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A Cost-Utility Analysis of Pacemakers For the Treatment of Neurally Mediated Syncope

by

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Abstract

Dual chamber pacing with rate drop sensing (DDD-RDS) is a novel, effective and expensive treatment for patients with very frequent neurally mediated syncope (NMS). Its cost-utility from the payer's perspective is unknown. We studied HRQL as measured with the EQ-5D, and the cost to the health care system, for the year before and the year after receiving a DDD-RDS. Physician billings were obtained from Alberta Health, and inpatient, outpatient and emergency costs including initial pacemaker implants were obtained from the CRHA. Recurring costs were extrapolated over 10 years to the expected life of the pacemaker. HRQL scores significantly improved with pacemaker therapy ($p<.001$). A low incremental cost per QALY gained was observed for pacemaker treatment of NMS ($9942 per QALY gained). This result was robust to variations of expected pacemaker life and treatment effect, and indicates that pacemaker therapy for this population merits public funding.

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Dedication

This thesis is dedicated to my wife Michelle, for her love and patience, and to my parents, for their love and support in all of my endeavors.

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1. INTRODUCTION

Introduction

Permanent dual-chamber cardiac pacemaker therapy is a highly effective therapy when compared to non-pacemaker treatments in more severely symptomatic neurally mediated syncope (NMS) populations (1-4). However, no study has previously determined the costs of pacemaker therapy as compared to conventional treatment, for this condition. This study determined the relative health benefits and costs of treating NMS with pacemaker therapy as compared to conventional non-pacemaker therapy, for varying levels of illness severity.

Rationale

As the health care system is one of limited resources, it is important to consider both effectiveness and cost data when making clinical guideline recommendations for health technologies (5). This is because a particular health technology may produce positive health outcomes, but the benefit may be gained only at substantial economic cost. How much cost is required to produce a particular benefit can be quantified, in part, with health economic evaluations.

Information on the costs and benefits of a particular treatment can be placed in the context of the costs and benefits of treating other diseases. Recommendations can then be made to developers of clinical practice guidelines on how to provide the mix of services within a particular program which will result in the most health benefit for a given set of resources (6). This mandate of maximizing health benefit and minimizing cost is found in the Alberta Health Three Year Business Plan, 1995-96 to 1997-98 (7).

As pacemaker therapy is a more effective treatment for NMS than conventional non-pacemaker treatment, two scenarios may arise in the current study. Pacemaker therapy may

be less costly than standard treatment for NMS, or pacemaker therapy may be more costly than conventional treatment for NMS. If the former, pacemaker therapy should obviously be recommended for funding. However, if pacemaker therapy is found to be more costly than conventional treatment, decision makers must make a decision as to whether the increased health benefit is worth the additional cost. The current study will inform decision makers of the cost required to produce the health benefit associated with pacemaker therapy for NMS.

In addition, the severity of NMS is diverse. As such, the costs and health outcomes of pacemaker therapy versus alternative treatments, for two different levels of illness severity, was determined. An overview of economic evaluation in health will be presented, followed by a literature review for the current study.

Overview of Economic Evaluation in Health

Economic evaluation in health has been defined by Drummond et al. as, "comparative analysis of alternative courses of action in terms of both their costs and consequences" (8). As such, economic evaluations provide information regarding which treatment alternative provides the optimal health benefit at the most reasonable cost. In general, economic evaluations are utilized to inform decision makers at the population level: such studies are not to be used by individual practitioners in making clinical judgments.

Before discussing the specific types of economic evaluations in health, three concepts which relate to all economic evaluations will be addressed. First, economic evaluations in health should focus on changes in health outcomes and costs (6). That is, by directly comparing two treatment alternatives, the incremental or additional cost and health outcome between two alternatives can be derived. This enables conclusions to be drawn about the relative changes in costs and health outcomes which result from using one treatment over the other. Second, economic evaluations require a relevant end point (9).

This is referred to as the analytic horizon, and is determined on the basis of what relevant point the trial is conducted to (i.e. discharge, death, etc.). Third, the costs that are to be measured in a given study are dependent on the perspective taken for that study. Commonly, the "societal perspective" is taken, which includes all productivity costs (i.e. lost wages) and all direct or health care system costs. Another perspective is the "payer perspective" which only includes direct costs (9).

There are four common types of economic evaluation in health care: cost minimization analysis (CMA); cost effectiveness analysis (CEA); cost benefit analysis (CBA); and cost utility analysis (CUA) (10). The first three will be briefly discussed, then the fourth will be examined more closely. First, CMA is appropriate when the health outcomes of two alternative treatments have been shown previously to produce equal benefit, and thus the goal is to determine which treatment is less costly. Second, CEA is utilized to determine the relative costs and health outcomes of two treatments, when the health outcome is in a directly measurable unit such as blood pressure or mortality. Third, CBA is an extension of CEA, where the health benefits are presented in monetary units. The advantage of CBA is it allows for inter-sectorial comparisons between, for example, a particular health treatment and an intervention in the education system.

The current study is a CUA, and thus more detail will be presented on this type of economic evaluation. When quality of life is the primary outcome measure, CUA is often the appropriate economic evaluation (8). CUA compares alternative treatments, based on the costs and a health outcome measurement called quality adjusted life years (QALYs). A QALY is a measure of the quality of life over some period of time. QALYs are formed by multiplying the expected length of life (or other specified time frame) by an indicator of quality of life, as measured with a health related quality of life (HRQL) instrument. QALYs gained can be understood as the number of life years saved, while taking into account quality of life (9). For example, if the mean HRQL of a group improved by 0.2 on a scale

from 0 to 1, over 1 year 0.2 QALYs would be gained on average. If this improvement was to hold over 10 years, 2 QALYs would be gained. The advantage of this type of analysis over analyses based solely on mortality, is that quality of life can vary even if length of life is equal.

CUA produces a ratio of incremental costs divided by incremental health outcomes as measured in QALYs gained (9). Thus, the cost utility ratio provides an incremental cost per QALY gained, which is simply the amount of resources, measured in dollars, required to produce one additional QALY. Laupacis et al. state there to be strong evidence for adoption of a technology if a cost per QALY gained of less than $20,000 is obtained (11). However, there are no set rules on how much is too much to spend per QALY gained. Further, decision making based on strict QALY league tables has been cautioned (12). Ultimately, such decisions are based on values which will differ depending on many factors including the prevalence and severity of the illness, the amount of resources available within the particular region and the political milieu of the time.

Essentially, a cost utility ratio provides a quantifiable measure of how much it costs to obtain an additional QALY. As with any parameter estimate, there is a degree of uncertainty with the calculated ratio. In economic evaluations, sensitivity analysis is conducted by systematically varying values used in the construction of the ratio, in order that the robustness of the derivation can be assessed (8).

Background

Syncope is "a reversible, temporary loss of consciousness due to a qualitative or quantitative disturbance of cerebral blood flow" (5). Recurrent NMS is estimated to effect 3% of the general population (13), and occurs in individuals of all ages. Although the underlying pathophysiology of syncope remains unclear (5, 6), it has been reported that NMS accounts for the majority of previously diagnosed "syncope of unknown cause" (14-

17). Although there has been no reported mortality associated with NMS, substantial physical and psychosocial morbidity, as measured on a health related quality of life (HRQL) scale, has been associated with this illness (18). Further, syncope is uncomfortable, inconvenient, embarrassing and can lead to injury (19). Clearly, research into effective treatment for NMS is warranted.

Research on the treatment of NMS has largely focused on medical therapies and cardiac pacing techniques. Beta blockers have shown mixed promise in the treatment of NMS (5, 8, 13-16), but no randomized control trial of beta blockers has been performed. Until this occurs, evidence for the effectiveness of beta blockers in treating NMS will remain inconclusive (20).

Several non-randomized studies have been conducted on pacemakers for the treatment of NMS. Benditt et al. (1997) report an overall reduction of syncope recurrence when patients were treated with the Thera DR, dual chamber pacemaker (3). Another study tested the effect of dual chamber pacing with automatic rate-drop sensing on NMS patients. This study found significant increases in time to first recurrence and decreases in frequency of spells when the 3 and 6 month post treatment periods were compared to the 3 month period from the tilt table test to the treatment (2). As well, this study found an associated rise in HRQL from pre to post-pacemaker treatment, with the overall perception of health on the EQ-5D thermometer scale rising from 55 (95% CI 45, 65) to 82 (95% CI 72, 92) ($p=.003$) (2). Similarly, Petersen et al. found symptomatic improvement in 89% of 35 patients who had a dual chamber pacemaker implanted (21).

A multi-centered, randomized North American study was conducted to assess the efficacy of dual chamber pacing for NMS (1). This study found the paced group to have a significantly increased time to first recurrence, as compared to the non-paced patients ($p<.001$) (1). In summary, permanent dual chamber pacemaker therapy is a promising treatment for patients with frequent NMS.

However, pacemakers are expensive: a dual chamber pacemaker with two leads costs approximately $7000 (personal communication, B. Metcalfe). Despite this high cost, no full economic evaluation has been performed on pacemaker treatment for NMS. Only one study focusing on the treatment costs of syncope was identified in the literature. This cost identification study of dual chamber pacemakers for the treatment of vasovagal syncope by Sutton and Petersen (22) presented no real subjects. A few potential costs that may be prevented with pacing were discussed, such as emergency visits and in-patient hospital stays, but actual patient data were not examined. Our study is the first to describe and analyze the costs and health outcomes resulting from the treatment of NMS with dual chamber pacemaker therapy.

In summary, pacemaker therapy is the leading candidate for the treatment of syncope and the effectiveness of this treatment has been established. The overall cost associated with this treatment is high and the cost utility from the payer's perspective is not known. The current study was conducted to determine the relative costs and health outcomes of dual chamber pacemaker therapy as compared to conventional non-pacemaker therapy for the treatment of NMS.

Hypotheses

1. A relatively low cost per QALY gained results from the treatment of NMS patients with pacemaker therapy as compared to conventional non-pacemaker therapy.
2. A lower cost per QALY gained is obtained in more severe NMS cases, as compared to less severe NMS cases, when pacemaker therapy is compared to conventional therapy.

Study Objectives

Research Questions

1. What are the direct medical costs associated with treatment of NMS?

2. What are the relative costs and relative health benefits of treating syncope patients with pacemaker therapy as compared to conventional treatment?

3. What is the incremental cost per QALY of pacemaker therapy as compared to conventional therapy, for varying levels of illness severity.

Specific Objectives

1. Identify the direct costs (payer perspective) associated with treatment of NMS.

2. Determine the cost per QALY gained in the comparison of pacemaker therapy with conventional therapy for the treatment of NMS.

3. Identify the cost per QALY gained for two study groups divided on the basis of frequency of spells. for pacemaker therapy versus conventional therapy.

2. METHODOLOGY

Study Design

This study employed a non-randomized, before and after design, which is illustrated in Figure 1.

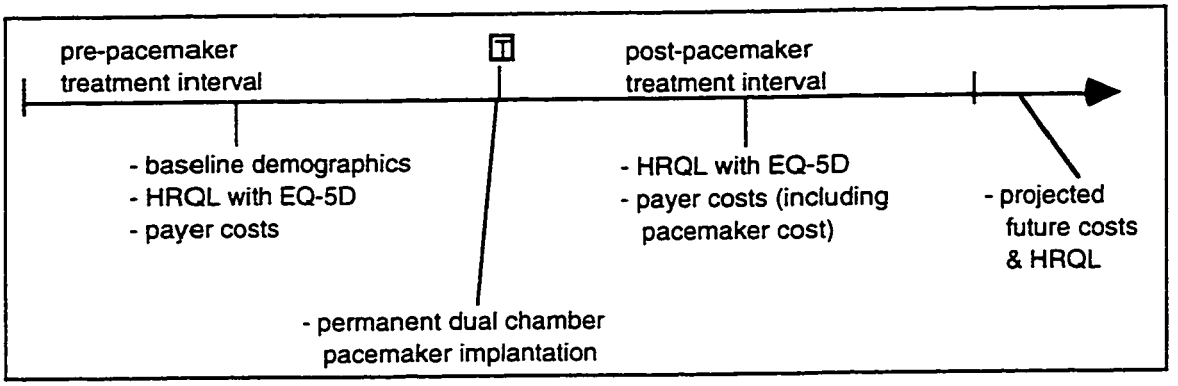

Figure 1: Study Design

Each patient was followed for a period before pacemaker treatment, and a period after pacemaker treatment. The pre-pacemaker interval consisted of the 12 months directly preceding pacemaker implantation. During this period the patients received conventional non-pacemaker treatment including drug therapy for NMS. This interval represented the control arm of the study, and provided information about patient baseline demographics, HRQL scores, illness history, and direct health care costs during a period in which no surgical intervention was conducted.

During the post-pacemaker interval, data was collected on direct health care costs for 12 months. As well, HRQL scores were obtained for each patient, at various points after pacemaker implantation, between 3 and 24 months.

Rationale for Study Design

The ideal study design for an economic evaluation for this type of intervention is a randomized clinical trial (RCT), where the costing data are collected prospectively along with the health outcome data. Although a randomized trial was conducted with subjects from the Calgary Syncope Clinic, most non-paced patients received a pacemaker once they had a recurrence of syncope. With this cross-over, valid long term follow-up comparisons were not possible. In addition, as pacemakers have been shown to be effective in a RCT, another RCT would not be ethical. As such, we retrospectively analyzed all patients pre and post-pacemaker treatment who received a pacemaker at the Calgary Syncope Clinic during the specified time period.

Each interval of observation was chosen to be 12 months as it was believed that this would be enough time to capture any differences in costs between the two study intervals, while remaining feasible. As this design is not readily used for this type of analysis, we estimated what interval length would provide data that would enable differences in costs between the intervals to be detected, while ensuring that the study could be completed in a timely manner.

Inclusion Criteria & Sample Size

The study sample consisted of adult patients (minimum age, 15 years) who received a dual chamber pacemaker for NMS from the Calgary Syncope Clinic from September 1995 to October 1997. The study inclusion criteria were: a positive tilt table test and a minimum of 6 syncopal spells prior to the tilt test, or at least one recurrence of syncope in the 6 months following the tilt table test. This criteria ensured a more frequent NMS sample. In total, 38 patients who received a pacemaker and met the inclusion criteria were included in the study.

A previous study by Sheldon et al. (2) found a significant decrease in frequency of spells per month and a significant increase in EQ-5D HRQL thermometer rating scores between pre and post-pacemaker insertion, with only 12 patients. Thus, even with a relatively small sample size, it was expected that the current study would have adequate power to detect statistically significant differences between the treatment intervals.

Treatment Comparators

In order to determine if a treatment produces a relatively favorable health benefit at a reasonable price, a treatment comparator must necessarily be chosen which reflects existing practice (9). Existing practice for the treatment of NMS is conventional medical therapy or no therapy.

During the 12 month period before receiving a pacemaker, the patients underwent medical therapy or watchful waiting. Medical therapy consisted of various beta blockers or other drugs, for various lengths of time. Some patients did not receive drug therapy prior to surgical treatment, and were instructed on how to recognize and act on prodromal pre-syncopal symptoms, and to increase salt and fluid intake. A listing of therapies received during the pre-pacemaker treatment interval is found in Appendix A.

The dual chamber pacemakers were a Diamond pacemaker (n=18) or a Thera DR pacemaker (n=20). In the 12 month post-treatment interval, the patients attended the Calgary Syncope Clinic at 4 to 6 month intervals. During these follow-up visits, various tests were conducted to ensure the normal functioning of the pacemaker. In some cases (n=10), patients continued with drug therapy once on the pacemaker.

Description of Study Groups

The study sample was broken into two groups to allow for more detailed cost utility analysis, based on illness severity. The median pre-treatment frequency of syncopal spells was calculated for the study sample. Those patients falling below the median frequency comprised the less severe study group, and those patients falling above the median frequency comprised the more severe study group. However, it should be noted that all of the subjects in this sample were relatively severe, as compared to the general syncope population.

An individual with a lower frequency of syncopal spells is probably less likely to be affected by one's illness and thus it was predicted that the utility relative to the costs of pacemaker treatment would not be as great for these less severe patients. This would be reflected in our analysis if a lower cost per QALY gained was obtained for the group falling above the median as compared to the group falling below.

Health Outcome Measure

Description of the EQ-5D

The primary health outcome was HRQL as measured with the EQ-5D (23). HRQL has been shown to be a valid indicator of worsening health in syncope populations (18, 24). In particular, patients meeting the selection criteria of our study have been shown to have significantly decreased HRQL EQ-5D scores as compared to the general population scores (18).

The EQ-5D is a standardized generic HRQL measurement tool designed to generate a single index value of an individual's health status (see Appendix B). The EQ-5D is a multi-dimensional measure of HRQL which contains a series of questions about one's health state, and includes a visual analogue scale (VAS) which enables the subject to

directly rate their health state between 0 (being 'worst imaginable') and 100 (being 'best imaginaable'). The index score is based on 5 questions and was derived from a time trade off weighting system presented by Dolan et al. (25). The primary features of the EQ-5D are that it is a simple measure, produces one numeric index of perception of overall health, creates low subject burden as it has a minimum number of questions, and was designed to be self-administered (23). Finally, the EQ-5D has been cross-validated numerous different European countries (25), and was recently validated in the U.S (26).

The VAS is not a true measure of utility, and thus may not be the best measure on which to base the quality component of the QALY. Brooks et al. state, "One of the key reasons for the choice of the VAS approach is its relative simplicity for scaling purposes... however, the VAS-scores are not meant by respondents to express trade-offs between longevity and the numbers of people helped" (27). For this reason, it was important to provide another measure on which to base the QALYs. Thus, the derived index based on the responses to the multi-dimensional questionnaire component of the EQ-5D was also utilized (8, 27). In addition, by including both the VAS and derived index scores, the agreement of the two methods could be examined statistically.

However, the full EQ-5D questionnaire was available for 25 of the 38 patients pre-pacemaker and for all 38 subjects post-pacemaker. For this reason, the VAS scores were used in the primary analysis, and the derived index scores were used for the CUA in the sensitivity analysis, described below. The derived index was calculated based on the time trade off scoring mechanism presented by Dolan et al. (25).

Rationale for the EQ-5D

The EQ-5D is one of the instruments recommended for cost utility analysis by the Canadian Center of Health Technology Assessment (CCOHTA) in the *Guidelines for Economic Evaluation of Pharmaceuticals: Canada* (9). It is an appropriate instrument because it produces a single numeric index which can be used to calculate QALYs, which

form the denominator of the cost utility ratio in cost utility analysis. As the *Guidelines for Economic Evaluation* state, "this score represents an estimate of the mean preference score that would be given to that health state by a random sample of the general public" (9). A preference is a concept which refers to the desirability of a health state (9). Thus, HRQL instruments like the EQ-5D provide a score which the general public would rate as the score for a given health state. As such, no preferences need to be collected directly from the sample when using such instruments. The EQ-5D is called an indirect preference measure, as it indirectly rates the desirability of a particular health state. This rating is measured as a score which, as mentioned, can be used to derive QALYs.

The EQ-5D has been shown to be a reliable and valid measure of HRQL when tested on a variety of populations. However, it has been shown to be less sensitive than the SF-36 health survey in the general population. Brazier et al. compared the EQ-5D and SF-36 health survey in a UK postal survey in 1980 (28). They found evidence for the construct validity of the EQ-5D dimension scores and total responses. There was an overall agreement of total EQ-5D scores and the SF-36 profile scores, but the SF-36 was found to be more sensitive to subtle changes in health status.

Rose et al. compared the EQ-5D against the SF-36 in patients with syncope (29). They examined the convergent validity, sensitivity and discriminant validity of the EQ-5D and SF-36 instruments. There were 145 syncope patients, with a mean age=41 (SD=18), and a mean frequency of syncopal spells of 0.21 spells per month. On most dimensions there was a high level of agreement between the two measures, and the two measures displayed similar ability to discriminate between differing levels of symptom burden on most dimensions. Importantly, on measures of overall health there was a large discrepancy between the instruments. The EQ-5D was a better predictor of the frequency of syncopal spells. Further, the EQ-5D was more sensitive in picking up increased anxiety or depression as compared to the SF-36, which did not detect increased impaired mental

health. In summary, the two instruments generally performed similarly, but the EQ-5D was more sensitive than the SF-36 in the overall health measure for this syncope population.

In conclusion, the EQ-5D is a sensitive and thorough measure of HRQL for the syncope population, and is recommended by CCOHTA in the *Guidelines for Economic Evaluation* for cost utility studies.

Cost Data

Description of the Cost Data

The cost analysis followed CCOHTA's *Guidelines for Economic Evaluation* and *A Guidance Document for the Costing Process* (5, 35). The cost data were obtained from the Calgary Syncope Clinic, Alberta Health billing records and from several administrative databases from the Corporate Data division of the Calgary Regional Health Authority (CRHA).

The direct costs associated with the following services or activities were obtained for the pre and post-treatment intervals: inpatient hospital care; day surgery; outpatient visits (clinic and emergency); laboratory, radiology and other diagnostic tests; medications; and medical devices, supplies and equipment (see Appendix C).

Rationale for Use of Direct Costs Only

As this study was from the payer perspective, only the direct costs associated with syncope were collected. There were several reasons for not including productivity costs. First, as productivity costs are only applicable for subjects who are of working age, some individuals in our sample (i.e. over 65 years) who were not working would not have lost wages. Thus, the results would depend on who works and who does not, thereby reducing the generalizability of the results from this study. Second, some authors have argued that lost productivity costs are reduced if society has unemployment. This is because, from a societal perspective, if an individual did not work, another individual who was previously

unemployed could theoretically work in place of the first individual, thereby resulting in a minimal net societal change in work production. Third, there has been disagreement over whether productivity costs should be valued in the numerator or denominator of the cost utility ratio (30).

Data Collection

Upon first admission to the Calgary Syncope Clinic, routine data were collected on all patients' basic demographics, baseline HRQL and information pertaining to illness history (duration, total number of spells). Post-pacemaker HRQL scores and frequency of syncopal spells were also obtained at the Syncope Clinic. Data on the pre and post-pacemaker direct cost of illness (payer perspective) were obtained retrospectively. Demographic and illness history data, health outcome data, and costing data are described in detail below.

Demographics & Clinical Characteristics

Demographics and clinical characteristics were collected for each patient. This included the patient's age, gender, number of syncopal spells pre-pacemaker, total duration of syncopal spells pre-pacemaker, frequency of syncopal spells pre-pacemaker, tilt table test results, number of syncopal spells post-pacemaker, and frequency of syncopal spells post-pacemaker. This information was used to describe the sample and to identify potential additional predictors of HRQL and costs.

EQ-5D Data

The HRQL EQ-5D scores were obtained pre and post-pacemaker from the patients at the Calgary Syncope Clinic. The patients completed the 2 page questionnaire and submitted it to the research nurse present. The questionnaire was then filed and scores were entered into a computer statistical program (SPSS) at a later date by an administrative

assistant. As routine practice, this occurred pre-pacemaker when the patient first presented at the Syncope Clinic.

Post-pacemaker HRQL scores were obtained between 3 and 24 months after surgery. As some patients (n=4) recently received pacemakers, post-pacemaker HRQL scores for these patients were only available for shorter intervals (i.e. 3 or 6 months). In addition, as some subjects (n=8) did not return to the Calgary Syncope Clinic at set intervals, later scores (i.e. greater than 12 months post-pacemaker) were not collected for all subjects.

The VAS component of the EQ-5D was the primary HRQL measure used in the current study, although the index derived from the multi-dimensional questions of the EQ-5D was also examined. The main reason the VAS was used as the primary measure is because pre and post-pacemaker VAS scores were available for all 38 subjects, whereas the index scores were available for only 25 subjects.

Cost Data

Administrative Databases

The Corporate Data administrative databases that were used for this cost analysis included the Inpatient File, Emergency File, and Day Procedures File. In July of 1996, the Emergency File and Inpatient File were combined to form the ACCS File, with all of the information from the separate files being available in the combined file. Every hospital visit in the CRHA (Alberta, Region 4) is recorded in these databases. As such, health care system utilization data for each of the 38 patients in our study sample was available.

These databases are administered by Corporate Data, CRHA. As the physician of the patients on whom data was requested is a part of our research team, consent at an individual patient level was not required. Each of the databases will be discussed in turn, including how costs were derived.

The Inpatient File records all inpatient hospital stays in Region 4 hospitals, as of April 1994. This includes Foothills Medical Center (FMC), Peter Lougheed Center (PLC), Alberta Children's Hospital (ACH), Rockyview General Hospital (RGH), and before closing in April 1997, Bow Valley Center (BVC). In these files, patients are individually identifiable through hospital ID numbers and Alberta Health personal health numbers. Output summaries for each patient are provided, and include the following information: age at time of admission, sex, admission and discharge dates, inpatient length of stay, the main unit on which service was provided, whether special care units were utilized (e.g. ICU, CCU), diagnostic related grouping codes, diagnosis codes, procedure codes with dates, and physician service codes.

These data were first used to determine whether the hospital stay occurred within the patient's pre or post-treatment interval. All hospital visits for the pacemaker insertion were included in the post-treatment interval.

Second, all visits not associated with syncope were excluded from our study. The primary objective of this study was to track treatment costs for NMS. As such, maternity costs and other obviously unrelated conditions[1] were excluded. Exclusions were made on a case by case basis, and reviewed in a blinded manner by the research nurse involved in this project. The majority of inpatient stays from our sample had diagnosis and procedure codes directly related to syncope.

Third, this file was used to determine which utilization represented "one time costs", and as such would not be included in the modeling of costs to 10 years. This was done again in consultation with the research nurse. In particular, utilization occurring before pacemaker treatment which were related to the diagnosis of syncope including tilt table testing and additional tests or procedures, were excluded from the modeling. Likewise, utilization in the post-treatment interval, including the pacemaker insertion itself

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[1]Other costs excluded were those associated with the following conditions or procedures: abortions; unspecified urethral stricture; open wound penis with complication; conjunctivitis; and trunk infection.

and related "one time" follow-up procedures or tests, were also excluded from the modeling (see Appendix D). Replacement costs which occurred in the first year post-surgery were not modeled, as replacement costs were factored in as per Gillis et al. (31), as described below.

A cost output summary for each FMC hospital stay was also obtained from Corporate Data. For each patient stay, an overall cost for that stay was provided, broken down into costs directly associated with patient care and costs associated with administration and overhead. These two types of costs were each broken down into the following categories: labs; diagnostic imaging; nursing; operating room; recovery room; respiratory therapist; cardiology lab; nutrition; physiotherapy; and social work. These summaries do not include physician activity and physician costs.

As Corporate Data only has costing data on FMC stays, costing of the stays at the other hospitals were estimated from the *Alberta Standard Cost List for Health Economics Evaluations* (32). The purpose of this cost list was to provide standardized health care service costs to be used in economic evaluations. They represent average Alberta costs, and as such may not necessarily represent procedure costs at one particular hospital. However, no other costing data was available on our patients, and as such using the standard costs was the best available option. Based on the procedure codes and diagnostic related grouping codes, each procedure was matched to the corresponding procedure from the cost list. These costs were then used as an estimate for each non-FMC hospital inpatient stay for our subjects. The costs for inpatient length of stays in the pre and post-pacemaker treatment intervals were linked with the costs associated with the emergency visits and day procedures, as described below.

The Emergency and Day Procedure Files (combined in July 1996 as the ACCS File) contain data on a patient by patient basis for all emergency visits and day procedures in Region 4 since September 1994. Output summaries for each patient, corresponding to

each emergency visit or day surgery, were obtained from Corporate Data. The outputs included: hospital ID and Alberta Health personal health number; admission and discharge date; age; gender; physician service code; diagnosis codes; procedure codes; and the site. Emergency visits and day procedures were costed as per the rate found in the *Alberta Standard Cost List for Health Economics Evaluations* (30).

Clinic Records

As the administrative databases do not include clinic data and physician activity data, other sources were used to ensure that all (or close to all) of the direct costs for each patient were obtained.

The second source of costing data was the patients' clinic records (see Appendix E for data collection form). First, the exact type of pacemaker and leads for each patient was recorded. Second, the pre and post-pacemaker treatment drugs were recorded for each patient. In most cases, prescribed drugs were for syncope. However, some patients received drugs for other, but potentially related, conditions such as migraines. All drugs which were prescribed for syncope or other potentially related conditions were included in the analysis, upon consultation with the research nurse. Third, the number of clinic visits in both the pre and post-treatment intervals was ascertained for each patient.

All medications prescribed were costed as per Canadian average wholesale pharmacy costs obtained from IMS Canada (personal communication, D. Rhodes), with an additional fee of $9.70 added to each prescription as per the *Alberta Stnadard Cost List for Health Economics Evaluations* (32). Based on the intent-to-treat principle, even if prescriptions were not filled, they were still included in the costs. Not all of these drugs were prescribed by physicians at the Syncope Clinic, but correspondence with general practitioners (GPs) and other physicians is generally recorded in the patient charts, and thus drugs prescribed elsewhere were likely captured through the clinic chart reviews.

The only way in which this data on drugs could alternatively be captured is through patient recall or going through GP office records. The first means would be subject to recall bias and inaccuracy, and the second means would be problematic in terms of both consent and feasibility.

For certain patients, the drug regime could not be clearly assessed by simply reviewing the clinic charts. For these cases, the research nurse was asked to estimate particular doses or length of time on certain drugs, and in some cases individual GP offices were contacted by the research nurse. Failing these measures, for a very small number of cases, the average Canadian prescription dose and associated average cost was obtained from IMS Canada and was utilized.

Tests conducted in GP offices could not be captured, and thus these costs were not included in this analysis. However, the cost of the GP assessment itself (if any) was captured in the data obtained from Alberta Health, described below.

As no detailed Syncope Clinic budget existed, the average clinic cost as per the *Alberta Standard Cost List for Health Economics Evaluations* was utilized. This value was multiplied by the number of clinic visits per patient for each interval, to derive an estimated clinic cost per patient per interval. This value was cross validated with previous crude Syncope Clinic budgets (personal communication, W. Wilson). The overall clinic costs per patient, for each interval, were recorded and reported.

Tests and procedures conducted outside of Region 4 were excluded. The inconsistency of reporting in the clinic charts with respect to such procedures would result in the potential for selection bias if any such procedures were included. Overall, the majority of patients received treatment within Region 4. In addition, no physician consultations which occurred in Alberta but outside of Region 4 were costed as these would have been captured in the data reported by Alberta Health in the Fee-for-Service File. Further, most hospital stays outside of Region 4 were not copied to the clinic files,

and thus these costs were not captured for our sample. Due to the exclusion of procedures and hospital visits outside of Region 4, the total direct costs for both the pre and post-treatment intervals were likely underestimated.

Alberta Health Costs

The third source of costing data was Alberta Health. For any data to be released, Alberta Health requires that an application for data be submitted. This application for data was submitted to Alberta Health on Oct. 3, 1997. The application was reviewed internally by C. Belanger and T. Fedoriw, and the researchers were informed that the application for data was successful in early December, 1997. The researchers were then asked to provide patient information so as the extraction of the required data could be conducted.

The researchers provided Alberta Health with a list of patient identifiers (Alberta Health Care personal health numbers), a pacemaker implantation index date for each patient, and a study group designation for each patient (values 1 and 2, representing the less and more severe study groups, respectively). This information was provided to Alberta Health in the form of a flat ASCII file on January 25, 1998. Every personal health number and implant date was confirmed with the following sources: cardiac diagnosis report; operative report; hospital discharge summary; hospital chart record of admission; and the Corporate Data administrative databases. The data requested from Alberta Health was in aggregate form, so no individual patients were identifiable from the data provided by Alberta Health.

The following data, for each interval and study group, were provided by Alberta Health on April 5, 1998: the sum of physician service units paid, the sum of the amount paid, the standard deviation of units paid, the standard deviation of the amount paid, and the mean and median of the service units paid and amount paid. The data requested from Alberta Health included all physician types.

Alberta health also conducted a validation check to ensure that the pacemaker insertion date in fact fell in the post-treatment interval (note, the first day of the post-treatment interval was the date of implantation). This was to ensure that the hospital and clinic records recorded the pacemaker implantation on the same date as was in the Alberta Health service records.

Imputation Methods for Physician Cost Data

Alberta Health had a service cut off date of January 1998, in order to provide the costing data to the researchers by March of 1998. Thus, those patients paced after January 1997 did not have Alberta Health costs recorded for the full 12 month post-treatment interval. As Alberta Health costs were provided aggregately, the individual costs for each patient could not simply be averaged over the 12 month period.

The aggregate mean cost provided by Alberta Health for the less severe study group was based on 177 of a total possible 192 months ([n=16]*[12 months]=192). Making the assumption that physician costs were uniformly distributed across the 12 month period, an average cost per month was derived by dividing the aggregate mean cost for the group by 177. This average physician cost per month was then multiplied by 15 months (the number of months which were not included in the Alberta Health data due to the cut off date), with the result added to the total cost provided for the 177 months. This resulted in a total physician cost for the less severe group, based on 192 months. This figure was then divided by the 16 in province subjects in this study group to derive a mean physician cost per patient, for the less severe group.

In a like manner, an average physician cost for the more severe group was calculated by dividing the total cost from Alberta Health by 191, the number of months the Alberta Health data was based on. This average physician cost per month for this group was then multiplied by the 13 months not included by Alberta Health, with the result being added to the total physician cost figure for this group from Alberta Health. This new total

cost was then divided by 17, the number of in-province patients in the more severe study group, to derive a mean physician cost for the more severe group.

In addition, 2 patients from Saskatchewan and 3 patients from B.C. met the inclusion criteria for this study. Alberta Health has no record of physician service units or amounts paid for these 5 patients, as Saskatchewan and B.C. Health, respectively, were billed. Although B.C. and Saskatchewan could have been approached for data, the additional effort required to obtain data on such a small number of patients was not deemed worthwhile. In order to utilize these patients in the overall cost analysis, the mean physician cost of the study group in which these patients belonged was assigned to each patient, respectively. With this, overall physician costs for the pre and post-pacemaker intervals, which included all study patients, were derived for each study group.

Linking of Cost Data from All Sources

The costs for each patient from each source for the pre and post-pacemaker intervals were summed, producing a cost per patient. The mean costs per patient overall and for the two study intervals were then calculated with the statistical software program Stata®.

Pacemaker Replacement Costs

As the patients in our study were followed-up in terms of costs for only 12 months, realistic replacement rates and subsequent costs could not be identified. As such, we obtained the expected pacemaker longevity from the pacemaker manufacturers (personal communication, B. Metcalfe and C. Lemay). From Gillis et al. (31), we then determined the expected survival of our sample, based on the 1875 patients who received a pacemaker and had been followed up at the Foothills Hospital Pacemaker Clinic between 1975 and 1996. At 10 years, which is the expected pacemaker life, the survival of patients over age 70 was 27% and those under age 70 was 64%. Thus, in 10 years time, it can be expected that only 27% of patients over age 70 will incur pacemaker replacement costs, whereas

64% under age 70 will incur these costs. As the general pacemaker population is not necessarily representative of the syncope pacemaker population in terms of mortality, the expected survival rates of the sample were varied in the sensitivity analysis.

The replacement costs were calculated by multiplying the replacement cost, as per the *Alberta Standard Cost List for Health Economics Evaluations*, discounted over 10 years at 5%, by the respective survival rates, (.64) and (.27). Then, the number in our sample under 70 years (n=34) was multiplied by the first figure, and the number in our sample over 70 years (n=4) was multiplied by the second figure. These two calculated figures were summed and divided by the total number in our sample (n=38) to derive a 10 year average per patient replacement cost.

Although replacement costs were included in the primary analysis as described, the analytic horizon was actually only the life of the first pacemaker. Viewed in this manner, a replacement pacemaker technically falls just beyond the analytic horizon. However, inclusion of replacement costs resulted in a conservative estimate of the cost utility of pacemakers for the specified analytic horizon. The scenario of not including replacement costs was examined in the sensitivity analysis, and was further discussed in the Discussion section below.

Summary of Cost Data

Gillis et al. state that long-term cost analysis of pacemakers should include the device costs, the procedural costs, the follow-up costs and the replacement costs (31). For our study, the procedural and follow-up costs were obtained directly from the sources described here. The device costs were available from the hospital, and were confirmed with Canadian average acquisition costs obtained from Medtronic, who manufactured the pacemakers. Finally, replacement costs were estimated as per the Gillis et al. model, based on patient survival rates and expected longevity calculations provided from Medtronic.

Statistical Analysis

Demographics & Clinical Characteristics

Mean and 95% confidence intervals (and geometric mean and 95% CIs for non-normal variables) were used to describe the following continuous variables: age, total number of syncopal spells pre-pacemaker treatment, pre-pacemaker frequency of spells, and post-pacemaker frequency of spells. These variables were depicted graphically with histograms, where appropriate. In addition, gender was described as a proportion with a 95% confidence interval, tilt table test results were described as proportions, and the median (IQR) was used to describe the duration of illness before pacemaker treatment. Finally, pre and post-pacemaker frequency of syncopal spells were compared with a paired t-test.

EQ-5D Scores

The HRQL EQ-5D scores for each patient pre and post-pacemaker were tabulated and an overall mean score was derived for the entire sample, and for each study group. The mean scores were reported, as per CCOHTA's published guidelines, in order that the absolute health state of the group would be transparent (9). Histograms and normal quantile plots were utilized to determine if the distributions were normal.

A 95% confidence interval was presented for each mean score. A paired t-test was conducted to determine if the differences between the mean scores for the two intervals, and within the study groups, was significant. To confirm that the two study groups represented more and less severe patients, a two sample t-test was conducted to test whether or not the pre-treatment mean HRQL scores were significantly different between the two study groups.

In order to examine the stability of the EQ-5D scores post-surgery, a paired t-test was utilized to determine if a difference between the first score obtained post-surgery and

the last score obtained post-surgery existed, for the 17 patients who had more than one score taken post-surgery. In addition, the mean±SD months post-surgery of the last score (i.e. the score used for the analysis in this study) was calculated and presented. Further, a two sample t-test was utilized to compare the mean score of the 21 patients with only one post-pacemaker score with the last score of the 17 patients with more than one post-pacemaker score. These tests were done to determine if a drop-off in post-pacemaker scores was apparent.

An incremental health outcome is the difference between two health outcomes, and indicates a change in health outcome across an intervention, or between two study groups. The incremental HRQL score comparing the pre and post-pacemaker intervals was derived by subtracting the mean HRQL score of the pre-treatment interval from that of the post-treatment interval. This was also done for each study group, so that the more severe group's pre-treatment interval mean HRQL score was subtracted from the more severe group's post-treatment interval mean HRQL score, and likewise for the less severe study group. The relative health benefit, as measured by the observed incremental HRQL mean score between the two intervals, was utilized in the cost utility ratios.

Next, the VAS scores were compared to the EQ-5D index scores based on the multi-dimensional questions. First, the mean index score, overall and for each study group, was presented. Second, a paired t-test was used to determine if the pre to post-pacemaker index scores were significantly different. Third, a Bland and Altman plot was utilized to examine the differences between the VAS and index scores. Fourth, incremental index scores, overall and for each study group, were calculated, in order that cost utility ratios based on the index scores could be derived, in the sensitivity analysis.

Finally, the relationship between HRQL and natural log (ln) frequency of spells was examined with simple linear regression. This regression was done to confirm, as shown in previous work, that ln frequency of spells is a significant predictor of HRQL, in

our sample. Baseline demographics were also modeled with regression against HRQL, to determine if any other variables were significant predictors of HRQL.

Pacemaker Type

The frequency and HRQL scores were compared on the basis of the type of pacemaker implanted. As two types of pacemakers were used, this testing was conducted to ensure that the two pacemaker groups could be combined in one sample. A two sample t-test was used to determine if a difference in frequency, and then EQ-5D scores, existed between those subjects with a Diamond pacemaker and those with Thera pacemakers.

Cost Data

First, pre to post-pacemaker treatment number of hospital visits were compared with McNemar's Test. This was done as one study had previously suggested that number of visits would likely decrease after pacemaker insertion (22).

Second, a two sample t-test was used to compare the pre-treatment mean cost of the two study groups, and to compare the post-treatment mean cost of the two study groups. This was done in order to determine if the costs for each of the study groups, pre and post-treatment, were significantly different. Further, a paired t-test and 95% confidence interval for the difference in means were used to compare the pre and post-treatment one year total costs, overall and for the two study groups.

Third, estimated replacement costs were added to the other costs obtained from our study, to derive an overall mean cost per patient which included replacement costs. Ignoring replacement costs could lead to a substantial underestimation of the costs of pacemaker therapy.

Finally, the relationship between direct costs and pre-pacemaker ln frequency of spells in each interval, and within each study group, was examined with simple linear regression. Cost was the outcome variable and ln frequency was the predictor variable.

Demographic variables were also modeled to determine if there were any other significant predictors of cost.

Modeling Health Benefits and Costs

The analytic horizon should extend to capture all relevant outcomes (5). In order to fully capture the cost savings of implanting an expensive device like a pacemaker, it is necessary to track the costs and health outcomes over the entire life of such a device. The relevant analytic horizon chosen for the cost utility analysis was 10 years, as this is the expected life of the pacemaker. The pre-treatment and post-treatment intervals were each extended an additional 9 years, so that each of the two intervals were 10 years in length (see Appendix D). Cost utility analysis was only carried out at the end of the modeled 10 year period.

Initially, the HRQL pre-treatment score was assumed to not change for the modeled 10 year pre-treatment interval, and thus this pre-treatment score was used for the cost utility analysis. The latest collected HRQL post-treatment score was assumed to be constant over the 10 year post-treatment period and was the score used for the cost utility analysis.

The pre-treatment costs were assumed to be constant over the 10 year interval, except for certain "one time costs" which were not included in the modeling. These one time costs included diagnostic costs and tilt-table testing costs which would not be incurred beyond the initial one year pre-treatment period. In a similar manner, the collected 12 month post-treatment costs were assumed to be constant over the 10 year post-treatment interval, except for identified one time costs, such as the pacemaker costs and the costs related to the pacemaker surgery. These "one time costs" were not extrapolated, but were counted in the first year. If they were counted in the additional years the actual costs over the 10 year period would be overestimated.

The one time costs were identified and the 10 year pre and post-treatment modeled cost figures were derived as per the calculations shown in Appendix D. The modeled mean cost per patient figures were described and were used in conjunction with the HRQL data for the cost utility analysis. First, the mean costs were presented for each interval separately, with 95% confidence intervals. These data were also presented for each of the study groups. As per CCOHTA's *Guidelines for Economic Evaluations* the mean costs were presented, in order that the absolute magnitude of costs per patient for each treatment regime could be observed (24).

Discounting

Pre and post-pacemaker costs were discounted at a rate of 5% per year. Costs which occur in the future are discounted because in general people prefer desirable consequences (like benefits) to occur earlier and undesirable consequences (like costs) to occur in the future rather than the present (9).

The 10 year modeled discounted incremental costs were used in the cost utility analysis. The calculations used for the discounting of costs are found in Appendix F. HRQL scores were not discounted (33). There is considerable debate in the literature regarding discounting of health benefits, and the CCOHTA guidelines recommend benefits to be discounted at the same rate as the costs (9). An argument against discounting benefits is that health prevention programs in which benefits may not be observed until several years in the future are inherently biased against when compared to acute sector treatments in which benefits are likely to occur more rapidly. Further, discounting health outcomes which are based on direct preference based measures like the time trade off would result in "double discounting" as individuals are likely already discounting benefits when making trade off decisions. Thus, it can be argued that QALYs formed from the EQ-5D derived

index measure (which is based on a time trade off system) should rightly not be discounted. Discount rates of 0% and 10% were examined in the sensitivity analysis (34).

Cost Utility Analysis

The cost utility ratio has two components, the incremental cost and the incremental QALY. This ratio results in an incremental cost per QALY gained. The methodology used to derive the components of the ratio, and the ratio itself, will be examined in this section.

A cost utility ratio is derived from the following formula, $\frac{C_2 - C_1}{Q_2 - Q_1}$, where C_2 and C_1 are the costs of the post-treatment interval and the pre-treatment interval respectively, and Q_2 and Q_1 are the QALYs of the two intervals, respectively.

A QALY is a measure of the quality of life over some period of time. Quality of life in our study was measured with the HRQL EQ-5D instrument. These scores, representing the "quality" component of the QALY, can be multiplied by a length of time to derive the QALY. As the treatment intervals in our study were modeled to 10 years, the "quantity" component of the QALY is 10. In order to construct the pre-treatment QALY, the pre-treatment mean HRQL score, scaled to a value between 0 and 1, was multiplied by 10. In the same manner, the post-treatment QALY was constructed by multiplying the post-treatment mean HRQL score by 10.

The two QALYs were inserted into the denominator of the cost utility ratio above. In subtracting Q_1 from Q_2, an incremental QALY gained between the post-treatment and pre-treatment interval results. This indicates how many additional QALYs are gained with pacemaker treatment as compared to conventional treatment. This procedure for calculating the QALYs of the two intervals, and the incremental QALY, was also conducted for each of the two study groups.

The derivation of the modeled mean cost per patient for the pre and post-pacemaker intervals, was described above. An incremental cost was then derived between the two

intervals by subtracting the pre-treatment mean cost from the post-treatment mean cost. The resulting incremental cost is the numerator of the cost utility ratio.

The cost utility ratio was then derived by dividing the incremental cost of the two intervals by the incremental QALY of the two intervals. This resulted in a figure which is the cost per QALY gained for pacemaker treatment as compared to conventional treatment.

Cost utility ratios were then derived for each of the two study groups. This allowed for comparison of the cost utility of pacemaker therapy versus conventional therapy at two levels of illness severity.

Sensitivity Analysis

Sensitivity analysis was used to evaluate the impact of the uncertainty of the precision of the estimates and for the uncertainty of modeling assumptions. How each of these uncertainties were controlled for will be discussed in turn.

As stated above, a 95% confidence interval was presented with each parameter estimated. For the pre and post-treatment mean HRQL scores, and within each study group, the upper and lower limits of the 95% confidence intervals were used to calculate the QALYs. This resulted in high and low incremental QALY estimates between the treatment intervals, and within the study groups. These incremental QALYs were then inserted in the cost utility ratio, resulting in varying cost per QALY gained figures.

In addition, the upper and lower limits from the 95% confidence intervals of the pre and post treatment mean cost estimates, and within the study groups, were used to determine a range of incremental costs between the intervals. In using the various incremental costs, a range of cost utility ratios resulted. Finally, the variations in costs were also changed simultaneously with changes in the QALYs. The range of resulting cost utility ratios were presented.

Further, sensitivity analysis was also used to evaluate the impace of the modeling assumptions inherent to our study design. First, the potential for a drop-off in treatment effect was accounted for by assuming that 25% of the sample would revert to their baseline HRQL scores within 2 years post-pacemaker, thus requiring a pacemaker replacement at this time. This percent was selected as this is the percentage of the sample for which only one post-pacemaker HRQL score was available for, not including those patients who were recently paced and were unable to have more than one score taken. This assumption considers that all of these patients had a drop-off of HRQL scores, and thus controls for the potential selection bias from these patients in not having post-pacemaker scores collected at intervals in line with the rest of the sample.

Second, as the physician cost data was received from Alberta Health in aggregate form, it was not possible to determine what physician costs were "one time" costs, and which costs would likely be incurred for the subsequent 9 years following the primary data collection interval. As such, in the initial analysis, the entire mean physician cost was modeled over the 10 year period, resulting in a 10 year total cost per patient.

If the positive treatment effect was maintained, it would be unlikely that the entire mean physician cost would be incurred in each year of the modeling. Thus, it was assumed that 80% of the physician costs were "one time" costs, and only 20% of the physician costs were modeled over the 10 year period. The percentage selected was a clinical estimate (personal communication, Dr. Sheldon), and was in line with the percent of the total regional costs which were deemed to be "one time" costs.

Third, as the syncope population is likely to have increased survival rates in comparison to the general pacemaker population, replacement costs were calculated assuming that in 10 years every subject would require another pacemaker. This provided the upper limit of costs expected due to pacemaker replacement, in 10 years time. In

addition, the CUA was conducted without replacement costs, which represented the cost utility of pacemakers just for the life of the first pacemaker.

Fourth, the 10 year expected life of the pacemaker was varied between 8 and 12 years (personal communication, B. Metcalfe). This was done by modeling the costs over 8 and 12 year periods, and factoring in replacement costs with respective survival rates at 8 and 12 years.

Fifth, as is stated in the literature (9, 34), the discounting rate for the pre and post-pacemaker costs were varied from 0% to 10%. With these discounting rates, the cost utility analysis was re-worked and resulting cost utility ratios were produced.

Sixth, cost utility ratios were derived using HRQL scores derived from multi-dimensional questions of the EQ-5D, to provide a comparison with the initial analysis which was based on the EQ-5D VAS scores.

3. RESULTS

Study Groups

The sample was split into two groups in order that analysis could be conducted on a more severe study group and a less severe study group. The cutoff point between the two groups was the pre-pacemaker treatment median frequency of syncopal spells. This value was .485 spells per month (IQR .104, 2), or just under 1 spell every two months. 19 subjects fell into each of the two study groups. Results are presented for the overall sample (n=38), and for each of the two study groups (n=19).

Demographic Variables

Age & Gender

The mean±SD age of the sample was 43.1±17.9 years. The age distribution of the sample is depicted in Figure 2. Twenty six of the 38 subjects in the sample, or 68% (95% CI 51%, 82%), were female.

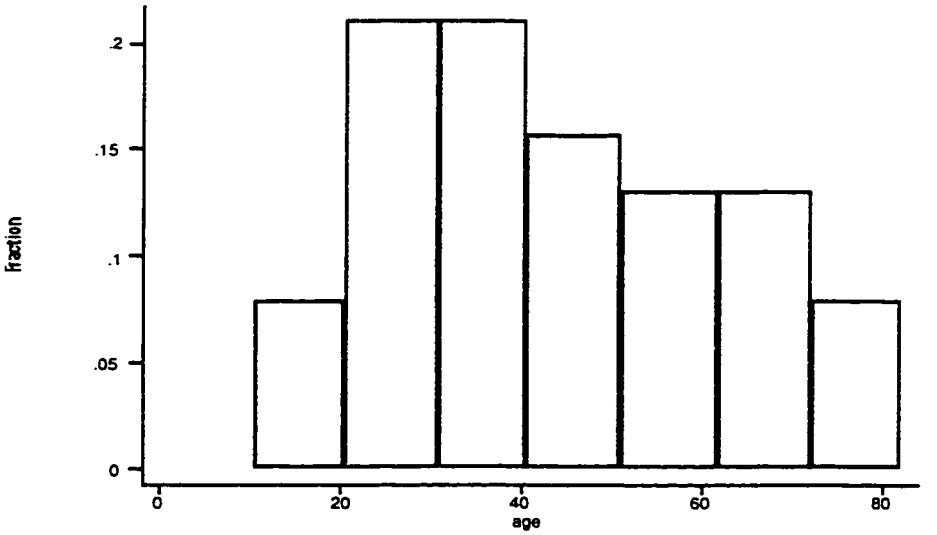

Figure 2: Age Distribution

Clinical Characteristics

Tilt Table Test

In this sample, 4/38 subjects had a negative tilt table test result, 4/38 subjects had pre-syncope and all 38 subjects had syncope.

Total Number of Spells and Duration

The geometric mean with 95% confidence interval of pre-pacemaker total spells was 40 (23, 69). The total duration of spells pre-pacemaker is another important indicator of symptom burden. The pre-pacemaker median duration of spells was 60 (IQR 13, 300) months, and is described with a histogram in Figure 3.

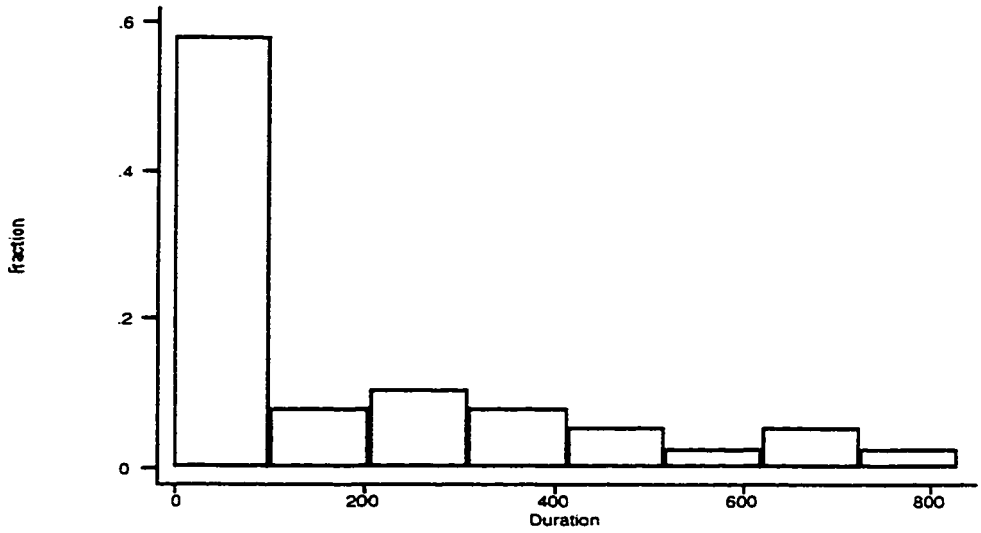

Figure 3: Duration of Syncopal Spells in months

Frequency of Spells

The frequency of syncopal spells was derived by dividing the total number of spells by the total duration of spells. This provides a value for each subject which describes the number of spells per month. Frequency of spells, before and after pacemaker insertion, are described in Figures 4 and 5.

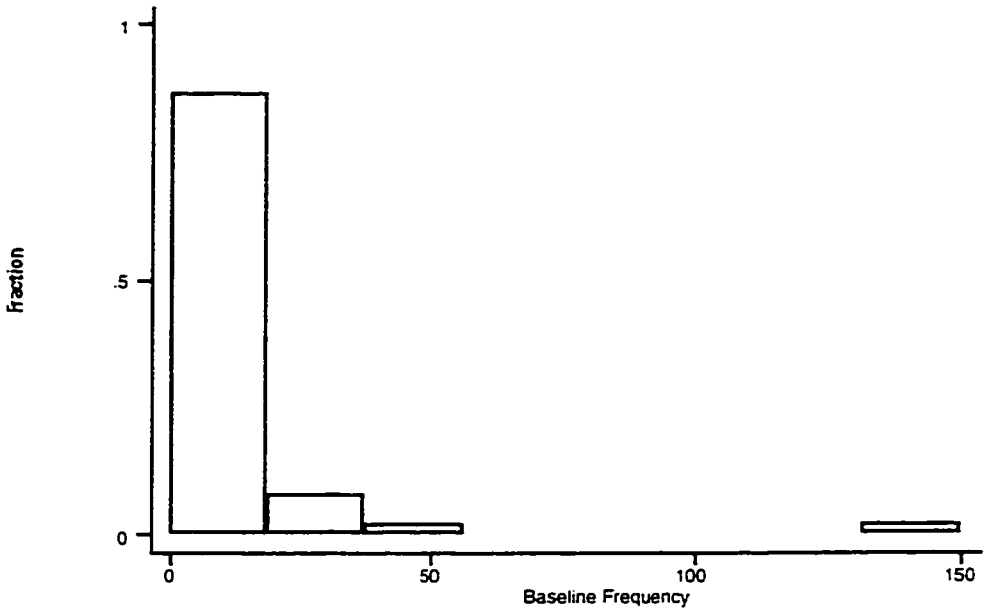

Figure 4: Baseline Frequency of Syncopal Spells (spells/ month)

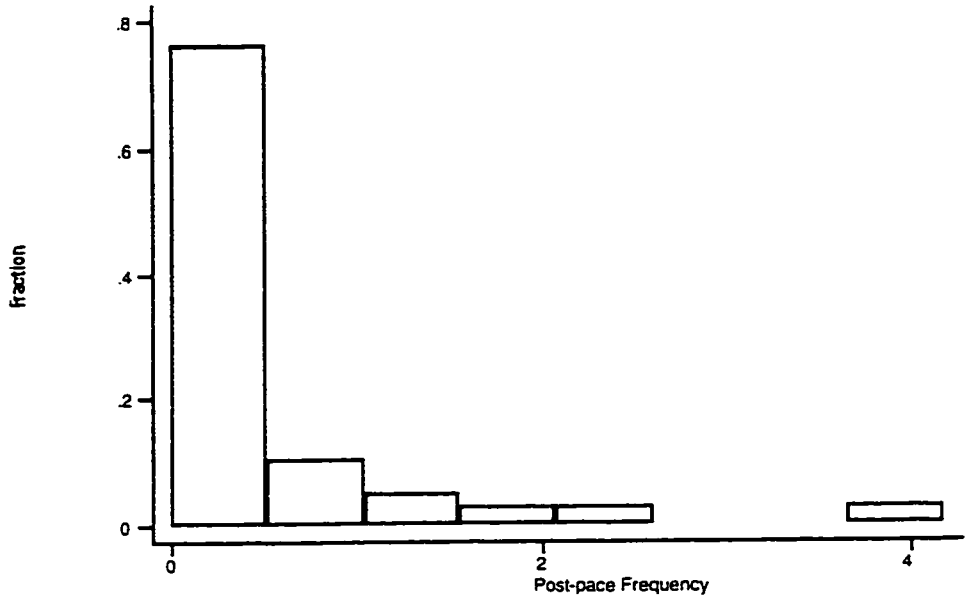

Figure 5: Post-Pacemaker Frequency of Syncopal Spells (spells/ month)

As frequency of spells has a non-normal distribution, a natural log transformation was performed. The geometric mean frequency of spells, before and after pacemaker insertion, are described in Table 1.

Table 1: Frequency of Syncopal Spells

Group	Baseline geometric mean frequency, 95% CI	Post-pace geometric mean frequency, 95% CI†
Overall	.60 (.28,1.3)	.07 (.04,.14)
High frequency	3.7 (1.6,8.2)	.14 (.05,.38)
Low frequency	.10 (.06,.16)	.04 (.02,.09)

†18 of 38 post-pace frequencies were 0, and thus .01 was added to each post-pace frequency in order that the natural log could be taken, enabling statistical testing on the transformed data to be performed

A paired t-test indicated that the difference pre to post-pacemaker on overall ln frequency of spells was highly significant ($t=5.19$, $df=37$, $p<.0001$).

EQ-5D Analysis

Description of EQ-5D scores

The distributions of baseline EQ-5D VAS scores are presented in Figure 6 for the sample overall, and for the high and low frequency study groups.

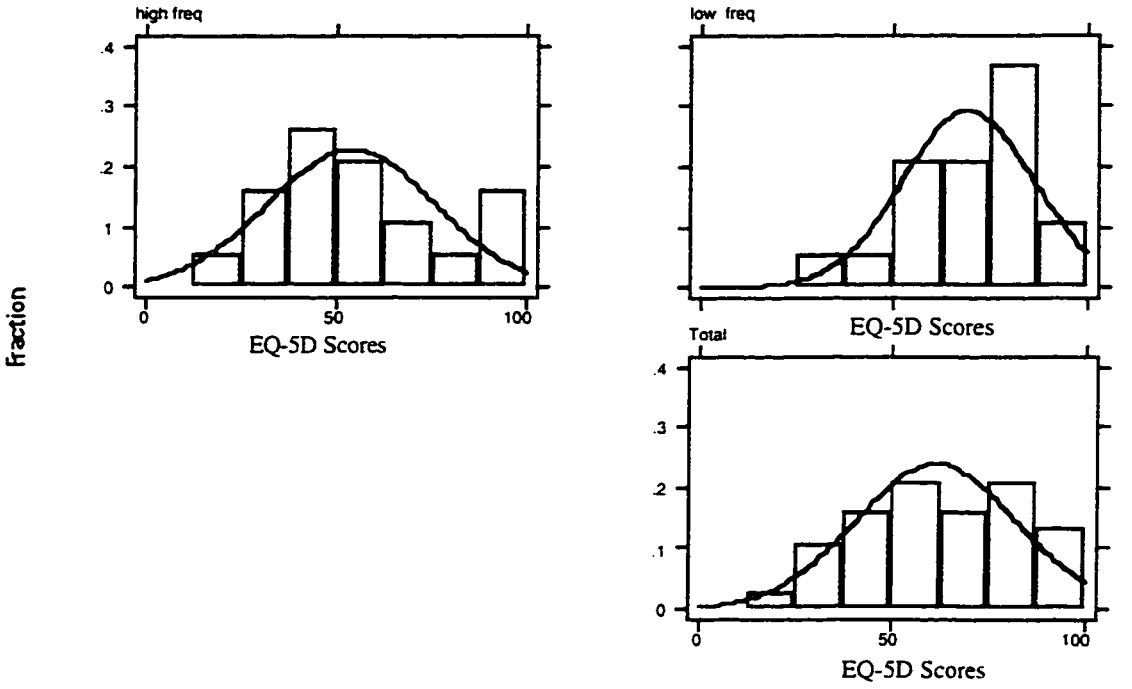

Figure 6: Pre-Pacemaker EQ-5D Distributions

The distributions of the post-pacemaker EQ-5D VAS scores, for the sample overall and for each of the study groups, are depicted in Figure 7. Some variation from normality is observed in the post-pacemaker distributions, and in the normal quantile plots (not shown). However, a suitable normalizing transformation could not be found, and thus all subsequent analyses were conducted with the non-transformed EQ-5D scores.

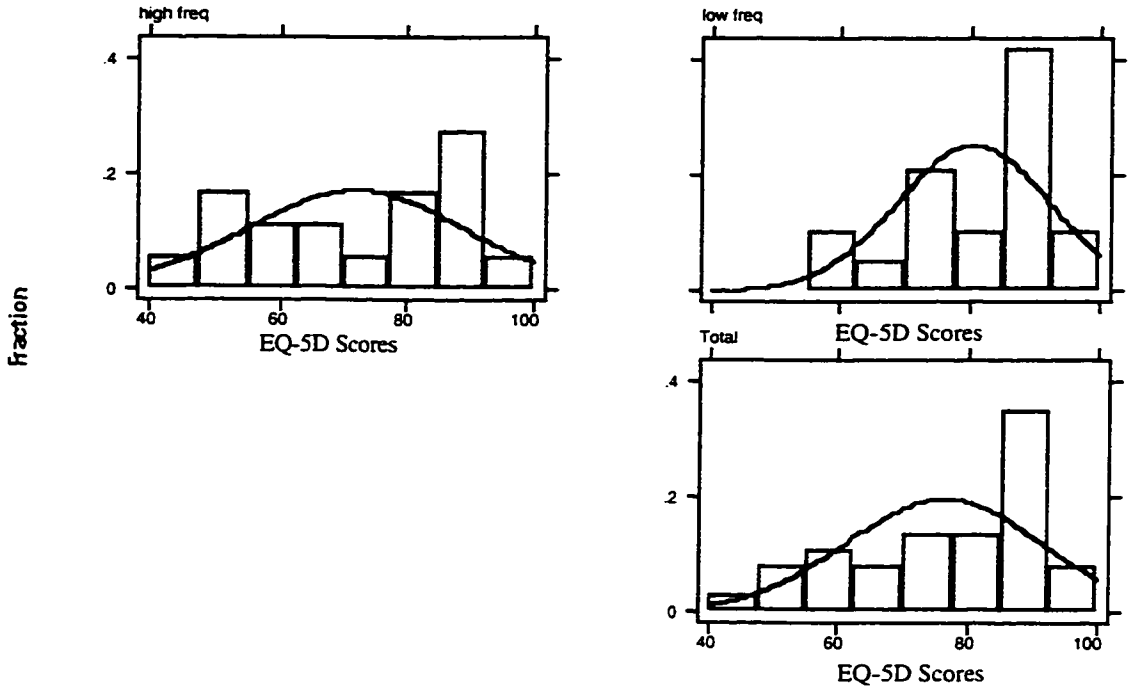

Figure 7: Post-Pacemaker EQ-5D Distributions

The pre and post-pacemaker EQ-5D VAS mean scores, with 95% confidence intervals, are described in Table 2. Although not wholly comparable with general population values due to differences in demographical distribution, a recent study found the general adult U.S. population to have an EQ-5D mean score of 81.7±14.9 (26).

Table 2: EQ-5D VAS Mean Scores

Group	Pre-pace EQ-5D VAS mean score with 95% CI	Post-pace EQ-5D VAS mean score with 95% CI	p-value	95% CI Difference in means	Incremental EQ-5D score
Overall	62.7 (56.1,69.2)	76.2 (71.2,81.3)	p<.0001	(7.4, 19.7)	13.5
High Frequency	53.7 (43.2,64.3)	72 (63.4,80.6)	p=.0046	(5.7, 26.5)	18.3
Low Frequency	69.1 (60.9,77.3)	80.3 (74.6,85.9)	p=.0066	(3.5, 18.8)	11.1

Significant differences between the pre and post-pacemaker HRQL scores, overall and for each study group, were observed. Further, incremental HRQL scores were calculated for the overall sample and for each of the study groups, by subtracting the pre-pacemaker EQ-5D score from the post-pacemaker EQ-5D score. A greater difference was found in the high frequency scores, indicating that pacing had the greatest effect in the more severe NMS patients. The incremental values will be utilized to form the QALYs.

Comparison of EQ-5D Scores Between the Study Groups

To confirm that splitting the sample on the pre-pacemaker median frequency of syncopal spells produced two study groups with significantly different HRQL, a two sample t-test was conducted on the EQ-5D scores between the high and low frequency study groups both pre and post-pacemaker. The analyses are presented in Table 3.

Table 3: Two Sample T-test on EQ-5D Scores Between the Two Study Groups

Interval	p-value	95% Difference in means	Mean Difference
EQ-5D scores between the study groups, pre-pacemaker	p=.02	(2.5, 28.3)	18.3
EQ-5D scores between the study groups, post-pacemaker	p=.10	(-1.6, 18.1)	11.1

A significant difference between the study groups on the pre-pacemaker EQ-5D score was observed, indicating that the two groups represented different levels of HRQL. No significant difference between the study groups on the post-pace EQ-5D scores was observed. However, the p-value is relatively low and the difference in means barely included 0, indicating that there may be a difference, but that is was not detected with this sample. Of note, the pre-pacemaker scores were a significant predictor of both post-

pacemaker scores ($p<.01$), and the difference in scores from pre to post-pacemaker ($p<.001$).

Stability of EQ-5D Scores Post-Pacemaker

The mean±SD months post-pacemaker of the last EQ-5D score obtained was 12±6.5 months post-pacemaker. Of those subjects for which more than one post-pacemaker EQ-5D score was available (n=17), no evidence existed that there was a drop off in scores (paired t-test, p=.94). These subjects had a mean 11.6±5.6 months between first and last score. As no evidence for a drop off in scores existed, the HRQL post-pacemaker data seemed stable, thereby providing some evidence that the long term assumptions regarding the HRQL scores were valid. A line graph representing the EQ-5D mean scores (with 95% CIs) during the post-pacemaker follow-up period is presented in Figure 8.

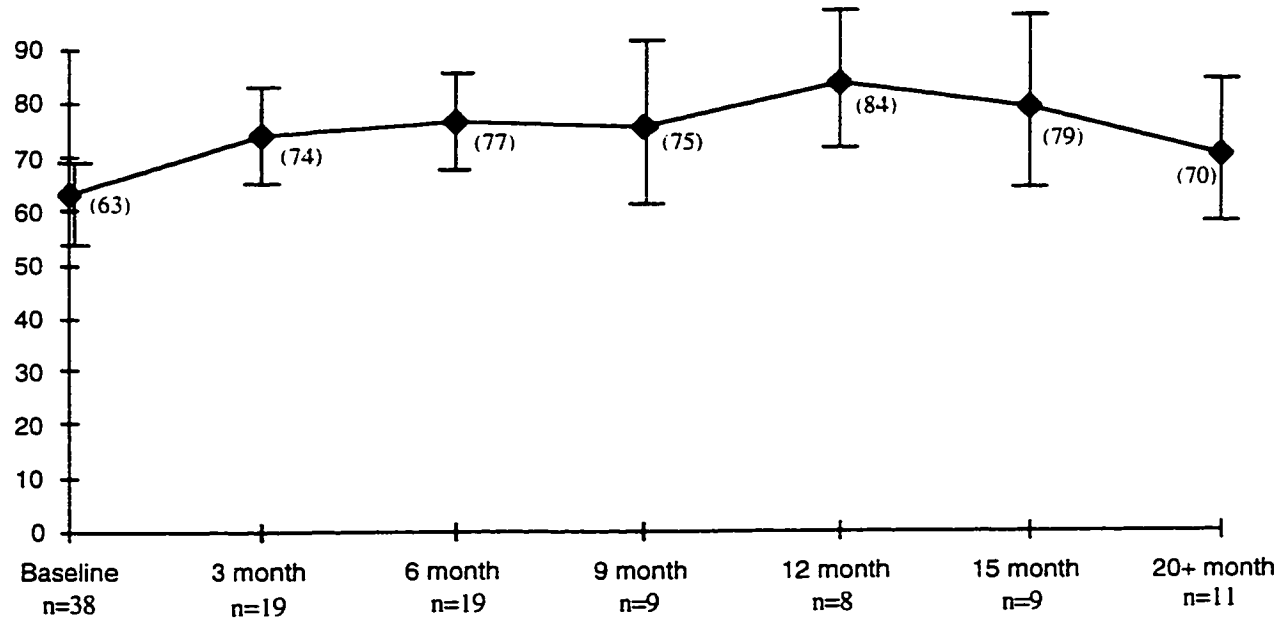

Figure 8: Line Graph of EQ-5D Post-Pacemaker Score Follow-up

Although there appears to be a drop-off in scores, it should be noted that the 20+ month point is based on only 11 subjects and the 15 month point on 9 subjects.

Further analysis was conducted between the 17 subjects who had more than one post-pacemaker score, and the 21 subjects who had only one post-pacemaker score. No significant difference was found between the last score available for the 17 subjects and the only score available for the 21 subjects (t=-.66, p=.512). This provided further evidence that the post-pacemaker EQ-5D scores were stable. In addition, there was no significant difference between the high and low frequency study groups when subjects with one and more than one post-pacemaker score was examined (p=.19), and no difference between baseline scores (p=.69) was present.

To further examine the stability of the data, an analysis comparing the pre to post-pacemaker EQ-5D scores, for all subjects with scores obtained at greater than 12 months was conducted. A paired t-test indicated that a highly significant difference between these pre and post-pacemaker EQ-5D scores existed (t=-3.25, p=.0038). The 95% confidence interval difference in means was (-24.6, -5.4). There was also no difference in mean baseline scores between subjects with post-pacemaker scores at 12 months or greater and those with scores at less than 12 months (p=.10). In summary, analysis of the longer term follow-up of subjects indicated that the EQ-5D improvement pre to post-pacemaker was maintained.

Comparison of VAS vs. Derived Index

The pre and post-pacemaker derived index distributions, overall and for the study groups, are presented in Figures 9 and 10, respectively.

Figure 9: Pre-pacemaker EQ-5D Derived Index Distribution

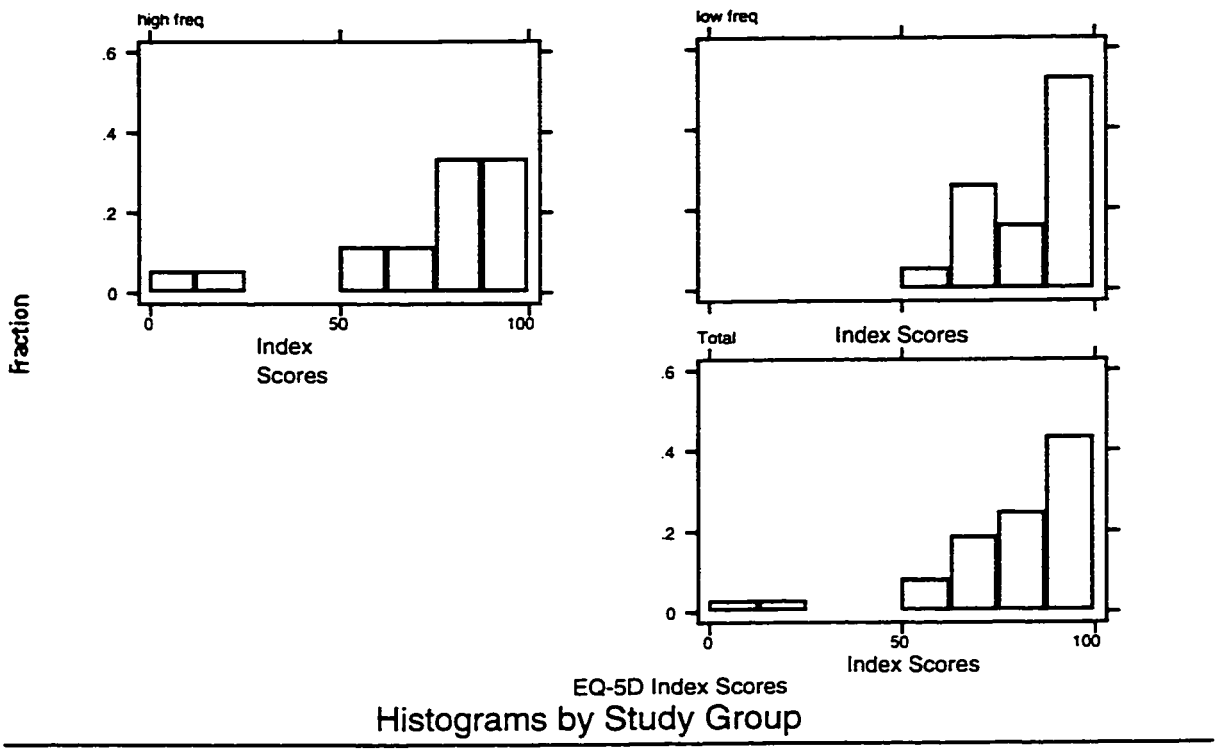

Figure 10: Post-pacemaker EQ-5D Derived Index Distribution

The pre and post pacemaker mean EQ-5D derived index scores are presented in Table 4.

Table 4: EQ-5D Derived index scores

Group	Pre-pacemaker derived index score, 95% CI	Post-pacemaker derived index score, 5% CI	Incremental EQ-5D	Incremental VAS
Overall	.748 (.646, .849)	.837 (.750, .923)	.089	13.5
High frequency	.644 (.473, .815)	.756 (.537, .974)	.111	18.3
Low frequency	.806 (.676, .936)	.883 (.805, .960)	.077	11.1

A significant difference was observed between the derived index score pre-pacemaker to post-pacemaker (t=-2.20, df=24, p=.037). The 95% confidence interval difference in

means was (.58, 17.3). The incremental scores will be used to derive the QALYs, in the sensitivity analysis, below.

A Bland and Altman plot was utilized to determine the level of agreement between the EQ-5D VAS and derived index scores. The pre-pacemaker plot is presented in Figure 11, and the post-pacemaker plot is shown in Figure 12.

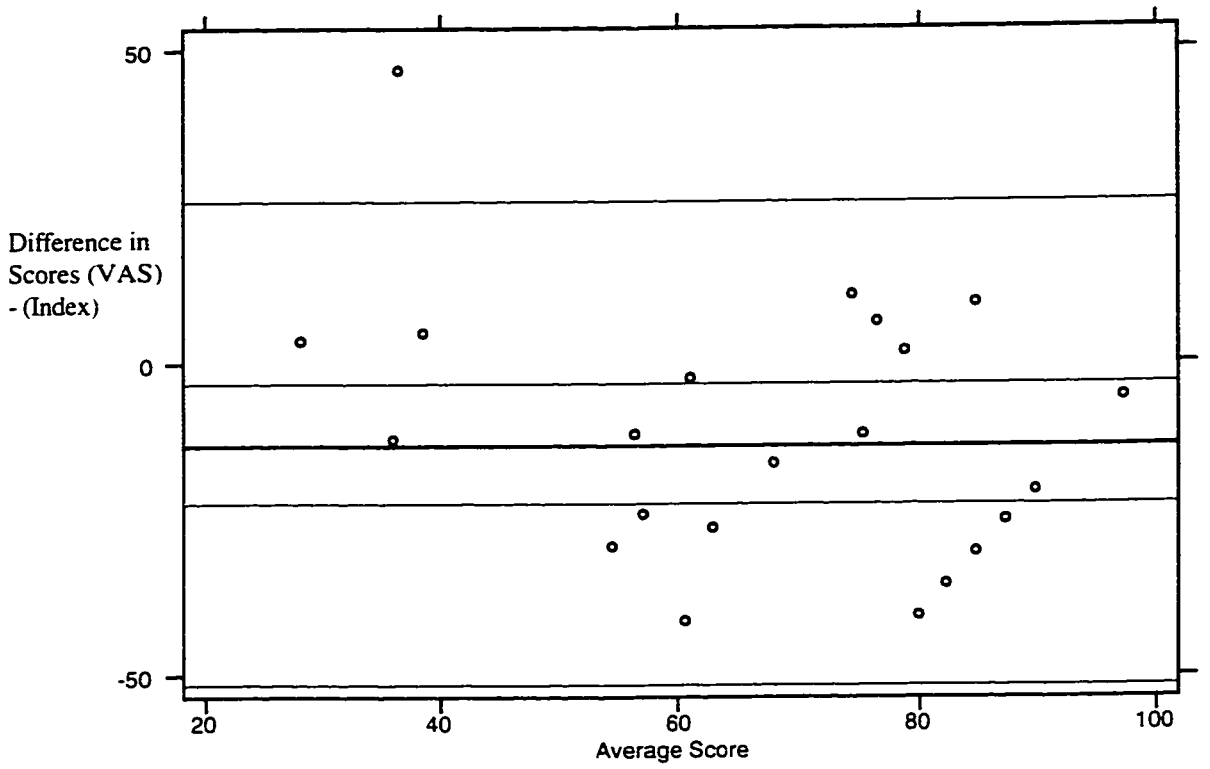

Figure 11: Bland and Altman Plot of the Pre-Pacemaker EQ-5D VAS and Index Scores

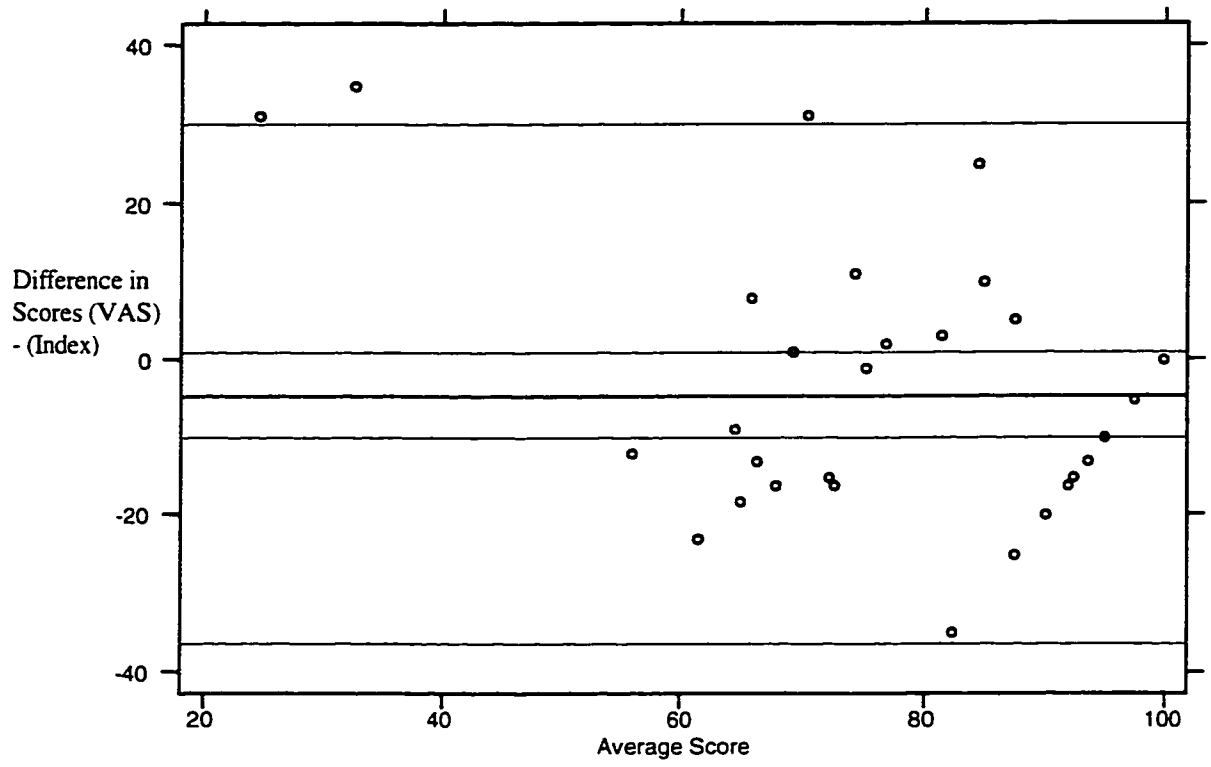

Figure 12: Bland and Altman Plot of the Post-Pacemaker EQ-5D VAS and Index Scores

For the pre-pacemaker scores, the Bland and Altman plot (35) indicates that on average the VAS and index scores do not agree. This is noted because 0 is not contained in the 95% difference in means interval, and because of the large difference which is observed for some individuals. For the post-pacemaker scores, it appears that the VAS and index scores do agree, as 0 is (barely) contained in the 95% difference in means interval. In both cases, the mean difference±2 SDs contains about 95% of the cases. However, there is again a great deal of individual variation between the two measures. Due in part to the low agreement between the two measures of HRQL, the CUA will be conducted in the sensitivity analysis using the index scores to derive the QALYs. Theoretical reasons for why the derived index should be considered are given in the Discussion, below.

Predictors of HRQL

The relationship between the ln baseline frequency of syncopal spells and the baseline HRQL EQ-5D scores was examined with simple linear regression. A highly significant relationship was observed in our sample ($p<.001$), as presented in Figure 13. The pearson's r coefficient was -0.6.

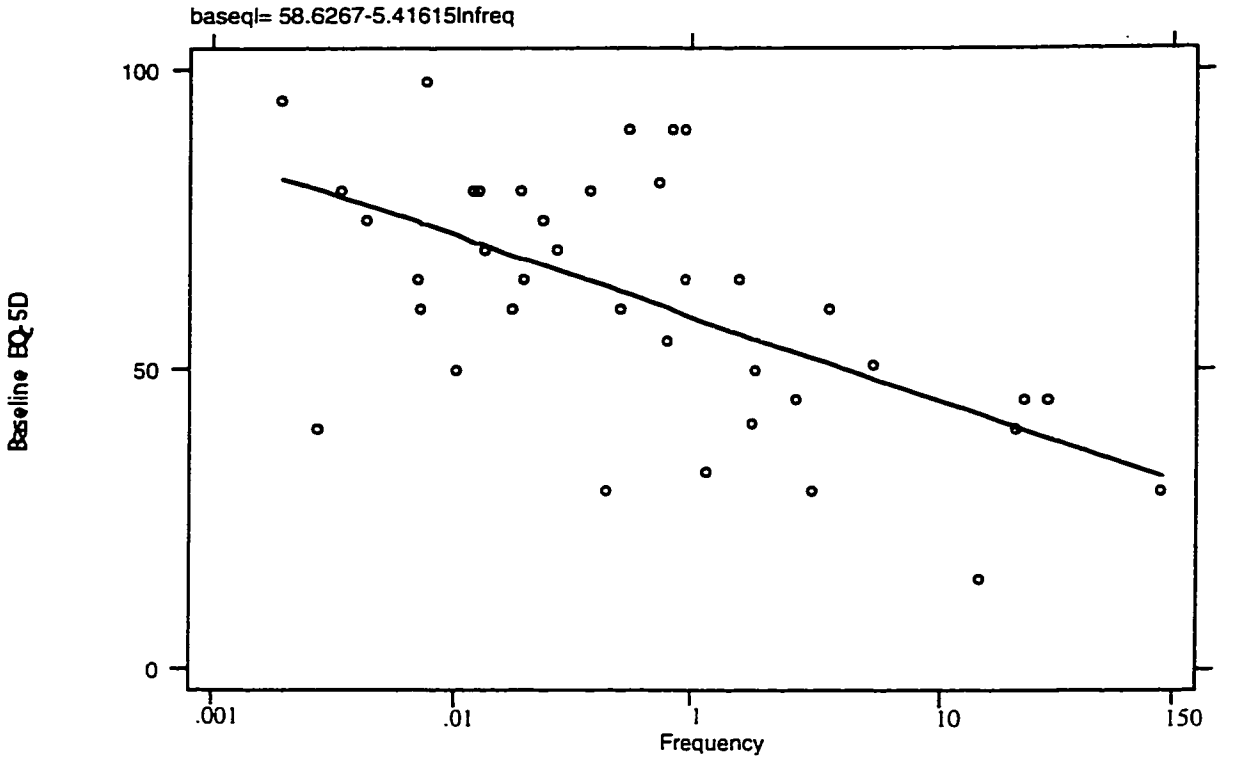

Figure 13: Scatterplot of Frequency of Syncopal Spells vs. HRQL

The demographic variables were examined against baseline HRQL with simple linear regression. Age was found to significantly predict baseline HRQL, and was then added to a multiple linear regression model with baseline ln frequency to determine if both

of these variables still significantly predicted baseline HRQL. Both age (p=.047) and ln baseline frequency (p<.001) were significant predictors of baseline HRQL.

Analysis of Pacemaker Type

Frequency of spells and HRQL were compared on pacemaker type to ensure that the two pacemaker groups could be combined in one sample. The analysis is described in Table 5.

Table 5: Frequency of spells and HRQL by Pacemaker Type

	Geo mean frequency (95% CI)	t-stat (p-value)	Difference in means	Mean HRQL (95% CI)	t-stat (p-value)	Difference in means
Baseline Diamond	.77 (.25, 2.3)	.72 (p=.47)	(.98, 2.06)	56.8 (47.4, 66.2)	-1.46 (p=.15)	(-23.3, 3.8)
Baseline Thera	.45 (.15, 1.3)			66.6 (56.1, 76.9)		
Post-pace Diamond	.098 (.03, .30)	.996 (p=.33)	(-.69, 2.02)	75.6 (67.4, 83.7)	.77 (p=.77)	(-11.8, 8.8)
Post-pace Thera	.05 (.02, .15)			77.1 (70.9, 83.2)		

A significant difference between pacemaker type on frequency of spells both pre or post-pacemaker was not observed. Further, there was no significant difference in HRQL between the two pacemaker groups before and after pacemakers were implanted. These results indicate that the pacemaker groups are sufficiently similar to combine in one group overall.

Costs

Administrative Databases

The mean pacemaker insertion cost, including associated lab tests and a minimum one night hospital stay was $7430±248. There was no difference in cost between the Thera and Diamond pacemakers. The pre-pacemaker mean hospital cost over the one year period of primary data collection was $432±696. The post-pacemaker mean hospital cost, including the pacemaker and insertion costs, over the one year period of primary data collection was $9420±4528. The pre to post-pacemaker number of hospital visits was compared with McNemar's test, for the one year pre and post-pacemaker primary interval of data collection. A non-significant difference was found (p=.5).

Clinic Records

The pre and post-pacemaker drug costs are depicted in Table 6. The lower frequency study group had a higher mean drug cost both pre and post-pacemaker than the high frequency group, but the confidence intervals overlap in both cases.

Table 6: Drug Costs

Group	Pre-pacemaker mean drug cost (95% CI)	Post-pacemaker mean drug cost (95% CI)	Paired t-test
Overall	$415 (208, 622)	$125 (0, 385)	p=.0026
High frequency	$338 (178, 497)	$40 (0, 98)	
Low frequency	$492 (246, 737)	$209 (0, 570)	

The number of Syncope Clinic visits pre and post-pacemaker, and the Syncope Clinic costs pre and post-pacemaker, are described in Table 7. As the Syncope Clinic visit data was non-normal, medians and IQRs were used to describe the data. Note that GP

Clinic costs are captured in the Alberta Health Fee-for-Service File, and thus are not included here.

Table 7: Syncope Clinic Costs

Group	Median visits pre-pace (IQR)	Median cost pre-pace (IQR)	Median visits post-pace (IQR)	Median cost post-pace (IQR)
Overall	1 (1,1)	$183 (183, 183)	2 (1,2)	$366 (183, 366)
High frequency	1 (0,1)	$183 (0, 183)	2 (1,2)	$366 (183, 366)
Low frequency	0 (0,1)	$0 (0, 183)	2 (1,2)	$366 (183, 366)

Alberta Health

The total physician costs per study group, obtained from Alberta Health, are described in Table 8. The median, mean and SD are also provided, for the one year pre-pacemaker and the one year post-pacemaker intervals. The post-pacemaker calculated mean includes the out of province patients and the additional months for those in province patients for which a total one year post-pacemaker interval was not available. The pre-pacemaker physician costs did not change, as data for the full one year interval was available for all subjects.

Table 8: Physician Costs

Interval/ Group	Total Amount (n=19 for each study group)	Median from Alberta Health	Mean from Alberta Health	Calculated Mean
pre-pacemaker high frequency	$19,713±548	$1182	$1159	n/a
pre-pacemaker low frequency	$17,887±731	$952	$1118	n/a
post-pacemaker high frequency	$20,850±613	$1020	$1226	$1310
post-pacemaker low frequency	$21,527±843	$1076	$1345	$1459

Total Costs at One Year Pre and Post-Pacemaker

Costs from all sources were summed to derive overall pre and post-pacemaker costs for the one year interval prior to pacemaker insertion. The mean cost and 95% confidence interval for the two intervals, overall and for the two study groups, are presented in Table 9.

Table 9: One Year Pre and Post-Pacemaker Costs

Group	Pre-Pacemaker Mean cost (95% CI)	Post-Pacemaker Mean cost (95% CI)
Overall	$2032 (1705, 2360)	$10,905 (9349,12446)
High frequency	$1915 (1441, 2453)	$9999 (8443, 11539)
Low frequency	$2085 (1653, 2582)	$11,812 (9012, 14596)

A significant difference was not detected between the two study groups on pre-pacemaker costs (t=-.52, p=.61). The 95% difference in means further supported this conclusion (-833, 493). A significant difference between the two study groups on post-

pacemaker costs was not observed (t=-1.2, p=.24). A difference in means (95% CI) resulted in an interval which included zero (-4894, 1269).

Further, a highly significant difference of one year costs pre to post-pacemaker, overall and for each study group, was observed (p<.0001 in each case). This is to be expected due to the high pacemaker cost, and illustrates the importance of modeling over the life of the pacemaker.

Replacement Costs

Pacemaker replacement costs were derived for subjects over 70 years and under 70 years. Gillis et al. (31) report the 10 year survival of pacemaker patients over 70 years in age to be 27%, and the survival of patients under 70 to be 65%. The average Alberta pacemaker replacement cost, as reported in the *Alberta Standard Cost List for Economic Evaluations* (32), is $5305. This is less than the initial implant cost largely due to the cost of the leads, which is incurred initially but not upon replacement. Discounting the replacement cost at 5%, and assuming the replacement cost will be incurred at 10 years, the replacement costs were $3256.

As per Gillis et al., it can be expected that only 65% of the 34 patients under age 70 and 27% of the 4 patients over age 70 in our sample will require a pacemaker replacement. Replacement cost calculations are shown in Table 10.

Table 10: Replacement Costs

Group	Discounted replacement cost * survival rate	Average replacement cost per group * (n)
Under 70 years (n=34)	(3256)*(.65)=$2116	($2116)*(34)=$71958
Over 70 years (n=4)	(3256)*(.27)=$879	($879)*(4)=$3516
Total	-	(71958+3516)/38= $1986 per patient

Thus, the average replacement cost of $1986 was applied to each subject in our sample, at 10 years. The CUA was re-analyzed in the sensitivity analysis by first assuming each subject received a replacement pacemaker, and second by not including any pacemaker replacement costs.

Modeling to 10 years

HRQL

The QALYs were derived by multiplying the quality component (EQ-5D score) by the quantity component (10 year expected pacemaker life). These derivations are presented in Table 11. Note, the EQ-5D scores are from Table 2 and are scaled between 0 and 1.

Table 11: Pre and Post-Pacemaker QALY Derivations

Group	Pre-pace EQ-5D score*quantity = pre-pace QALY	Post-pace EQ-5D score*quantity = post-pace QALY
Overall	(.627)*(10)=6.27	(.762)*(10)=7.62
High frequency	(.537)*(10)=5.37	(.720)*(10)=7.20
Low frequency	(.691)*(10)=6.91	(.803)*(10)=8.03

Costs

The costs were also modeled to 10 years, pre and post-pacemaker. The future costs were discounted at 5% per year, and the post-pacemaker 10 year cost includes the replacement costs as calculated above. These values, with 95% confidence intervals, are depicted in Table 12.

Table 12: Pre and Post-Pacemaker Costs Modeled to 10 Years

Group	10 yr. cost pre-pacemaker†	10 yr. cost post-pacemaker†
Overall	$11,982 (10180,13783)	$25,404 (22974,27818)
High frequency	$11,723 (9056,14390)	$24,557 (20947,28251)
Low frequency	$12,239 (9556,14922)	$26,241 (22797,29689)

†Discounting at 5%

Predictors of Cost

The relationship between the ln baseline frequency of syncopal spells and the square root of the pre pacemaker regional costs was examined with simple linear regression. Square root ransformations on both the x and y variables were necessary for the assumption of normality to be met. This non-significant relationship (p=.82) is depicted in Figure 14.

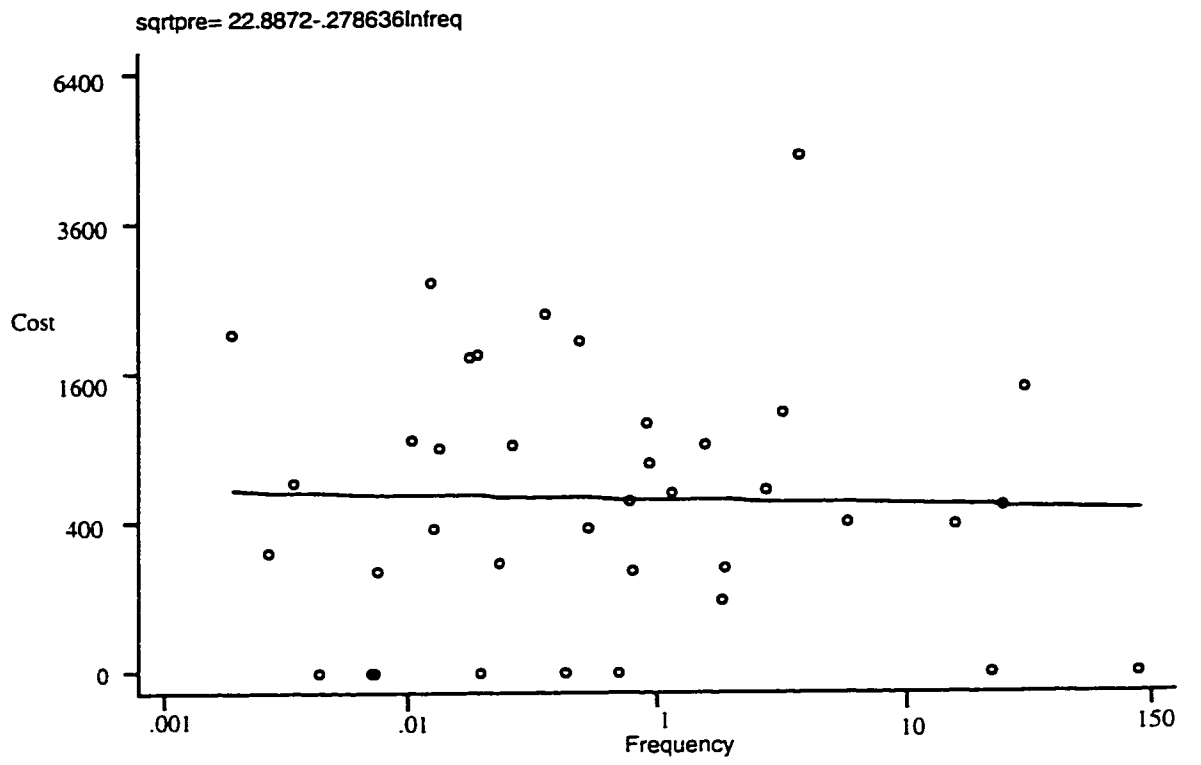

Figure 14: Scatterplot of Frequency of Syncopal Spells vs. Pre-Pacemaker Regional Costs

The relationship between ln frequency and post-pacemaker regional costs was also examined. The relationship appeared to be non-significant, but the assumption of normality for each value of the predictor variable was not met, making the interpretation of the model problematic. In summary, it was found that illness severity as measured by the frequency of syncopal spells did not significantly predict pre or post-pacemaker regional cost.

Cost Utility Analysis

The incremental QALYs and costs were derived, and are presented in Table 13. This was done by subtracting the pre-pacemaker QALYs, and pre-pacemaker costs, from the post-pacemaker QALYs and costs, respectively. The incremental QALYs and costs

were then used to derive the cost utility ratios, also shown in Table 13. These ratios indicate the amount of resources, measured in dollars, required to obtain one additional QALY. The sensitivity analysis conducted below will provide a series of ranges for each ratio.

Table 13: Calculation of Incremental QALYs and CUA

Group	Incremental QALY gained	Incremental cost	CUA
Overall	1.35	$13,422	$9942/ QALY gained
High frequency	1.83	$12,834	$7013/ QALY gained
Low frequency	1.12	$14,012	$12,511/ QALY gained

Sensitivity Analysis

Confidence Intervals

The cost and HRQL 95% upper and lower confidence interval limits were used to calculate a range of cost utility ratios. These ranges are presented in Table 14.

Table 14: Cost Utility Ratio Boundaries

Group	Cost utility ratio range
Overall	($8494, $11626)
High frequency	($5902, $8523)
Low frequency	($9688, $17208)

Additional combinations of the lower and upper confidence intervals can be used to derive further cost utility ratio boundaries. However, only these combinations are presented here, in order to gain a sense of variation which potentially could occur around the original cost utility ratios.

Treatment Effect Drop-off

25% of the sample had only one post-pacemaker HRQL score taken due to not returning to the clinic at regularly scheduled intervals. A worst case scenario was assumed that all of these subjects had a drop-off in treatment effect and required a pacemaker replacement in 2 years. The re-worked CUA, based on the increased cost in the post-pacemaker period, is presented in Table 15. It was assumed the HRQL score of these subjects returned to their pre-pacemaker levels, resulting in lower incremental QALYs gained.

Table 15: CUA Based on 25% Treatment Effect Drop-Off

Group	10 Year Post-Pace Cost	10 Year Pre-Pace Cost (unchanged)	Incremental QALYs	Re-worked CUA
Overall	$30,216	$11,982	1.04	$17,532
High frequency	$29,369	$11,723	1.36	$12,975
Low frequency	$31,063	$12,239	.72	$26,144

Physician Costs Reduced

In the initial analysis, the entire mean physician cost for each subject was modeled over the 10 year period, producing a conservative total post-pacemaker cost. Here, it was assumed that only 20% of the physician costs would be incurred for each year beyond the first year, over the 10 year modeled period. The CUA was reworked with the newly

calculated 10 year post-pacemaker costs, along with the unchanged pre-pacemaker costs and incremental QALYs. The results are presented in Table 16.

Table 16: CUA with Physician Costs Reduced

Group	10 year Post-Pace Costs	10 year Pre-Pace Costs (unchanged)	Incremental QALYs (unchanged)	Re-worked CUA
Overall	$18,034	$11,982	1.35	$4483
High frequency	$17,545	$11,723	1.83	$3181
Low frequency	$18,524	$12,239	1.12	$5612

Replacement Costs

As described in Table 17, the CUA was re-worked with the assumption first that pacemaker replacement costs were incurred by all subjects, and second that replacement costs were not incurred by any of the subjects. The incremental QALYs would, of course, not change. The post-pacemaker costs increased when the full discounted replacement costs were included, resulting in higher incremental costs than the initial analysis, and higher cost utility ratios. When replacement costs were excluded, the post-pacemaker costs were reduced, resulting in lower incremental costs then the initial analysis, and lower cost utility ratios.

Table 17: CUA with Full and No Replacement Costs

Group	Incremental QALYs	Incremental costs with full replacement	CUA with full replace costs	Incremental costs with no replacement	CUA with no replace costs
Total	1.35	$14,688	$10,880	$11,436	$8471
High frequency	1.83	$14,037	$7670	$10,848	$5923
Low frequency	1.12	$13,696	$12,229	$12,026	$10,738

Pacemaker Longevity

As the length of the pacemaker life may vary, the CUA was conducted assuming pacemaker longevity of first 8, and then 12 years. For this analysis, the total replacement cost will be applied to all subjects, making the assumption that there was no mortality over the 8 and 12 year periods. Discounting was assumed to be at 5% per year. Table 18 describes the CUA for an 8 year period, and Table 19 presents the 12 year CUA.

Table 18: Eight Year CUA

Group	Incremental QALY	Incremental Cost	8 Year CUA
Overall	1.08	$14,468	$13,396
High frequency	1.46	$13,792	$9447
Low frequency	.896	$15,145	$16,902

Table 19: Twelve Year CUA

Group	Incremental QALY	Incremental Cost	12 Year CUA
Overall	1.62	$14,889	$9191
High frequency	2.196	$14,258	$6493
Low frequency	1.344	$15,520	$11,548

Discounting

The discounting rate utilized in the calculation of the original cost utility ratios was 5%. This rate was varied between 0 and 10%, and the cost utility ratios were re-calculated. The CUA assuming 0% discounting are presented in Table 20, and the CUA with 10% discounting is found in Table 21.

Table 20: CUA with 0% Discounting

Group	Incremental QALY (unchanged)	Incremental Cost	CUA with 0% Discounting
Total	1.35	$16,070	$11,903
High frequency	1.83	$15,421	$8427
Low frequency	1.12	$16,720	$14,929

Table 21: CUA with 10% Discounting

Group	Incremental QALY (unchanged)	Incremental Cost	CUA with 10% Discounting
Total	1.35	$13,691	$10,141
High frequency	1.83	$13,107	$7162
Low frequency	1.12	$14274	$12,745

With 0% discounting, the cost utility ratios were higher than the original cost utility ratios. When 10% discounting is applied, the ratios are lower than the original ratios.

EQ-5D Derived Index

The EQ-5D derived index was available for 25 of the 38 subjects in our sample. For comparison to the cost utility analysis based on the VAS scores, an analysis was also conducted based on the derived index scores. The analysis is presented in Table 22.

Table 22: CUA with EQ-5D Index Scores

Group	Incremental QALY†	Incremental costs for the 25 subjects (post-pre costs)	CUA (incremental cost/ incremental QALY)
Total	.89	$25,927-$13,105=$12,774	$14,353
High frequency	1.11	$24,297-$13,765=$10,492	$9452
Low frequency	.77	$26,831-$12,734=$17,577	$22,827

†These values are based on the incremental index scores from Table 4.

The cost utility ratios based on the derived index score were higher than those produced in the original analysis, as the incremental QALYs gained as calculated with the derived scores were less than those in the original calculations. This resulted in smaller denominators and thus larger cost utility ratios, overall and for each of the study groups.

Summary

A summary of the various CUA which were conducted for the sensitivity analysis is presented in Table 23. For comparison, the initial base case CUA ratios are also provided.

Table 23: Summary of Initial CUA and CUA for the Sensitivity Analysis

Group	Initial CUA	Tmt Effect Drop-off	Phys Cost Reduced	Full Replace	No Replace	8 year horizon	12 year horizon	0% Discount	10% Discount	Index Score
Overall	$9942	$17,532	$4483	$10,880	$8471	$13,396	$9191	$11,903	$10,141	$14,353
High freq	$7013	$12,975	$3181	$7670	$5923	$9447	$6493	$8427	$7162	$9452
Low freq	$12,511	$26,144	$5612	$12,229	$10,738	$16,902	$11,548	$14,929	$12,745	$22,827

Overall, the CUA results were robust to variations in the assumptions, as described. In two cases, the low frequency group did have a cost utility ratio above $20,000 per QALY

gained. Although notable, there is no great cause for alarm as these results are worst case scenarios, and the $20,000 / QALY gained figure is not absolute, but rather a general guideline. Finally, the sensitivity analysis conducted here did not consider simultaneous variation of different assumptions (i.e. two way sensitivity analysis). If done, it is possible that less favorable cost utility ratios would result. However, this is unlikely due to the generally favorable ratios that did result with the sensitivity analysis that was conducted.

4. DISCUSSION

Cost Utility Analysis Results

This study found pacemaker therapy for the treatment of NMS, in comparison to conventional non-pacemaker therapy, to have a very low cost per QALY gained. This result was found in our sample overall, and for more and less severe study groups. In addition, the high frequency (i.e. more severe) study group was found to have a lower cost per QALY gained than the low frequency (i.e. less severe) study group. These results indicate that pacemaker therapy for very frequent NMS merits public funding.

In CUA, a cost utility ratio is derived which can be interpreted as the amount of resources required, measured in dollars, to produce one additional QALY. In the current study, this can be expressed as the extra cost per QALY gained for pacemaker therapy relative to the alternative conventional therapy. Laupacis et al. state that if the extra QALY gained can be reached at a cost of less $20,000, than the program or treatment should be recommended. If the cost per QALY gained is $20,000-$100,000 it has been suggested that the program should be recommended but that it must be followed closely. If the cost per QALY gained is >$100,000 than the program or treatment should not be implemented (11). Some examples of the cost utility of other treatments include GP advice to stop smoking ($600/ QALY), diet and exercise interventions in non-insulin-dependent diabetes mellitus ($12,000/ QALY), coronary artery bypass graft two-vessel disease ($32,700/ QALY), and hospital hemodialysis ($65,500/ QALY) (8, 11, 36).

As the overall cost per QALY gained of pacemaker therapy in comparison to conventional therapy in the current study was $9942, funding for pacemaker therapy clearly should be recommended. In addition, this result can be set in the context of the cost utility of treatments for other illnesses. In so doing, varying treatments within or even across programs can be compared. Through this process, the mix of treatments or services

which provide the maximal health benefit for a given set of resources can be recommended.

In addition to the overall cost utility ratio of pacemakers being very low, this result was also obtained for both the high and low frequency study groups ($7013 and $12,511 per QALY gained, respectively). These further results have two major implications. First, as both ratios were favorable, pacemaker therapy for both the more and less severe patients in our study merits public funding. Second, the cost per QALY is lower for the high frequency study group, compared to the low frequency group. This was the case not because there was a difference in cost of treatment for the two groups, but because the health benefit with pacemaker therapy was much larger for the more frequent group.

In summary, the cost per QALY gained of pacemaker therapy for NMS, overall and for the high and low frequency study groups, was very favorable. The results also indicate that the cost utility of pacemaker therapy is dependent on illness severity, as observed by the lower cost per QALY gained for the high frequency group. These results indicate that pacemaker therapy for frequent NMS is a reasonable manner in which to spend scarce resources.

Robustness of Results

Sensitivity analysis is conducted in order to determine the amount of variation that can be expected around the cost utility ratios. Uncertainty can arise in economic evaluations from both sampling error and assumptions. Numerous statistical approaches have been presented for determining a confidence interval around cost-effectiveness and cost utility ratios (9). Some of these statistical methods will be examined in future research on the current data. For the purposes of this work, one way sensitivity analysis was conducted, in that only one variable was changed at a time. While this method did not result in a full range of possible ratios, it did provide an indication of the possible variation which could be expected for the original cost utility ratios.

By using the various upper and lower 95% confidence interval limits around the mean cost and the mean EQ-5D score to form the cost utility ratios, a range of ratios resulted. In each case, even the worst scenario (i.e. the highest cost per QALY gained) still resulted in a favorable cost per QALY gained. As such, it can be concluded that the results were robust to variations in the cost and HRQL parameters based on the confidence interval limits.

Generally, the more serious threat to the validity of the conclusions in an economic evaluation is due to the use of unsubstantiated assumptions. Five major assumptions were made in this study. First, it was assumed that the treatment effect would be constant over the 10 year life of the pacemaker. Second, the entire mean physician costs were modeled over the 10 year period. Third, it was assumed that our frequent NMS sample had similar survival rates to that of the general pacemaker population at Foothills Hospital. Fourth, the pacemaker longevity was assumed to be 10 years. Fifth, future costs were discounted at 5% per year.

The assumptions made for the initial analysis were varied in the sensitivity analysis, resulting in new costs and HRQL scores. From the new costs and HRQL scores, additional cost utility ratios were derived. In each case, the ratios were not substantially different from the original cost utility ratios. Most importantly, the conclusions were robust even when it was assumed that 25% of the sample would revert to pre-pacemaker HRQL levels within 2 years. Overall, the conclusions were robust to variations of the underlying assumptions.

In addition to these variations, cost utility ratios were also derived based on the EQ-5D derived index score. This was done in order to have evidence on hand if our study was criticized on the formation of QALYs based on the measure used in the study. Again, the initial conclusions were robust, as substantial increases in the cost utility ratios were not observed.

In summary, one way sensitivity analysis was conducted for this cost utility analysis to provide evidence for the robustness of our conclusions. Overall, the initial conclusions were robust to cost utility ratios constructed based on cost and HRQL score confidence intervals, variations in underlying assumptions, and use of a second HRQL construct to form the QALYs.

Threats to Internal Validity

The major threat to internal validity with a before-and-after study design which has no control group is the possibility of spontaneous recovery if treatment was not received. As no suitable control group was available, it simply was not possible to compare the paced group to a non-paced group.

There are several ways that this threat to the validity of the study was minimized. First, this group of patients had recurrent syncope which pre-existed for a median time of 60 (30, 300) months before pacemaker insertion. Second, no patients responded positively to previous pharmacological and non-pharmacological therapy. Third, some patients had an early recurrence of syncope following tilt testing before pacemaker implantation, which strongly predicts a high frequency of syncope recurrence (37). Finally, the effect of pacemaker treatment was large, with almost all patients showing large improvements of reduced fainting frequency, and highly significant changes in HRQL ($p<.001$).

As the study was non-randomized, there was the possibility that some external factor influenced the therapeutic pathway and caused the changes in health outcomes and costs. However, no significant predictors of post-treatment HRQL were identified exept pre-treatment HRQL.

In summary, there were some threats to the internal validity of the current study. However, with the dramatic improvement in HRQL pre to post-pacemaker treatment that

was observed, and very low cost per QALY gained figures that were derived, it is unlikely that these threats could have been great enough to account for the findings.

Threats to External Validity

One threat to the external validity of the proposed study is that the patients included in this sample were a clinic referral population, and had a more severe case of NMS than the general Canadian NMS population. Thus, the generalizability to the Canadian syncope population as a whole is somewhat limited. However, it is the more severe patients who would be considered for pacing and thus it was this group that had to be targeted for the economic evaluation. Despite this, the results do indicate that the cost utility of pacemakers for NMS is dependent on illness severity. Thus, while the results are not directly generalizable to populations with less frequent NMS, they do suggest that the cost per QALY gained will be higher in groups with less frequent NMS.

Further, the pacemaker and drug therapy costs would not be expected to vary substantially across Canada. Thus, if HRQL studies are conducted in other Canadian regions, and pacemakers are shown to produce less health benefit in less frequent NMS populations, it would be likely that the cost per QALY gained would increase.

Finally, one must be cautioned in directly transferring these results to U.S. NMS populations. While similar effectiveness of pacemakers for frequent NMS groups may be observed, costs in Canada do not equal costs in the U.S. This is because in the U.S., economic costs are often measured as charges which are generally higher than the actual cost, and which are not easily translated into actual costs (38).

Effectiveness Data

HRQL and Frequency

A significant difference in EQ-5D scores pre to post-pacemaker was observed for the overall sample and for each of the study groups. This result provides further evidence for the effectiveness of pacemakers for the treatment of frequent NMS. As well, the pre to post-pacemaker incremental score was greater for the high frequency group as compared to the low frequency group. The post-pacemaker scores between the two study groups were not significantly different, although there was a tendency for the high frequency group to have a lower post-pacemaker HRQL score. These results indicate that pacemaker therapy had the greatest effect in more severely ill patients, but that those who started with a better HRQL would probably have a better HRQL post-pacemaker.

In addition to the improvement of HRQL scores, pre to post-pacemaker frequency of syncopal spells dropped dramatically. Regression analysis indicated that pre-pacemaker frequency of syncopal spells was a significant predictor of both pre and post-pacemaker HRQL. These results support previous findings of the negative relationship between frequency and HRQL in the frequent NMS population (18).

Length of Follow-up

The conclusions of this study are based on a mean±SD follow-up of 12±6.5 months. Analysis of all HRQL scores available at greater than 12 months post-pacemaker indicated a highly significant pre to post-pacemaker difference in scores. As well, there was no difference in baseline HRQL score between the subjects with post-pacemaker scores at greater than 12 months and those at less than 12 months. These results indicate that the post-pacemaker HRQL scores were stable over the length of follow-up in this study, and supported previous findings (2).

It is possible that some subjects for whom the treatment failed did not complete post-treatment HRQL tests at regular intervals, which could lead to selection bias. However, there was no difference between pre or post-pacemaker scores for subjects with only one post-pacemaker score compared to those with more than one.

These findings illustrate that regardless of when the post-pacemaker scores were taken, the overall positive effect of the pacemaker in terms of HRQL is observed. Of course, it is possible that the treatment failed in some patients, and because of the varying post-treatment data collection points, the "true" effect may not have been captured with the current design. For this reason, the sensitivity analysis allowed for treatment failure, but the conclusion of a favorable cost utility was robust.

In this study, the assumption was made that the improvement in HRQL scores would be maintained over the 10 year life of the pacemaker. At this time, it is simply not known if this assumption will be correct, but based on the evidence available, this seems likely. Long term follow-up studies are underway to assess this assumption.

Syncope Specific HRQL

In some cases, changes in HRQL pre to post-pacemaker may not have been due to changes in syncope but due to changes in other health problems. This was particularly apparent in some cases where the subject asked the research nurse if they were to record their HRQL as it relates to syncope or as it relates to their health state overall (personal communication, M. Koshman). As the EQ-5D measures the overall perception of health, the research nurse correctly informed subjects to record their HRQL overall, even if this meant that their HRQL may be decreased due to a health problem other than syncope.

Two points in defense of using a generic HRQL instrument can be made. First, as the overall perception measure of the EQ-5D likely includes syncope, and the major health problem with each subject in our sample was syncope, the major portion of change observed should be due to changes in syncope. Second, as the primary outcome variable

was change in HRQL score, if another health condition was present both before and after pacing, the change can likely be attributed to the pacemaker treatment for syncope.

Overall, these issues highlight that a syncope specific measure might be a useful tool for effectiveness studies, but not for cost utility studies. As has been done previously (29), by determining what specific factors of health may explain the impact of syncope on HRQL, a syncope specific tool could be developed. However, for cost utility analysis, a generic instrument which produces a single HRQL index is required in order to construct a QALY. Thus, despite the possibility of other health conditions effecting the HRQL score, there is currently no good alternative to the overall perception measure on generic HRQL instruments like the EQ-5D when QALYs are the primary outcome.

VAS and Derived Index

The EQ-5D HRQL instrument has two components: the 5 dimensional questionnaire and the VAS. The VAS instructions ask the individual to mark on a thermometer scale, with 0 being the worst and 100 being the best, the place which best represents their own health state at that moment. From the questionnaire component, an index score can be derived with a weighting system developed from the general public. One such commonly used weighting system is found in Dolan et al. (25), which was constructed based on a sample of the general public in the U.K. Recently, Johnson et al. produced a weighting system based on the results of a U.S. postal survey (39).

Utility is defined by CCOHTA as "the desirability of a specific level of health status or a specific health outcome" (9). It has been argued that the derived index score of the EQ-5D, based on a time trade off weighting system, is a true utility measure, whereas the VAS is a proxy utility measure (8, 27). Specifically, the VAS is not preference based and is not anchored on 0 as death. However, the VAS has been shown to be positively correlated with the index score, indicating the reliability of this component of the EQ-5D (39).

Although, in our study, as is discussed below, there was disagreement between the VAS and derived index components.

In our study, the main reason the VAS component of the EQ-5D was utilized was because all 38 patients had a pre and post-pacemaker VAS score recorded, whereas a pre and post-pacemaker derived index score was available for only 25 subjects. In using the VAS as the quality adjustment factor to derive the QALYs, it was recognized that it was a proxy to the true utility it was attempting to measure (27).

In order to determine if the two measures were in agreement, a Bland and Altman plot was utilized. The Bland and Altman plot is the correct statistical method for measuring agreement, not the correlation co-efficient which is commonly used (35). The VAS and index scores did not have good agreement pre and post-pacemaker.

A possible explanation is that the VAS and derived index are measuring HRQL in different ways. As has been reported, when VAS scores are compared to time trade off or standard gamble methods, different results arise (27). For CUA, the key point is that even if both methods are attempting to measure HRQL, the derived index, based on a time trade off or similar method, is likely a better measure of utility. Due to the lack of agreement in our sample between the two comonents of the EQ-5D, and based on the considerations stated here, it was important to conduct the CUA based on the derived index scores as well as the VAS scores.

In the sensitivity analysis, the cost utility ratios based on the derived index were higher than those based on the VAS scores, but were still favorable. Thus, although there was an indication that the CUA based on the VAS scores underestimated the cost per QALY gained, the sensitivity analysis provided evidence for the robustness of the conclusions.

Pacemaker Type

Two brands of dual chamber pacemakers with rate drop sensing were used in this study, the Thera DR and the Diamond 800. The two pacemaker groups were compared on HRQL scores and frequency of syncopal spells to determine if it was valid to combine the groups in one sample. As it was found that there was no significant difference on HRQL scores and frequency, all subjects regardless of pacemaker brand were combined in one sample. Although the Diamond patients were younger, the primary outcome was HRQL. As no difference on this variable was found, the groups were combined.

Cost Results

Cost Exclusions

Several costs were not captured with this study. First hospital costs incurred outside of Region 4 and tests which occurred in GP offices were not obtained. As the Syncope Clinic is a referral clinic, it can be expected that these additional costs would be minimal. Further, only a small number of the sample lived outside of Region 4.

Second, this study did not attempt to capture any productivity costs. These are costs associated with lost wages. It was not feasible to capture these costs with the retrospective study design. However, with the significant improvement in HRQL observed post-pacemaker in our sample, it would be expected that lost productivity costs due to missed work days would have been greater in the pre-treatment interval. As such, the cost per QALY gained would have been even lower than was observed. Thus, by not including productivity costs, the cost per QALY gained figures were very likely overestimated and that with the productivity costs included, an even better picture of pacemakers would have resulted.

In summary, although certain costs were excluded, the effects would have been minimal or would have resulted in strengthening the argument for pacemaker therapy for frequent NMS groups.

Replacement Costs

The analytic horizon chosen for this study was 10 years, the expected life of the pacemakers. Pacemaker replacement costs were included in the primary analysis, and were excluded in the sensitivity analysis. Conceptually, it is helpful to consider each pacemaker life as a cycle, with the analytic horizon of this study being one cycle. Even though costs associated with replacement pacemakers were incurred in the second cycle, their inclusion produced a higher estimate of the costs associated with pacemaker treatment of NMS. This resulted in a conservative estimate of the cost utility of pacemakers for the treatment of NMS, in comparison to conventional therapy.

From an economic perspective, it could clearly be argued that inclusion of these costs biased the results against pacemakers. Further, it could also be argued that if these costs from the second cycle were included, then all costs from the second cycle should be included, for both the pacemaker and drug groups. However, including all costs for the second cycle would be problematic as it would require modeling the data over a 20 year period, resulting in even greater uncertainty in the results. Further, as the assumptions for the second cycle are based on the same data that the first cycle are based on, the CUA modeled to 20 years would likely produce the same results as the CUA over 10 years. Thus, the ideal choice economically would be to not include pacemaker replacement costs at all. For this reason, although the initial analysis was conducted with the replacement costs included, in the sensitivity analysis these costs were removed. As was observed in Table 17, the exclusion of these costs changed the results minimally.

Future Costs

Like most economic evaluations, the major threat to the internal validity of the study is due to certain assumptions that the cost analysis is based upon. In the current study, the cost and HRQL scores were modeled to 10 years, the expected life of the pacemaker. The assumption was made that the HRQL scores would not change over this period, and that the costs, with the exception of certain "one time" costs, also would not change. The issues related to the modeling of the HRQL scores was discussed above.

The difficulty in making this assumption with the costs is that it is really not known if these patients will continue utilizing the health care system in the same manner in which they did in the year of primary data collection. Even though "one time" costs were excluded in the modeling, it is entirely possible that if the patients HRQL continued to increase, they could realistically have only minimal health care system utilization in future years. Conversely, HRQL may decrease and additional costs would be incurred in the 10 year period. These factors were varied in the sensitivity analysis, and the initial conclusions were robust.

As has been stated, certain "one time" costs were not included in the modeling. As physician costs were provided by Alberta Health in aggregate form, these costs were unable to be dissected into "one time" and expected recurrent costs. As such, the full one year pre and post-pacemaker mean physician costs were modeled over the 10 year period. As the majority of subjects in our sample had been ill for lengthy periods prior to pacemaker treatment, it is more likely that the modeling of costs in the pre-treatment interval accurately reflected the true costs over the 10 years. If the assumption holds that HRQL does not decline in the future, it is likely that including the full physician costs over the 10 year post-treatment period resulted in an overestimation of the true future costs. This means that the true incremental cost pre to post-treatment would be smaller, resulting in more favorable cost per QALY gained results. This was supported by the sensitivity analysis.

Another related issue is choosing the analytic horizon to be the life of the pacemaker or the life of the patient. A previous study interested in long term pacemaker costs chose the relevant endpoint to be the patient lifetime (31). The problem with this is that in 10 years a new treatment for NMS may be available which has greater effectiveness than pacemakers, and thus a replacement pacemaker would not even be considered. As well, with a 10 year time frame, assumptions regarding utilization based on a one year period are tenuous for 10 year modeling. If these costs need to be modeled for more than 10 years, this could lead to uncertainty which sensitivity analysis could not even account for. In summary, in our opinion, the most reasonable analytic horizon was that of the life of the pacemaker.

As the pacemaker life was chosen as the analytic horizon, the pacemaker life had to be determined. A 10 year period was chosen in part because of data provided by the pacemaker manufacturers and in part due to choosing a standard interval used in pacemaker studies. This time frame for this sample was a conservative one. As the percentage of time the pacemaker was pacing in this sample was on average only about 15%, the pacemakers in our sample may last up to 15 years. Thus, in choosing a conservative pacemaker life, the cost utility ratios again potentially overestimate the true cost utility ratios.

Alberta Health Data

The data on physician costs were obtained from Alberta Health on an aggregate level. That is, the cost data was provided for the sample overall, and for each study group, but not for each patient individually. In order to get data on an individual level, informed consent from each subject was required. This would have been difficult to obtain with the retrospective sample, and some subjects may not have wanted to release their cost data. However, in hindsight, attempting to gain consent from each individual, thereby enabling access to cost data on an individual level, may have been useful.

There would have been several advantages to having the physician cost data on an individual level. First, there would not have been a need to make an arbitrary split to create

two study groups based on the median pre-pacemaker frequency of syncopal spells. Second, the relationship between the regional cost data and the physician data could have been examined. Research in this area could potentially lead to the development of regression models which would enable physician costs to be predicted from regional data. Third, because the physician data was not on an individual level, when costs were modeled over the 10 year periods, there was no way to remove the "one time" physician costs (only regional "one time" costs were removed in our study). Thus, in particular for the 10 year post-pacemaker period, an overestimation of physician costs likely resulted. Further, the individual regional data was examined and those hospital stays and procedures which were deemed to be not related to syncope were not included in the analysis. With the physician data this was not possible, and thus again there was likely an overestimation of the physician costs, as the costs which were provided from Alberta Health undoubtedly included some physician billings that were not related to syncope.

Imputation Methods

As described in the Methods section, in-province patients who did not have physician costs for the full one year post-pacemaker interval, and those out of province patients who had no physician costs available at all, were still included in the analysis. This was because the mean physician costs for the study group that the subject was in was applied to that subject. This was an approximation, and although not ideal, large scale variations from the true physician costs for these individuals was unlikely. This is because the physician costs were only one component of the overall costs pre and post-pacemaker, and relatively few subjects were not included in the physician cost data provided by Alberta Health.

Ideally, a regression model with various illness history and HRQL variables would have been developed to predict physician costs. As physician costs were not available on an individual level, this was not possible. Further, when these variables were used to develop

a multiple regression model to predict overall costs, no significant predictors were found. This is probably because the overall costs were composed of the physician grouped data. As individual regional data was available, another option would have been to determine the regional costs for these patients and then to compare each subject's cost to the mean regional cost. From the variation from the mean of the regional costs, the variation from the physician costs could have been imputed. However, this method was not utilized as it relied on the assumption that regional costs were related to physician costs. Although this would be an interesting project for future research, at this time this assumption is not substantiated.

Regression Analysis

Several regression models were developed to determine if significant predictors of HRQL and costs could be identified. First, ln frequency of syncopal spells was found to significantly predict HRQL. This result had been found previously (18). No other significant predictors of HRQL were identified with simple linear regression except age. When age was added to the model including ln frequency, both were found to significantly predict HRQL. This should not be surprising, for as people age their quality of life decreases.

Second, a simple linear regression model was developed to determine if ln frequency of syncopal spells predicted cost. The non-significant relationship between frequency and pre-pacemaker regional costs was surprising, as intuitively it would make sense that more severe cases would utilize the health care system more and thus would be expected to have incurred increased costs. However, the major component of the regional costs was the cost of the pacemaker and hospitalization costs associated with the pacemaker implantation, which were relatively constant for all subjects in the sample, regardless of illness severity. Thus, any variation in costs overall, if present, were likely "masked" by

the pacemaker cost and associated implantation costs. An interesting future study would be to look at all utilization costs except those costs associated with the pacemaker and pacemaker implant, for a larger sample, to determine if illness does in fact predict cost.

Benefits of the Study Design

There are several benefits to carrying out this study with retrospective data. First, all of the data pertaining to the illness itself (i.e. frequency of spells, HRQL measurements etc.) was previously collected and was available for this study. As such, only the information pertaining to the costs had to be collected. This enabled the study objectives to be reached in a timely and feasible manner. Second, although the study is not randomized, the pre-treatment to post-treatment analysis occurred within the same patients. Thus, unless the lives of subjects change in some drastic way other than having received pacemaker therapy, it was surmised that the effects observed (changes in costs and health outcomes) were due to the pacemaker intervention. Of course, this illustrates the importance of randomized trials. Third, the study was not subject to recall biases as all of the data was obtained from records and administrative databases.

Ethical Considerations

No individual patient consent was required for this study. Dr. E. Burgess from the Department of Bioethics, Faculty of Medicine, stated individual consent was not required for several reasons (personal communication, E. Burgess). First, the data was collected retrospectively from patient hospital charts with no patient contact. Second, one of the co-investigators in this study, Dr. Robert Sheldon, was the cardiologist of each patient in the sample. The principal investigator was viewed as an agent acting on the behalf of Dr. Sheldon in obtaining the information in the charts for the cost analysis. Third, Dr. Burgess

stated that there was no reason why a patient would object to this information being released. Alberta Health stated they would release the required billing information in group form, with no individual identifiers attached to the data, without individual patient consent as long as approval from the University Ethics Board was obtained (personal communication, T. Fedoriw).

As this study had no patient contact, there was no burden on the patients. As well, there was no potential for subject harm as the study was based entirely on previously collected data and on records. The privacy and confidentiality of all patients involved in the study was maintained, and no individual patient names were attached to any published or presented material related to this study.

General Cost Utility Ratio Considerations

A key point regarding cost utility ratios, and in general cost-effectiveness ratios, is often overlooked in economic evaluations. This is that no recommendation for funding should ever be made solely on the basis of a single calculation. It is not appropriate for a decision maker in a Regional Health Authority or hospital to simple allocate funding to a particular treatment or service on the basis of a single ratio. This is not to take away from the importance of micro-economic, evidence based evaluations. But rather to emphasize that issues such as illness prevalence must also be taken into consideration when funding is considered. This point is highlighted by Caro et al. in stating that an activity with an unfavorable ratio may be worth doing if it occurs rarely (40). In addition, morbidity and mortality rates are important considerations which must also be included in deciding to increase or decrease funding in particular areas.

Further, these issues must also be put into the context of the local health care system. Dependent on particular health care lobbyist or political agendas, despite sound evidence from economic evaluations, a treatment or service still may not receive public

funding. Finally, provincial or national emphases regarding health care direction also play a part in allocation decisions.

Thus, an important realization when presenting cost utility ratios is that there are many things on which funding decisions in health care are based, only one of which is the result of a particular CUA. Methods are currently being undertaken to use ratios calculated in economic evaluations in a supportive rather than singular manner in the decision making process (40). These issues highlight that more work is required on how cost utility and cost effectiveness ratios are to be used, and certainly imply that uninformed hospital or regional decision makers should not allocate funding on the sole basis of a cost utility ratio.

Future Studies

Three major areas for future research were identified from the current research. First, as already discussed, longer term follow-up on NMS patients is underway to determine the long term effect of cardiac pacing on HRQL and cost. As HRQL scores are continuing to be taken from the patients in the current sample, longer term HRQL data will be available. Cost data could be collected at a future point, and used in conjunction with the HRQL data to conduct another cost utility analysis. This would provide great insight into the longer term effects and cost utility of pacing frequent NMS patients.

Second, cost and effectiveness literature on the treatment of other heart conditions should be reviewed. Where applicable, these additional studies could be utilized to determine, along with the current study, the mix of services which would provide the most health benefit for the resources available. This could occur first within the cardiology program at Foothills Hospital, with the potential for the results to be generalized to other Calgary and Canadian hospitals. This type of research is the natural outflow from micro economic evaluations like the current study. As mentioned above, a cost utility ratio provides evidence pertaining to the costs and health benefits of a particular treatment in

comparison to another treatment. By then using these results in the broader context of treatments and services provided within or across programs, decision makers have the potential to make evidence based decisions leading to maximal health benefits for available resources.

Third, in the current study, traditional sensitivity analysis was used to determine the uncertainty of the cost utility ratios. Recently, different statistical techniques which can be applied to capture this uncertainty have been discussed (41-43). Such methods include probabilistic Monte Carlo simulations, the Taylor series, and non-parametric bootstrapping. With the data from the current study, such statistical methods could be compared to the sensitivity analysis conducted in this study. This would provide evidence as to which methods are best able to describe the uncertainty of cost utility ratios.

Conclusions

In conclusion, pacemaker therapy for frequent NMS is a highly effective treatment with a very favorable cost per QALY gained, in comparison to conventional non-pacemaker therapy. Cost utility analysis indicated the cost per QALY gained to be $9942 for the overall sample, and $7013 and $12,511 for the high and low frequency study groups, respectively. These results were tested with sensitivity analysis and the results were robust. The difference between the study groups suggested that the cost utility of pacemakers is more favorable for more severely ill NMS patients, but funding for pacemaker therapy should be recommended for both study groups in this sample. Further work is required to determine the long term HRQL and cost implications of pacemaker therapy for NMS. As well, this study can be used in conjunction with other studies to determine the mix of services within a cardiology program which will maximize the health benefits for the given resources. Based on the results in this study, we conclude that dual chamber cardiac pacemaker therapy for frequent NMS merits public funding.

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Appendix A: Pre-pacemaker therapy

Table 25: Pre-Pacemaker Therapy

ID#	Meds - dose - schedule[†]
1	Inderal 60mg po tid Atenolol 50mg po OD Atenolol 100mg po OD Pindolol 5mg po bid Sudafed 60mg po bid Sertraline 50mg po qam
2	Amatine 5mg tid Amatine 10mg OD Zoloft 50mg
3	Imitrex prn Tylenol #3 prn
4	- no meds
5	Dilantin 100mg 5OD Tegretol 200mg 5OD Rhythmodan LA 750mg po bid Sudafed 15mg po tid Sandomigran .5mg po tid Midodrine 2.5mg po tid Zoloft 50mg OD Zoloft 50mg bid Zoloft 50mg qid Metoprolol 50mg Disopyramide 250mg po bid Scopolamine 1g
6	Tylenol #3 prn
7	Zoloft 50mg OD Florinef .1mg po OD Pseudoephrine 120mg qid Atenolol 25mg po bid Atenolol 75mg OD Sertraline 50mg OD
8	Sertraline 50mg OD pseudoephedrine 180mg OD
9	Naprasine 250mg qid
10	Pseudoephedrine 180mg OD Tegretol 200mg 5OD Dilantin 100mg 5OD Epival 500mg AM/PM; 250mg noon Disopyramide 100mg po qid Disopyramide 250mg po bid
11	- no meds

12	Dilantin 100mg AM; 200 mg PM Mysoline 125mg tid Entrophen 325mg OD Lasix 40mg BD Paxil 20MG BD Slowk 600mg OD Plendil 2.5mg bid Tylenol #3 1 tab q4h Calcium 500mg qh Lanoxin .125mg OD Clamozipam .5mg OD
13	- no meds
14	Metoprolol 50mg po bid Disopyramide 250mg po bid Scopolamine Verapamil 80mg po tid Verapamil 120mg po tid Verapamil 160mg po tid Sudafed 15mg po tid Clonadine 50ug qid Sandomigran .5mg qhs Fluoxetine 20mg OD Andixoret 25ug po bid
15	- no meds
16	- no meds
17	Propranolol 120mg OD Florinef 100mg bid Norpace CR - 150mg tid Metoprolol 50mg bid Metoprolol 100mg bid Amatine 2.5mg bid
18	- no meds
19	Amatine 2.5mg tid Florinef .1mg OD Inderal LA 60mg OD Inderal LA 60mg bid
20	Inderal 20mg OD
21	Pindolol 5mg po bid Acebutolol 100mg bid Sertraline 50mg OD Nadolol 80mg OD Zoloft 50mg OD
22	Inderal 40mg po bid Rythmodan LA 500mg bid Hytrin 1mg OD Synthroid 50ug OD Prozac 20mg po OD Zantac 300mg po OD Eltroxin 50ug po OD
23	Inderal 60mg OD
24	- no meds

25	Florinef .1mg OD NaCl 1g po tid
26	Imovane 7.5mg OD
27	NaCl 1g tid
28	- no meds
29	Atenolol 25mg po bid Tenorim 50mg OD Atenolol 25mg po bid Atenolol 75mg OD
30	Vaotec 5mg OD Moduret 1 tab OD
31	Atrovent 250ug/ puff bid prn Becolvent 50ug/ puff bid prn Ventolin 100ug/ puff bid prn
32	Lipidil Micro 200mg OD Hytrin 1mg OD Arthrotec 1tab OD ASA 325mg OD Metroprolol 50mg po bid Isoptin 180mg OD Verapamil 120mg
33	Metoprolol 50mg po bid Lozide 2.5mg po OD
34	Eltroxin .1mg OD Losec 2mg Zantac 300mg
35	Lozide 2.5mg OD Adalat XL 30mg OD
36	Premarin .9mg OD Diclofenac 50mg bid Ranitidine 150mg bid Amitriptylline 75mg OD Folic Acid 1mg OD Atenolol 25mg OD Atenolol 50mg OD Hydroxychloroquine 400mg OD Prednisone 5mg bid Voltaren 100mg bid Tylenol #3 - 3 tabs OD Elavil tid 12.5mg Plaquenil 200mg bid Zantac 300mg Sulcrate 1g bid Isoproterenol 120ug/ puff
37	- no meds

38	Fenofibrate 200mg bid Niacin 1g bid Losec 20mg qam Eltroxin 150ug OD EC ASA 325mg OD Nicotinamide 1.5g qid Lipidil 200mg Metoprolol 100mg bid

†The following abbreviations are used: po - oral administration; OD - once daily; bid - twice daily; tid - three times daily; qid - four times daily; qam - once in the morning

Appendix B: HRQL EQ-5D measurment tool

Please indicate which statement best describes your own health state today by placing a checkmark in one box for each group below. 90

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 with washing or dressing myself
- I am unable to wash or dress myself

Usual Activities

- I have no problems with performing my usual activities (e.g. work, study, housework, family or leisure 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

Compared with my general level of health over the past 12 months, my health state today is:

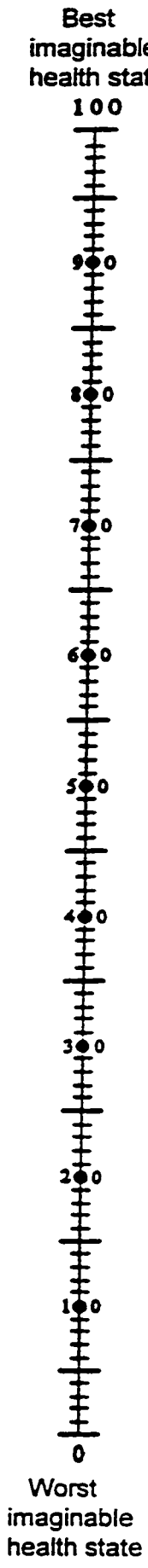
PLEASE CHECK ONE BOX

- Better
- Much the same
- Worse

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

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

Your own health state today



Appendix C: Resource units and unit value costs

Description of resource units and unit value costs for each activity or service category recorded from the hospital & clinic records, Corporate Data databases, and from Alberta Health.

Table 26: Resource Units and Unit Value Costs by Activity or Service Category

Category	*Source of Information*	*Resource Unit*	*$ Value*
Inpatient Care	Corporate Data	weighted case or weighted day	cost per weighted case or weighted day
Day Surgery	Corporate Data	weighted case	cost per weighted case
Outpatient Visits - Clinic (including phys component, excluding labs/xrays)	Syncope Clinic	visits physician services	cost per clinic visit physician fee
Outpatient Visits - Emergency	Corporate Data	same as clinic	same as clinic
Phys & Other Prof Services	AB health, Syncope Clinic, Corporate Data	services	fee for service
Lab, Rad, Diag Tests	Syncope Clinic, Corporate Data	services	cost per service
Devices	Syncope Clinic, Hospitals	device	retail
Medication	Syncope Clinic, Hospitals	prescription	national average

Appendix D: Analytic horizon and modeling

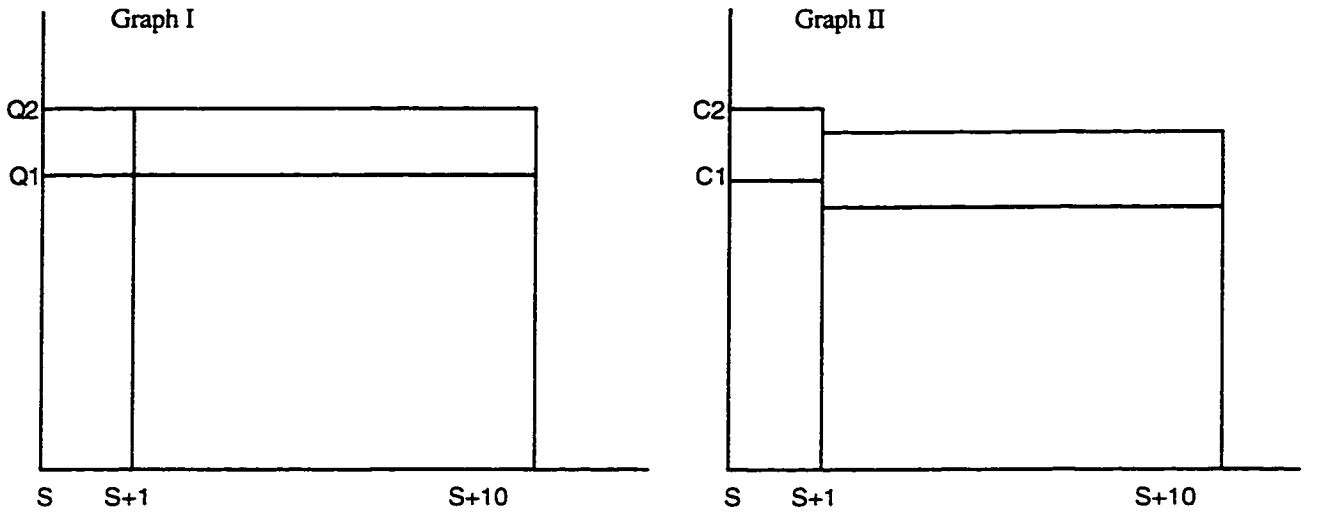


Figure 15: Analytic Horizon and Modeling

Q1=HRQL EQ-5D score in pre-treatment interval
Q2=HRQL EQ-5D score in post-treatment interval

C1=direct costs in pre-treatment interval
C2=direct costs in post-treatment interval

S=time marking the start of each interval
S+1=time marking the end of primary data collection
S+10=time marking 10 years after start of each interval

Graph I depicts the assumption that the HRQL scores measured in each primary data collection 12 month interval will not change for the proceeding 9 years.

Graph II indicates that costs after the first year will drop due to exclusion of diagnostic and tilt table testing costs for C1 and exclusion of pacemaker surgery and related "one time costs" for C2. Assumption is made that other than exclusions, costs will remain constant.

Both pre-treatment and post-treatment intervals are modelled to extend to 10 years; cost utility analysis will be performed with the resulting 10 year data. The 10 year analytic horizon was chosen as this is the minimum expected life of the pacemaker and leads. Sensitivity analysis will be conducted to account for possible variations in these assumptions.

Appendix D cont.

Modelling 12 month intervals to derive a 10 year average cost per patient for pre-treatment and post-treatment intervals.

1. (Mean cost of one year post-treatment interval) + (mean cost of discounted year two)+(mean cost of discounted year three)+...+ (mean cost of discounted year 10) = 10 year modelled post-treatment cost

2. (Mean cost of one year pre-treatment interval) + (mean cost of discounted year two) + (mean cost of discounted year three) +...+ (mean cost of discounted year 10) = 10 year modelled pre-treatment cost

Appendix E: Clinic Record Data Collection Sheet

Table 27: Data Collection Sheet for Syncope Clinic Records

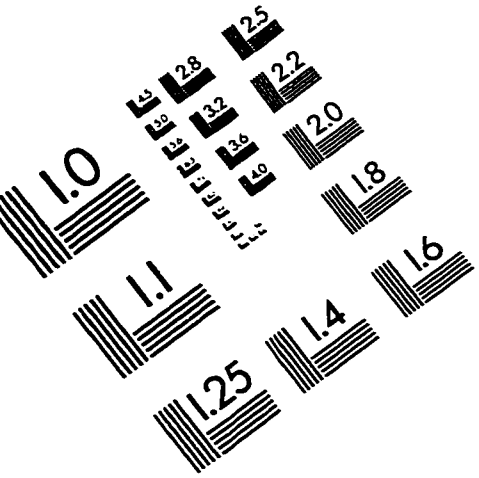
ID#	Pre-tmt interval:_____ Post-tmt interval:_____
Pacemaker:	Atrial Lead:_____ Vent Lead:_____
Pre-pace drugs: Start Finish Med/ Dose Schedule - - - - - - - - -	# of mg's taken in pre-pace interval: # of days Daily Dose Subtotal - - - - - - - - -
Pre-clinic visits: Date - -	Post-clinic visits: Date - -
Pre-treatment diagnostic tests - -	Post-treatment one time tests (including pace) - -

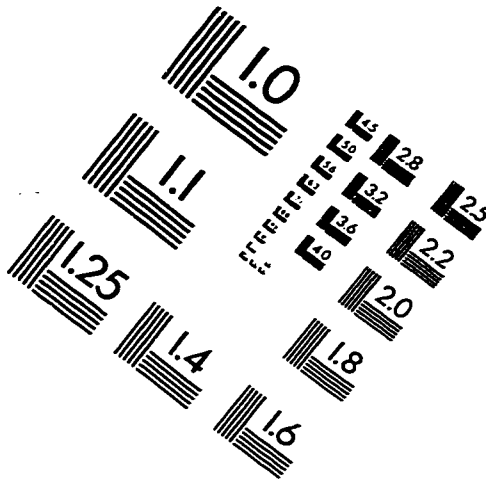
Appendix F: Schedule for Discounting of Future Costs

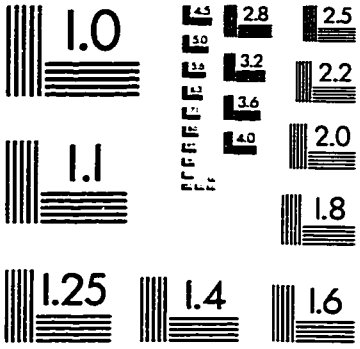
Table 28: Discounting Costs (at 5% per year)

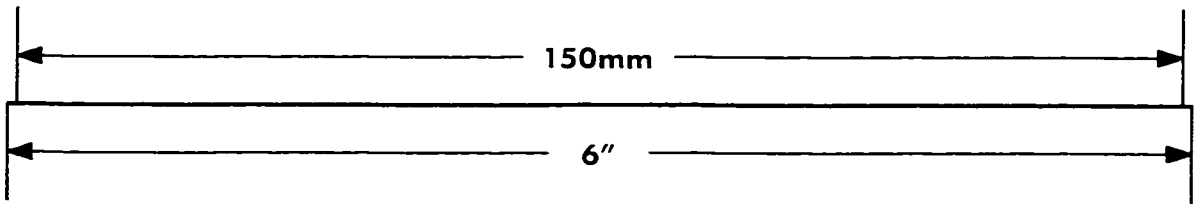
Year	0-1	2	3	4	5	6	7	8	9	10
Discount	(1.05)	$(1.05)^2$	$(1.05)^3$	$(1.05)^4$	$(1.05)^5$	$(1.05)^6$	$(1.05)^7$	$(1.05)^8$	$(1.05)^9$	$(1.05)^{10}$
Cost/yr	$x	$x	$x	$x	$x	$x	$x	$x	$x	$x
Calc.	$\frac{\$x}{(1.05)}$	$\frac{\$x}{(1.05)^2}$	$\frac{\$x}{(1.05)^3}$	$\frac{\$x}{(1.05)^4}$	$\frac{\$x}{(1.05)^5}$	$\frac{\$x}{(1.05)^6}$	$\frac{\$x}{(1.05)^7}$	$\frac{\$x}{(1.05)^8}$	$\frac{\$x}{(1.05)^9}$	$\frac{\$x}{(1.05)^{10}}$

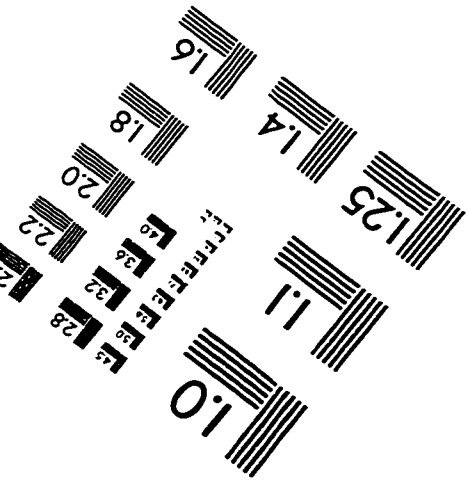
IMAGE EVALUATION TEST TARGET (QA-3)

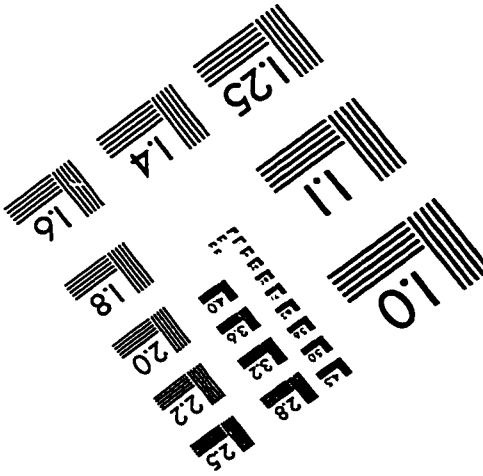












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