.98), and $833.33 (CI: $453.87 to $1,263.45) for patients receiving pharmaceutical care, home visit, and SAT, respectively.

GLMs with identity link regardless of the distribution did not converge. The AICs (Table 4) and the graphical analyses (Figure 4) clearly showed that the gamma distribution with log link was a better performed model. After adjustment for baseline characteristics (Table 5), the ratios of mean costs were 1.904 (CI: 0.754 to 4.802) and

0.792 (CI: 0.289 to 2.175) for the home visit and SAT groups, respectively, when pharmaceutical care was set as a reference.

On average, the OOP expenditures accounted for 7.93%, 2.00%, and 1.29% of the reported patient's annual income, while the indirect costs were 12.35%, 27.05%, and 11.35% of the reported patient's annual income for patients receiving pharmaceutical care, home visit, and SAT, respectively (Figure 5).

4.4.3 HRQoL

When followed patients until March 2015, a total of 104 and 90 patients completed the questionnaire at the end of intensive and continuous phases, respectively. The overall study dropout rate was 13.5%.

Percentage of patients who had no problem with mobility at the baseline and at the end of treatment were 72.4% and 84.6%, 78.9% and 88.9%, as well as 64.9% and 100% in pharmaceutical care, home visit, and SAT groups, respectively. There were 90% and almost 100% of all patients who had no problem with self-care at the baseline and at the end of treatment, respectively. At the baseline, 60% of all patients had no problem with usual activities, while the percentage of those had increased to more than 80% at the end of treatment. At the baseline, 10.3%, 5.3%, and 5.4% of patients receiving pharmaceutical care, home visit, and SAT, respectively, had extreme pain or

discomfort. Four patients (10.5%) and one patient receiving home visit and SAT, respectively, also reported extreme anxiety or depression, whereas at the end of treatment, no patients reported either extreme pain/discomfort or anxiety/depression. The mean EQ-5D scores at the baseline and at the end of treatment were 0.679 and 0.830, 0.713 and 0.905, and 0.708 and 0.913, while the mean VAS scores at the baseline and at the end of treatment were 66.90 and 89.92, 61.68 and 91.94, and 65.41 and 94.00 for the patients receiving pharmaceutical care, home visit, and SAT, respectively (Table7).

Table 8 shows the differences in paired mean scores between the beginning and the end of treatment. All three treatment strategies had significant increases in utility scores at the end of treatment. Home visit resulted in the highest difference in paired mean EQ-5D and VAS scores.

4.5 DISCUSSION

Although patients are covered under one of three public insurance schemes and access to TB care is free of charge in Thailand, this prospective study highlights the financial burden imposed by TB on patients and the society. As percentage of reported patient's annual income, the OOP expenditures (primarily transportation costs) for patients receiving pharmaceutical care were four-fold higher than those receiving the

other two strategies. Productivity loss was a large contributor to the financial burden. Patients receiving home visit had the highest indirect costs. All three strategies resulted in significant improvement in patients' HRQoL. The financial burden varied markedly across different treatment strategies due to the influence of several factors such as public insurance coverage, socioeconomic status, disease severity, distance to TB services.

The pharmaceutical care group incurred the highest OOP expenditures is not surprising as many patients came from other provinces, in order to seek TB treatments, they incurred six-fold higher transportation costs compared with the other two strategies. In addition, 38% of these patients paid their medical care themselves because the healthcare at the study hospital was outside their service area. Consequently, costs due to outpatient visits and hospitalizations became the second large contributor for OOP expenditures among these patients. This issue has been discussed in our previous retrospective cohort study [19].

People with TB-related symptoms may pay to seek care in a private unit before the TB diagnosis is made by a public healthcare provider. In all treatment strategies, average costs due to visiting private facilities before TB treatment were much higher than those incurred during TB treatment period. Before TB diagnosis, a larger proportion of patients receiving pharmaceutical care visit the private facilities, presumably due to

the higher average income in this group. After TB diagnosis, patient costs were much lower, because the health care costs were mostly covered under patients' health insurance.

Productivity loss posed a substantial financial burden to patients receiving home visit due to the high proportion of patients who were too sick to work and of those who were unemployed because of TB. The home visit group had the highest number of hospitalized patients. One possible explanation may be the home-visit study hospital was the main provincial referral hospital under the Ministry of Public Health. The other reason may be the lower education level in patients receiving home visit, compared with those receiving pharmaceutical care. A previous study in Thailand indicated that lower education levels were associated with poorer TB knowledge [(36)]. These patients may be more likely to delay visiting a hospital and choose other options instead (e.g. purchasing medications from drugstores, visiting community health centers). In such cases, disease is likely to be more advanced before hospital care begins.

Indirect costs affect both patients and the society. Income loss due to TB affects patients directly, while production loss due to time seeking treatment, illness, disability or premature mortality affects the society as well. A large proportion of patients in home visit and SAT had no fixed income, an absence from work due to seeking treatment or illness resulted in income loss.

The period of pre-diagnosis and first two months of TB treatment are very important for TB care. The financial burden incurred during these periods may delay TB diagnostic, lead to the spread of disease in the community, and become barriers to treatment adherence [3]. For both patients and societal benefit, it is necessary to ensure that public healthcare services are provided in a way that decrease OOP expenditures and indirect costs, especially during seeking care, TB diagnosis, and treatment initiation. During seeking care, improving access to the community health centers (e.g. providing the overtime services, ensuring use of effective screening and referral procedures) could increase accessibility and reduce patient congestion at the hospital. In the diagnostic process, ensuring use of fast and precise diagnostic test is necessary for reducing transportation costs and work time loss incurred to patients.

At the baseline, TB impaired patients' HRQoL in both physical and psychological domains across all five EQ-5D attributes. TB treatment, under all three strategies, resulted in significantly improved patients' quality of life over time. Our findings demonstrated the longitudinal changes in TB patients' quality of life over at least six months which has been rarely reported. Most studies on the HRQoL of TB patient have been based on a cross-sectional design [4]. Of the seven studies with a prospective longitudinal design that assessed quality of life during the various stages of treatment, most had a follow-up less than 6-month. Only two of the seven studies (one from China and the other from Malaysia) followed patients until the treatment was completed and

reported improvement of patients' quality of life over time. However, both used a different non-utility based quality of life measure: the SF-36 [37,38]. Only one study used SF-36 alongside EQ-5D, but they investigated the change in health status only at the beginning and at 2-month [39].

The use of patient interviews in this prospective study allowed us to explore the effects of TB on patients' employment status and the differences in socioeconomic characteristics (e.g. income levels, educational attainment) among different treatment strategies which were not examined due to the limitations of the hospital database review in our previous retrospective study [18].

Nevertheless, there were some limitations in our study. Given the nature of a prospective cohort study, it generally follows patients for a long time, which can lead to dropouts, and consequently require a large initial sample size. However, due to the time constraints, the longer recruitment period requires an excessive amount of time to complete the data collection. As a result, we were only able to analyze a limited number of patients. In addition, although we found that the treatment success in patients receiving SAT was below the WHO's target of 85% [35] and this accentuated the necessity of the supportive approach for enhancing adherence in pulmonary TB patients, the small sample obtained may not be representative of the population intended to be analyzed. Another limitation is related to the long treatment duration of

TB. We initially planned to follow our participants for at least six months or until the treatment course was completed. Eventually, the interview was stopped in March 2015. In addition, although we had followed the treatment outcomes for almost two years, two patients who had developed to MDR-TB were still going through treatment at the end of December 2015. Lastly, we had a few number of MDR-TB cases. Future larger-scale study would be useful to confirm our findings and to inform the costs related to MDR-TB patients.

4.6 CONCLUSION

The patients receiving pharmaceutical care experienced the highest OOP expenditures, compared with those receiving home visit and SAT. Patients receiving home visit had the highest indirect costs as well as the highest improvement in utility scores. Differences in patient characteristics among patients receiving different strategies had a high impact on a large variation in financial burden. Reducing the financial burden incurred during seeking care, TB diagnosis, and treatment initiation is necessary.

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Conflict of interest: All authors declare that they have no conflict of interest.

Author contributions: All authors developed conception and design of study; P.T. performed the data collection, analyzed the data, and prepared the manuscript; F.X., M.L., and J.D. performed critical revision of the manuscript

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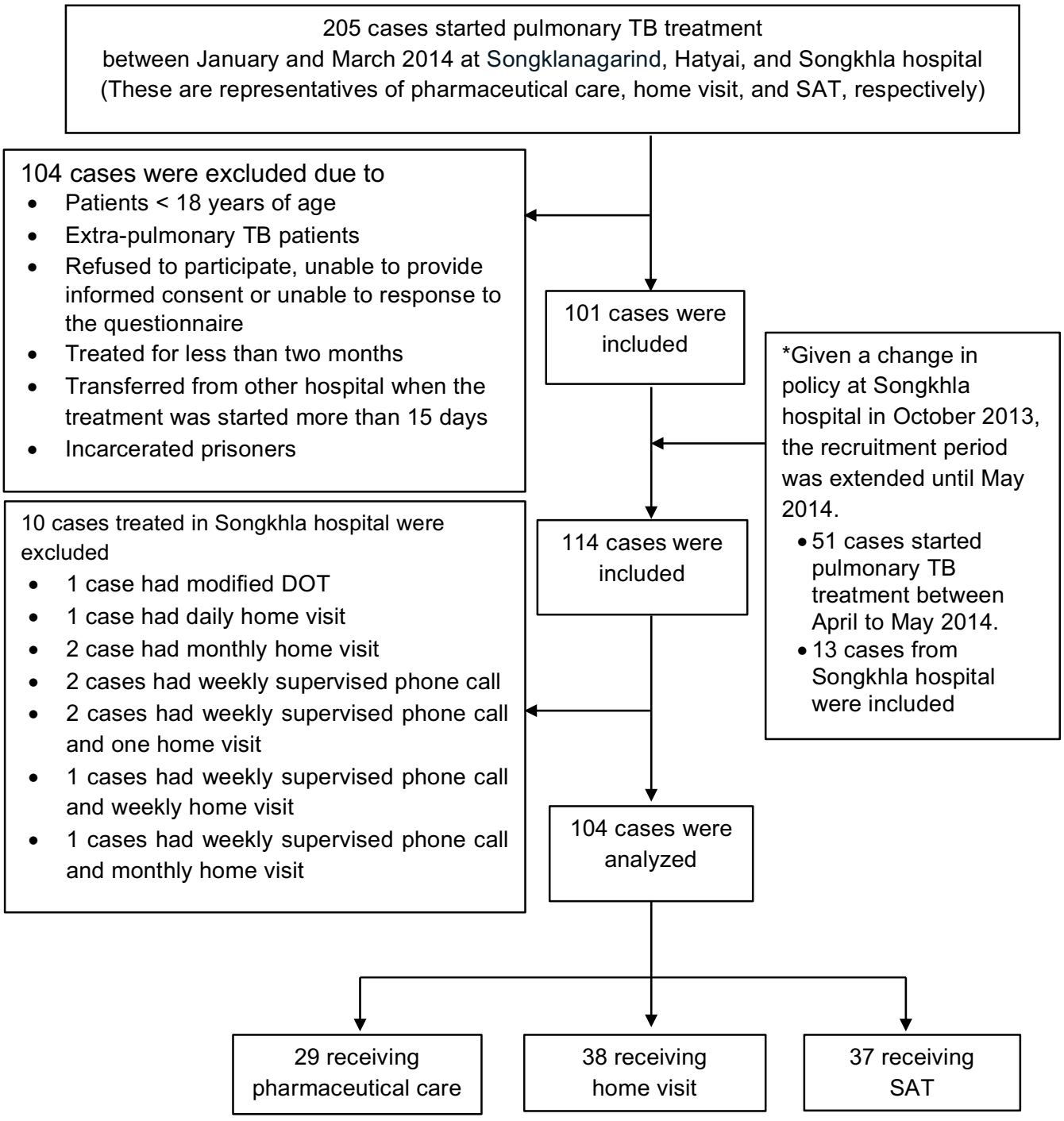
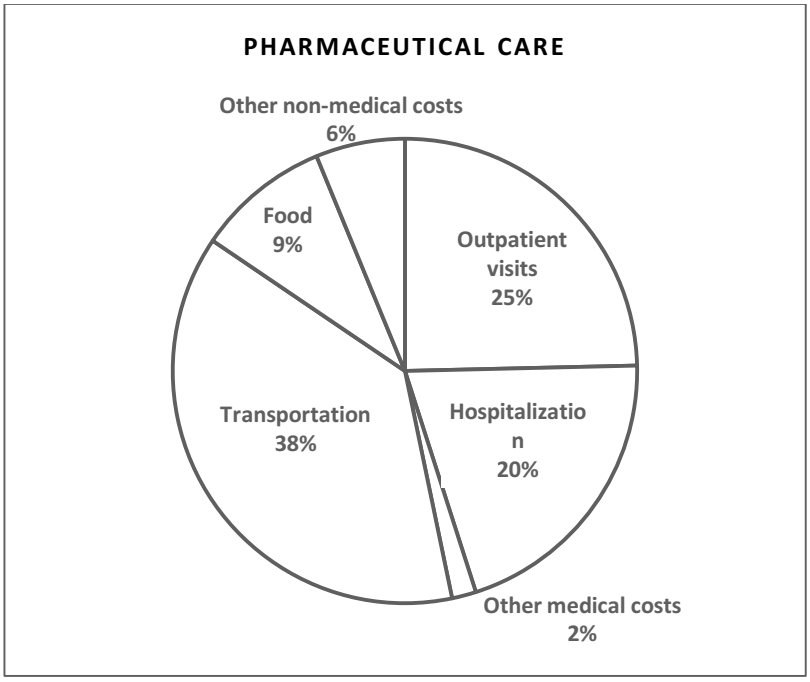
Figure1: Flowchart of study participants



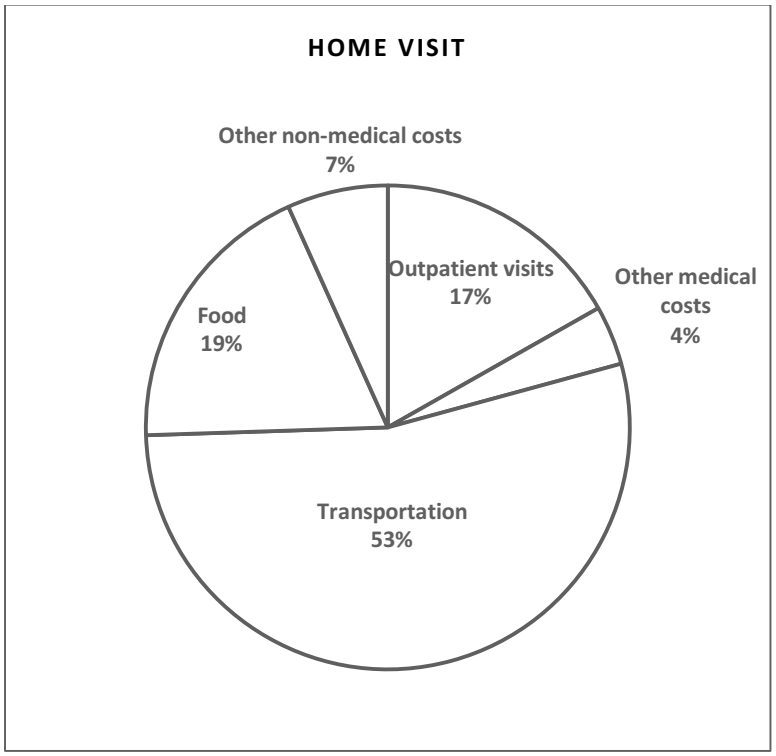
NOTE: *Previously, Songkhla hospital adopted the modified DOT (a combination of short-course DOT and home visits) as an adherence enhancement strategy. However, given the change in treatment policy in October 2013, most patients had SAT instead of receiving modified DOT. Therefore, the recruitment period was extended until May 2014 in order to observe the performance of hospital's new policy and recruit more patients.

Figure 2: Breakdown of OOP expenditures incurred in each treatment strategy: a.) Pharmaceutical care, b.) Home visit, and c.) SAT. Percentages are proportion of respective sub-component cost out of the total costs.

a.)



b.)


HOME VISIT
Other non-medical costs
7%
Outpatient visits
17%
Other medical
costs
4%
Food
19%
Transportation
53%

c.)

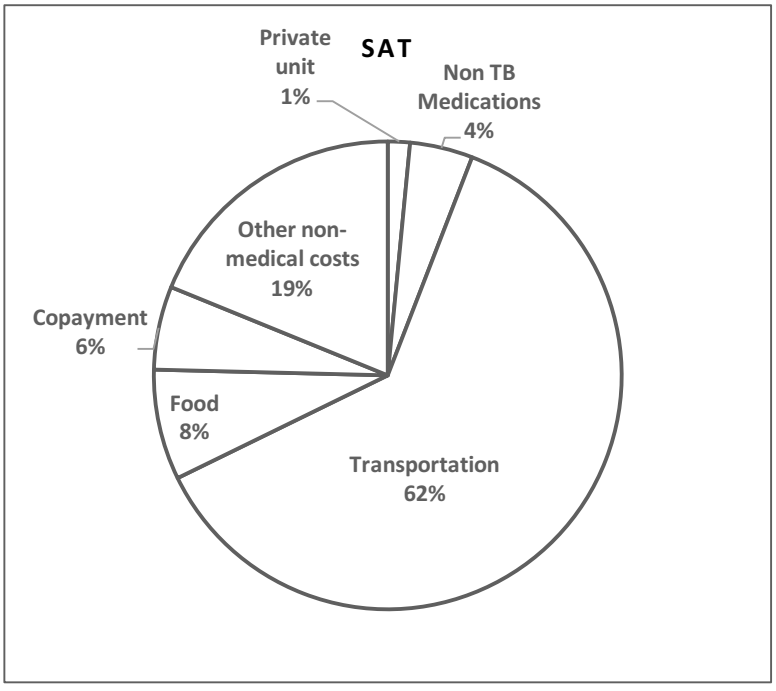
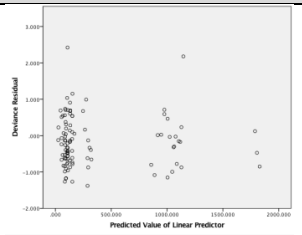
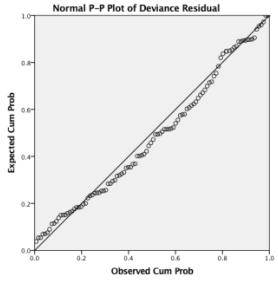
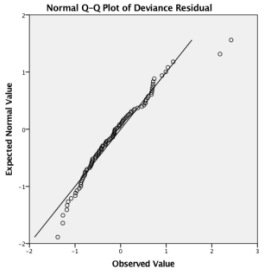
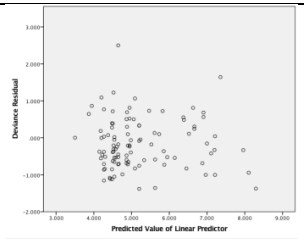
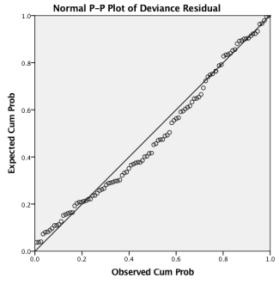
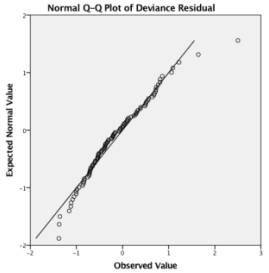

SAT
Private
unit
1%
Non TB
Medications
4%
Other non-
medical costs
19%
Copayment
6%
Food
8%
Transportation
62%

Figure 3: Total OOP expenditures categorized by the distributions and link functions: Model performance assessment using graphical analyses including scatter plots of the deviance residuals versus the fitted values, normal probability plots (P-P plots) of the deviance residuals, and normal quantile plots (Q- Q plots) of the deviance residuals.

Distributions	Link functions	Scatter plots	P-P plots	Q-Q plots
Gamma	Identity			
	Log			

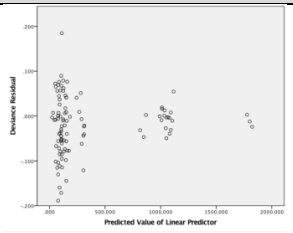
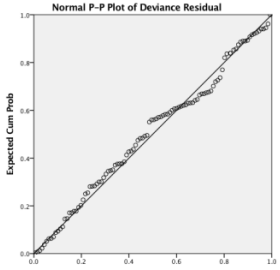
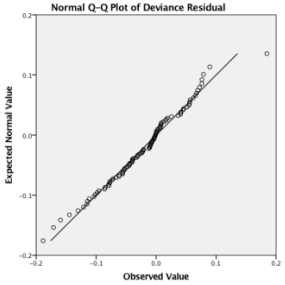
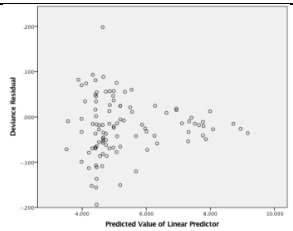
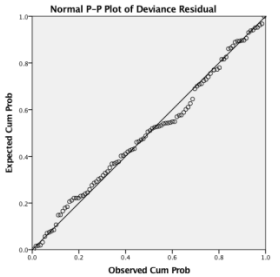
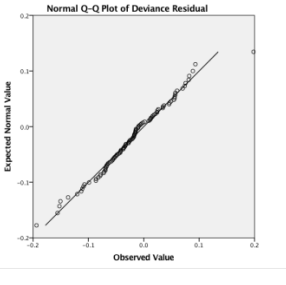
Distributions	Link functions	Scatter plots	P-P plots	Q-Q plots
Inverse Gaussian	Identity			
	Log			

Figure 4: Total indirect costs categorized by the different distributions: Model performance assessment using graphical analyses including scatter plots of the deviance residuals versus the fitted values, normal probability plots (P-P plots) of the deviance residuals, and normal quantile plots (Q- Q plots) of the deviance residuals.

Note: GLMs with identity link regardless of the distribution did not converge.

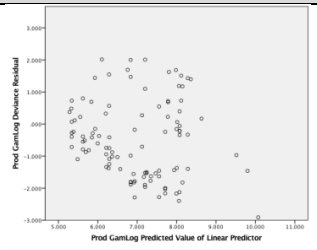
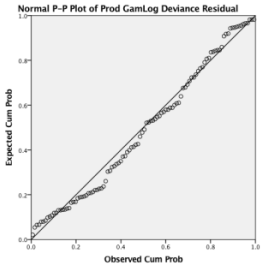
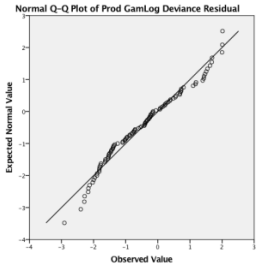
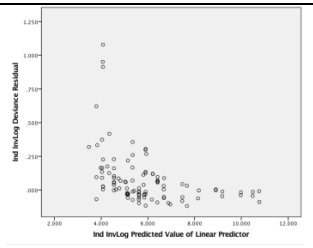
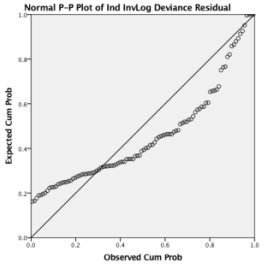
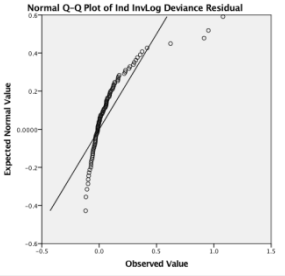
Distributions	Link functions	Scatter plots	P-P plots	Q-Q plots
Gamma	Log			
Inverse Gaussian	Log			

Figure 5: Costs as percentage of the reported patient's annual income

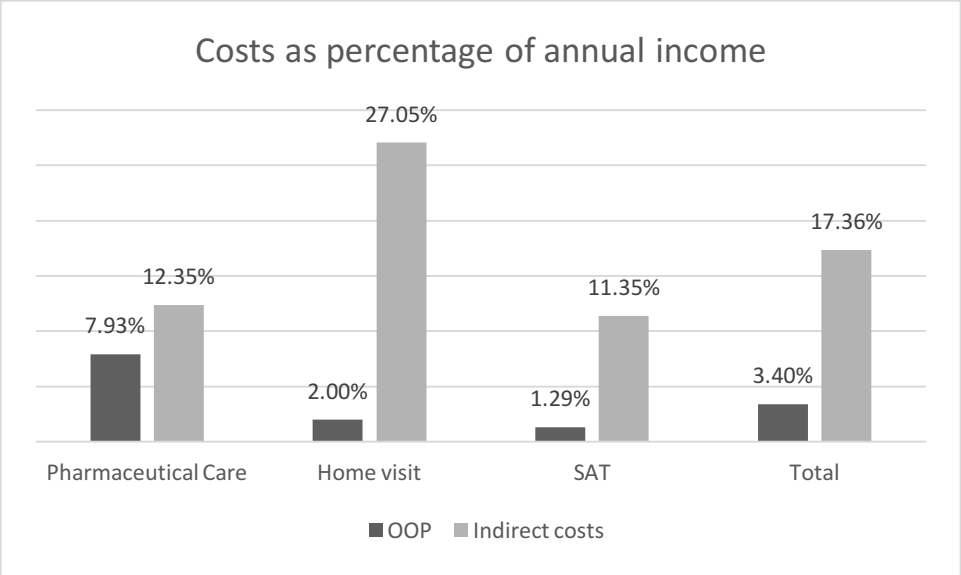


Table 1: Baseline characteristics and complications in TB treatment of 104 included patients received different treatment strategies

Note:

- *Fisher's Exact test, † Oneway-ANOVA
- CSMBS = Civil servant medical benefits scheme; SSS = Social security scheme; UC = Universal coverage

Variable		104 cases			p-value
		Pharm care (n=29)	Home visit (n=38)	SAT (n=37)	
		n (%)	n (%)	n (%)	
Gender	Male	21 (72.4)	26 (68.4)	26 (70.3)	0.939
	Female	8 (27.6)	12 (31.6)	11 (29.7)	
Age group, years	18-24	1 (3.4)	2 (5.3)	5 (13.5)	0.490*
	25-34	4 (13.8)	5 (13.2)	7 (18.9)	
	35-44	5 (17.2)	13 (34.2)	5 (13.5)	
	45-54	8 (27.6)	7 (18.4)	8 (21.6)	
	≥55	11 (37.9)	11 (28.9)	12 (32.4)	
Live in Songkhla	Yes	18 (62.1)	38 (100)	37 (100)	<0.001*
	No	11 (37.9)	0	0	
Education attainment	Less than high school	12 (41.4)	30 (78.9)	25 (67.6)	0.040*
	High school	9 (31.0)	4 (10.5)	7 (18.9)	
	Diploma	3 (10.3)	0	2 (5.4)	
	University	5 (17.2)	4 (10.5)	3 (8.1)	
CURRENT employment status	Employed	16 (55.2)	17 (44.7)	18 (48.6)	0.370*
	Unable to work due to TB	2 (6.9)	9 (23.7)	7 (18.9)	
	Unemployment due to TB	1 (3.4)	5 (13.2)	1 (2.7)	
	Unemployed	0	1 (2.6)	1 (2.7)	
	Student	1 (3.4)	1 (2.6)	2 (5.4)	
	Retired	9 (31.0)	5 (13.2)	8 (21.6)	
Monthly income BEFORE TB, $international dollars	*Mean (SD)*	1,381.97 (1,509.98)	738.67 (497.51)	569.48 (486.01)	0.001†
	< $500	7 (24.1)	11 (28.9)	14 (37.8)	0.001*
	$500 - $999	5 (17.2)	20 (52.6)	17 (45.9)	
	$1,000 - $1,999	10 (34.5)	5 (13.2)	6 (16.2)	
	> $1,999	7 (24.1)	2 (5.3)	0	
CURRENT monthly income,	*Mean (SD)*	1,184.59 (1,510.60)	421.76 (523.46)	417.79 (499.25)	0.001†
	< $500	11 (37.9)	21 (55.3)	22 (59.5)	0.001*

Variable		104 cases			p-value
		Pharm care (n=29)	Home visit (n=38)	SAT (n=37)	
		n (%)	n (%)	n (%)	
$international dollars	$500 - $999	3 (10.3)	14 (36.8)	10 (27.0)	
	$1,000 - $1,999	9 (31.0)	2 (5.3)	5 (13.5)	
	> $1,999	6 (20.7)	1 (2.6)	0	
Health Insurance	UC	7 (24.1)	23 (60.5)	18 (48.6)	<0.001*
	CSMBS	10 (34.5)	0	4 (10.8)	
	SSS	1 (3.4)	12 (31.6)	15 (40.5)	
	Not covered by public health insurance	11 (37.9)	3 (7.9)	0	
HIV	Yes	0	4 (10.5)	0	<0.001*
	No	20 (69.0)	34 (89.5)	37 (100)	
	Unknown	9 (31.0)	0	0	
Co-morbidity	Yes	16 (55.2)	8 (21.1)	12 (32.4)	0.014
	No	13 (44.8)	30 (78.9)	25 (67.6)	
Sputum smear	Positive	27 (93.1)	24 (63.2)	21 (56.8)	0.001
	Negative	2 (6.9)	14 (36.8)	16 (43.2)	
Baseline chest X-ray	Normal	0	0	0	0.061*
	Lesion without cavity	21 (72.4)	32 (84.2)	23 (62.2)	
	Lesion with cavity	8 (27.6)	5 (13.2)	14 (37.8)	
	No baseline available	0	1 (2.6)	0	
Registration	New	27 (93.1)	37 (97.4)	33 (89.2)	0.373*
	Relapse	1 (3.4)	0	2 (5.4)	
	Treatment after default	1 (3.4)	0	2 (5.4)	
	Other	0	1 (2.6)	0	
Initial treatment regimen	Standard treatment regimen	28 (96.6)	38 (100)	36 (97.3)	0.532*
	Re-treatment regimen	1 (3.4)	0	1 (2.7)	
Complications in TB treatment					
Develop to MDR-TB	Yes	2 (6.9)	0	2 (5.4)	0.256*
	No	27 (93.1)	38 (100)	35 (94.6)	
Re-Challenge anti-TB drug use	Yes	2 (6.9)	5 (13.2)	1 (2.7)	0.272*
	No	27 (93.1)	33 (86.8)	36 (97.3)	
	Yes	2 (6.9)	4 (10.5)	0	

Variable		104 cases			p-value
		Pharm care (n=29)	Home visit (n=38)	SAT (n=37)	
		n (%)	n (%)	n (%)	
Hepatotoxicity with anti-TB drugs	No	27 (93.1)	34 (89.5)	37 (100)	0.128*
Adverse events	No adverse events	15 (51.7)	24 (63.1)	10 (27.0)	0.003*
	Severe	2 (6.9)	5 (13.2)	2 (5.4)	
	Mild	12 (41.4)	9 (23.7)	25 (67.6)	
Hospitalization for TB	Yes	1 (3.4)	10 (26.3)	5 (13.5)	0.024
	No	28 (96.6)	28 (73.7)	32 (86.5)	

Table 2: Treatment outcome of included patients received different treatment strategies

Note: *Fisher's Exact test, † Oneway-ANOVA, ‡ When followed patients until March 2015

Variable		104 cases			p-value
		Pharm care (n=29)	Home visit (n=38)	SAT (n=37)	
		n (%)	n (%)	n (%)	
Treatment outcome	Cure	25 (86.2)	23 (60.5)	16 (43.2)	0.001*
	Complete	2 (6.9)	14 (36.8)	15 (40.5)	
	Death	0	1 (2.6)	2 (5.4)	
	Defaulted	0	0	4 (10.8)	
	The treatment was not completed at the end of December 2015	2 (6.9)	0	0	
		Mean (SD)	Mean (SD)	Mean (SD)	
Number of outpatient visits‡, n		7 (2)	8 (2)	7 (2)	0.079†
Duration of intensive phase, months		2.5 (0.8)	2.7 (1.0)	2.2 (0.5)	0.026†
Duration of continuation phase, months		4.3 (1.3) (n=27)	5.5 (2.4)	4.6 (3.9)	0.222†

Table 3: Summary of OOP expenditures (in 2015 international dollars) incurred by 104 patients before and during TB treatment categorized by treatment strategy.

Note: N = number of patients receiving each treatment strategy; n = number of patients who paid any cost

Variable		104 patients											
		Pharm care				Home visit				SAT			
		Patients reporting cost		Total patients (N=29)		Patients reporting cost		Total patients (N=38)		Patients reporting cost		Total patients (N=37)	
		n	Arithmetic mean (SD)	Arithmetic mean (SD)	95% CI	n	Arithmetic mean (SD)	Arithmetic mean (SD)	95% CI	n	Arithmetic mean (SD)	Arithmetic mean (SD)	95% CI
PRE-TB treatment period	**Health care costs**												
	Health care costs not covered by public health insurances												
	• Outpatient visits	13	154.80 (33.77)	69.39 (81.40)	38.57 - 101.20	2	21.37 (1.84)	1.12 (4.85)	0 - 2.78	0	0	0	-
	• Hospitalizations	0	0	0	-	1	517.60	13.62 (83.97)	0 - 36.97	0	0	0	-
	Health care costs occurred in the private healthcare units	5	155.36 (124.73)	26.79 (76.09)	5.95 - 56.81	1	89.20	2.35 (14.47)	0 - 6.86	2	81.77 (42.05)	4.42 (20.01)	0 - 10.61
	Non-essential drugs (NEDs)	1	1.34	0.05 (0.25)	0 - 0.14	0	0	0	-	0	0	0	-
	Other medications (e.g. vitamins, antibiotics, anti-cough)	9	19.66 (23.27)	6.10 (15.50)	1.83 - 12.13	7	27.00 (53.80)	4.97 (24.12)	0.48 - 13.25	9	13.71 (12.29)	3.34 (8.31)	1.03 - 6.46
	Non-medical costs												
	Transportation	28	50.04 (51.84)	48.32 (51.75)	31.28 - 68.88	37	7.20 (4.28)	7.01 (4.38)	5.73 - 8.43	37	8.45 (6.11)	8.45 (6.11)	6.67 - 10.67

Variable		104 patients											
		Pharm care				Home visit				SAT			
		Patients reporting cost		Total patients (N=29)		Patients reporting cost		Total patients (N=38)		Patients reporting cost		Total patients (N=37)	
		n	Arithmetic mean (SD)	Arithmetic mean (SD)	95% CI	n	Arithmetic mean (SD)	Arithmetic mean (SD)	95% CI	n	Arithmetic mean (SD)	Arithmetic mean (SD)	95% CI
	Food	23	16.45 (11.28)	13.05 (12.08)	8.80 - 17.36	13	6.52 (2.13)	2.23 (3.36)	1.21 - 3.30	13	7.46 (4.48)	2.62 (4.44)	1.29 - 3.97
	Copayments	2	2.23	0.15 (0.58)	0 - 0.37	13	2.91 (1.06)	1.00 (1.53)	0.52 - 1.48	4	2.60 (0.74)	0.28 (0.85)	0.06 - 0.56
	Other costs (e.g. food supplement, accommodation)	2	81.77 (10.51)	5.64 (21.18)	0 - 13.89	2	185.84 (52.56)	9.78 (42.93)	0 -23.47	0	0	0	-
	Total OOP expenditures	28	175.54 (148.75)	169.48 (149.67)	120.04 - 233.31	37	43.23 (95.40)	42.09 (94.36)	19.81 - 72.17	37	19.11 (21.28)	19.11 (21.28)	13.52 - 26.71
TB treatment period	Health care costs												
	Health care costs not covered by public health insurances • Outpatient visits	13	405.52 (271.98)	181.78 (271.71)	94.19 - 281.89	3	226.34 (66.90)	17.87 (63.78)	0 - 37.86	0	0	0	-
	• Hospitalizations	1	4372.77	150.79 (812.00)	0 - 416.45	0	0	0	-	0	0	0	-
	Health care costs occurred in the private healthcare units	2	25.27 (27.33)	1.74 (8.32)	0 - 4.25	1	22.30	0.59 (3.62)	0 - 1.75	1	43.12	1.17 (7.09)	0 - 3.08
	Non-essential drugs (NEDs)	2	6.24 (2.73)	0.43 (1.69)	0 - 1.10	0	0	0	-	0	0	0	-
	Other medications (e.g. vitamins, antibiotics, anti-cough)	7	42.49 (80.40)	10.26 (41.56)	1.07 - 24.28	5	27.58 (25.30)	3.63 (12.59)	0.52 - 7.55	13	9.44 (9.02)	3.32 (6.93)	1.47 - 5.53

Variable	104 patients											
	Pharm care				Home visit				SAT			
	Patients reporting cost		Total patients (N=29)		Patients reporting cost		Total patients (N=38)		Patients reporting cost		Total patients (N=37)	
	n	Arithmetic mean (SD)	Arithmetic mean (SD)	95% CI	n	Arithmetic mean (SD)	Arithmetic mean (SD)	95% CI	n	Arithmetic mean (SD)	Arithmetic mean (SD)	95% CI
Non-medical costs												
Transportation	29	278.53 (333.98)	278.53 (333.98)	173.94 - 400.67	38	57.15 (48.64)	57.15 (48.64)	43.81 - 72.55	37	47.19 (41.45)	47.19 (41.45)	36.75 - 60.48
Food	27	73.77 (105.08)	68.69 (103.02)	38.64 - 105.02	26	29.20 (28.71)	19.98 (27.31)	12.15 - 28.49	19	11.33 (14.91)	5.82 (12.00)	2.97 - 9.55
Copayments	2	11.15 (3.15)	0.77 (2.94)	0 - 1.91	18	15.13 (4.34)	7.17 (8.20)	4.64 - 9.80	14	11.62 (7.09)	4.40 (7.13)	2.36 - 6.77
Other costs (e.g. food supplement, accommodation)	10	130.76 (115.57)	45.09 (91.07)	15.56 - 81.52	0	0	0	-	3	177.17 (161.86)	14.37 (62.12)	0 - 35.69
Total OOP expenditures	29	738.07 (1,011.49)	738.07 (1,011.49)	458.96 - 1095.58	38	106.38 (95.73)	106.38 (95.73)	79.24 - 136.36	37	76.24 (102.00)	76.24 (102.00)	50.90 - 109.50
Total OOP expenditures	-	-	907.56 (1,073.97)	603.80 - 1,269.41	-	-	148.47 (160.55)	109.49 - 194.89	-	-	95.35 (105.53)	69.11 - 129.63

Table 4: Comparison of GLMs with two different types of distributions and either identity or log link for models including seven baseline covariates. Two types of costs were investigated: mean total OOP expenditures and mean total indirect costs

Distributions	Link functions	AICs	
		Outcome: OOP expenditures	Outcome: Indirect costs
Gamma	Identity	1285.65	GLM did not converge
	Log	1,284.89	1,676.24
Inverse Gaussian	Identity	1,298.08	GLM did not converge
	Log	1,299.97	3,845.76

Table 5: Ratios of mean costs between the specified group compared with reference group when impact of differences in baseline characteristics was adjusted by GLMs with gamma distribution and the log link.

Note:

- Ratios of the mean costs presented were the exponential of coefficients from the GLMs with gamma distribution and the log link.
- References used in each category were supervision strategy (pharmaceutical care), gender (female), age group (≤54), habitat (non-local), Education attainment (less than high school), current monthly income (< $500), health Insurance (UC)
- Significance for all statistical analysis was at $p < 0.05$.
-

Variable		Total OOP expenditures			Total indirect costs		
		Ratio of mean costs	95% CI	p-value	Ratio of mean costs	95% CI	p-value
Supervision strategy	Home visit	0.247	0.142 to 0.427	<0.001	1.904	0.754 to 4.802	0.173
	SAT	0.318	0.187 to 0.540	<0.001	0.792	0.289 to 2.175	0.652
Gender	Male	1.379	1.020 to 1.865	0.037	0.931	0.551 to 1.571	0.788
Age group, years	>55	0.507	0.369 to 0.697	<0.001	0.694	0.401 to 1.200	0.190
Habitat	Local	0.467	0.262 to 0.829	0.009	0.124	0.047 to 0.329	<0.001
Education attainment	high school or higher education	0.866	0.639 to 1.174	0.352	1.327	0.740 to 2.380	0.342
CURRENT monthly income, $international dollars	≥$500	0.715	0.523 to 0.978	0.036	0.168	0.095 to 0.296	<0.001
Health Insurance	CSMBS	1.318	0.780 to 2.230	0.303	1.106	0.447 to 2.735	0.827
	Social Security Scheme	1.034	0.705 to 1.516	0.864	0.926	0.493 to 1.740	0.812

Variable		Total OOP expenditures			Total indirect costs		
		Ratio of mean costs	95% CI	p-value	Ratio of mean costs	95% CI	p-value
	Not covered by public health insurance	3.781	2.246 to 6.373	<0.001	1.311	0.547 to 3.146	0.543

Table 6: Summary of indirect costs (in hours and 2015 international dollars) incurred by 104 patients before and during TB treatment categorized by treatment strategy.

Note:

- N = number of patients receiving each treatment strategy; n = number of patients who paid any cost
- *Times reported as indicated in brackets next to the variable name
- The indirect costs due to productivity loss were calculated by multiplying the amount of time lost due to TB illness by patient's or the family member's hourly wage rate. If the wage was not available, we used daily minimum wage in Songkhla province (300 baht per day, in 2015) (15). Patients and their accompanying family members were assumed to work 8-hour per day, and 40-hour per week.
-

Variable		104 patients														
		Pharm care					Home visit					SAT				
		Patients reporting times		Total patients (N=29)			Patients reporting times		Total patients (N=38)			Patients reporting times		Total patients (N=37)		
		n	Mean (SD)*	Mean hours (SD)	Mean cost (SD)	95% CI	n	Mean (SD)*	Mean hours (SD)	Mean cost (SD)	95% CI	n	Mean (SD)*	Mean hours (SD)	Mean cost (SD)	95% CI
PRE-TB treatment period	Time loss incurred by patients															
	Travel time (hours)	29	2.6 (2.2)	2.6 (2.2)	20.39 (30.52)	10.58 - 33.20	38	0.8 (0.5)	0.8 (0.5)	2.91 (2.38)	2.24 - 3.63	37	0.9 (0.5)	0.9 (0.5)	3.57 (2.64)	2.82 - 4.54
	Waiting and consultation time (hours)	29	5.8 (2.0)	5.8 (2.0)	42.33 (40.59)	28.77 - 58.78	38	4.3 (1.9)	4.3 (1.9)	17.21 (12.95)	13.61 - 21.31	37	4.3 (1.5)	4.3 (1.5)	17.91 (13.52)	14.17 - 22.89
	Time for being unable to work due to TB (days)	5	12.0 (3.4)	96.0 (27.1)	170.86 (514.24)	24.12 - 383.06	10	36.6 (27.5)	292.8 (220.4)	344.62 (816.49)	118.05 - 614.41	5	24.0 (12.3)	192.0 (98.6)	87.58 (246.75)	21.81 - 162.43
	Time lost during hospitalization (days)	0	0	0	0	-	4	4.3 (1.0)	34.0 (7.7)	22.93 (87.88)	3.43 - 50.27	3	7.7 (6.4)	61.3 (50.8)	15.83 (61.65)	0 - 36.90

Variable		104 patients														
		Pharm care					Home visit					SAT				
		Patients reporting times		Total patients (N=29)			Patients reporting times		Total patients (N=38)			Patients reporting times		Total patients (N=37)		
		n	Mean (SD)*	Mean hours (SD)	Mean cost (SD)	95% CI	n	Mean (SD)*	Mean hours (SD)	Mean cost (SD)	95% CI	n	Mean (SD)*	Mean hours (SD)	Mean cost (SD)	95% CI
	Time loss incurred by accompanying family members															
	Waiting and consultation time (hours)	14	7.6 (4.8)	7.6 (4.8)	10.19 (14.14)	5.68 - 15.38	15	4.9 (2.8)	4.9 (2.8)	5.43 (8.30)	2.83 - 8.40	15	4.7 (3.4)	4.7 (3.4)	5.35 (8.85)	3.02 - 8.06
	Time lost during hospitalization (days)	0	0	0	0	-	4	4.3 (1.0)	34.0 (7.7)	9.98 (30.10)	2.52 - 19.14	3	7.7 (6.4)	61.3 (50.8)	13.86 (57.90)	0 -33.45
	Total indirect costs	-	-	28.6 (39.3)	243.77 (551.40)	85.12 - 470.47	-	-	91.2 (175.9)	403.07 (833.38)	172.76 - 688.29	-	-	43.0 (87.1)	144.09 (288.92)	60.50 - 237.21
TB treatment period	Time loss incurred by patients															
	Travel time (hours)	29	16.2 (17.3)	16.2 (17.3)	151.01 (299.45)	67.56 - 279.86	38	5.6 (3.7)	5.6 (3.7)	21.60 (15.92)	17.42 - 26.15	37	4.6 (2.4)	4.6 (2.4)	17.90 (10.21)	14.77 - 21.12
	Waiting and consultation time (hours)	29	23.9 (12.3)	23.9 (12.3)	203.72 (288.94)	115.07- 329.85	38	28.5 (11.0)	28.5 (11.0)	112.64 (56.94)	94.27 - 130.33	37	19.9 (12.8)	19.9 (12.8)	76.17 (46.23)	61.43 - 91.48
	Time for being unable to work due to TB (days)	12	53.6 (54.8)	428.7 (438.6)	1,255.79 (2,335.12)	475.96 - 2,197.14	18	106.8 (87.5)	854.2 (700.2)	1,669.78 (2,724.84)	954.79 - 2,485.99	10	76.1 (58.8)	608.8 (470.7)	568.13 (1,281.31)	231.57 - 962.02
	Time lost during hospitalization (days)	1	17.0	136.0	21.79 (117.33)	0 - 59.24	7	13.9 (19.0)	110.9 (152.3)	99.97 (366.37)	17.53 - 229.77	2	4.0 (1.4)	32.0 (11.3)	5.32 (23.78)	0 - 13.11
	Time loss incurred by accompanying family members															

Variable	104 patients														
	Pharm care					Home visit					SAT				
	Patients reporting times		Total patients (N=29)			Patients reporting times		Total patients (N=38)			Patients reporting times		Total patients (N=37)		
	n	Mean (SD)*	Mean hours (SD)	Mean cost (SD)	95% CI	n	Mean (SD)*	Mean hours (SD)	Mean cost (SD)	95% CI	n	Mean (SD)*	Mean hours (SD)	Mean cost (SD)	95% CI
Waiting and consultation time (hours)	21	18.1 (15.6)	18.1 (15.6)	36.52 (43.53)	22.44 - 53.49	25	16.1 (12.6)	16.1 (12.6)	29.67 (35.83)	18.06 - 42.61	18	12.4 (12.3)	12.4 (12.3)	16.88 (29.57)	9.53 - 25.45
Time lost during hospitalization (days)	1	17.0	136.0	13.07 (70.40)	0 - 35.54	7	13.9 (19.0)	110.9 (152.3)	56.93 (209.69)	11.77 - 123.88	2	4.0 (1.4)	32.0 (11.3)	4.82 (21.11)	0 - 11.80
Total indirect costs	-	-	239.9 (372.7)	1,681.92 (2,727.60)	766.86 - 2,833.78	-	-	490.2 (735.8)	1,990.58 (3,132.21)	1,164.32 - 2,911.41	-	-	198.5 (372.5)	689.24 (1,310.14)	347.52 - 1,090.67
Total indirect costs	-	-	268.6 (382.9)	1,925.68 (3,049.88)	922.06 - 3,284.94	-	-	581.4 (815.0)	2,393.66 (3,594.64)	1,435.01 - 3,501.98	-	-	241.6 (414.6)	833.33 (1,438.73)	453.87 - 1,263.45

Table 7: Descriptive statistics of EQ-5D attributes, the EQ-5D scores, and the VAS scores categorized by the treatment strategy and stages of treatment. Patients were followed until March 2015.

Note:

- *Fisher's Exact test; † One-way ANOVA
- At the end of March 2015:
- Pharmaceutical care group: two patients were still going through treatment and one case was cured, but missed the last interview.
- Home visit group: one patient was still going through treatment and one patient had died.
- SAT group: two patients was still going through treatment. One case completed the treatment but missed the last interview. There were also two died and four defaulted patients.

Attributes	Frequency											
	At the start of intensive phase N = 104				At the end of intensive phase N = 104				At the end of continuous phase N = 90			
	Pharm care (N=29)	Home visit (N=38)	SAT (N=37)	p-value	Pharm care (N=29)	Home visit (N=38)	SAT (N=37)	p-value	Pharm care (N=26)	Home visit (N=36)	SAT (N=28)	p-value
	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	
Mobility												
No problem walking	21 (72.4)	30 (78.9)	24 (64.9)	0.396	21 (72.4)	29 (76.3)	26 (70.3)	0.836	22 (84.6)	32 (88.9)	28 (100)	0.113*
Some problem walking	8 (27.6)	8 (21.1)	13 (35.1)		8 (27.6)	9 (23.7)	11 (29.7)		3 (11.5)	4 (11.1)	0	
Confined to bed	0	0	0		0	0	0		1 (3.8)	0	0	
Self-care												
No problem	27 (93.1)	38 (100)	36 (97.3)	0.192*	28 (96.6)	38 (100)	37 (100)	0.279*	25 (96.2)	36 (100)	28 (100)	0.289*
Some problems washing or dressing self	2 (6.9)	0	1 (2.7)		1 (3.4)	0	0		0	0	0	

Attributes	Frequency											
	At the start of intensive phase N = 104				At the end of intensive phase N = 104				At the end of continuous phase N = 90			
	Pharm care (N=29)	Home visit (N=38)	SAT (N=37)	p-value	Pharm care (N=29)	Home visit (N=38)	SAT (N=37)	p-value	Pharm care (N=26)	Home visit (N=36)	SAT (N=28)	p-value
	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	
Unable to wash or dress self	0	0	0		0	0	0		1 (3.8)	0	0	
Usual activities (e.g., work, study, housework, family or leisure activities)												
No problem	20 (69.0)	26 (68.4)	24 (64.9)	0.924	22 (75.9)	27 (71.1)	26 (70.3)	0.867	22 (84.6)	35 (97.2)	26 (92.9)	0.327*
Some problem	9 (31.0)	12 (31.6)	13 (35.1)		7 (24.1)	11 (28.9)	11 (29.7)		3 (11.5)	1 (2.8)	2 (7.1)	
Unable to perform	0	0	0		0	0	0		1 (3.8)	0	0	
Pain/discomfort												
No pain or discomfort	11 (37.9)	17 (44.7)	18 (48.6)	0.864*	20 (69.0)	25 (65.8)	17 (45.9)	0.071*	19 (73.1)	30 (83.3)	22 (78.6)	0.620
Moderate	15 (51.7)	19 (50.0)	17 (45.9)		8 (27.6)	13 (34.2)	20 (54.1)		7 (26.9)	6 (16.7)	6 (21.4)	
Extreme	3 (10.3)	2 (5.3)	2 (5.4)		1 (3.4)	0	0		0	0	0	
Anxiety/depression												
Not anxious or depressed	11 (37.9)	20 (52.6)	22 (59.5)	0.082*	18 (62.1)	30 (78.9)	24 (64.9)	0.257	19 (73.1)	29 (80.6)	26 (92.9)	0.161*
Moderate	18 (62.1)	14 (36.8)	14 (37.8)		11 (37.9)	8 (21.1)	13 (35.1)		7 (26.9)	7 (19.4)	2 (7.1)	
Extreme	0	4 (10.5)	1 (2.7)		0	0	0		0	0	0	
EQ-5D scores, Mean (SD)	0.679 (0.215)	0.713 (0.207)	0.708 (0.188)	0.779†	0.786 (0.206)	0.806 (0.179)	0.743 (0.166)	0.324†	0.830 (0.269)	0.905 (0.149)	0.913 (0.130)	0.198†

Attributes	Frequency											
	At the start of intensive phase N = 104				At the end of intensive phase N = 104				At the end of continuous phase N = 90			
	Pharm care (N=29)	Home visit (N=38)	SAT (N=37)	p-value	Pharm care (N=29)	Home visit (N=38)	SAT (N=37)	p-value	Pharm care (N=26)	Home visit (N=36)	SAT (N=28)	p-value
	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	
VAS scores, Mean (SD)	66.90 (15.14)	61.68 (23.67)	65.41 (21.65)	0.567†	78.79 (14.80)	77.76 (15.67)	77.51 (17.56)	0.946†	89.92 (9.62)	91.94 (8.39)	94.00 (7.51)	0.218†

Table 8: Differences in paired mean EQ-5D and the VAS scores between the beginning of treatment (the start of intensive phase) and the end of treatment (the end of continuous phase), categorized by the treatment strategy.

Note: *Paired t-test

Variable		Pharm care (N=26)	Home visit (N=36)	SAT (N=28)
EQ-5D scores	At the beginning of treatment, mean (SD)	0.661 (0.206)	0.720 (0.210)	0.738 (0.178)
	At the end of treatment, mean (SD)	0.830 (0.269)	0.905 (0.149)	0.913 (0.130)
	Paired mean differences (SD)	0.169 (0.349)	0.185 (0.208)	0.176 (0.212)
	95%CI of the difference	0.028 to 0.310	0.115 to 0.255	0.093 to 0.258
	p-value*	0.021	<0.001	<0.001
VAS scores	At the beginning of treatment, mean (SD)	68.46 (15.15)	61.50 (24.06)	66.43 (23.60)
	At the end of treatment, mean (SD)	89.92 (9.62)	91.94 (8.39)	94.00 (7.51)
	Paired mean differences (SD)	21.46 (18.67)	30.44 (23.82)	27.57 (23.51)
	95%CI of the difference	13.92 to 29.00	22.38 to 38.50	18.45 to 36.69
	p-value*	<0.001	<0.001	<0.001

APPENDIX 4.I: Questionnaire (translated from Thai version)

The cost and quality of life questionnaire

This questionnaire is part of a PhD study in Health Research Methodology at McMaster University, Canada. The research aims to compare out-of-pocket (OOP) expenditures, indirect costs, and health-related quality of life (HRQoL) among TB patients who received pharmaceutical care compared to home visit and self-administered therapy (SAT) in Thailand.

Respondent estimated time: 5-10 minutes.

Your information will be confidential. This data will be used for academic purposes only

We would like to thank you for providing the information herein.
This research could not be completed without your kindness.

Pimwara Tanvejsilp
Faculty of Pharmaceutical Sciences,
Prince of Songkla University
Tel: 6681 679 1141

Section1: General information

Please fill in the blank or mark ✓ in the appropriate answer for the following questions

1. Gender □ Female □ Male

2. Age**.....**years

3. Address: District**.....** Province.....

4. Occupation**.....**
   □ Unemployed

5. Education
   □ Less than high school
   □ High School
   □ Diploma
   □ Bachelor's degree
   □ Postgraduate (Please specify) .....

6. Your income before TB is approximately …… Baht *per month.*
   (Please skip to question 8 if you have a daily income).

7. Your current income is approximately …… Baht *per month.*
   (Please skip to question 9 if you have a daily income).

8. Your income before TB is approximately …… Baht *per day.*

9. Your current income is approximately …… Baht *per day.*

Please complete the section 2 on the next page

Section 2 Costs and time loss due to TB illness

Please fill in the blank or mark ✓ in the appropriate answer for the following questions

1. Today, you pay for travelling to and from hospital approximately……. Baht

2. You pay for;
   □ Food approximately…….. Baht
   □ Accommodation approximately…….. Baht
   □ Non-TB medication that was not covered by your health insurance (e.g. vitamins, antibiotics, anti-cough and others)
   Please specify……approximately……Baht
   □ Other costs
   Please specify……approximately……. Baht
   □ I didn't pay any other costs

3. *Today, do you come with your family member?*
   □ No (Please skip to question 5)
   □ Yes

4. *How many of your family members who have to be absent from work in order to come to hospital with you today? ……*

5. *Today, you spent*
   a. *Travel time* to and from hospital for ……..hours
   b. *Waiting time and consultation time for* …….hours

6. *Today, you are absent from work;*
   □ Half-day □ Whole-day □ Unemployed

7. *Due to this illness*;
   □ I have …… days per month lost from work. (Except the absence for doctor visit)
   □ I was not absent from work.

*** Please complete the section 3 on the next page***

Section 3 Health-related quality of life

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

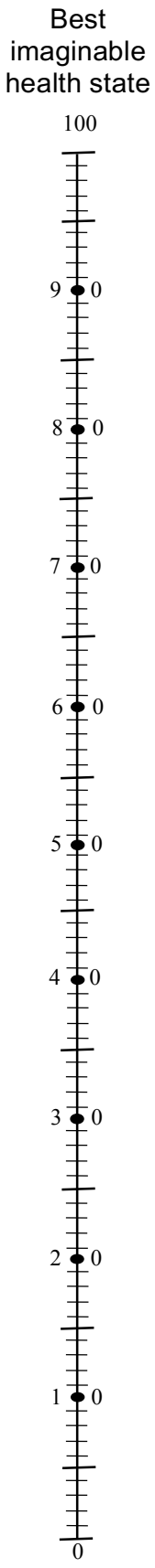
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Thank you for completing the questionnaire

APPENDIX 4.II: Analysis of utility scores

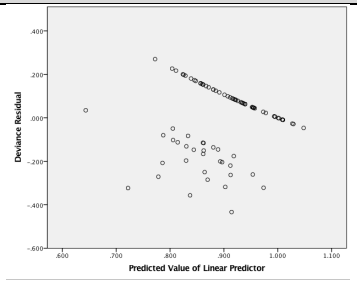
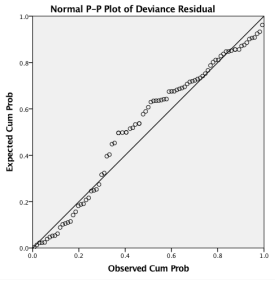
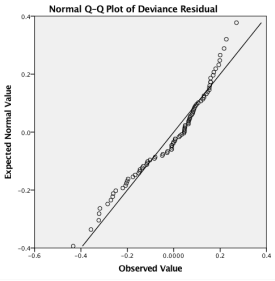
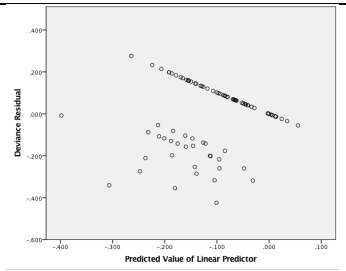
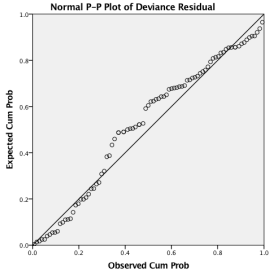
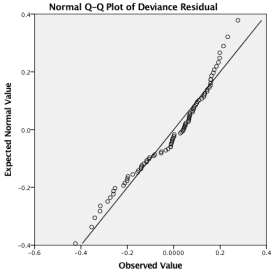
In this Chapter, the standard parametric methods were used in the analysis of the EQ-5D and VAS utility scores (e.g. means and SDs for the utility scores were calculated, differences in means utility scores among different treatment strategies were evaluated using ANOVA, and differences in means utility scores between the start and the end of treatment were compared using paired t-test). However, the Shapiro-Wilk test indicated that the EQ-5D-3L and VAS utility scores were not normally distributed. Therefore, non-parametric bootstrap technique was thus used to check on the robustness of the standard parametric methods, and to derive the 95% CI [28] (Table 9).

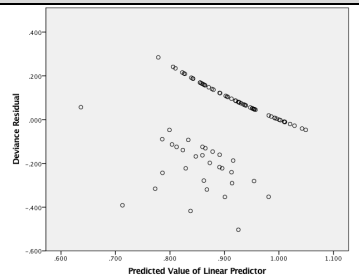
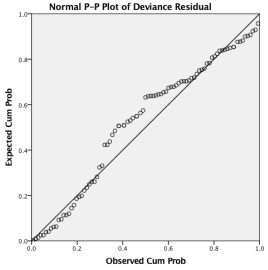
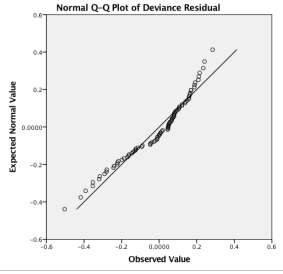
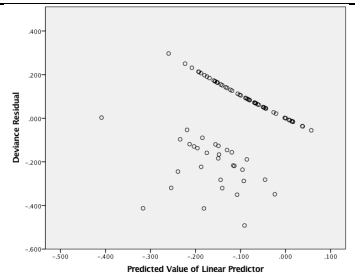
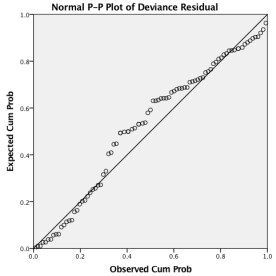
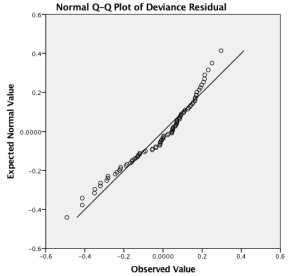
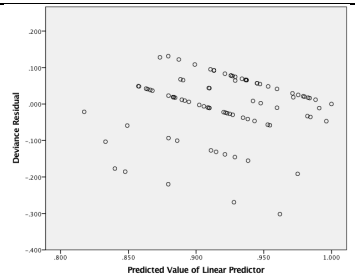
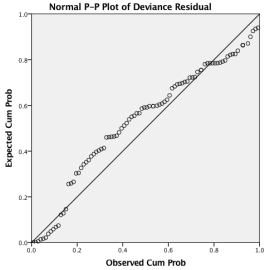
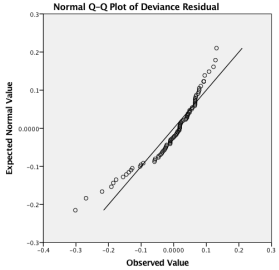
At the end of treatment, differences in means utility scores (e.g. the EQ-5D and the VAS) among treatment strategies adjusted for baseline utility scores and baseline characteristics were investigated by GLMs [29,30]. The model included eight baseline covariates, namely, treatment strategy, baseline utility score, sex, age, habitat, education, income, and health Insurance. The AICs (Table 10) and the graphical analyses (Figure 6) clearly showed that the gamma distribution with identity link was a better performed model. After adjustment for eight baseline characteristics (Table 11), the differences in mean EQ-5D scores were 0.013 (CI: -0.098 to 0.125) and 0.006 (CI: -0.113 to 0.124) for the home visit and SAT groups, respectively, when pharmaceutical care was set as a reference. There were also no statistically significant differences in mean VAS scores for patients receiving either home visit or SAT (2.00, CI: -4.20 to

8.20, and 4.30, CI: -2.10 to 10.60, respectively), when compared to the patients receiving pharmaceutical care.

Table 12 shows the differences in paired mean utility scores between the beginning and the end of treatment. The non-parametric bootstrap was used for assessing robustness of the standard paired t-test method to non-normality data of the utility scores. Results from both the standard paired t-test and the bootstrap method provide P-values of less than 0.05. This indicated that the standard paired t-test method is robust to the non-normality for utility scores. The possible explanation may be because the data was not severely skewed. All three treatment strategies had significant increases in utility scores at the end of treatment.

Figure 6: The EQ-5D and the VAS scores categorized by the distributions and link functions: Model performance assessment using graphical analyses including scatter plots of the deviance residuals versus the fitted values, normal probability plots (P-P plots) of the deviance residuals, and normal quantile plots (Q- Q plots) of the deviance residuals.

	Distributions	Link functions	Scatter plots	P-P plots	Q-Q plots
The EQ-5D scores	Gamma	Identity			
		Log			

	Distributions	Link functions	Scatter plots	P-P plots	Q-Q plots
	Inverse Gaussian	Identity			
		Log			
The VAS scores	Gamma	Identity			

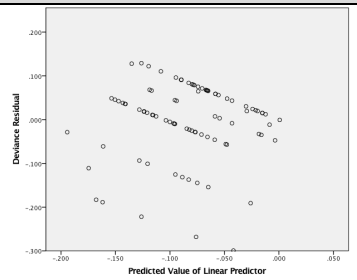
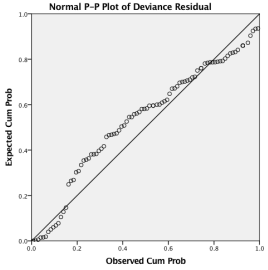
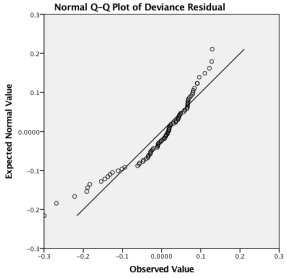
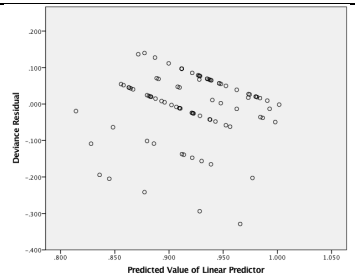
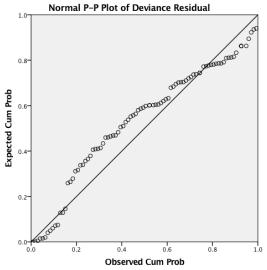
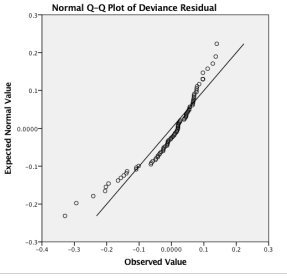
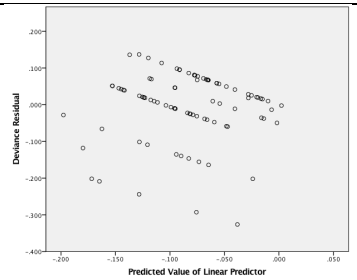
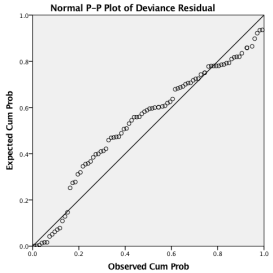
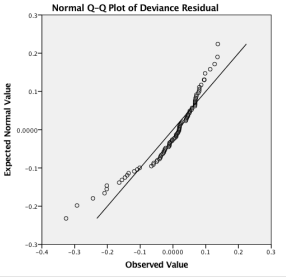
	Distributions	Link functions	Scatter plots	P-P plots	Q-Q plots
		Log			
	Inverse Gaussian	Identity			
		Log			

Table 9: The EQ-5D and VAS scores categorized by the treatment strategy and stages of treatment. Patients were followed until March 2015.

Note:

- *One-way ANOVA, † Non-parametric bootstrap technique
- At the end of March 2015:
  - Pharmaceutical care group: two patients were still going through treatment and one case was cured, but missed the last interview.
  - Home visit group: one patient was still going through treatment and one patient had died.
  - SAT group: two patients was still going through treatment. One case completed the treatment but missed the last interview. There were also two died and four defaulted patients.

Attributes		Frequency											
		At the start of intensive phase N = 104				At the end of intensive phase N = 104				At the end of continuous phase N = 90			
		Pharm care (N=29)	Home visit (N=38)	SAT (N=37)	p-value	Pharm care (N=29)	Home visit (N=38)	SAT (N=37)	p-value	Pharm care (N=26)	Home visit (N=36)	SAT (N=28)	p-value
		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	
EQ-5D scores	Mean (SD)	0.679 (0.215)	0.713 (0.207)	0.708 (0.188)	0.779*	0.786 (0.206)	0.806 (0.179)	0.743 (0.166)	0.324*	0.830 (0.269)	0.905 (0.149)	0.913 (0.130)	0.198*
	†Bootstrap 95%CI	0.604 to 0.758	0.649 to 0.776	0.647 to 0.767		0.713 to 0.864	0.749 to 0.863	0.692 to 0.800		0.715 to 0.914	0.856 to 0.950	0.863 to 0.962	
VAS scores	Mean (SD)	66.90 (15.14)	61.68 (23.67)	65.41 (21.65)	0.567*	78.79 (14.80)	77.76 (15.67)	77.51 (17.56)	0.946*	89.92 (9.62)	91.94 (8.39)	94.00 (7.51)	0.218*
	†Bootstrap 95%CI	61.00 to 72.50	53.54 to 69.58	58.90 to 72.16		73.44 to 83.89	72.50 to 82.78	71.85 to 82.62		86.15 to 93.46	89.24 to 94.57	90.97 to 96.62	

Table 10: Comparison of GLMs with two different types of distributions and either identity or log link for models including eight baseline covariates. Two types of utility scores were investigated: the EQ5D and VAS scores

Distributions	Link functions	AICs	
		EQ5D scores	VAS scores
Gamma	Identity	-73.42	-176.06
	Log	-72.95	-175.58
Inverse Gaussian	Identity	-66.76	-171.98
	Log	-66.18	-171.46

Table 11: Differences in mean EQ-5D and VAS scores at the end of treatment compared between the specified group and reference group when impact of differences in baseline characteristics was adjusted by GLMs with gamma distribution and the identity link.

Note:

- References used in each category were supervision strategy (pharmaceutical care), gender (female), age group (≤54), habitat (non-local), Education attainment (less than high school), current monthly income (< $500), health Insurance (UC)
- Significance for all statistical analysis was at $p < 0.05$.
- One case with baseline EQ-5D score less than zero was invalid for the gamma probability distribution, and was not used in the analysis.

Variable		EQ-5D scores			VAS scores		
		Difference in mean	95% CI	p-value	Difference in mean	95% CI	p-value
Supervision strategy	Home visit	0.013	-0.098 to 0.125	0.818	2.00	-4.20 to 8.20	0.522
	SAT	0.006	-0.113 to 0.124	0.924	4.30	-2.10 to 10.60	0.191
Baseline utility scores	none	0.176	0.015 to 0.336	0.032	3.80	-4.20 to 11.80	0.350
Gender	Male	-0.056	-0.122 to 0.010	0.097	-5.10	-8.90 to -1.30	0.008
Age group, years	>55	-0.046	-0.119 to 0.028	0.223	-0.80	-5.00 to 3.40	0.717
Habitat	Local	0.095	-0.021 to 0.211	0.110	2.20	-4.50 to 8.90	0.527
Education attainment	high school or higher education	-0.009	-0.083 to 0.066	0.819	-3.20	-7.20 to 0.90	0.122
CURRENT monthly income, $international dollars	≥$500	0.038	-0.027 to 0.103	0.248	3.40	-0.20 to 7.00	0.062
Health Insurance	CSMBS	0.075	-0.047 to 0.197	0.231	2.30	-4.30 to 8.90	0.492

Variable		EQ-5D scores			VAS scores		
		Difference in mean	95% CI	p-value	Difference in mean	95% CI	p-value
	Social Security Scheme	0.047	-0.032 to 0.147	0.244	2.40	-2.00 to 6.80	0.289
	Not covered by public health insurance	0.069	-0.035 to 0.174	0.192	5.10	-0.70 to 11.00	0.086

Table 12: Differences in paired mean EQ-5D and VAS scores between the beginning of treatment (the start of intensive phase) and the end of treatment (the end of continuous phase), categorized by the treatment strategy.

Note: * Paired t-test
† non-parametric bootstrap for paired t-test

Variable		Pharm care (N=26)	Home visit (N=36)	SAT (N=28)
EQ-5D scores	At the beginning of treatment, mean (SD)	0.661 (0.206)	0.720 (0.210)	0.738 (0.178)
	At the end of treatment, mean (SD)	0.830 (0.269)	0.905 (0.149)	0.913 (0.130)
	Paired mean differences (SD)	0.169 (0.349)	0.185 (0.208)	0.176 (0.212)
	95%CI of the difference	0.028 to 0.310	0.115 to 0.255	0.093 to 0.258
	*p-value	0.021	<0.001	<0.001
	† Bootstrap 95%CI of the difference	0.022 to 0.279	0.111 to 0.252	0.099 to 0.259
	† Bootstrap hypothesis test (p-value)	0.040	0.001	0.002
VAS scores	At the start of intensive phase, mean (SD)	68.46 (15.15)	61.50 (24.06)	66.43 (23.60)
	At the end of continuous phase, mean (SD)	89.92 (9.62)	91.94 (8.39)	94.00 (7.51)
	Paired mean differences (SD)	21.46 (18.67)	30.44 (23.82)	27.57 (23.51)
	95%CI of the difference	13.92 to 29.00	22.38 to 38.50	18.45 o 36.69
	*p-value	<0.001	<0.001	<0.001
	† Bootstrap 95%CI of the difference	14.05 to 29.12	23.13 to 38.46	19.05 to 36.75
	† Bootstrap hypothesis test (p-value)	0.001	0.001	0.001

CHAPTER 5:

DISCUSSION AND CONCLUSION

5.1 SUMMARY AND MAJOR CONTRIBUTIONS

This thesis was conceptualized when pharmaceutical care was introduced to an academic tertiary hospital as an alternative supervision approach to improve adherence to pulmonary tuberculosis (TB) treatment in southern Thailand. This new approach is relatively simple and entirely differs sharply from directly observed therapy (DOT), a World Health Organization (WHO)'s recommended strategy, which emphasizes the importance of direct supervision in the initial two months of treatment [(1)]. The unique component of pharmaceutical care is that the clinical pharmacist provides timely services on patient education at every outpatient visit and supports patient-centered communication by providing consultation at any time through mobile phone. However, evidence on performance of pharmaceutical care for enhancing adherence in pulmonary TB patients is based on very limited data. We investigated two other referral hospitals in the vicinity and found that, due to health care resource constraints, DOT was not implemented in those hospitals. Their supervision approaches were tailored to fit their specific contexts, including home visit (regular home visits until treatment completion) and modified DOT (short-course of DOT and regular home visits). We designed this PhD work with three consecutive studies comparing these three different approaches for enhancing adherence to pulmonary

TB treatment in referral hospitals in southern Thailand: i.e., pharmaceutical care, home visit, and modified DOT. Several specific aspects were investigated, including the clinical effectiveness, health care resource uses and costs, financial burden borne by patients and the society and health-related quality of life (HRQoL).

The provision of pharmaceutical care for TB patients was initially started due to the study hospital's limitation. With accumulated experience and expanded capacity of the university hospital, a large proportion of non-local patients traveled for seeking TB care at the study hospital. Therefore, providing the DOT or other supervision activities (e.g. home visit) at patients' home was beyond the hospital's capacity. Unlike most hospitals in Thailand that need to follow a policy of the Ministry of Public Health by providing TB care with supervision activities, the study hospital under Prince of Songkla University (PSU) enhances patients' adherence by delegating responsibility of patient education service to their clinical pharmacists in the TB outpatient clinic. Our findings have provided evidence for the potential role of pharmacists in improving adherence in TB patients who took medications by themselves at home. Although the findings have shown that TB treatment success rates for pharmaceutical care are very similar to those for home visit or modified DOT, the cost analysis indicates that the pharmaceutical care approach requires less health care resources compared with the other strategies studied because the intervention requires no direct supervision which was one of the three main resource uses for both home visit and modified DOT groups.

Differences in patient characteristics among patients receiving different strategies had a high impact on a large variation in financial burden borne by patients and the society. The pharmaceutical care group incurred the highest out of pocket (OOP) expenditures, which is not surprising as almost half of patients treated in this group came from neighboring provinces. In addition to the costs of long-distance transportation, these patients paid for their medical care because the study hospital was outside their service area and was thus not covered by their public health insurance. Moreover, due to the higher income, a larger proportion of patients receiving pharmaceutical care can afford to visit private facilities before the TB diagnosis is made by a public healthcare provider.

Possible reasons for OOP expenditures incurred by local patients may be the awareness of TB, the accessibility of healthcare services, and patients' income. Although health care costs for TB diagnosis and treatment were mostly covered by patients' public insurance, in Thailand, people with TB related symptoms generally perceive that the symptoms are low severity and undertake their initial relief through purchasing medications from drugstores because of better accessibility and to avoid long waiting times at hospital [(2)]. Moreover, people who get paid daily may opt for visiting drugstores instead of spending their time at hospital and losing daily wage.

Indirect costs affect both patients and the society. Income loss due to TB affects patients directly, while production loss due to time seeking treatment, illness, disability or premature mortality affects the society as well. Productivity loss was a large

contributor to the incurred financial burden. Productivity loss posed a substantial financial burden to patients receiving home visit due to the high proportion of patients who were absent from work or who were unemployed because of TB. This implies that these patients who received home visit had more severe symptoms, compared with those receiving the other two approaches. We observed that patients receiving home visit had significant lower education level. These patients are more likely to wait and visit a hospital when the disease has progressed to a more advanced stage [(2)].

Public healthcare services should be provided in a way that provides timely and effective treatment, decreases OOP expenditures and indirect costs, especially during seeking care, TB diagnosis, and treatment initiation because the financial burden incurred during these periods may delay TB diagnosis and treatment, and pose barriers to treatment adherence, thus increasing spread of disease in the community [(3)].

5.2 IMPLICATIONS

This thesis is the first step towards investigating the potential value of pharmaceutical care for improving adherence in pulmonary TB treatment. Our findings shed light on the potential role of the clinical pharmacist in pulmonary TB outpatient service. Pharmaceutical care is a more recent and relatively simple supervision approach compared with home visits and modified directly observed therapy (DOT). Although this approach differs from the WHO's recommended strategy, which

emphasizes the importance of direct supervision in the initial two months of treatment [1], timely pharmacist-led patient education for every outpatient visit and pharmacist-provided telephone consultation were clinically effective and required less health care resources.

However, it may not be realistic to expect rapid changes in TB care policy in Thailand based on such data, since the provision for home visits and modified DOT is funded by the Ministry of Public Health, in alignment with the WHO's recommended strategy and the global fund's incentives for patient supervision. A larger scale, prospective study is warranted to generate more robust evidence to support Thai decision makers.

The financial burden varied markedly across different treatment strategies due to several factors such as public insurance coverage, socioeconomic status, disease severity, distance to TB services. In particular, the socioeconomic characteristics appear to differ substantially, which is not surprising since the three groups came from different areas of the province. In addition, the willingness of non-local patients to pay out of their own pockets for seeking TB care at the university hospital outside their district may be atypical in other settings. Thus, caution should be exercised when generalizing the research findings to other populations.

The evidence from this thesis shows that strategies to improve financial risk protection are essential for TB patients. During seeking care, improving access to quality public

healthcare facilities by decentralizing the services to the community health centers (e.g. providing the overtime services, ensuring use of effective screening and referral procedures) could increase accessibility and reduce patient congestion at the hospital. In the diagnostic process, ensuring use of fast and precise diagnostic test is necessary for reducing transportation costs and work time loss incurred to patients.

This work also provides additional evidence for the longitudinal changes in TB patients' quality of life over at least six months, which has rarely been studied. The utility based quality of life measure (EQ-5D-3L) facilitates the calculation of quality-adjusted life years (QALYs) which could support economic evaluations of different supportive approaches in the future work.

5.3 Limitations and Future areas of research

There are a few limitations with the studies. First, since the aim of this thesis is to compare the performance of different TB treatment supervision approaches that have been currently used under the usual health care practice, the study design was not a randomized controlled trial, but an observational study of patients who differ in some demographic characteristics. In Chapter 2, there have been attempts to statistically correct for some of these differences through the logistic regression and the propensity score method. Although we finally decided to use the propensity score method as a main analysis because this approach was better in adjusting for the confounders than

logistic regression, we acknowledged that there are limitations which were not overcome by matching a few specified variables. Other differences (e.g. income levels, educational attainment) between the groups have not been assessed due to limitations of the retrospective review and these could influence adherence to drug therapy. Nevertheless, propensity score matching was used only for comparing effectiveness, but not the costs. Since information about the costs of alternative treatments is to be used to guide health care policy decisions. It is the total cost of treating all patients with the disease that is relevant. Thus, the use of propensity score matching may be associated with underrepresentation of patients who utilize large amounts of resources (e.g. patients who are particularly ill or who pay out of their pocket for medical costs because the care is not covered by their public health insurance), due to unavailability of the match in the other groups. Consequently, the cost analysis included all patients and compared the differences in health care resource uses and costs between each treatment strategy.

The provision of pharmaceutical care at the study hospital by a small number of well-trained clinical pharmacists is challenging. Although, the team delegates one clinical pharmacist standing by for providing timely patient education for each TB patient at outpatient TB clinic visit and all members in the team can provide effective care based on the standard procedures for pulmonary TB management. The efficiency of this intervention depends highly on knowledge, experiences, and motivation of individual clinical pharmacist.

Another limitation is related to hospital databases in Thailand. The data used for assessing the clinical effectiveness and the resource utilization came from a retrospective hospital database review. However, we found that some clinical information such as patients' comorbidities, and adverse drug reactions (ADRs) was recorded differently across the hospitals. There was also missing data for some variables (e.g. HIV status, baseline chest radiography) due to the differences in the format of hospital database (e.g. some paper based medical documents were not converted to the computer based yet). Moreover, in the process for estimating health care resource uses and costs from hospital costs database, a number of patients had missing information (e.g. missing of resource use items for laboratory investigation, diagnostic radiology, and quantities of medication uses). Imputation has been made to minimize the impact of the missing information. This huge endeavor to handle the missing information was very time consuming.

To investigate some of the factors that were not available in the hospital database (e.g. patients' employment status, patients' income, and educational attainment, other costs that incurred to patients and their families, health-related quality of life (HRQoL), we conducted a perspective study based on patient interviews. However, this prospective component had a relative small sample size. Due to the long treatment duration of TB and the time constraints, recruiting a large number of TB cases was very challenging. Thus, the findings that indicate the treatment success in patients receiving self-administered therapy (SAT) below the WHO's target of 85% [4] are highly preliminary and need to be confirmed by a future large-scale, prospective study.

Lastly, a very small number of multidrug-resistance TB (MDR-TB) cases were included in the analysis. Research findings from this PhD work were derived from mostly drug-susceptible pulmonary TB patients. Caution should be exercised when generalizing the research findings to other populations with high proportion of MDR-TB. Current knowledge of the economic impact and the change in HRQoL associated with these different approaches in MDR-TB patients is limited. In 2015, a systematic review on costs to health services and the patient for treating TB reported that literatures on the costs of MDR-TB treatment are limited [5]. MDR-TB substantially impairs patients' HRQoL because the disease is associated with the debilitating conditions, long duration of treatment, high rates of ADRs, likelihood of anxiety and depression, stigma, income loss and unemployment [6]. However, there has been less attention given to MDR-TB patients. A few available studies were a small cross-sectional or prospective design with a follow-up period shorter than 6-month [6,7].

MDR-TB treatment has been changing rapidly [5]. Treatment regimens for MDR-TB typically last for 20 months of complex combinations of second-line agents, including long period with injectable medications, which are more expensive and may increase the likelihood of ADRs compared with the first-line agents [6,8]. In May 2016, given new evidence from several countries, WHO launched a shorter MDR-TB regimen lasting less than 12 months. The cost of MDR-TB treatment was reduced from US$ 2000–5000 per patient with the 20-month regimen to about US$ 1000 per patient with a

shortened regimen [8,9]. However, since the inappropriate use of the shorter regimen (e.g. in extensively drug-resistant TB (XDR-TB)) leads to serious risks for worsening resistance, this new regimen has not widely adopted in clinical practice yet and still needs the ongoing clinical trials to confirm its effectiveness [9].

As a result, further work needs to be carried out in the neglected area of MDR-TB management. Future larger-scale longitudinal studies would be useful to assess the costs and HRQoL associated with the three different approaches in MDR-TB patients, in order to better understand the sources of financial burden over time, to improve the strategies for financial risk protection, and to evaluate the impact of TB treatment on quality of life until the treatment completed in MDR-TB patients. In addition, these further works will be necessary to assess the budgetary impact of the ongoing changes in MDR-TB treatment and to support economic evaluations of new approaches for MDR-TB management.

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