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Cost utility analysis of balloon kyphoplasty and vertebroplasty in the treatment of vertebral compression fractures in the United States

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A Thesis

entitled

**Cost Utility Analysis of Balloon Kyphoplasty and Vertebroplasty in the Treatment
of Vertebral Compression Fractures in the United States**

by

Mrudula Borse

Submitted to the Graduate Faculty as partial fulfillment of
the requirements for the Master of Science Degree in Pharmaceutical Sciences

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May, 2013

An Abstract of
Cost Utility Analysis of Balloon Kyphoplasty and Vertebroplasty in the Treatment of
Vertebral Compression Fractures in the United States

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Vertebral compression fractures are associated with chronic pain, decreased health related quality of life and high health care costs. Balloon kyphoplasty and vertebroplasty are vertebral augmentation procedures, widely used by spine surgeons to relieve pain in these patients. A number of studies have been conducted to compare and contrast the effectiveness of both these techniques and have reported that balloon kyphoplasty offers a long lasting pain relief compared to vertebroplasty. However, kyphoplasty procedure is also more expensive than vertebroplasty. With the limited resources and the need of justification of patient selection, it is important to address whether the additional benefits offered by kyphoplasty are worth the additional costs. We performed a cost utility analysis from a payer's perspective using a Markov model to assess the cost utility of balloon kyphoplasty compared to vertebroplasty. Health utility data was obtained from previously conducted clinical trials. Direct medical cost associated with each of these procedures were obtained through an observational study conducted from the payer's perspective. Sensitivity analysis was performed to assess the robustness of the results around uncertainties in cost and utility parameters. The incremental cost utility of balloon kyphoplasty was \$ 29,027. The results were found to be robust. In conclusion, balloon

kyphoplasty is a cost-effective option for treating patients with vertebral compression fractures in the United States.

For my parents. Thank you for your love and support.

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Chapter 1

Introduction

This chapter gives an introduction of vertebral compression fractures, the various treatment options to relieve pain associated with them and a brief overview of pharmacoeconomic analysis. The chapter further provides the aims and objectives of the study.

1.1 Background

1.1.1 Vertebral Compression Fractures

Osteoporosis is a metabolic bone disorder in the elderly characterized by the loss of bone mass that leads to an increased risk of fracture and associated comorbidities. Each year, more than two million osteoporotic fractures occur in the United States.¹ Of these, the most common ones are spinal fractures also referred as vertebral compression fractures (VCFs) and hip fractures. Vertebral compression fractures can be extremely painful and can decrease the quality of life. They can also occur due to neoplasia or trauma. Around 547,000 vertebral fractures occur in the United States each year.² The risk of VCFs increases rapidly with age for both males and females and affects more than one fourth of all post-menopausal women. It costs the United States around 17 billion dollars each year.^{3,4,5} With the ageing of the United States population, an increase in occurrence of

VCFs is expected, leading to a growing burden on the health care system, owing to the high cost of treatment. Spinal fractures are associated with high morbidity and mortality in the elderly, leading to alarming consequences. Patients with VCFs suffer from chronic back pain, decreased physical function, depression, and decreased pulmonary function.⁶ It decreases the quality of life and also increases dependence on others. They can also lead to permanent long term degenerative effects. Patients with multiple compression fractures may begin to notice kyphotic deformity or curving of the spine, like a “hunchback” as shown in Figure 1.1 on p 3. Due to this curvature, the center of gravity moves forward, thereby creating a large bending stature. This increased bending stature must be counterbalanced by the back muscles and ligaments, which results in muscle fatigue, gait abnormalities, and consequently an increased risk of falls and additional fractures.⁷ Vertebral fractures are also a cause of significant mortality in the elderly population. A recent study conducted among the female Medicare population showed that patients with a vertebral fracture had an overall mortality rate that was approximately twice that of the controls.⁸ The chronic pain associated with symptomatic vertebral compression fractures can lead to decreased mobility and a marked decrease in the health-related quality of life (HRQoL). The management of such patients includes measures to reduce pain, improve mobility and initiation of osteoporotic treatment.

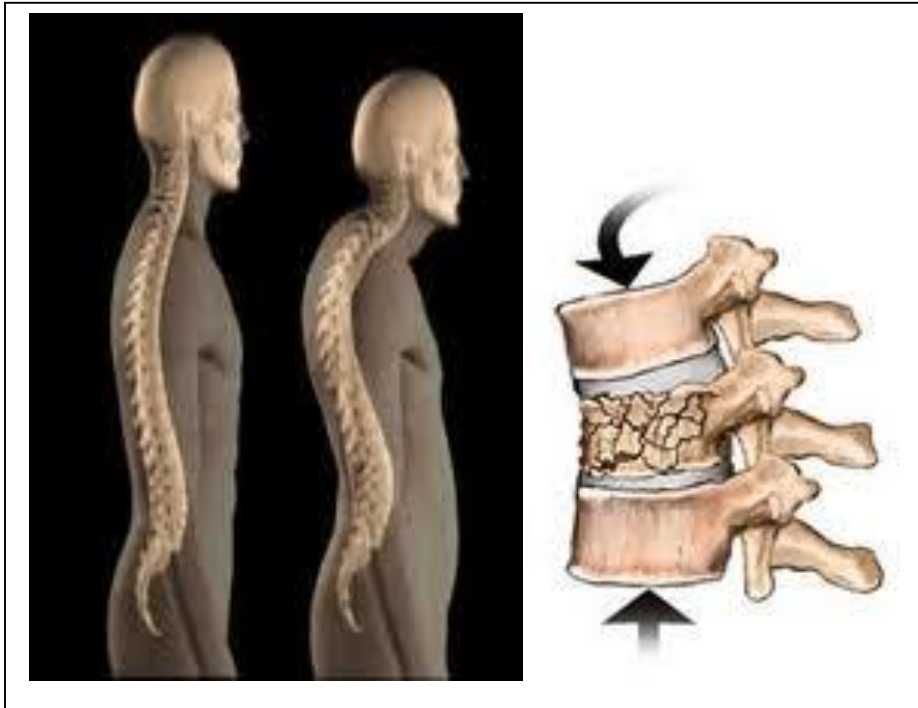


Figure 1.1: Kyphotic deformity in vertebral compression fracture

1.1.2 Treatment of pain in patients with spinal fracture

Conventional medical management for these patients can take two forms. The first one involves bed rest, and sufficient use of pain medications. However, bed rest decreases activity and accelerates bone loss and may cause deep venous thromboses. Also, the use of opioids for treatment of pain can occasionally result in opioid dependence and can also alter the mood and mental status of elderly patients, thus worsening their condition.⁹ Another form of conventional treatment is physical therapy, and external back-bracing.^{10,11} External braces may, however, be inconvenient for the elderly patients. While the conventional treatment helps relieve pain in some patients, in others chronic pain may persist. Two minimally invasive treatment options- percutaneous vertebroplasty and

balloon kyphoplasty are available for treatment of chronic pain (lasting more than two months) in cases where conventional treatment fails.¹²

Vertebroplasty is recommended for the treatment of chronic and disabling pain in patients with spinal fractures.^{13,14,15} It was first performed in the United States in 1994 and has gained increasing popularity since 1997 as a treatment for pain associated with VCFs.¹⁶ It is performed by interventional radiologists in an inpatient as well as outpatient setting using local anesthesia (Figure 1.2 on p 4).

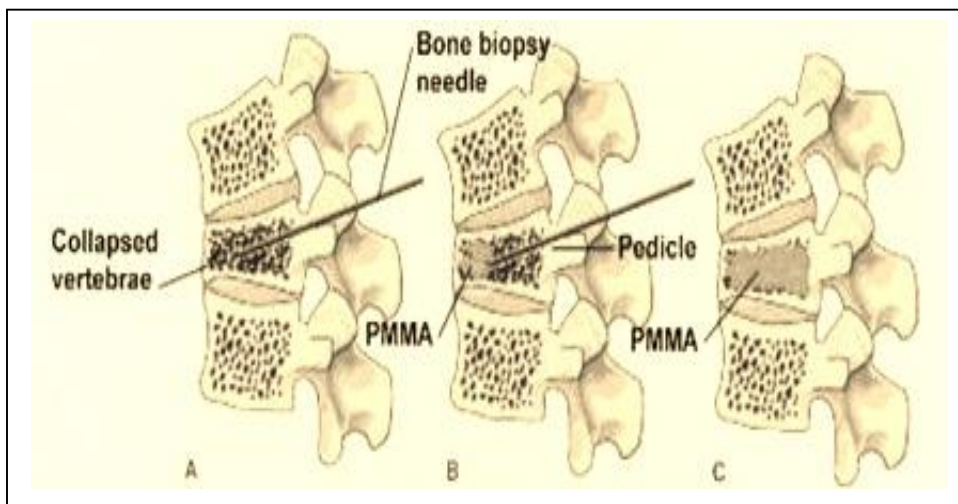


Figure 1.2: Procedure of vertebroplasty

A needle is inserted through an incision in the skin in the back into the fractured vertebral body. When the needle is in appropriate position, surgical-grade bone cement is injected into the vertebra under fluoroscopic guidance. The cement (usually polymethylmethacrylate) hardens within 15 minutes and forms a support structure within the vertebra that provides stabilization and strength. It also prevents pain caused by one vertebra rubbing against another. The entire procedure takes one to two hours to perform depending on how many bones are treated. After the procedure, the patient is allowed to move carefully and can usually go home within several hours. After vertebroplasty, most

patients experience pain relief within a day or two. Several studies have reported a significant reduction in pain and an improvement in functional mobility with vertebroplasty.¹⁷⁻¹⁹ However, in vertebroplasty, the cement is injected into the fractured vertebra under high pressure and may be difficult to control. This leads to a potentially higher risk of cement leakage compared to kyphoplasty.²⁰ However, various studies conducted to evaluate the safety of vertebroplasty report an overall good safety profile.

Kyphoplasty is a procedure similar to vertebroplasty except that it involves the use of an inflatable balloon called a bone tamp. (Figure 1.3 on p 5)

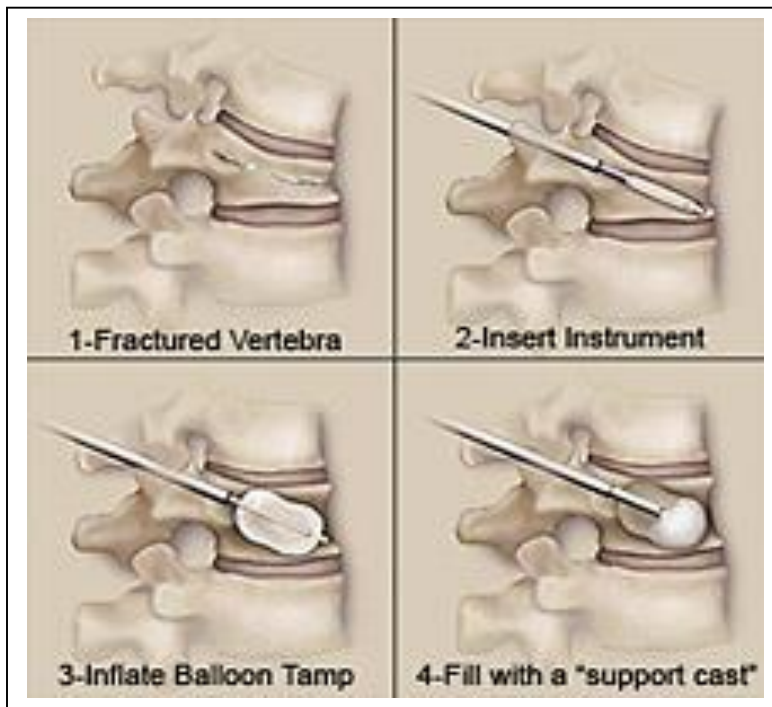


Figure 1.3: Procedure of balloon kyphoplasty

In kyphoplasty, the patient is sedated using general anesthesia. Through two small incisions made in the back, a probe is inserted into the body of the fractured vertebra using image guidance X-rays. The bone is then drilled and the bone tamp is inserted on each side. These balloons are then inflated with a contrast agent until they expand to the desired

height and removed. As the balloon inflates, it can help to restore the height of the compressed bone due to the fracture and can also correct abnormal wedging of the broken vertebra. The cavity created by the balloons is then filled with polymethylmethacrylate (PMMA), the same orthopedic cement used in vertebroplasty, binding the fracture. The cement hardens in place, providing strength and stability to the vertebra, restoring height, and relieving pain.

A significant decrease in pain level and an improvement in physical function are observed after balloon kyphoplasty.²¹⁻²³ Kyphoplasty offers the additional benefit of correcting the kyphotic deformity (hunchback) by restoring the spine to a more normal alignment compared to vertebroplasty.^{20,23} Various observational studies have been performed to compare and contrast the effectiveness of both these techniques. Some studies have noted a significant difference in the long-term efficacy of these techniques with balloon kyphoplasty offering a long lasting pain relief compared to vertebroplasty.²⁴⁻²⁶ However, kyphoplasty costs approximately 2.5 times higher than vertebroplasty.²⁷ While a typical vertebroplasty procedure costs anywhere from \$3,300 to \$9,800 based on the setting, a kyphoplasty can cost between \$8,100 and \$13,000 in a similar setting.²⁸ Given the vast difference in the cost of vertebroplasty and kyphoplasty, one may question the cost-effectiveness of kyphoplasty over vertebroplasty. With the limited resources and the need of justification of patient selection, it is important to address whether the additional benefits offered by kyphoplasty are worth the additional costs. Cost effectiveness analysis in health care is used to evaluate such health care interventions to help justify resource allocation.

1.1.3 Pharmacoeconomics

In the recent years, there have been breakthroughs in the area of health technology research that have increased longevity and quality of life. Advances in the medical field have made it possible to improve disease conditions and health outcomes. However, most of the current treatment options are still “mid-way” technologies which help improve a disease state but do not cure. For example, in HIV patients, there are many new, useful treatment options that help fight the infection, but do not cure it. Most often, these technological developments are also associated with an increase in cost. This complex web of diagnostic and therapeutic uncertainties, increased costs, and limited resources makes health care decisions more challenging.

In recent years, the scarcity of resources and increased threat of monetary cutbacks have amplified the importance of economic evaluation of health care services. A large number of economic evaluations have been published, which serve as a guide to determine optimal resource allocation. Such studies provide information on the effectiveness of an intervention in comparison to the cost of its implementation. Pharmacoeconomic studies concurrently evaluate the clinical and economic consequences of a treatment option thereby helping to determine wise allocation of resources.

Pharmacoeconomic studies use four basic forms of economic evaluation to assess the benefits and effectiveness of an intervention. The four basic forms of economic evaluation are cost-minimization analysis, cost-effectiveness analysis, cost-benefit analysis, and cost-utility analysis. Cost minimization analysis is a type of partial economic evaluation in which two or more treatment options that are identical in their health benefits are compared in terms of their costs. Since the outcomes are considered equivalent, the

least expensive option is generally chosen. However, in reality, very few alternate treatments have equivalent outcomes and hence, other types of economic analysis are prevalently employed. Cost effectiveness analysis (CEA) is a type of full economic analysis that allows policy makers and health planners to compare the cost and health gains that various interventions can achieve. CEA helps determine the intervention that leads to the greatest improvement in some health indicator (mortality or morbidity) for the smallest increase in costs. Costs are measured in monetary units whereas health gain/ effectiveness is measured based on the consequences, such as improvement in clinical and humanistic outcomes, improved patient quality of life, years of life saved, etc. The goal is to find the most effective treatment at the least cost. Cost utility analysis is a type of cost effectiveness analysis which measures the health benefits in terms of quality adjusted life years (QALYs). Cost benefit analysis is generally used when it is possible to attach a monetary value to all the effects of the interventions which are then compared.

1.1.4 Cost utility analysis (CUA)

Cost utility analysis allows the comparison of different health outcomes (such as addition of life years, prevention of pain or relief from suffering) by measuring them all in terms of a single unit – the QALY. QALYs measure health as a combination of the duration of life and the health-related quality of life and are hence considered a better outcome indicator. Health related quality of life is measured on a preference scale with 1 being the perfect or best imaginable health and 0 being a quality of life as bad as being dead. QALYs are obtained by asking individuals to trade off improvements in their health status against either life expectancy (time trade-off) or risk of death (standard gamble). These are reported as key values called ‘utilities’. A number of valuation methods for utility

measurement have been used; with the most common ones being the time trade-off (TTO) method and the standard gamble (SG) method. Various standardized and validated health status instruments like EuroQol 5 Dimension (EQ-5D), short form 6D (SF-6D), Health Utilities Index Mark-3 (HUI-3), etc. have been widely used to measure QALYs.

Results of a cost utility analysis are primarily expressed as a ratio called incremental cost-utility ratio (ICUR) or in other terms – cost per QALY, which is calculated as the difference in the expected cost of two alternate therapies, divided by the difference in the expected QALYs gained. The results of CUA are compared with a predefined standard (i.e. a maximum acceptable cost-utility ratio or an acceptability criterion against which they can be compared) also referred to as the willingness to pay for health gain. Interventions below the threshold ICUR are normally funded whereas as an intervention with an ICUR above the threshold value tends not be. Interventions with a high ICUR may be funded on the basis of other considerations such as the severity of the condition and the availability of alternative treatments.

1.1.5 Selecting the viewpoint of Pharmacoeconomic Analysis

To fully evaluate any pharmacoeconomic study, it is important to understand the perspective from which it is conducted. The viewpoint chosen can change the judgment on the best value obtained for money. The costs that are considered in any pharmacoeconomic analysis are influenced by the perspective under consideration. A health care provider's perspective includes only the true cost of service. For example, from a hospital's perspective; the cost of resources required for the treatment, physician fees, cost of hospital beds, etc. are evaluated. Whereas a payer's perspective, such as that of an insurance company accounts for the reimbursable charges like reimbursement rate for hospital

services or physician fees or cost of medications, etc. The patient's perspective includes out of pocket costs in addition to other opportunity costs such as decreased earning ability or cost of loss of work and cost of premature death. The societal perspective is a broad perspective that accounts for all the above costs in addition to the cost of lack of use of resources for overall benefit of the society. The characteristics of the costs and benefits are affected by the choice about what perspective to adopt and is likely to influence the interpretation of results and conclusion of an economic analysis.

1.2 Need for study

As the baby boomers continue to age, the United States continually faces the surge in demand for medical care thereby putting a strain on its resources. Given the prevalence of vertebral compression fractures and its predicted increase in the future, combined with the dilemma of resource allocation for its treatment, economic evaluation of vertebroplasty and balloon kyphoplasty is important from the payer's perspective. Although both these techniques are similar in their biomechanical principle, literature shows that there is a significant difference in their outcomes. In order to justify reimbursement and rationalize patient selection, it is essential to determine the cost-utility of these techniques.

This study will be conducted in order to assess from a payer's perspective the cost-utility of kyphoplasty compared with vertebroplasty in the United States. The study will help determine the most effective alternate in treating patients with VCFs.

1.3 Objective

The main objective of this study is to determine from a payer's perspective whether the additional cost of balloon kyphoplasty is worth the benefits associated with it when

compared to vertebroplasty in the treatment of vertebral compression fractures in the United States.

We hypothesize that:

1. Balloon kyphoplasty will be more effective than vertebroplasty for treating VCFs. It will improve the HRQoL and utility.
2. The total direct costs associated with balloon kyphoplasty will be higher than the total direct costs associated with vertebroplasty.

1.4 Specific aims

1. To determine the cost per QALY gained after balloon kyphoplasty
2. To determine the cost per QALY gained after percutaneous vertebroplasty
3. To determine the incremental cost effectiveness ratio of balloon kyphoplasty compared to vertebroplasty in the treatment of patients with a painful, vertebral compression fracture, from a payer's perspective.

1.5 Research question

Is balloon kyphoplasty cost-effective compared to vertebroplasty in treatment of vertebral compression fractures in the United States?

Chapter 2

Literature Review

2.1 Epidemiology of Disorders leading to Vertebral Compression Fractures

Vertebroplasty and kyphoplasty are emerging effective approaches for pain relief and improvement of function in the treatment of VCFs. While osteoporosis is the most common cause of VCF, they may also be caused by trauma or metastatic tumors.

2.1.1 Osteoporosis

Osteoporosis is a bone condition characterized by thinning of bone tissue and loss of bone density, thereby leading to an increased risk of fracture. It is defined by World Health Organization as bone mineral density that is 2.5 standard deviations or more below the mean peak bone mass (average of young, healthy adults) as measured by DXA; the term "established osteoporosis" includes the presence of a fragility fracture.²⁹ Fragility fractures are those that occur in conditions where a healthy person would not normally break a bone such as stepping out of the shower, sneezing vigorously or lifting a light object. Most common fragility fractures are hip fractures, vertebral fractures and wrist fractures.³⁰

More than 10 million people in the United States aged 50 years and above are estimated to be diagnosed with osteoporosis. With the aging population of United States, this number is expected to increase to 121.3 million by the year 2025.¹ Osteoporosis increases the risk of fractures thereby causing significant morbidity and mortality. It has been shown that an initial fracture increases the risk of subsequent fracture by 86%.³¹ Likewise, patients with a history of VCF have a 5-fold increased risk of future vertebral fracture.³²

2.1.1.1 Risk factors for osteoporosis related VCFs

Epidemiological data shows that the risk for vertebral fractures increases with age for both, men and women.³³ Furthermore, women are twice as likely to incur osteoporosis-related VCFs compared to men.³³ The age-standardized incidence of fractures is 10.7 and 5.7 per 1,000 person-years in women and men, respectively.³⁴ However, men in their fifties have a much higher prevalence of VCFs compared to women, probably due to more strenuous activities.³⁵ A population study carried out in Minnesota reported incidence rate as high as 29.6 per 1,000 person-years of new vertebral fractures in women aged ≤ 85 years.³⁶ Studies show that there is a variation in fracture incidence across various ethnic groups as well. Caucasians and Asians have higher prevalence of VCFs whereas African-Americans and Hispanics have lower incidences of VCFs.³⁷⁻³⁹

2.1.1.2 Consequences of VCFs

Spinal fractures are associated with significant morbidity and mortality. They cause acute pain which can limit a person's physical activities. However, more severe are the long-term side effects of VCFs like kyphotic deformity, reduction in pulmonary function,

etc. A single thoracic vertebral fracture can decrease the lung function by 10%.⁴⁰ Women with one or more VCF have an age-adjusted relative risk of mortality related to pulmonary causes 2 - 2.7 times higher compared to women without VCF.⁴¹ Vertebral fractures are also associated with an increase in mortality. A study conducted by Van Staa et al reported survival rates of 86.5% and 74.3% at the end of one year and survival rates of 56.5% and 42.1% at the end of five years following a fracture among women and men, respectively, aged ≥ 65 years.⁴²

2.1.2 Metastatic cancer related VCFs

Metastatic cancer may cause changes in bone structure, making them brittle and weak. Each year, around 75,000 to 100,000 VCFs related to cancer occur in the US, the most common causes being myeloma, prostate and lung cancer.^{43, 43} Factors contributing to VCFs in cancer patients include continued bone loss due to tumor invasion, poor nutritional status, immobilization, and prolonged steroid use. The outcomes associated with VCFs in cancer patients are similar to those observed in the osteoporotic population.

2.1.3 Trauma related VCFs

High-energy trauma such as a motor vehicle accident or fall from a great height may also lead to VCFs. Most of the VCFs that occur in patients below the age 50 years are trauma-related. The primary cause of morbidity in these patients is deep venous thrombosis and pulmonary embolism and hence such fractures are beyond the scope of this study.

2.2 Forms of care for the management of VCFs

VCFs lead to vertebral collapse and can cause a significant amount of pain. The main aim of the treatment is, hence, to ease the pain and to decrease and stabilize the fracture. VCFs can be treated either by following the conservative treatment or the surgical care option. The selection of treatment regimen is subjective to the level of pain and percentage of vertebral collapse. Vertebral augmentation techniques are employed when the pain is greater than four on a ten-point scale (zero indicates no pain and ten indicates the worst pain imaginable) or if the vertebral bodies are more than 40% collapsed. Conservative treatment is preferred in other cases.

Since, a majority of the fractures can heal naturally; the conservative treatment employs the use of bed rest, analgesic medication and orthotics. For osteoporosis-related VCFs, the pharmacotherapy includes use of anti-catabolic medications such as calcitonin, raloxifene, risedronate, alendronate, etc or anabolic medications such as teriparatide. However, conservative treatment is often ineffective for pain relief. In such cases, minimally invasive techniques i.e. vertebral augmentation techniques such as vertebroplasty and balloon kyphoplasty are considered.

2.3 Vertebroplasty

Vertebroplasty is a minimally invasive technique that can be employed to treat spinal fracture patients who are in constant pain and cannot manage everyday activities.

2.3.1 Selection for vertebroplasty

The primary indication for vertebroplasty is severe pain emanating from VCFs. Vertebroplasty should be opted as early as possible in cases of failing conservative therapy, or in cases of intense pain requiring hospitalization since patients with pain of more than three months duration are less likely to benefit from vertebroplasty.⁴⁴ Respiratory or severe cardiac failure are contraindicated for vertebroplasty.⁴⁵ In addition, the coagulation profile is checked before vertebroplasty; it must be normal or near normal, and the use of anticoagulants must be ceased prior to the procedure.⁴⁵ Fever or infection is another contraindication for vertebroplasty. Vertebroplasty is also avoided in cases with severe loss of vertebral body height, but it can yield good results even in severely compressed vertebrae.⁴⁶

A week or two before the actual procedure, a formal pre-operative assessment is performed by the interventionist to distinguish pain from other causes than VCF. Magnetic resonance imaging dating from the time of symptom onset is reviewed to assess for osteolysis, marrow edema in the target levels, degree of collapse, and compression of neural tissue. Vertebroplasty is contraindicated if bone marrow edema is absent. Severe degree of collapse of the pedicle and posterior vertebral body cortex increases the risk of symptomatic cement leakage and thus vertebroplasty is contraindicated in such patients.⁴⁵

2.3.2 Post-operative care for vertebroplasty

The patient is asked to remain in a supine position (lie on the bed with face up) or semi-recumbent position for one hour after the procedure. The patient's neurovascular status is checked every 15 minutes and a wound inspection is conducted every 30 minutes.

The patient is then gently mobilized. The patient can be discharged home after two hours if his/her status is stable. Sometimes, the patient may experience an increase in pain which is usually of benign etiology and self-limiting. For osteoporotic fractures, follow-up treatment of the patient's underlying osteoporosis is essential.

2.3.3 Post- vertebroplasty morbidity

Although, there may be a few complications after vertebroplasty, overall, it is a safe and effective procedure. Some of the possible complications post-vertebroplasty include cement leakage, pulmonary embolism, infection, bleeding, increased back pain and neurological symptoms such as numbness or tingling.^{47, 48-53} Paralysis is extremely rare.⁵⁴ Some studies mention that vertebroplasty can cause another fracture in adjacent spine or ribs.^{51,55,56} A possible explanation for adjacent fractures is that, most of the VCF cases are osteoporosis-related and if osteoporosis is left untreated, it results in fragile bones. The friction between fragile bones and stiff and strong treated vertebral bones could lead to future fractures due to which may not necessarily be a direct consequence of vertebroplasty.⁵⁰

2.3.4 Post- vertebroplasty causes of mortality

The incidence of death after vertebroplasty is very rare and based on a review article, seven deaths in approximately 140,000 –175,000 procedures occurred after vertebroplasty between 1999 and June 2003 in the United States. Four of the seven deaths were described as an anaphylactic reaction to the bone cement resulting in cardiac and/or respiratory arrest and death whereas the other three were attributed to surgical error.⁵³ Another case study that was performed in Austria reported patient death after

vertebroplasty as a result of cement leakage into the extra-vertebral space leading to pulmonary failure.⁵⁷

2.3.5 Post- vertebroplasty health-related quality of life (HRQoL)

Various studies have evaluated the decrease in pain scores and improvement in HRQoL after a vertebroplasty procedure. Various validated instruments have been used to measure these humanistic outcomes. A majority of the studies analyzed pain score using a visual analogue score (VAS). Most commonly used instruments for measuring HRQoL were the EQ-5D Questionnaire, Short Form-36 (SF-36) questionnaire, Osteoporosis Quality of Life Questionnaire, etc.

Different studies have reported a significant reduction in pain after vertebroplasty.^{17,20,58-60} However, two recently published randomized studies have reported vertebroplasty and sham procedure to be equally effective.^{61,62} However, these findings have been challenged by other clinicians due to the bias in their patient selection. Some of the potential flaws include small sample size, low rate of enrollment, lack of evidence for VCFs as the cause of pain, patients with lower levels of pain and disability than those normally treated by vertebroplasty and a high rate of crossover from placebo to vertebroplasty in one of the studies.⁶³⁻⁶⁶ Overall, vertebroplasty is a widely accepted procedure for pain reduction in patients with VCF. Also, there is a significant improvement in the quality of life after vertebroplasty for up to 6 months. However, vertebroplasty has shown to lose its benefits in the long term. Studies with longer follow-up time (more than 2 years) have shown no significant difference in pain reduction due to vertebroplasty.

2.3.6 Economic evaluation of vertebroplasty

VCFs are highly debilitating and cause a considerable amount of pain and morbidity. Vertebroplasty is known to be effective in reducing pain and morbidity associated with VCFs. However, it is comparatively an expensive procedure and hence economic evaluation is necessary to justify its reimbursement. Two cost effectiveness studies have been conducted to evaluate the cost effectiveness of vertebroplasty with conservative treatment. One of the studies found that vertebroplasty causes a significant reduction in pain compared to conservative treatment and is cost effective when evaluated in terms of reduction of pain (VAS).⁶⁷ Another study evaluated the cost effectiveness of vertebroplasty over conservative treatment with regards to improvement in quality of life and found vertebroplasty to be cost effective.⁶⁸

2.4 Balloon Kyphoplasty

Balloon kyphoplasty is a vertebral augmentation technique similar to vertebroplasty with the exception of the use of a balloon to create a cavity in the vertebra before filling it with bone cement.

2.4.1 Selection for kyphoplasty

Patient selection for kyphoplasty is similar to vertebroplasty in terms of history, physical examination and imaging evaluation. Like vertebroplasty, primary indication for kyphoplasty is pain as a cause of VCF. To distinguish pain from other causes, a careful assessment of patient history and clinical examination is performed. Imaging reports are used to assess the level of vertebral collapse. Kyphoplasty is recommended for acute

fractures (1 to 3 weeks old) as they are much less likely to have healed significantly, and therefore kyphoplasty can better provide height restoration.⁶⁹ Completely collapsed vertebrae may be more difficult to treat with kyphoplasty because the insertion of the balloon tamp requires more residual vertebral body height than the devices required for vertebroplasty. Twenty five to thirty percentage of the original vertebral height is generally required for kyphoplasty.⁷⁰ The exclusion criteria for kyphoplasty are similar to vertebroplasty. Kyphoplasty is contraindicated if there is a local or systemic infection, if the vertebral compression fracture is not painful, or if there is respiratory or cardiac failure.⁷¹

2.4.2 Post-operative care of kyphoplasty

After kyphoplasty, the patient is taken to a recovery area and monitored for 2 to 3 hours. The patient lies in the supine position for an hour during which the bone cement (PMMA) usually hardens to 90% of its strength. During this time, the patient is monitored for neurological and hemodynamic changes. If any such changes occur, especially neurological, prompt imaging, usually with CT, is warranted. Post-procedural pain is assessed and managed with nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics.⁷²

2.4.3 Post- kyphoplasty morbidity

Kyphoplasty is associated with significantly less morbidity than vertebroplasty or open surgery.⁷³ Some of the reported complications with kyphoplasty include extravasation of the bone cement, neurological symptoms, pulmonary embolism, and

infections.⁵³ However, the risk for embolization is very low.⁷³ Also, most of the cement leakages are asymptomatic.^{74,75}

2.4.4 Post- kyphoplasty causes of mortality

As reported by Food and Drug Administration, only one case of death occurred as a result of kyphoplasty among 40,000 –50,000 kyphoplasty procedures performed between 1999 and 2003 in the United States.⁵³ In studies conducted in other countries, the incidence of death after kyphoplasty is very low. A comprehensive meta-analysis of complications associated with kyphoplasty conducted by Taylor et al. reported an overall mortality rate of 4.4%, peri-operative mortality was 0.13%.⁷⁶

2.4.5 Post-kyphoplasty HRQoL

VCFs cause severe physical, functional and psychological consequences that can dramatically impact the patient's HRQoL.²⁰ Studies show that patients show a significant improvement in their functional ability after balloon kyphoplasty, gaining independence and improving quality of life. A study conducted by Coumans et al. reported a significant improvement in the HRQoL persistent for one year after kyphoplasty as measured using the SF-36 instrument.⁷⁵ These results are in concordance with another study conducted by Eidt-Koch et al. in Germany.⁷⁷ Various other studies have measured HRQoL at different time points after kyphoplasty and have reported a similar improvement.⁷⁸⁻⁸⁰

2.4.6 Economic evaluation of kyphoplasty

Although balloon kyphoplasty has proven effective in the treatment of pain associated with VCFs, it is an expensive procedure. The cost of kyphoplasty procedure

ranges from \$8100 to \$16,000 depending upon the setting.²⁸ Hence, cost effectiveness evaluation is necessary to justify the allocation of resources. A cost utility analysis was conducted by Strom et.al using HRQoL outcomes from the FREE (Fracture Reduction Evaluation) clinical trial. A comparison of kyphoplasty to conservative treatment of VCFs indicated that balloon kyphoplasty was a cost effective alternative for treating such patients.⁸¹

However, to our knowledge, no studies have compared the cost effectiveness of balloon kyphoplasty with vertebroplasty. Both of these being vertebral augmentation procedures, they are similar in many aspects terms such as patient selection, post-procedure care, etc. Yet they vary in their safety and efficacy profiles and costs. For wise resource allocation, a cost effectiveness analysis of these two procedures is warranted.

Chapter 3

Methods

An economic analysis of vertebroplasty and balloon kyphoplasty was conducted from a payer's perspective such as Medicare using TreeAge Pro Software, Williamston, MA. Health effects were measured as quality-adjusted life-years (QALYs) gained. Costs were measured in United States Dollars (USD). A computer simulated Markov Model was used to calculate the cost per QALY for each procedure and the findings were reported as an incremental cost-utility ratio (ICUR).

3.1 General Description of the Study Design

A historical cohort study was undertaken in order to study the HRQoL and economic impact of vertebroplasty and balloon kyphoplasty. HRQoL data were obtained from previously conducted clinical trials. The cost of intervention was obtained from a study conducted from the payer's perspective in patients with vertebral compression fractures and treated with vertebroplasty or kyphoplasty. Cost and utility associated with vertebroplasty and kyphoplasty were then modelled in a hypothetical population cohort using a Markov model to obtain ICURs.

3.2 Study Population

The base case population was 70 year old US adults with a T-score of -2.5 who had incurred one initial vertebral fracture. HRQoL effects were measured as QALYs gained which were modeled on the EQ-5D data estimated by the previously published studies detailed below.

3.3 Markov Model

Markov models are often used to represent stochastic processes i.e. random processes that evolve over time. A Markov's model represents a changing set of health states over time, where there is a known probability or rate of transition from one health state to another. Health states in a Markov's model represent clinically and economically important events in the disease process. These different health states are mutually exclusive i.e. a patient cannot exist in more than one health state at any one time and there always exists the probability of death. The probability of moving from one health state into the other is called as the "transition probability". A patient can move from one health state into the other except when a patient is in the "dead" health state which is sometimes also referred to as the absorbing state. The disease which is studied is divided into distinct health states and transition probabilities are assigned for movement between these states over a discrete time period called a "Markov Cycle". Estimates of resource utilization and health consequences are attached to the different health states and transitions in the model and then the model is run over a large number of cycles to estimate long term costs and consequences associated with the disease and a particular health intervention. A change of state can occur only once in each cycle.

3.4 Development of Markov Structure Model

The cohort simulation model used in this study is based on a previously published study evaluating the cost effectiveness of balloon kyphoplasty compared with non-surgical management in hospitalized patients with painful VCFs.⁸¹ The original Markov model was developed by a team of clinicians frequently performing the procedure primarily in Europe and United States. Since, the treatment guidelines and transition from one health state to another are similar in Europe and United States, the model was considered suitable for the US setting. It was designed to compare treatment of painful osteoporotic fracture with vertebroplasty or kyphoplasty. The redesigned model was validated by consulting a research team comprising of orthopedic surgeons, spine surgery specialists and members from the orthopedic research center at University of Toledo

It simulates the various possible health events over time after undergoing a vertebroplasty or a balloon kyphoplasty. The cycle length was set at 6 months and all the patients were followed through the model until they reached 100 years of age or they died. A schematic picture of the model is shown in Figure 3.1 on p 26.

All patients started with an initial VCF and were either treated with vertebroplasty or balloon kyphoplasty. The base case cohort age was considered to be the same as in the clinical trials i.e 70 year old men and women. After being treated with vertebroplasty or balloon kyphoplasty, each patient could have three possible health outcomes – either they could remain in their current state (associated with an improvement in their health) or they could sustain an additional VCF, or they could die. If a patient stays in the vertebroplasty or balloon kyphoplasty or additional VCF state without incurring a fracture event or dying, the patient moves to the first sub-state. The sub-states are temporary states that account for

the time-dimension as the patients recover, and the fracture-related mortality decreases from the initial level in the first six months in each state. A patient with an additional spinal fracture after either of the two procedures, can have only three possible outcomes, they can either sustain an additional VCF or they can improve their health or they can die. If a patient dies, he/she will move to the absorbing dead health state. Sustaining an additional VCF means that the patients will be suffering from pain associated with the new spinal fracture and were hence considered to have lost all QoL benefits associated with vertebroplasty or balloon kyphoplasty if they sustained an additional VCF.

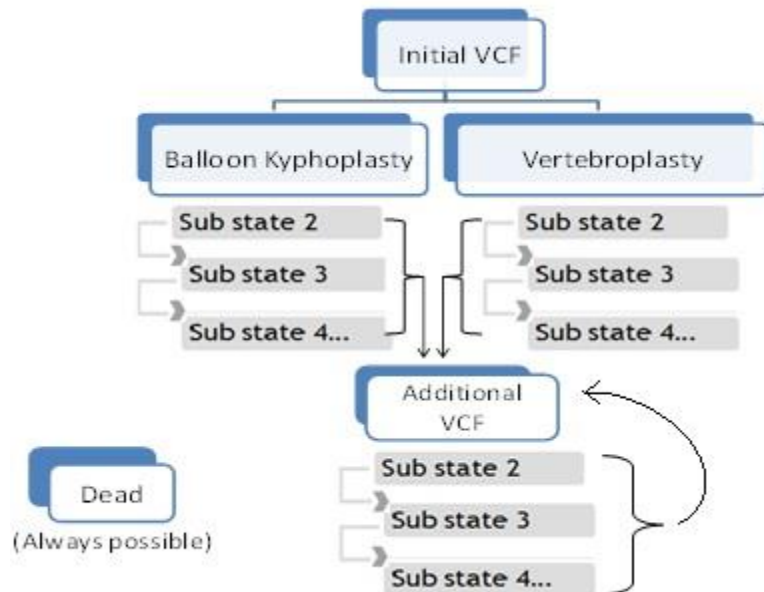


Figure 3.1: Schematic picture of transition states used in the Markov model

3.5 Building the model in Treeage Pro Suite Software

The theoretical model structure was then built in Treeage Pro Suite software to run a computer generated simulation on a hypothetical cohort. A graphical presentation of the model is shown in Figure 3.2 on p 27. A Markov process assumes that the behavior of the model in one time period (i.e., cycle) does not depend on the previous time period.

However, in our model the amount of time spent in each cycle affects the utility in sub-states. The sub-states are time dependent processes and hence they were modelled as “tunnel states”. Hence, to allow for transition probabilities, costs and health utilities to reflect the actual duration of a patient's stay in a specific health state, tunnel states were used. A tunnel state is an array of temporary Markov states that can be visited only in a specific sequence. They allow for the time dimension as the patient recovers in the sub-states.

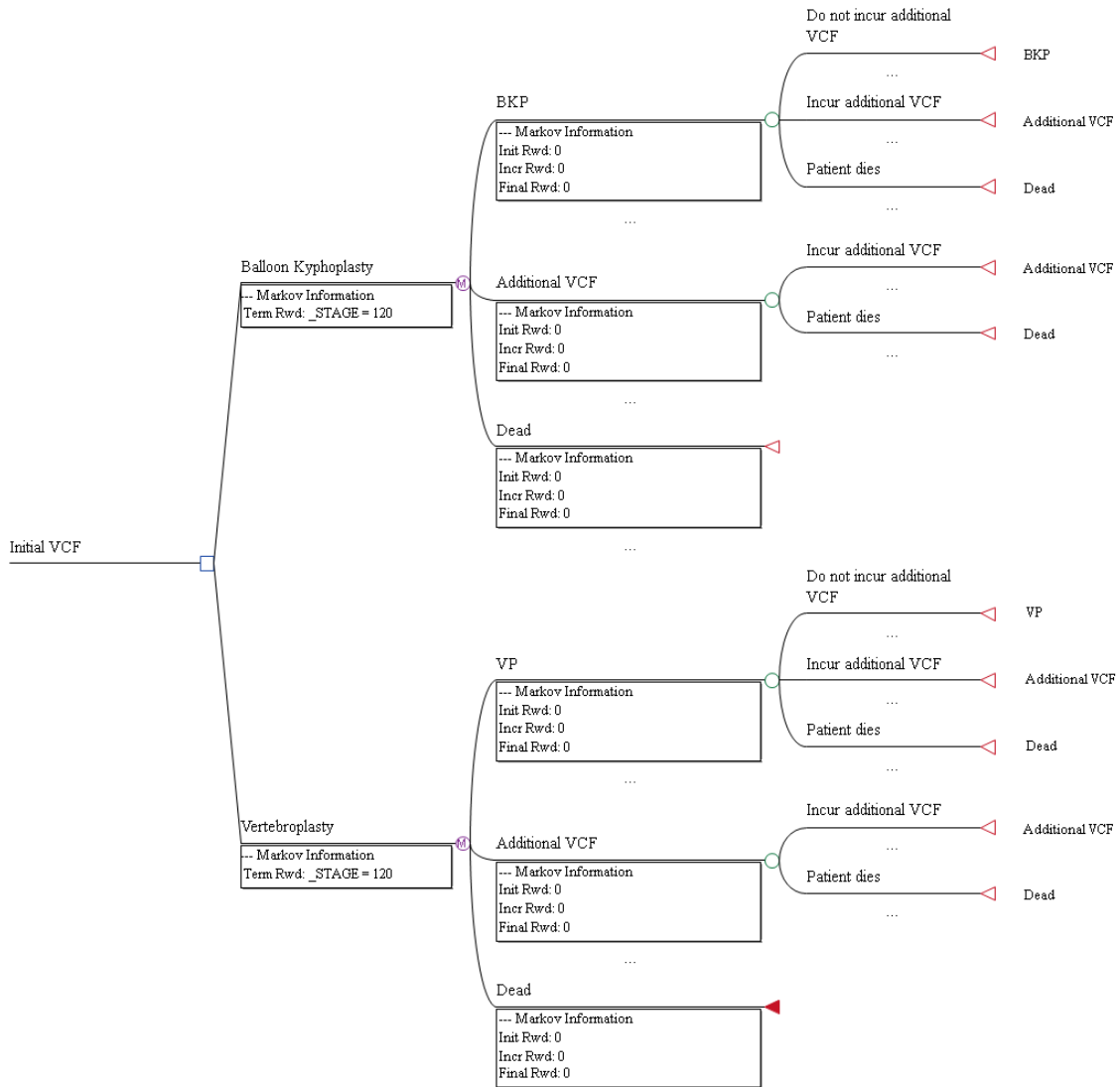


Figure 3.2. Markov Model build in Treeage Pro Suite software

3.6 Health Utility: QALY

The quality of life was assessed based on data found in the literature. QALYs were measured using the EuroQol 5 Dimension (EQ-5D) questionnaire. The EQ-5D is a validated, multi-attribute, preference-based health status measure. Currently, EQ-5D is being widely used in different countries as a standardized measure of health for clinical and economic appraisal. It comprises of five dimensions: (i) mobility, (ii) self care, (iii) usual activities, (iv) pain/discomfort, and (v) anxiety/discomfort. The EQ-5D records the respondents' self-rated health on a level of one to three for each domain. Further details on the survey instrument are reported elsewhere.⁸² The EQ-5D scores are then converted into a single summary index using an algorithm to apply weights. They can be expressed as QALYs with values ranging from zero to one, with one indicating “perfect health” and zero being equivalent to “death”.

Data available from two previously published randomized control trials on vertebroplasty and balloon kyphoplasty were used to estimate the health utility i.e gain in QALYs as calculated using EQ-5D. Both these studies were considered as Level 1 evidence based on the US Task Force definition of level of evidence of clinical data. The gain in QALYs after balloon kyphoplasty was derived from the FREE trial which is a multi-center, randomized control trial comparing kyphoplasty with conservative treatment in patients hospitalized with vertebral compression fractures.⁸³ A randomized clinical trial, VERTOS II, compared effectiveness of vertebroplasty to non-surgical management of VCFs and was used to model gains in QALY after vertebroplasty.⁴⁴ The study design of the VERTOS II trial was based on the FREE trial making them identical in various parameters such as inclusion-exclusion criteria, outcome endpoint, survey instrument, data

collection time points, etc. The population, and the measurement of health outcomes in both these trials were very similar making them comparable to each other.

3.6.1 The FREE trial

The FREE study was a two-year randomized controlled trial comparing balloon kyphoplasty and non-surgical care for treating spinal fractures. It was funded by Medtronic Spine LLC, the manufacturer of balloon kyphoplasty equipment. Two hundred and two patients with a mean age 75 years and with 1 to 3 acute vertebral fractures were enrolled at 21 sites in 8 countries. They were randomly assigned to balloon kyphoplasty (n=101) or conservative treatment (n=101). For participation in the study, patients had to meet specific criteria, including:

- (a) They had at least one vertebral compression fracture that had caused edema assessed by magnetic resonance imaging (MRI),
- (b) Vertebral height loss of at least 15% and
- (c) Back pain that the patient described as greater than 4 on a visual analogue scale of 0-10 (0 meaning no pain, and 10 being the worst pain ever) for 6 weeks or less.

The FREE trial collected data on various primary (example back pain reduction, physical functioning, etc) and secondary indicators (example HRQoL and QALY gains). EQ-5D scores were one of the secondary outcomes and were used to model QALY gains.

3.6.2 The Vertos II trial

The Vertos II trial is a multicenter, open label randomized control trial. Two hundred and two patients with a mean age of 75 years were screened and randomly assigned to balloon kyphoplasty (n=101) or conservative treatment (n=101). Patients were

required to have at least one vertebral compression fracture that had caused edema assessed by magnetic resonance imaging (MRI), at least 15% height loss, and back pain for 6 weeks or less. EQ-5D scores were one of the secondary outcomes and were used to model QALY gains.

3.7 Costs

In an economic analysis, based on the study perspective, various costs are considered (such as direct medical cost, direct non-medical cost, indirect costs, and intangible cost). Direct medical costs include medical expenditure for treatment of illness and medical care for associated complications, if any. It includes cost of medical procedure, inpatient hospital stay, outpatient service charges, physician fees, diagnostic tests, pharmacy costs and costs of medical supplies. They are the most relevant when analyzing the costs from a payer's perspective. Our study was conducted from a payer's perspective and hence direct medical costs were considered. Cost data was derived from a study conducted in a routine clinical setting in the United States.²⁸ Hospital discharge and billing records were analyzed retrospectively from the Premier Perspective database. Inpatient hospitalizations were identified using primary ICD-9_CM procedure codes (Table 3.1 on p 31) for vertebroplasty and kyphoplasty whereas outpatient services were identified using primary ICD-9_CM procedure codes and at least one CPT code for vertebroplasty or kyphoplasty. Patients with claims for both, vertebroplasty and kyphoplasty were excluded from the analysis. The study utilized cost data or cost to charge ratios derived from the hospital accounting system to estimate costs for vertebral augmentation procedures.

Table 3.1. ICD-9-CM procedure and CPT procedure codes for identification of vertebroplasty and balloon kyphoplasty patients

Procedure	ICD-9-CM	CPT codes
Vertebroplasty	81.65	22520
		22521
		22522
Balloon kyphoplasty	81.66	22523
		22524
		22525

Costs were adjusted for covariates such as age, sex, marital status, ethnicity, comorbidities, APR-DRG severity, admission status (elective or emergency), hospital characteristics, etc. More than 80% of the patients had Medicare as their payer and around 7% of the patients were insured through managed care which resembles a typical composition of coverage type for osteoporotic population. The study accounted for medical costs due to VCF such as cost of each procedure, cost of follow up, medications, hospital stay, lab tests, radiology, and specialty care etc. The cost for treating additional VCFs was considered to be the same for both the procedures and was not accounted in the model.

Data on effectiveness and cost were synthesized to populate the model. The cumulative effectiveness of balloon kyphoplasty and vertebroplasty for all the cycles were calculated. An incremental cost effectiveness ratio was calculated for balloon kyphoplasty.

3.8 Sensitivity analysis

The present model estimates the cost utility in patients with acute fractures (inclusion-exclusion criteria of FREE and VERTOS II trial), based on the results of two large, randomized clinical trials. Given the variability in the health utility as observed through other studies, a one way-sensitivity analysis was performed where the HRQoL gain with vertebroplasty varied with balloon kyphoplasty.

Uncertainty in parameter estimates was explored through the use of deterministic and probabilistic sensitivity analyses (PSA). The deterministic sensitivity analysis covered one-way sensitivity analysis which included uncertainties around the effectiveness of balloon kyphoplasty & vertebroplasty. To represent the uncertainty around the QoL benefits found in the FREE and VERTOS II trial, distributions of the utility gains were created with bootstrapping method. Health utility benefit associated with balloon kyphoplasty were assumed to have a beta distribution and the standard deviation was considered to be 0.02 as obtained from the trial data. In addition, uncertainties around costs were addressed simultaneously using PSA. A total of 1,000 Monte Carlo simulations were generated from the PSA. Sensitivity analyses around costs considered the ‘best-case’ and the ‘worst-case’ scenario that considered the effect of the extreme values of cost. A 25% variation in the cost of treatment with balloon kyphoplasty on both ends was considered. A cost-utility acceptability (CUA) curve was plotted at a willingness-to-pay of \$50,000.

Chapter 4

Results

4.1 Effectiveness

The study population were 70-year old US adults with at least one painful vertebral compression fracture. Vertebroplasty was associated with a cumulative QALY gain of 0.24, whereas balloon kyphoplasty was associated with a cumulative QALY gain of 0.37. The FREE trial was a two-year study and had utility data available up to 24 months. Studies suggest that health benefits of kyphoplasty persist well beyond two years; however due to lack of long-term randomized data, it was assumed that balloon kyphoplasty was associated with QoL benefits for three years if no additional fractures were incurred. The cumulative effectiveness of balloon kyphoplasty after 24 months was obtained by linear interpolation. Figure 4.1 on p 34 reflects the modelled persistence of utility benefits after balloon kyphoplasty.

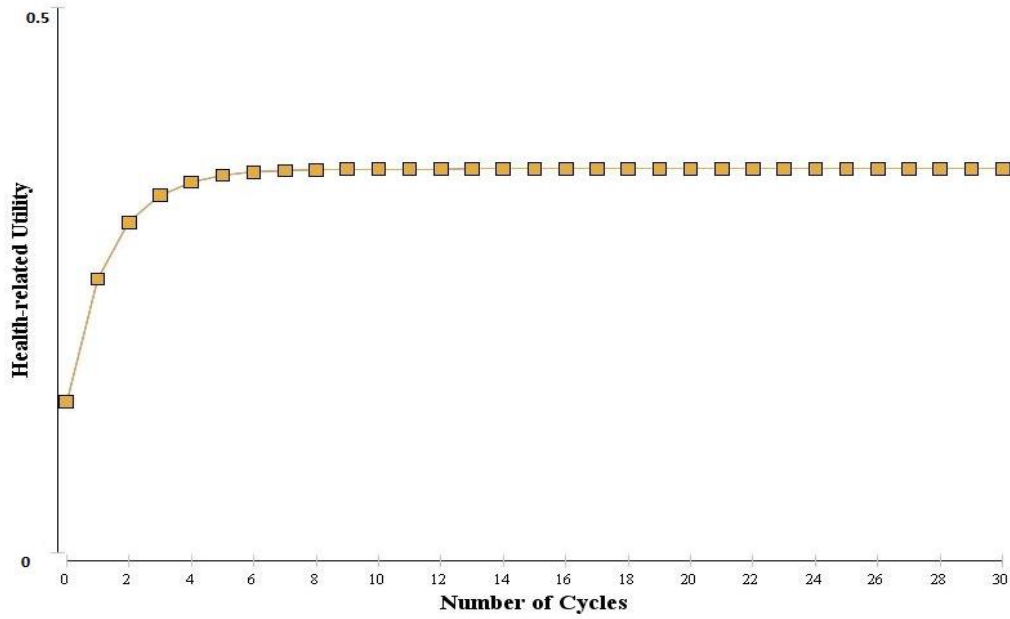


Figure 4.1: Modelled persistence of utility benefits with balloon kyphoplasty

Similar to the FREE trial, VERTOS II was a two-year study and data for vertebroplasty were obtained through similar calculations and under similar assumptions. Figure 4.2 on p 34 reflects the modelled persistence of utility benefits after vertebroplasty procedure.

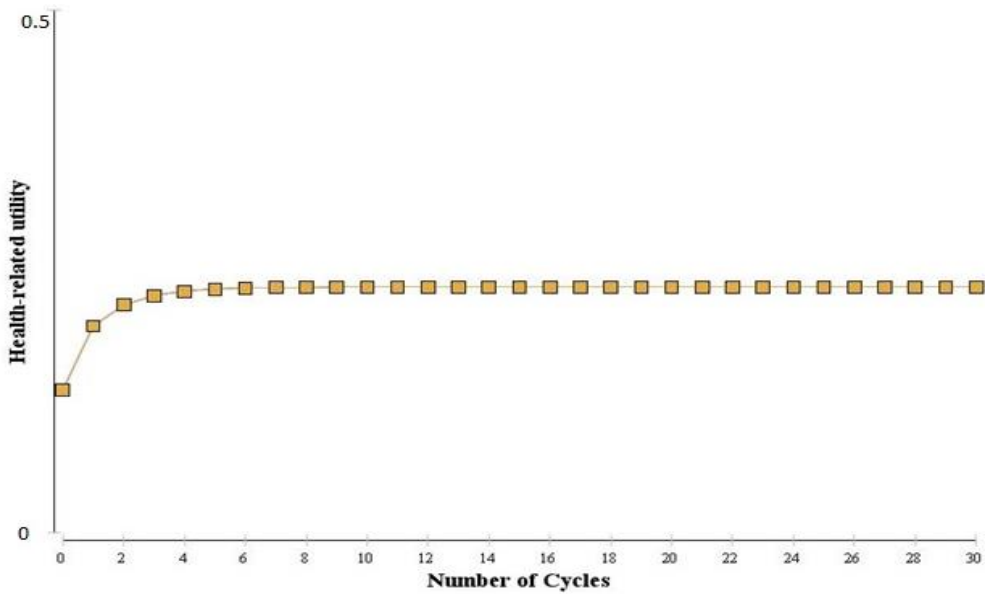


Figure 4.2: Modelled persistence of utility benefits with vertebroplasty

4.2 Cost

Since, the study was conducted from the payer's perspective only direct medical costs were included in the model. These included the cost of procedure, follow up, medications, hospital stay, lab tests, radiology, and specialty care. Details on the measurements of these costs are mentioned in the original article.²⁸

The costs of vertebroplasty and balloon kyphoplasty were found to vary by the setting in which they were conducted. Inpatient costs were higher due to the cost of hospital stay. Balloon kyphoplasty was conducted in an outpatient setting 46% of the times and in an inpatient setting 54% of the times. The mean adjusted outpatient cost associated with a balloon kyphoplasty was \$7, 010 and the mean adjusted inpatient cost was \$16, 182. The mean total adjusted cost for balloon kyphoplasty was \$11, 963.

Percutaneous vertebroplasty was conducted in an outpatient setting 36% of the times and in an inpatient setting 64% of the times. The mean adjusted outpatient cost associated with a vertebroplasty was \$2, 997 and the mean adjusted inpatient cost was \$11, 386. The mean total adjusted cost for balloon kyphoplasty was \$8, 366. Differences in the costs were largely due to differences in the OR costs. A break-down of the total inpatient and outpatient OR costs by category is shown in Table 4.1 on p 36.

Table 4.1. Unadjusted OR costs by charge category for vertebroplasty and kyphoplasty²⁸

Mean costs	Vertebroplasty	Kyphoplasty
Inpatient OR costs		
Anesthesia	\$73.60	\$172.16
Recovery Room	\$112.06	\$257.47
Surgery	\$990.12	\$1471.49
Outpatient OR costs		
Anesthesia	\$74.16	\$182.98
Recovery Room	\$213.69	\$289.35
Surgery	\$974.22	\$1,520.24

4.3 Base case analysis

In the base case analysis, the cost utility ratio for a vertebroplasty was \$34,688 per QALY gained and that for a balloon kyphoplasty was \$32,767 per QALY gained. In an incremental comparison between kyphoplasty and vertebroplasty, balloon kyphoplasty was cost effective compared to vertebroplasty (Table 4.2 on p 37). BKP/VP cost \$29,027/QALY gained compared with vertebroplasty.

Table 4.2 Results of Markov Analysis

	Vertebroplasty (VP)	Kyphoplasty (BKP)	Difference
Effectiveness (QALY)	0.24	0.37	0.12
Cost (Dollars)	\$8,365.93	\$11,962.88	\$3,596.95
Cost-utility ratios ^a	\$34,688.24	\$32,766.57	-
ICUR ^b		\$29,026.97	-

^a Cost per QALY

^b ICUR (Cost/QALY per person)

Figure 4.3 on p 38 depicts the cost and effectiveness of vertebroplasty and balloon kyphoplasty for patients with VCF.

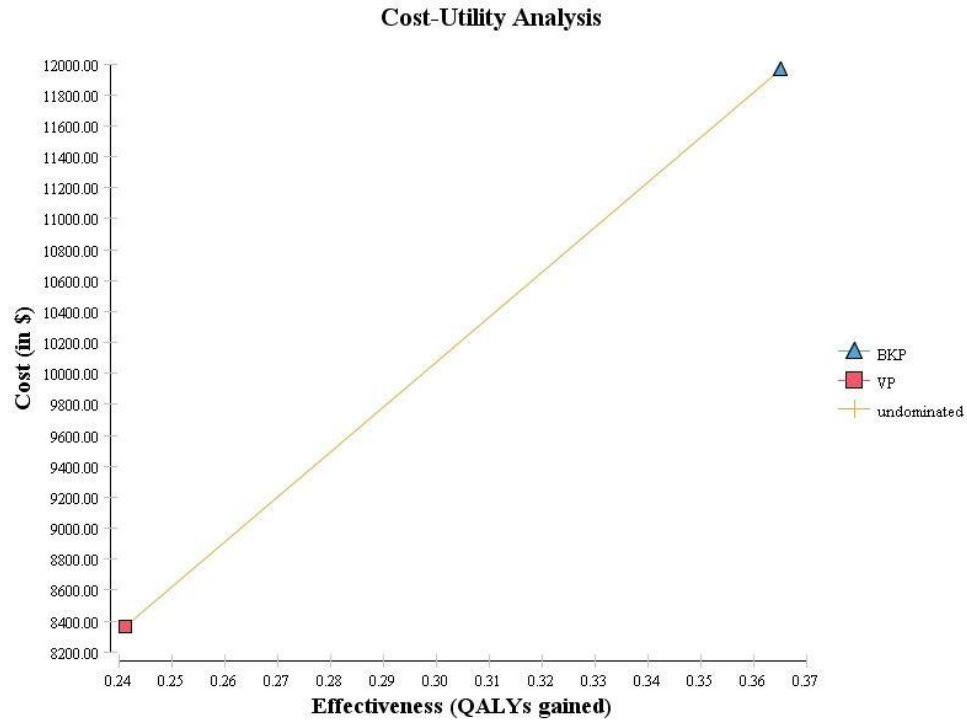


Figure 4.3: Effectiveness of vertebroplasty and balloon kyphoplasty for patients with VCF

4.4 Sensitivity analysis

Deterministic sensitivity analysis was carried out around parameters with known uncertainty. In the one-way sensitivity analysis of the HRQoL benefit, the health utility benefit with balloon kyphoplasty compared to vertebroplasty in the base scenario was varied between a minimum value of 0.263 and a maximum value of 0.311 (as obtained through the 95% CI in FREE trial). Figure 4.4 on p 39 and Table 4.3 on p 39 show the impact of the variation in parameter estimates (one-way analysis) on the cost-utility of balloon kyphoplasty. At a minimum value of utility (0.263), BKP has an ICUR of \$34, 226 and at a maximum utility value (0.311), BKP has an ICUR of \$24, 220.

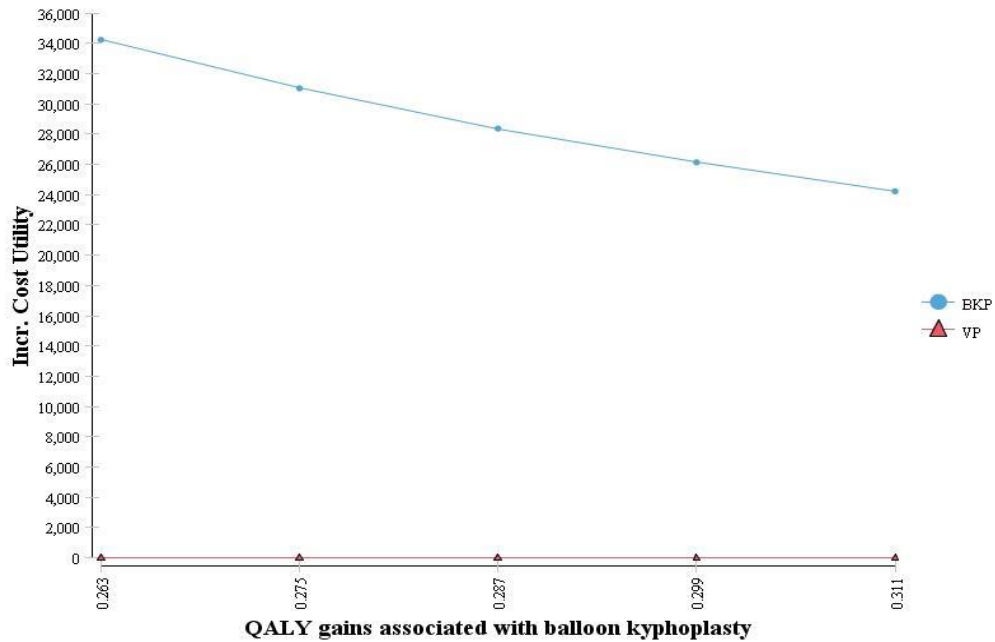


Figure 4.4: Incremental Cost utility results (after one-way sensitivity analyses) comparing balloon kyphoplasty with vertebroplasty

Table 4.3: Results of one-way sensitivity analysis

Parameter	Incremental cost per person (USD)	Incremental effect per person (QALY)	ICUR (USD)
Base-case assumptions	\$3,596.95	0.12	\$29, 027
Effectiveness of BKP (based on lower limit of 95% CI)	\$3,596.95	0.11	\$34, 226
Effectiveness of BKP (based on upper limit of 95% CI)	\$3,596.95	0.15	\$24, 220

A scatterplot of the probabilistic findings, showing simulated estimates of cost difference against QALY difference between balloon kyphoplasty and vertebroplasty, is provided in Figure 4.5 on p 40. The scatterplot shows that all the simulations generated an improved effectiveness of balloon kyphoplasty, but also a higher cost than vertebroplasty (i.e. all points were in the north-east quadrant of the cost-effectiveness plane). This reflects the estimates of effect size.

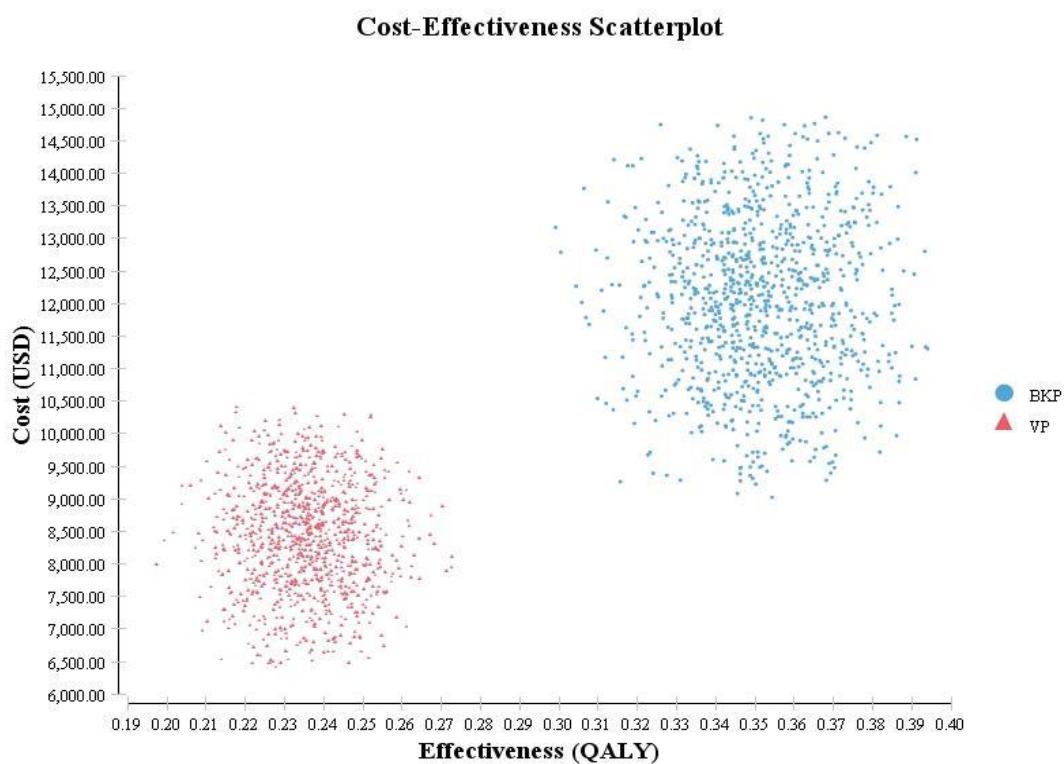


Figure 4.5: Cost-effectiveness plane showing the scatterplot 1,000 Monte Carlo simulations for balloon kyphoplasty compared with vertebroplasty.

The decision as to whether or not these findings can be considered cost-effective depends on the maximum amount decision-makers are willing to spend to obtain an additional unit of effectiveness (in this case, a QALY). This can be best presented in the form of a cost-utility acceptability curve, as presented in Figure 4.6 on p 41. At a threshold of

\$40,000 there is a 0.708 probability that balloon kyphoplasty is cost-effective. This increases to 0.873 when a threshold of \$50,000 is considered.

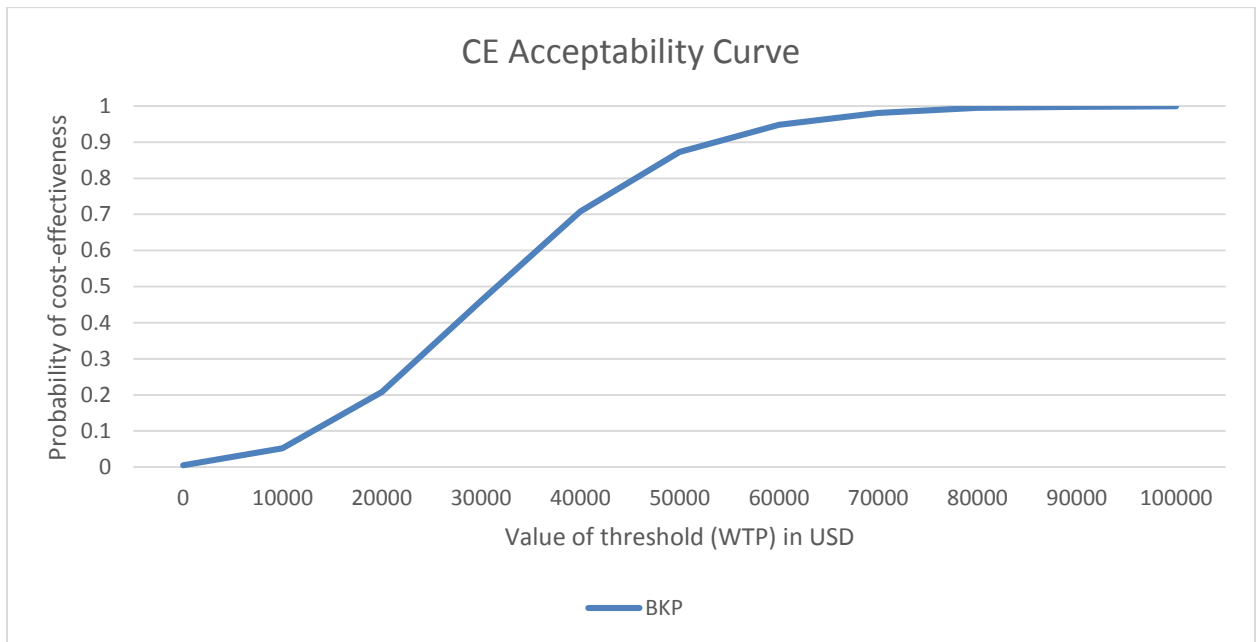


Figure 4.6: Cost-effectiveness acceptability curve showing the probability of cost-effectiveness for balloon kyphoplasty at varying levels of threshold.

4.5 Summary of findings

Our analysis attempts to estimate the cost-utility of balloon kyphoplasty using a Markov framework similar to that used in previous analyses.⁸¹ Our base-case assumptions result in a favorable cost-utility ratio of \$29, 027 per QALY gained from balloon kyphoplasty compared with vertebroplasty. It should be acknowledged that our base-case estimate includes some optimistic assumptions with respect to cost and effectiveness. However, our deterministic and PSAs suggest that there is a low possibility of the ICUR increasing above \$50,000 when these assumptions are relaxed.

Chapter 5

DISCUSSION

Our contemporary health economic evaluation of minimally invasive procedures in the treatment of vertebral compression fracture addresses the cost effectiveness of vertebroplasty and kyphoplasty in an elderly US population, in light of data on VCFs, including results from randomized control trials. Balloon kyphoplasty was found to be cost effective in comparison to vertebroplasty at a willingness to pay threshold of \$50,000/QALY. Our findings are similar to another study that was conducted recently in an UK setting which reported that balloon kyphoplasty was more effective than vertebroplasty or non-surgical treatment in the management of pain in VCFs.⁸⁴ However, the values of ICURs obtained are different, owing to the subtle differences in the modelling of both these studies. The study by Svedbom et al included only hospitalized patients with VCFs as their study population. As depicted in Mehio et al' study, the cost of treatment varies considerably by the setting in which the procedures are conducted. Also, more than half of the patients in United States undergo vertebral augmentation procedures in an outpatient setting leading to differences in costs between those observed in the UK and those in the US. Furthermore, the cost data for their study was based on the National Health Service Hospitals in UK which had a different reimbursement rate than Medicare. All these

factors could explain the differences in the values of the ICURs reported by our study and that by Svedbom et al.

Although our cost-utility estimates suggest that balloon kyphoplasty is a cost-effective use of payer's resources, it should be noted that the individual-level lifetime QALY gains are relatively modest (< 0.0001 in our base-case analysis). This estimate is predicted on the evidence of effectiveness derived from the clinical trials. We believe that the Level I evidence has provided the most robust estimate to date of the effectiveness of balloon kyphoplasty compared with vertebroplasty. However, it should be acknowledged that the cost-utility analysis is attempting to capture lifetime benefits based on evidence of relatively modest effect sizes derived from short-term studies. Any such analysis inevitably involves some assumptions about the degree to which utility change is lasting and fails to consider other health behaviors that may impact long-term outcomes. The result is that the cost-utility analysis estimates that balloon kyphoplasty has a modest lifetime cost and a marginal lifetime QALY gain. Even small changes in the source data used to populate the model, particularly evidence of effect size and cost, may lead to significant changes in the resulting ICUR.

Although sensitivity analysis has sought to address this point, it should be acknowledged that, source data were derived from a single studies and it was necessary to fit distributions to parameters to allow for PSA. Although every effort has been made to explore uncertainty, there is a possibility that the uncertainty around parameter estimates may be greater than predicted within our analysis, which would have a sizeable impact on the ICUR.

Costs are an important parameter and cost considerations can significantly affect the results of an economic study. Various cost effectiveness studies have been conducted comparing each procedure to non-surgical management of vertebral compression fractures. For example, the VERTOS II trial conducted a cost-effectiveness analysis comparing vertebroplasty to conservative treatment as one of their secondary outcomes. They reported an incremental cost- effectiveness ratio of €22 685 per QALY gained for vertebroplasty.⁴⁴ Another study conducted by Masala in 2008 reported vertebroplasty to be a more cost effective option than conservative treatment.⁶⁷ This study included costs for drug therapy, specialist consults and radiological examinations. A study comparing balloon kyphoplasty with non-surgical treatment reported a cost effectiveness of £8,840/QALY gained for balloon kyphoplasty.⁸¹ Both these studies have accounted for similar categories of costs as those considered in our study. In our study, we considered cost of procedure, cost of medications, cost of stay at hospital, cost of laboratory tests and specialist consultation charges.

We found that balloon kyphoplasty was associated with higher effectiveness compared to vertebroplasty. Similar findings have been reported by various other studies. A systematic review conducted by Taylor et al reported a better documentation of QALY gains and improvement in quality of life after kyphoplasty compared to vertebroplasty.²⁵ However, another systematic review published in the Ontario Health Technology Assessment Issue reported that two of the four studies assessing quality of life improvements after balloon kyphoplasty using SF-36 Health Survey found decline in benefits over long term. A recent meta-analysis conducted by Ma et al, also reported that there were no significant difference in the long term effectiveness between vertebroplasty

and kyphoplasty.⁸⁵ This is suggestive that there are possible differences in the short term effectiveness between the two procedures, however, these differences decline over time. In our study we modelled the long term effects based on a two-year data obtained from clinical trials.

The FREE trial also evaluated various other primary health indicators such as reduction in pain scores by Visual Analogue Scale, Oswestry Disability Index, Roland Morris score, health related quality of life as measured though SF-36, and days of reduced mobility. These could also serve as end points in a cost-effectiveness study. However, we chose only EQ-5D scores to assess QALY gain as QALYs are considered as an ultimate endpoint in a cost-utility study. Future studies evaluating these primary end-points would help us understand the impact of balloon kyphoplasty and vertebroplasty on intermediate outcomes.

The FREE trial and the observational study conducted by Kumar et al were not sufficiently powered to detect the differences in mortality following these procedures. Should there be a significant mortality reduction offered by one technique over the other, this would have a significant impact on the results. However, both these techniques are safe and for ethical reasons, no studies have been conducted so far evaluating the mortality reduction.

Also, both these procedures are relatively new and there is limited amount of available data describing long term quality of life effects, the risk of additional fracture, the effect on mortality, and possible reduction in the use of pharmaceutical services over long term. It would be interesting to note the how these techniques perform relatively over

the long term and what potential cost savings could be offered with respect to the above mentioned parameters.

In summary, we found that balloon kyphoplasty is associated with a better utility compared to vertebroplasty, but is also associated with an increase in overall costs. When comparing the increase in cost over the increase in effectiveness, it was found that there is a very slight improvement in utility compared to the large increase in costs. The willingness to pay lies within the range of \$50, 000-\$100, 000/QALY in the United States.⁸⁶ ICURs above \$50, 000 can be acceptable if the innovation offers distinctive benefits of a substantial nature which may not have been captured in the QALY measure. Given the results of our study, the budgetary impact of treating a kyphoplasty patient would cost \$29, 027 per person per additional gain in QALY. However, our approach generates a partial analysis that does not consider the impact of balloon kyphoplasty on a number of morbidities known to be associated with VCFs. On this basis, the authors would wish to emphasize that our estimates of cost-effectiveness should be regarded as conservative, as we have made no attempt to quantify these benefits within our analysis.

5.1 Study Limitations

There are a number of limitations to our analysis which should be acknowledged. Firstly, it was not possible to include any adverse events/ negative outcomes (such as subsequent fractures, falls etc.) that may be affected by vertebral augmentation procedures owing to uncertainty over the relationship between vertebral augmentation procedures, incidence and quality-adjusted life expectancy. Another limitations was that the study conducted by Mehio et al observed more inpatient procedures than outpatient procedures

in their analysis and this may not be a true representative of the nation-wide distribution of these procedures. Further research is necessary to understand the distribution of the vertebral augmentation procedure. Another limitation is that the survival rate following VCFs could be different for men and women. However, due to lack of sufficient literature on gender-specific survival rate in patients with vertebral compression fracture, we accounted for an average survival rate following VCF in our analysis.

Chapter 6

CONCLUSION

The cost–utility analysis presented herein was an attempt to adhere to best practice principles in economic evaluation⁸⁷ and also replicate the methods adopted in previous research.⁸¹ Using this method our base-case analysis in adults aged 70 years and above undergoing treatment for painful, vertebral compression fractures in a US setting shows an indicative ICUR for balloon kyphoplasty versus vertebroplasty of \$29,027 /QALY. This result was sensitive to changes in key input parameters, particularly the estimate of effectiveness of balloon kyphoplasty (change in QALY). There was a 71% probability that balloon kyphoplasty was cost-effective at \$40,000/QALY and 87% probability that balloon kyphoplasty was cost-effective at \$50,000/QALY.

However, there is a need for further developments of this model to incorporate long-term benefits in HRQoL, negative outcomes, comorbidities, differences in survival and post-fracture resource utilization. Consideration needs to be given to the trade-off between developing a simple model (as we have done here) which can be populated and acknowledges its limitations versus a more complex model which may be a better representation of reality but can only be partially populated, which might result in even

greater uncertainty. In both cases, necessary revisions should be made to the cost-utility of kyphoplasty as more evidence on long-term outcomes becomes available.

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Appendix A

Economic evaluation checklist

Drummond adapted criteria

Criteria	Did the study meet the criteria?
1. Was a well-defined question posed in answerable form?	Yes
2. Was a comprehensive description of the competing alternatives given?	Yes
3. Was the effectiveness of the program or services established?	Yes
4. Were all the important and relevant costs and consequences for each alternative identified?	Yes
5. Were costs and consequences measured accurately in appropriate physical units?	Yes
6. Were the cost and consequences valued credibly?	Yes
7. Were costs and consequences adjusted for differential timing?	No
8. Was an incremental analysis of costs and consequences of alternatives performed?	Yes
9. Was allowance made for uncertainty in the estimates of costs and consequences?	Yes
10. Did the presentation and discussion of study results include all issues of concern to users?	Yes