Policy Analysis of the Continuous Subcutaneous Insulin Infusion – Access With Evidence Development Scheme in Alberta: A Cost Effectiveness, Value of Information and SWOT Analysis

by

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Abstract

Health systems aim to maximize patient access to health technologies on a fixed budget. Reimbursement decisions are increasingly complex and need to capture perspectives of multiple stakeholders. Decision makers must weight different types of evidence, much of which involves significant uncertainty. On May 30, 2013, Alberta Health announced the availability of continuous subcutaneous insulin infusion (CSII) for Alberta residents with type 1 diabetes mellitus (T1DM). At the time of announcement, evidence had shown that CSII is neither clearly inferior nor clearly superior to multiple daily injections (MDI) for the treatment of T1DM. Given the uncertainty surrounding CSII, an access with evidence development (AED) scheme was funded to gather the information needed to inform a definitive reimbursement decision.

Using a continuous subcutaneous insulin infusion case study (CSII) compared with multiple daily injections (MDI), this thesis has three objectives: (1) to examine the role of cost effectiveness analysis (CEA) in reducing value for money uncertainties of CSII, (2) to explore the role of value of information analysis in decision making and whether or not delaying a decision to employ CSII and collecting more information will resolve decision uncertainty and (3) to examine the strengths and weaknesses of an access with evidence development scheme that addresses uncertainties surrounding government funded implementation of CSII in Alberta.

CSII requires ongoing pump maintenance, the purchase of equipment and supplies, and incurs more ongoing cost that MDI. Although there are benefits to CSII, the cost is greater than the cost of MDI. Given the uncertainty surrounding CSII, it would be worthwhile to collect additional information on the quality adjusted life years associated with CSII and the effectiveness of CSII in reducing severe hypoglycemic events. The implementation of CSII

under an AED scheme allows decision makers to (1) meet patient demand through managed entry, (2) improved patient safety and (3) control public funds.

The use of AED schemes reflects pressures for increasing accountability, transparency, and timeliness of decision making. The trend toward conditional coverage suggest a growing need for conditional approval and integration of data collection into coverage and reimbursement schemes. Access with evidence development schemes have the potential to alter the reimbursement landscape for health technologies.

Dedication

For my late parents, Patricia Kan Sum Lau and Chiu Fu Lau, thank you for the support that I needed to build a dream to chase after. Thank you for believing that I have the talent to reach my goals. Thank you for all the love and encouragement.

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List of Abbreviations

AACHT	Alberta Advisory Committee on Health Technologies
ADSS	Alberta Diabetes Surveillance System
AED	Access with Evidence Development
AH	Alberta Health
AHS	Alberta Health Services
CADTH	Canadian Agency for Drugs and Technologies in Health
CDM	Core Diabetes Model
CEA	cost effectiveness analysis
CEAC	cost effectiveness acceptability curve
CI	confidence interval
CORE	Centre for Outcomes Research
CSII	continuous subcutaneous insulin infusion
DKA	diabetic ketoacidosis
ENBS	expected net benefit of sampling
EQ-5D-5L	EuroQol
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
EVSI	expected value of sample information
HAAF	hypoglycemia-assisted autonomic failure
HTA	health technology assessment
HUI3	Health Utilities Index Mark 3
ICER	incremental cost effectiveness ratio

IDF	International Diabetes Federation
IIT	intensive insulin therapy
IPT	insulin pump therapy
MC	Monte Carlo
MDI	multiple daily injections
NHB	net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
NSHE	nonsevere hypoglycemic event
QALY	quality adjusted life year
SA	sensitivity analysis
SE	standard error
SHE	severe hypoglycemic event
SWOT	strengths weaknesses opportunities threats
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
VOI	value of information

Chapter 1: Introductory Chapter

1.1 Introduction

The rapid development of new technologies, the establishment of regulatory approval processes that facilitate early access to innovative therapies, and the need to capture perspectives from multiple stakeholders, has made reimbursement decisions increasingly complex. Reimbursement authorities strive to maximize patient access to new health technologies, but must operate within limited budgets. Their decisions are often binary – a technology is either funded or it is not funded. Decision makers must weigh different types of evidence, much of which involves significant uncertainty. As a result, there is interest in approaches to reduce that uncertainty through the use of innovative decision options.

Attempts to develop such approaches have largely focused on frameworks and models that break a complex decision problem into parts. Examples are economic evaluations and value of information analysis, which rely on mathematical models comprised of several variables and explore uncertainties through sensitivity analyses [1]. However, at some point, those pieces need to be put back together to make a decision. This requires consideration of other factors (e.g., organizational priorities, system capacity, stakeholder perspectives, and broader societal values), each of which might contribute to additional decision uncertainty. Thus, there is interest in decision options that take account of such uncertainties and provide ways of addressing them. One example is access with evidence development (AED). In Alberta, Canada, an AED scheme was initiated by Alberta Health (AH) to address the uncertainties in the value of certain health technologies. Continuous subcutaneous insulin infusion (CSII) is the first health technology funded under the AED scheme.

An existing report reviewing CSII [2] identified three main areas of uncertainty: (1) safety and health effectiveness, (2) cost-effectiveness, and (3) system/resources required [3]. The

AED involved a decision to fund CSII for a fixed time period while the evidence is collected to reduce such uncertainties. Uncertainties related to the effectiveness and efficiency of the technology, the budget for providing the technology, and practice and implementation of the technology [4].

The number and complexity of uncertainties to be reduced in an AED scheme might require significant research resources to be employed before it can be determined whether an investment is worthwhile. Is there enough evidence for a definitive funding decision? Is further research worthwhile? Which uncertainties should be pursued for further research? The goal of this dissertation is to investigate AED schemes operating in a real-world organizational decision making context, that is, the introduction of a government reimbursed program of CSII and its uncertainties.

1.2 Research Objectives: Continuous Insulin Infusion in Alberta

This case study has three objectives:

(1) To examine the role of cost effectiveness analyses in reducing the "value for money" uncertainties of CSII. The cost effectiveness analysis will establish \

   a. whether CSII demonstrates a greater monetary value than multiple daily injections (MDI) for Albertans with type 1 diabetes mellitus (T1DM).
   b. the economic impact of CSII technology analyzed from the perspective of
      i. the health payer to capture direct health costs associated with use of the technology
      ii. society to capture direct and indirect costs associated with the use of the technology.

(2) To explore the potential role of value of information (VOI) analysis in decision making. The VOI analysis will establish whether or not delaying a decision to employ CSII and collecting more information resolve decision uncertainty. The following will be explored:

   a. the value of research: if further research is worthwhile, which uncertainties should become research priorities?

   b. the value of pursuing research.

(3) To examine the strengths and weaknesses of an AED scheme that addresses uncertainties surrounding the government funded implementation of CSII in Alberta, and to suggest potential improvements to future AED schemes.

1.3 Summary of Thesis Format

The thesis is organized in paper format. Chapters 2, 3, and 4 are separate manuscripts that address the three objectives of the case study. Chapter 2 compares the cost effectiveness of CSII and MDI. Chapter 3 is a VOI analysis of CSII compared to MDI. Chapter 4 is a strengths, weaknesses, opportunities, and threats (SWOT) analysis of AED schemes that addresses evidence gaps in costs and health benefits of CSII in Alberta. In chapter 5 the research presented in chapters 2 through 4 is summarized, and conclusions are drawn regarding the research questions.

Chapter 2: Cost Effectiveness of Continuous Subcutaneous Insulin Infusion (CSII) compared with Multiple Daily Injections (MDI) for Type 1 Diabetes Mellitus

2.1 Introduction

On May 30, 2013, Alberta Health (AH) announced the availability of insulin pump therapy (IPT), also known as continuous subcutaneous insulin infusion (CSII) therapy, for Alberta residents with type 1 diabetes mellitus (T1DM) who meet eligibility and clinical requirements (see Appendix A for eligibility criteria for children and adolescents to be started on CSII; see Appendix B for a list of indications for CSII for adults with T1DM) [5, 6]. The program provides funding for the cost of the insulin pump and supplies. To enroll, patients must (1) obtain a referral to the program from a physician or nurse practitioner, (2) participate in a pre-pump information session, and (3) have a clinical assessment completed at a participating clinic. In Alberta, the two main reasons for the launch of CSII were to decrease hypoglycemic episodes and improve hypoglycemia awareness (see Appendix C).

At the time of the announcement of the program, evidence had shown that CSII is neither clearly inferior nor clearly superior to multiple daily injections (MDI) for the treatment of T1DM, but that there may be some benefits in terms of decreased hemoglobin A1c (HbA1c) and decreased insulin dosage[1] [7-15] in T1DM patients. Given the uncertainty surrounding the value of CSII, the Alberta Advisory Committee on Health Technologies (AACHT) decided through the Alberta Health Technologies Decision Process that T1DM patients would benefit from further research concerning the real world effectiveness of CSII, and an access with evidence development (AED) scheme was funded to gather the information needed to inform a definitive reimbursement decision. Based on an existing report reviewing IPT [2], three main areas of uncertainty were identified: (1) safety and health effectiveness, (2) cost-effectiveness, and (3)

[1] Due to increased insulin sensitivity.

system/resources required [3]. CSII is the first health technology to be funded under an AED scheme in Alberta.

Study Questions

Study questions related to the areas of uncertainty were: (1) What is the effectiveness of CSII to reduce severe hypoglycemic events in T1DM patients? (2) What are the costs associated with CSII compared with MDI (gold standard) in Alberta? (3) Does CSII demonstrate a greater monetary value than MDI for Albertans with T1DM? The economic impact of CSII technology was analyzed from the perspective of the health payer to capture direct costs and health care costs associated with the technology and from the perspective of society to capture direct and indirect costs (productivity losses) associated with the use of the technology.

Objectives of the Study

This paper focuses on Question 3 above. It reports on two analyses.

1) CSII and MDI were compared regarding their safety and health effectiveness (quality adjusted life years) using existing evidence.
2) CSII and MDI were compared regarding their cost effectiveness, using Markov models

2.2 Background

Type 1 Diabetes Mellitus (T1DM)

T1DM is an autoimmune destruction of the insulin producing β-cells in the pancreas caused primarily by T-cell mediated pancreatic islet β-cell destruction. T1DM results in deficient insulin production [16]. The subsequent reduction or lack of insulin in the body results in an inability to regulate blood sugars and an increase in blood and urine glucose (hyperglycemia). T1DM becomes clinically symptomatic when approximately 90% of the pancreatic β-cells are

destroyed or fail to produce insulin [17]. T1DM causes polyuria, polydipsia, blurring of vision, weight loss, and in its most severe form, ketoacidosis, which can lead to stupor, coma, and death [16]. Long term complications related to untreated or improperly managed diabetes include retinopathy, neuropathy, and microvascular diseases that cause visual impairment, renal failure, and hypertension, pain, paraesthesiae, muscle weakness, and autonomic dysfunction, cardiac disease, peripheral vascular disease, and stroke [18]. T1DM continues to be a major cause of morbidity and mortality [19] and is the most common chronic disease among children and adolescents, comprising approximately 90% of childhood and adolescent diabetes cases [16]. More than half of the individuals with T1DM are diagnosed before 15 years of age [16]. However, the long-life course, the decreased quality of life, the monetary and nonmonetary lifetime burden, and the absence of interventions to prevent or delay this disease, warrant an increased attention to T1DM.

Management of T1DM and Iatrogenic Hypoglycemia

Once diagnosis of T1DM is established, the initial focus is on glycemic management and restoring euglycemia[2] through insulin therapy and on teaching the patient and the family the skills necessary to regulate the patient's blood sugar levels. Three basic objectives of insulin therapy are: (1) facilitate metabolism and storage of consumed food, (2) normalize hyperglycemia, and (3) maintain euglycemia during fasting [20]. The ultimate goal of glycemic management is to maintain euglycemia without hypoglycemia [21]. However, a common drawback to insulin regimens, which seek to tightly control blood sugars, is iatrogenic hypoglycemia [22, 23].

[2] Euglycemia – normal concentration (70–100 mg/dL) of glucose in the blood, also known as normoglycemia.

Hypoglycemia is characterized by abnormally low blood glucose and is a complex interplay of insulin levels and a compromised physiological defense against falling plasma glucose [21]. Occasional insulin excess is due to the result of pharmacokinetic imperfections of insulin preparations used in the context of food intake, exercise, drug interactions, altered sensitivity to insulin, and insulin clearance to regulate blood sugars [21]. Falling plasma glucose levels combined with pathophysiological impairment[3] results in a loss of warning symptoms or hypoglycemia unawareness, where the patient is unable to recognize hypoglycemia and take corrective action [21]. Frequent hypoglycemic events reduce glucose levels, and that leads to a counter-regulatory response to restore euglycemia and results in hypoglycemia-assisted autonomic failure (HAAF) [21, 24]. Frequent hypoglycemic episodes are a major barrier to the effective management of T1DM.

Thresholds for symptoms of hypoglycemia shift to lower plasma glucose concentrations after a recent hypoglycemic episode and to higher plasma glucose concentrations in patients with poorly controlled diabetes and infrequent hypoglycemia and a single threshold value for plasma glucose concentration that defines hypoglycemia in diabetes cannot be assigned [24]. Often, hypoglycemia is inconsistently defined in the literature due to a lack of a single threshold value. An alert value of ≤ 70 mg/dL (≤ 3.9 mmol/L) is suggested to bring attention to the possibility of developing hypoglycemia and to take corrective action. Therefore, the goal of new health technologies (drugs, devices, or disease management strategies) for glycemic management is to improve both glycemic control and to reduce the frequency and severity of hypoglycemia [21].

Optimal glycemic control is often challenging in different age groups (infants, children, adolescents, adults). In infants and children, challenges include insulin dosing issues, variable

[3] (1) insulin levels not decreasing, (2) glucagon levels not increasing, and (3) epinephrine increase being attenuated.

eating patterns, erratic physical activity, limited ability to detect hypoglycemia, and communication difficulties [24]. In adolescents, glycemic control is complicated by insulin resistance and the hormonal and psychosocial changes associated with puberty [24]. In adults, glycemic control can be influenced by lifestyle factors, such as diet, exercise, and interpersonal relationships, and may be associated with a decreased quality of life.

Subcutaneous injection of insulin is the basic therapy for T1DM, and a wide range of insulin formulations and regimens exist. Intensive insulin therapy (IIT) to attain a near a normal blood glucose range[4] has been shown to delay and slow the onset of microvascular complications [23, 25], and persistent efforts of intensive insulin therapy (IIT) to attain a near normal glycemic concentration have extended benefits over time in delaying the progression of diabetic nephropathy [26, 27] and retinopathy [26]. Currently, two strategies exist in the management of T1DM, MDI (the gold standard) and CSII. CSII requires the purchase of equipment and has higher maintenance costs compared with MDI. Regardless of the strategy, successful management of T1DM requires effective diabetes and nutritional education, insulin replacement therapy, blood glucose monitoring, nutritional planning, physical activity, a psychological adjustment of the whole family, and care teams that include doctors, nurses, pharmacists, dietitians, and diabetes educators.

Multiple Daily Injections (MDI)

MDI consists of three or more insulin injections each day. Injection may consists of long acting basal insulin and a rapid acting prandial insulin formulation. A glycated hemoglobin test (HbA1c) reveals the average blood sugar level over the past 2–3 months. The goal is to achieve an HbA1c < 7% to lower the risk of developing microvascular complications. However,

[4] Preprandial glucose concentration between 70 and 120 mg/dL (3.9 and 6.7 mmol/L), postprandial concentrations of < 180 mg/dL (10 mmol/L), and a HbA1c measured monthly within the normal range (< 6.05%).

glycemic targets should be individualized based on the patient's age, the duration of diabetes, the risk of severe hypoglycemia, the life expectancy of the patient, and the presence or absence of cardiovascular disease [28]. The goal of maintaining the blood glucose in a normal range must be balanced with the risk of hypoglycemia [28]. Therefore, MDI protocols depend on patient discipline, skill, and adherence, and require continuing education, dietary management, instruction on insulin delivery and blood glucose monitoring, emotional and behavioral support, and access to expertise in diabetes care. The MDI protocol combined with frequent blood glucose monitoring, carbohydrate counting, and an insulin dose (determined using an insulin-to-carbohydrate ratio) that allows for flexible food choice are the conditions that comprise the gold standard for intensive T1DM management.

Continuous Subcutaneous Insulin Infusion (CSII)

CSII, or IPT, is a pseudo-physiologic method of insulin dosing that allows for more flexibility and precision in glycemic control than multiple daily injections. CSII continually infuses (at a basal rate) rapid acting insulin into the skin, and a bolus dose of insulin programmed by the user is delivered at meal times to counteract an increased glycemic load. Additional bolus doses can be used to correct high blood glucose levels [20]. Most insulin pumps consist of a pump, a disposable insulin reservoir, and a disposable infusion set (including the tubing that connects the cannula to pump and reservoir) [20]. The current generation insulin pumps allow a user to calculate an appropriate bolus dose according to the number of carbohydrates consumed and a correction factor based on the user's insulin:carbohydrate ratio [20]. In addition, the pump mathematically estimates the amount of active insulin in circulation at the time of bolus dose administration [20]. Potential but infrequent complications to the CSII technology include adverse reactions and infections in the cannula site, tube blockage, pump malfunction (depleted

batteries, electrical or mechanical malfunction, and problems with the insulin reservoir, blockage in the insulin infusion set tubs) [2]. Severe hyperglycemia or diabetic ketoacidosis are likely to occur if the pump is malfunctioning or when insulin infusion is interrupted [2].

The potential advantages of CSII over MDI are: (1) greater convenience of insulin administration, (2) less variability in blood glucose and insulin levels, and (3) an opportunity to vary the rate of insulin infusion (the pump can be programmed during the basal period as well as around meals) [2]. Successful CSII requires and depends on the same patient factors (discipline, skill, adherence, access to diabetes professionals) as MDI. In addition, CSII requires ongoing pump maintenance, the purchase of equipment and supplies, and incurs more ongoing cost than MDI. Although there are benefits to CSII, the cost is greater than the cost of MDI [29, 30].

Currently, there are no standard patient eligibility requirements for intensive insulin therapy in Alberta and it is difficult to estimate how many people would take advantage of CSII [2].

Funding Coverage of CSII in Canada

In Canada, funding coverage is variable for different age groups [31], with varying age requirements across provinces for the use of (a) a CSII pump and (b) CSII supplies.

Province	Insulin Pumps[5]	Pump Supplies
British Columbia	25 and under	All ages
Alberta	All ages	All ages
Saskatchewan	25 and under	17 and under
Manitoba	17 and under	17 and under
Ontario	All ages	All ages

[5] As of March 1, 2015

Quebec	18 and under	18 and under
New Brunswick	18 and under	18 and under
Nova Scotia	19 and under	25 and under
Prince Edward Island	25 and under	19 and under
Newfoundland	All ages	All ages
Yukon/NWT/Nunavut	All ages	All ages

Incidence and Prevalence of T1DM in Canada and Alberta

The Alberta Diabetes Surveillance System (ADSS) has estimated that there are approximately 8193 to 16,385 Albertans living with T1DM[6] [2]. In 2013, the International Diabetes Federation (IDF) Diabetes Atlas estimated that the incidence rate of T1DM in Canadian youth 0–14 years of age was 25.9 per 100,000 [32] and that the T1DM incidence increased at rates of 14.7, 24.0, and 26.3 per 100,000 for 0–4 year olds, 5–9 year olds, and 10–14 year olds, respectively [2].

Economic Costs Associated with Type 1 Diabetes

The economic burden of diabetes (T1DM and T2DM combined) in Canada is expected to rise from $12.2 billion in 2010 to $16.9 billion in 2020, with the direct costs of diabetes accounting for 3.5% of public health care spending; this trend is expected to increase as the prevalence of diabetes continues to rise [33]. T2DM accounts for 90–95% of diabetes cases. The significant difference in economic costs of type 1 and type 2 diabetes is hidden when such costs are combined. The economic burden per case of diabetes is greater and the per capita use of

[6] The Alberta Diabetes Surveillance System does not differentiate between type 1 and type 2 diabetes; the estimated number of individuals with type 1 diabetes ranges from 5% to 10% of all individuals with diabetes.

health care services is higher for T1DM than for T2DM [34]. Medical costs increase faster for T1DM patients than for T2DM patients [34]; T1DM patients are diagnosed at an earlier age and therefore live longer with the disease, which puts them at a higher risk of microvascular and macrovascular complications and results in increased utilization of health care services compared T2DM (which is usually diagnosed after 40 years of age) [34, 35]. Diabetes complications account for 80% of diabetes costs in Canada [36].

Burden of Out of Pocket Costs and Funding Coverage of CSII in Canada

Managing diabetes places a large financial burden on individuals with diabetes and their families. The inability to afford medical devices and medical supplies may result in noncompliance with diabetes therapy, compromising diabetes management and increasing the risk of costly and life threatening diabetes complications (heart attack, stroke, blindness, kidney failure, and depression) and mortality [37-39]. Fifty seven percent (57%) of Canadians with diabetes report that they do not adhere to their prescribed therapy because they cannot afford the prescribed medication, devices, and medical supplies [37]. The burden of out of pocket expenses varies across Canada; out of pocket expenses are especially burdensome for low income Canadians and those without adequate insurance coverage [37].

Canadians with T1DM who utilize an insulin pump face higher out of pocket costs than T2DM patients and T1DM patients who do not use an insulin pump [37]. The high cost of diabetes devices and supplies may result in technologies being inaccessible to Canadians with low income [37]. A coordinated response from health care providers, government, the insurance industry, and patient advocacy groups is essential to ensure that care for patients with type 1 diabetes is not compromised because of financial constraints.

2.3 Research Design and Methods

The ultimate goal of glycemic management in T1DM patients is to maintain euglycemia without hypoglycemia [21]; therefore the economic model that reflects the objective of optimal glycemic management – reduction in the rate of hypoglycemic and diabetic ketoacidosis events – was considered to be appropriate to the reimbursement decision of CSII technology in Alberta. To investigate the cost effectiveness of CSII compared to MDI, and to aid such decision making in Alberta, a cost utility analysis utilizing a Markov model was performed.

Time Horizon and Perspective

The time horizon for the cost analysis is assumed to be five years which is the lifetime of the CSII pump. To capture costs to the health care system and society, a health payer perspective and a societal perspective were investigated.

Markov Model

The Markov model consists of two health states: well and dead. A number of short term transitions can occur in the well state, including a nonsevere hypoglycemic event (NSHE), a severe hypoglycemic event (SHE), and the development of diabetic ketoacidosis (DKA). Severe hypoglycemic events and diabetic ketoacidosis have two outcomes: recover (return to being well) and die (Figure 1). The effectiveness of therapy was measured using quality adjusted life years (QALYs).

Health Payer Perspective (Alberta Health Services/Alberta Health)

In the primary cost utility analysis, performed from a health payer perspective, only direct costs to the health care funder (Alberta Health Services/Alberta Health) were included (Table 3). Short-term transitions that can occur from the health payer perspective include (1) severe hypoglycemic events (SHE) and (2) diabetic ketoacidosis (Figure 1). The cost of the

pump, insulin, and pump supplies for the estimated life span of the pump (5 years) and the direct medical costs of (1) severe hypoglycemic events and (2) diabetic ketoacidosis events are included (Table 3; Table 5). Monthly cycles were used to model the frequency of hypoglycemia and diabetic ketoacidosis events for the time horizon of the pump therapy.

The decision tree for the cost effectiveness analysis from the health payer perspective is presented in Figure 2. The branches for MDI and CSII are identical, but the transition probabilities differ.

Societal Perspective

A secondary cost utility analysis including direct costs and indirect costs was performed from the societal perspective (Figure 3, Figure 4, Table 3). Indirect costs include productivity losses due to nonsevere hypoglycemic events (NSHE) and severe hypoglycemic events (SHE) (Table 3). From the health payer perspective, short-term transitions include: (1) nonsevere hypoglycemic events, (2) severe hypoglycemic events, and (3) diabetic ketoacidosis. The costs of the pump, insulin, and pump supplies for the estimated life span of the pump, and the direct medical costs of severe hypoglycemic events and diabetic ketoacidosis events were included in the cost utility analysis. Lost productivity resulting from nonsevere hypoglycemic and severe hypoglycemic events was taken into account in indirect costs. Monthly cycles were used to model the frequency of hypoglycemia and diabetic ketoacidosis events during the time horizon of the pump therapy.

The decision tree for the cost effectiveness analysis from the societal perspective is presented in Figure 4. The branches for MDI and CSII are identical, but the transition probabilities differ.

Effectiveness, Rates, Transition Probabilities, Quality Adjusted Life Years, Costs

Transition Probabilities

Transition rates[7] to and from various health states were obtained from a literature review [7-15]. These were discussed with health professionals, including doctors, nurses, pharmacists, dietitians, and diabetes educators to ensure they are relevant to the Alberta situation.

Yearly transition rates (events per person per year) were converted to monthly transition probabilities[8] based on the following formula:

$$p = 1-\exp(-rt), \quad (1)$$

where p is the probability, r is the rate, and t is the time period of interest [40].

A probability can be converted back to a rate with the following formula:

$$r = -[\ln(1-p)]/t, \quad (2)$$

where p is the probability, r is the rate, and t is the time period of interest [40].

Direct Costs and Indirect Costs

Data on the cost of the CSII pump and CSII accessories and consumables (lancets, test strips, etc.) were drawn from the Alberta Blue Cross Insulin Pump Therapy Program Monthly Product Utilization Report [41]. Indirect costs associated with nonsevere hypoglycemic events (NSHE) and severe hypoglycemic events (SHE) were drawn from literature [42, 43].

Health Care Utilization

The proportion of patients with T1DM utilizing paramedic services, emergency room services, and hospital inpatient health services was obtained from the Alberta IPT study.

[7] A rate is defined as the "instantaneous potential for the occurrence of an event, expressed as the number of patients at risk in a given period of time."
[8] Probabilities are a "number ranging from 0 to 1, that represents the likelihood of an event happening over a specific period of time."

Quality Adjusted Life Years (QALYs)

The main outcome for the Markov model was quality adjusted life years (QALYs) derived from the Alberta IPT Study.

Estimation of Cost Effectiveness

Costs incurred and quality adjusted life years were estimated for the CSII and MDI arms over the lifetime of the CSII pump. For CSII and MDI, 10,000 Monte Carlo simulations were performed to identify the distribution of costs, the cost effectiveness and to enable the calculation of standard deviations, confidence intervals, probability that the interventions are cost-effective, and the proportion of the population for whom the technology is cost effective. Incremental costs and benefits were used to calculate the incremental cost effectiveness ratio (ICER):

$$ICER = (cost_{csii} - cost_{mdi}) / (QALY_{csii} - QALY_{mdi}), \quad (3)$$

where $cost_{csii}$ and $cost_{mdi}$ are the costs of CSII and MDI, respectively, and $QALY_{csii}$ and $QALY_{mdi}$ are the quality adjusted life years of CSII and MDI, respectively.

Discounting to Allow for Differential Timing of Therapy Costs and Health Consequences

Decision makers need to compare programs at one point in time (usually the present); however, program costs and consequences do not usually occur in one time period or the same time period, but over a set time horizon [44]. “Time discounting” is the current relative valuation placed on receiving a good (or a service) at an earlier date compared with receiving it at a later date.

In health care, time discounting has been applied to the costs of treatment and the health consequences of programs [45]; for example, screening programs have immediate costs, however, the benefits of the screening may not be recognized until a later date. The appropriate

rate of time discounting is controversial and is continuously debated when applied to health outcomes.

For the sensitivity analysis, a discount rate (base case scenario) of 5% was applied to costs and health outcomes as recommended by CADTH guidelines [46]. The discount rate was varied in the sensitivity analysis at 0% and 3% as recommended in the CADTH guidelines [46].

Sensitivity Analyses

One-Way Sensitivity Analysis

A one-way sensitivity analysis was conducted using best and worst case values of each relevant model parameter to identify parameters that influence the ICER. The best and worst case values were drawn from the literature review on mortality and incidence rates of hypoglycemic and diabetic ketoacidosis events (Table 2), costs of a CSII pump and CSII supplies (Table 3), and the patient's health related quality of life (Table 4).

Probabilistic Sensitivity Analysis

Since cost analysis models require certain assumptions about the inputs, there is inherent uncertainty around the true parameters (costs, consequences, and health outcomes) of health technologies. Therefore, Monte Carlo simulations were used to understand the impact of the uncertainty around the incremental costs and incremental benefits from a cost effectiveness analysis by providing a range of estimates. The first step in the Monte Carlo simulation is the assignment of probability distributions (e.g., gamma, beta, normal, binomial, uniform, etc.) to model parameters. The simulation is accomplished by drawing a random sample from the predetermined probability distributions and recording the outputs from the model cost and health benefit [29].

Gamma Distribution for Treatment Costs and Hypoglycemic and Diabeic Ketoacidosis Events

Since treatment costs and hypoglycemic and diabetic ketoacidosis events are distributed around a nonzero mean with a low probability of incurring high costs or high rates of events, the gamma distribution was utilized. It is a nonsymmetric distribution that is skewed to the right, with most of the area located near the origin, with a long right tail [47].

The method of moments approach was used derive the gamma distribution parameters, α and β, and can be calculated using the following formulas [40]:

$$\alpha=\mu^2 s^2 \quad (4)$$

$$\beta=s^2/\mu \quad (5)$$

Beta Distribution for Proportion of Patients Admitted (as outpatient or inpatient into a emergency room and assisted by family/colleagues)

The proportion of patients admitted: as an outpatient, as an inpatient, into an emergency room and assisted by family/colleagues is bounded between 0 and 1, the beta probability distribution was used. The beta probability distribution is a two-parameter density function defined over the interval $0 \leq y \leq 1$, and is often used to model proportions [47].

The method of moments approach was used derive the beta distribution parameters, α and β, and can be calculated using the following formulas [40]:

$$\alpha=\mu(\alpha+\beta) \quad (6)$$

$$\beta=\alpha(1-\mu)/\mu \quad (7)$$

2.4 Results

Literature on the Mortality and Incidence Rates of Hypoglycemic and Diabetic Ketoacidosis Events (Table 2)

Incidence of Hypoglycemic Events

Hypoglycemic events are often categorized into severe and mild hypoglycemic events. A severe hypoglycemia event (SHE) is an event that requires the assistance of another person to administer carbohydrates and/or glucagon, or to deploy other corrective action to restore blood glucose to normal. A nonsevere hypoglycemic event (NSHE) is an event that does not require assistance from another person; the NHSE is self-manageable.

Cohort studies in adults 17–75 years of age have shown that NSHE events range from 29 to 42.89 per person year [48-50] and severe hypoglycemic events range from 0.12 to 3.20 events per person year [49-53] (Table 2). The major risk factors for severe hypoglycemia in adult patients with T1DM include a previous episode of severe hypoglycemia, hypoglycemia awareness, a long duration of diabetes, and autonomic neuropathy. Adolescents, and preschool children are also at risk for severe hypoglycemic events as they are unable to detect and/or treat mild hypoglycemia on their own [54].

Incidence of Diabetic Ketoacidosis

Diabetic ketoacidosis is an episode of hyperglycemia or ketoacidosis leading to an emergency department visit or a hospital admission [55]. Cohort studies of children and adolescents [51, 53, 55] have shown that incidence rates of diabetic ketoacidosis range from 2.7 to 9 episodes per 100 person years (Table 2). Risk factors for diabetes ketoacidosis include increasing age, higher glycated hemoglobin levels, higher reported insulin doses, and the presence of psychiatric disorders [55].

Mortality Rates of Severe Hypoglycemic and Diabetic Ketoacidosis

Severe hypoglycemia mortality rates range from 0.02 to 0.33[9] events per 1000 person years and diabetic ketoacidosis mortality rates range from 0.12 to 0.28 events per 1000 person years (Table 2) [29, 56-58]. The incidence rate of hypoglycemia is higher than the incidence rate of diabetic ketoacidosis. However, diabetic ketoacidosis is associated with a higher rate of mortality [55]. The model parameters were adjusted to reflect this trend.

Obtaining Standard Errors From Confidence Intervals

Authors who reported hypoglycemic event (nonsevere and severe) rates, diabetic ketoacidosis (DKA) rates, and hypoglycemia and DKA mortality rates [29, 56-58] did not report the standard errors required to calculate the probability distribution for the Monte Carlo simulations, however, 95% confidence intervals were reported. Standard errors (SE) were calculated from the 95% confidence intervals using the following formula:

$$SE = (\text{upper 95\% CI limit} - \text{lower 95\% CI limit})/3.92. \qquad (8)$$

For 90% confidence intervals the SE was divided by 3.92; for 99% confidence intervals the SE was divided by 5.15.

Where confidence intervals and standard errors were not reported, assumptions were made about plausible standard errors and reported in the results section (Table 6).

Literature on the Effectiveness of Continuous Subcutaneous Insulin Infusion Compared to Multiple Daily Injections

Studies have shown that CSII results (HbA1c, rates of hypoglycemia, rates of diabetic ketoacidosis) range from no effect to some effect depending on patient characteristics and

[9] 0.33 deaths due to severe hypoglycemia per 1000 person years was drawn from the Scuffham and Carr (2003) article. The study assumed 7 deaths in 21000 person years. The study did not separate severe hypoglycemic deaths and diabetic ketoacidosis deaths (Muhlhauser et al. 2000), and the reported mortality rate is likely to be above average.

behavior, the existence of support groups, and the health resources infrastructure. Table 1 contains a summary of 10 published systematic reviews and meta-analyses that compared CSII to MDI in different age groups with respect to clinical outcomes such as glycemic control (HbA1c), hypoglycemic events, insulin requirements, diabetic ketoacidosis, adverse events, and discontinuation rates. Three studies [8, 9, 15] focused on an adult population, two studies [7, 12] focused on children, adolescents, and young adults, two studies [11, 59] focused on pregnant women, and three studies [10, 13, 14] focused on individuals of all ages with T1DM.

Summary of findings

Children, Adolescents, and Young Adults

Compared to MDI, CSII was associated with significant improvement in HbA1c and reduced insulin dosage (Table 1) [7, 12]. Pankowska et al. (2009) [12] found no difference in incidence of hypoglycemia in children, adolescents, and young adults, and Churchill et al. (2009) [7] found a decreasing trend of hypoglycemia in young children (1 to 6 years of age) treated with CSII.

Adults

Two studies [8, 9] (Table 1) showed that CSII was associated with significant improvements in HbA1c when compared to MDI; a third study [15] found no significant difference in HbA1c between CSII and MDI. In addition, CSII was effective at a lower total daily insulin dose than MDI [9, 15]. All three studies [8, 9, 15] reported no significant difference in the number of hypoglycemic events between CSII and MDI.

Pregnant women

There was no significant difference between CSII and MDI in HbA1c, hypoglycemic risk, and reduction of insulin dose in the two studies of pregnant women [11, 59] (Table 1).

All ages

CSII was associated with a reduction in HbA1c and a reduction in total daily insulin dose when compared with MDI [10, 13, 14] (Table 1). Pickup et al. (2002) [13] found that CSII was associated with a lower insulin dose, less variation in blood glucose concentration, and a decrease in severe hypoglycemic events when compared with MDI (Table 1). Monami et al. (2010) [10] found no significant difference in the rates of severe hypoglycemic events between CSII and MDI treatment groups (Table 1).

Systematic reviews and meta-analyses comparing CSII with MDI showed that a difference in the frequency of hypoglycemic events was ambiguous. This could be due to inconsistent definitions of hypoglycemia [7, 9], short trial durations [12], inconsistent reports of hypoglycemia [10], and missing data [9], all of which result in the inability to capture long term health outcomes of CSII and MDI. Currently, the only conclusive evidence in favor of CSII over MDI is CSII's ability to reduce the mean level of glycated hemoglobin and to achieve glycemic control with reduced insulin usage in adolescents and adults. However, the long-term health benefits of such a small reduction in glycated hemoglobin with CSII treatment compared to MDI treatment is unknown. The effects of CSII on the rates of hypoglycemic events remain inconclusive.

Reduction in Hypoglycemic Events

CSII is associated with a reduction in hypoglycemic events. Boland et al. (1999) [60] reported a 50% reduction in severe hypoglycemic events compared to MDI and Hoogma et al. (2006) [61] reported a 11%[10] reduction in mild hypoglycemic events and a 60%[11] reduction in severe hypoglycemic events compared to MDI. However, CSII's ability to reduce hypoglycemic

[10] MDI: 55.4 events per patient year; CSII: 49.3 events per patient year
[11] MDI: 0.5 events per patient year; CSII: 0.2 events per patient year

events compared to MDI remains inconclusive, due to inconsistent definitions of hypoglycemia, short trial duration, and small sample sizes [9].

After consulting with local clinical experts, it was decided that for the cost effectiveness analysis, the model would assume CSII is associated with a 30% risk reduction of hypoglycemic (SHE and NSHE) events compared to MDI.

Reduction in Diabetic Ketoacidosis.

Studies by Boland et al. (1999) and Bode et al. (2002) [60, 62], reported a 100%[12] increase and a 66%[13] reduction compared to MDI, respectively. After consulting with local clinical experts, it was decided that evidence that CSII reduces DKA events is insufficient. Therefore, in the analytic model, it is assumed that CSII is not associated with a reduction in diabetic ketoacidosis events.

Reduction in Insulin Usage

CSII is associated with lower daily insulin requirements than MDI. In a systematic review of 14 studies by Jeitler et al. (2008) reporting total insulin requirements, 12 studies reported lower insulin doses in CSII treated patients compared to MDI treated patients; 7 studies reported a statistically significant reduction in daily insulin requirements with CSII compared to MDI [9]. In a meta-analysis by Pankowska et al. (2008) [12], CSII was associated with a 15 to 22% reduction in insulin requirements compared to MDI. CSII was associated with a 14% reduction in insulin requirements compared to MDI in a 12-month cohort study [60].

The cost of insulin is not covered for MDI patients enrolled in the IPT program and therefore there is no cost to the health payer. For the cost effective analysis, the model assumed

[12] MDI: 1 event per 100 patient years; CSII: 2 events per 100 patient years.
[13] MDI: 0.1 events per 100 patient years; CSII: 0.01 events per 100 patient years for adults

an identical insulin dosage in CSII and MDI, and therefore no cost savings to the health payer from decreased insulin usage in CSII compared with MDI.

Direct and Indirect Costs Associated with CSII and Hypoglycemic Events

Direct Costs

The price of a new CSII pump is $6577.88[14] (Table 3). The monthly average cost of consumables per claimant was found to be $916.02 for new pump users and $765.18 for existing CSII pump users, with the total average cost – for all pump users – being $845.43 (Table 3). The cost of MDI consumables was assumed to be zero because the health payer (Alberta Health) does not pay for supplies for MDI patients.

Insulin usage[15] for CSII patients was found to cost $332.60 for new pump users and $182.71 for existing pump users, with the total average cost for new and existing pump users being $266.07. Direct health care costs were drawn from an Alberta IPT study. The costs used in the model for (1) a severe hypoglycemic event requiring outpatient visit, (2) a severe hypoglycemic event resulting in an emergency room visit, (3) a severe hypoglycemic event resulting in an inpatient visit, and (4) a diabetic ketoacidosis event were assumed to be $179.89, $392.68, $4995.81, and $4995.81, respectively (Table 5); a diabetic ketoacidosis event was assumed to cost the same amount as an SHE that resulted in a hospital inpatient visit.

Indirect Costs

Type 1 Diabetes and Productivity Loss

Hypoglycemic events carry costs to health care systems and to a society, resulting in additional health care spending, a lower quality of life, and a loss of productivity in that society [42, 43, 63-65]. A survey by Brod et al. (2011) [42] of 713 T1DM patients in four countries

[14] As of December 2015 in Canadian dollars.
[15] Insulin usage for CSII patients were excluded from the model. The costs of insulin are not covered.

(USA, UK, Germany, France) found that 51.4% of the patients had "daily to about one hypoglycemic event per week," 27.1% had "one hypoglycemic event per month" to "several hypoglycemic events per month," and 21.7 % reported having a hypoglycemic event "a few times per year to very rarely." Concerning the productivity losses in diabetes patients (T1DM and T2DM) following a nonsevere hypoglycemic event (NSHE) during working hours, the authors found that 18.3% missed work for an average of 9.9 hours per month. Of diabetes (type 1 and type 2) patients that experienced a NSHE outside of work, 22.7% arrived late for work or missed the full day. Lost productivity following a NSHE was estimated to be $15.26 to $93.47[16] per NSHE, or 8.3 to 15.9 hours of lost work per month.

A literature review (Foos et al. 2015) [43] of the costs (direct and indirect) of hypoglycemia in T1DM and T2DM patients in the United States estimated that direct medical costs associated with severe and nonsevere hypoglycemic events were $1161[17] per severe hypoglycemic event and $66[18] (type 1) and $11 (type 2) per nonsevere hypoglycemic event. The indirect costs (productivity losses) associated with (1) a severe hypoglycemic event requiring nonmedical assistance, (2) a severe hypoglycemic event requiring medical assistance, and (3) a non-severe hypoglycemic event were estimated to be $242, $160, and $11 for patients with T1DM and $579, $176, and $11[19,20] for patients with T2DM.

For the cost effective analysis, the productivity loss associated with an NSHE was assumed to be $75.00. Severe hypoglycemic events requiring medical assistance and severe hypoglycemic events requiring nonmedical assistance were estimated to cost $242.00 and

[16] Estimated using the Human Capital Method [61, 63].
[17] 2012 USD.
[18] Methodological differences resulted in varying numbers. Foos et el. (2015) performed a literature review, while Brod et al. (2011) calculated productivity losses from a survey administered to patients, and assessed the impact of NSHEs.
[19] 2012 USD.
[20] Estimated using the Human Capital Method (HCM).

$160.00 dollars, respectively [43]. To determine the total indirect costs associated with productivity losses caused by NSHEs and SHEs, the numbers of NSHEs and the number of SHEs were multiplied by their respective productivity losses.

Health Care Utilization

From the Alberta IPT study, the proportion of T1DM patients utilizing paramedic services, emergency room services, and hospital inpatient health services was found to be 76%, 3%, and 0.5%, respectively; the remaining 20.5% of patients with T1DM were assumed to be assisted by family and colleagues (Table 7). To determine the costs accrued by the utilization of health care services, health care utilization costs (by service type) were calculated by multiplying the proportion of SHE events by their respective health care (utilization) costs.

Continuous Subcutaneous Insulin Infusion (CSII) and Quality of Life

CSII is associated with a better health related quality of life (HRQL) than MDI. Lukacs et al. (2013) reported significant differences between CSII and MDI groups in both child self-reported and parent proxy reported HRQL. Youth using CSII reported higher scores in emotional functioning, and physical functioning, and better school functioning than youth using MDI [66]. In addition, youths using CSII worry less about the efficiency of the medical treatment and the long term complications [66]. Patients using CSII had higher levels of treatment satisfaction, higher levels of autonomy in diabetes management, and lower levels of daily activity interferences than patients using MDI [51, 67].

As part of the Alberta IPT study, data on the HRQL from T1DM patients with and without the pump were collected using EQ-5D-5L and HUI3 surveys. Surveys were administered every three months; one year of HRQL data were analyzed. The EQ-5D survey reported CSII pump users had a QALY of 0.88875 and nonpump users (who used MDI) had a QALY of

0.83875. The HUI3 survey revealed that CSII pump users had a QALY of 0.82375 and that nonpump users (who used MDI) had a QALY of 0.70000. CSII therapy was associated with a 0.05 and a 0.1238 QALY improvement over nonpump users (who used MDI), according to EQ-5D and HUI3 surveys, respectively (Table 4).

For the cost effective analysis, the Markov model assumed that MDI is associated with a 6.0% worse quality of life compared with CSII. To obtain crude utility weights for calculating QALYs, the CSII group will be indexed to an HRQL of 1.0 (1.0 = full health and 0.0 = dead), and the MDI group esd indexed to an HRQL of 0.94. Monthly HRQL values were obtained by dividing the yearly QALY by 12 months.

A monthly disutility weight associated with a severe hypoglycemic event or a diabetic ketoacidosis event was drawn from a study by Scuffham and Carr (2003) [29] and assumed to be 0.067 (SE 0.023).

Cost Effectiveness Analysis Results - Health Payer Perspective

The ICER was calculated using equation 3 (Eq. 3), with cost and outcomes inputs obtained from Tables 2, 3, and 4. For the simulated 10,000 cases over five years, the mean cost per QALY (baseline) for CSII compared to MDI was $123,041. CSII was estimated to cost an average of $53,095.21 (SD $5,292.12; range: $36,361.91, $76,135.96) per patient, where $44,953.45 (SD $5,261.25; range: $27,786.35, $68,460.12) was for pump consumables, and $1,349.70 (SD $537.75; range $112.72, $4,300.23) was attributable to a diabetic ketoacidosis episode requring hospital inpatient services, or a severe hypoglycemic event requiring paramedic, emergency room, or hospital inpatient services (Table 8). Patients using CSII could expect to have 3.95 QALYs (SD 0.25; range; 2.301, 4.38) (Table 8).

MDI was estimated to cost $1,538.96 (SD $574.48; range: $173.94, $4,580.89) per patient (Table 8). The costs accrued in the MDI were attributable to diabetic ketoacidosis episodes requiring hospital inpatient services or severe hypoglycemic events requiring paramedic services, emergency room services, or hospital inpatient services. MDI patients could expect to have 3.53 QALYs (SD 0.32; range 1.81, 4.25) (Table 8).

CSII was estimated to cost an additional $51,566.25 (SD $5,264.72; range: $34,449.47, $75,313.27) per patient compared with MDI (Table 8). CSII was associated with decreased health care utilization with an average cost savings of $179.26 (SD $144.19; range: $0.77, $1,459.57) and CSII was associated with 0.41 more QALYs (SD 0.17; range: 0.04, 1.48) compared with MDI. The QALYs gained by CSII resulted from an improved quality of life. CSII was more expensive and associated with an increased quality of life compared to MDI in all cases (Figure 5).

Cost Effectiveness Analysis Results – Societal Perspective

Indirect costs

For the simulated 10,000 cases over five years, the mean cost per QALY (ICER) from the societal perspective for CSII compared to MDI was $122,155. The indirect costs due to lost productivity from NSHEs and SHEs requiring medical and nonmedical assistance were calculated and CSII was associated with $3,695.74 (SD $1,310.10; range: $531.17, $10,611.48) of lost productivity, whereas MDI were associated with $3,989.47 (SD $1,332.75; range: $880.30, $11,085.49) of lost productivity. CSII saved on average $293.73 (SD $273.28, range: $-516.27, $3,481.14) of lost productivity compared with MDI (Table 8).

Sensitivity Analysis

A one-way sensitivity analysis identified three dominant factors in the comparison of CSII and MDI: (1) additional utility from CSII compared to MDI, (2) the rate of SHE, and (3) the effectiveness of CSII compared to MDI (to reduce the number of severe hypoglycemic events (Table 9: Figure 7, Figure 8). The large ICER ranges were a result of HRQL gains from CSII compared to MDI. First, additional utility generated from CSII produced the most obvious and direct effect on the ICER through an improved quality of life compared to MDI. Second, a high rate of hypoglycemic events (e.g., 3.2 SHEs per person-year) resulted in large QALY gains, from CSII, reducing the number of SHEs (and the avoidance of disutility from SHEs). Reduction in SHEs was also achieved through increased effectiveness of CSII, which resulted in a higher HRQL compared to MDI (Table 9). A time horizon of 10 years for CSII reduced the ICER from the baseline ICERs of $123,041 and $122,155 to $115,970 and $115,046 for the health payer and societal perspectives, respectively (Table 9: Figure 7, Figure 8).

Discount Rate

The discount rate had an effect on both costs and health outcomes (Table 9). A zero discount rate for health outcomes produced ICERs of $108,973 per QALY and $108,153 per QALY from health payer and societal perspectives, respectively. A 3% discount rate for health outcomes produced ICERs of $117,360 per QALY and $116,477 per QALY from health payer and societal perspectives, respectively. Varying the discount rates for costs increased the ICER from baseline. A zero discount rate for costs produced ICERs of $136,911 per QALY and $135,866 per QALY from health payer and societal perspectives, respectively. A 3% discount rate for health outcomes produced ICERs of $128,424 per QALY and $127,272 per QALY from health payer and societal perspectives, respectively. Figure 9 shows the effects of the discount

rates on cost effectiveness acceptability curves (CEACs) and the probability that CSII is cost effective from a health payer perspective.

2.5 Discussion

The results of the study were compared with previously published cost effectiveness analysis. A systematic review [68] of cost effectiveness studies comparing CSII to MDI identified two models that investigated the cost effectiveness of CSII compared with MDI. This review identified 11 studies in eight countries; nine of the 11 studies were performed using the CORE (Centre for Outcomes Research) Diabetes Model (CDM) and two studies used the Markov model analysis of CSII versus MDI [68]. The perspective of the analyses was from a third-party health payer [68]. The CDM assumed 50 years, 60 years, or a lifetime time horizon for the technology, and most of the studies derived HbA1c reduction estimates of 10–13 mmol/L in favor of CSII (vs. MDI) from Weissberg-Benchell et al. (2003) [69]. The reduction in HbA1c is assumed to reduce the incidence of micro- and macrovascular complications over the time horizon of the technology (50+ years). The objective of the CDM cost effectiveness models was to capture CSII's improvement in HbA1c on micro- and macrovascular complications over the lifetime of a patient. Common clinical assumptions across the CDM models likely contributed to the similar findings across settings [68].

The two Markov model analyses assumed an eight or ten year time horizon for the technology and assumed no HbA1c benefit for either CSII or MDI. The model analyses were based exclusively on the incidence of hypoglycemic and ketoacidosis events. The Markov model approach is considered more conservative than the CDM as it does not assume HbA1c improvements and a reduction in the incidence of micro- and macrovascular complications. The Markov model's objective was to capture CSII's improved glycemic management through a

reduction in the number of hypoglycemic and diabetic ketoacidosis events. The results of the systematic review concluded that CSII is cost effective compared to MDI with a mean ICER of US$40,143 (range: $23,409-$56,876) in patients with high rates of hypoglycemic events [68].

This cost effectiveness study comparing CSII with MDI using a Markov model found an ICER of C$123,041 and C$122,155 from health payer and societal perspectives, respectively. The cost effectiveness analysis in Alberta found that CSII consumables are a major driver of costs, with pump consumables costing an average of $44,953.45 over five years and accounting for 85% of the total cost of providing CSII (over the lifetime of the technology) in Alberta. The three main drivers of the increased QALYs are: (1) the rate of SHEs, (2) the effectiveness of CSII to reduce SHEs, and (3) the utility weights of improved quality of life associated with CSII. Therefore, a cost-effective implementation of CSII would require knowledge of the rate of SHEs in the T1DM population and would need to identify the most appropriate users (patients with high rates of SHEs) of CSII. This suggestion poses two problems. First, the rate of SHEs is difficult to assess due to a lack of a standardized definition and different methods of data collection [70] and a high rate of SHEs is not a sufficient criterion for CSII implementation, since many other factors contribute to successful diabetes management (e.g., the patient must be suitable, highly motivated, and possess the necessary health care support systems). Second, the results of this study support previous claims that if CSII technology can reduce the number of SHEs, it may be cost effective [29]. However, evidence for the effectiveness of CSII in reducing SHEs is ambiguous and inconclusive due to methodological limitations [7, 9, 10, 12].

Strengths and Limitations

This study has several strengths. First, the cost effectiveness analysis was calculated with local data, where applicable and available. Data were collected from an Alberta specific insulin

pump therapy study that examined the costs of the insulin pump and consumables, the number of T1DM patients utilizing outpatient services, an emergency room, and inpatient care, and the health related quality of life[21] of pump users and pump nonusers. Second, a two-perspective (health payer and societal) approach was taken to capture costs to the health care system and society. Productivity losses due to nonsevere hypoglycemic and severe hypoglycemic events requiring medical and nonmedical assistance were included. Third, a Markov model was developed that offered a more conservative approach with fewer assumptions and a shorter time horizon than the Core Diabetes Models (CDM); the latter assumes a lifetime time horizon and long term effects of hemoglobin A1c reduction, which are currently unknown. To address uncertainties around parameter estimates, a Monte Carlo simulation was used to estimate the distribution of cost effectiveness and the probability that the technology is cost effective at various levels of willingness to pay.

The study has several limitations. First, the model omits death from all-cause mortality in both the CSII and MDI arms, and this has a potential to bias the results. However, all-cause mortality affects each arm equally and thus has no overall effect on the model outcome. Second, the narrow definition of productivity measured in the study using the human capital method [42, 43] may not capture all of the indirect costs in individuals with T1DM. For example, CSII may aid in better glycemic control and reduce hypoglycemic events, allowing individuals with T1DM or parents with T1DM children to return to work (part time or full time) or enabling children and adolescents to have a more flexible lifestyle (e.g., participate in sports). Third, the Alberta insulin pump study was based on very strict eligibility criteria, where individuals with T1DM admitted to the Alberta insulin pump program were very well managed (Appendix A, Appendix B). The

[21] The quality of life scores utilize T1DM patient experiences with and without CSII therapy.

model using these inputs may produce a higher ICER than would be calculated for the general T1DM population because of the reduced effectiveness of the technology in a well-managed T1DM population compared to a more general patient population.

Policy Implications

There is no doubt that relevant information regarding the cost effectiveness of diabetes intervention can assist in decision making, but awareness of the larger issues and assumptions behind such intervention are needed to evaluate the applicability of the results and the long-term sustainability of increased health care spending [71, 72]. Cost effectiveness studies aid decision making by distilling the decision problem into variables that can be manipulated by public policy to achieve health system goals. Cost effectiveness studies (1) explicitly state the underlying problem to be addressed, (2) lay out the potential alternatives, (3) predict the consequences of each alternative, and (4) evaluate potential outcomes. However, cost effectiveness studies are often difficult to interpret. First, the decision models involved are assumed to capture all relevant variables that are important to decision makers, health care providers, and patients. At the same time, the process of simplifying a complex issue into a decision model (e.g. decision tree, Markov chain) involves many assumptions about what is important to (1) decision makers, (2) health care providers, and (3) patients affected by the decision. Decision models and cost effectiveness acceptability curves may omit information that would be required for successful planning and implementation of CSII in Alberta to achieve societal goals.

For example, in CSII, the decision model assumes that only SHEs are important, and the only aspects of the technology that are of value are (1) the ability of CSII to prevent (direct and indirect) costs associated with SHEs and (2) the ability of CSII to increase a health-related quality of life. Decision makers are faced with conflicting objectives in their efforts to allocate

scarce health care resources to improve population health. Decision makers are interested in the value of a health technology and how it meets the needs of the population. Health care providers have to figure out how to deliver health care services on a limited budget without decreasing the quality of existing services.

T1DM patients in different age groups have different needs regarding its management. Optimal glycemic control in infants and children with T1DM is difficult because of insulin dosing, variable eating patterns, erratic activity, and communication difficulties, whereas optimal glycemic control of T1DM in adolescents and adults is complicated by insulin resistance, hormonal and psychosocial changes associated with puberty, and varying lifestyle factors (level of activity, diet, interpersonal relationships, and self-image). While these may be personal barriers to optimal glycemic control, should they be valued and included in the decision-making process?

In general, use of an ICER in decision making depends on the legitimacy of the QALYs as good indicators of the benefits of health care [73]. Central to this debate is the ongoing dialogue of whose preferences should be used – patients who have experience with the disease or individuals from the general population whose revealed preferences are assumed to maximize expected utility [74]. Use of different preference based measurement systems and value sets in decision making may result in different courses of action, each of which has a large resource allocative efficiency implication [75, 76].

For example, a study by Luo et al. (2005) [77] utilized three multiattribute preference based measures—the EQ-5D, the Health Utilities Index Mark 2 (HUI2), and the Health Utilities Index Mark 3 HUI3)—to describe self-reported health in the U.S. population. The authors concluded that the measures (EQ-5D, HUI2, and HUI3) generate different health index scores

and are not interchangeable. Thus, they recommended consideration of the component attributes/dimensions of health when choosing a measure for specific applications. The choice of HRQL measures depends on (1) the characteristics of the disease, (2) the ability of the measure to detect changes, and (3) the purpose of administering an HRQL measure (how will the information be used). In this case study of CSII, very different reimbursement decisions might have resulted from basing a decision on a cost effective analysis that utilizes EQ-5D versus a cost effective analysis that utilizes HUI3.

Third, interpretation of the ICER, for the allocation of scare health care funds, has no meaning without reference to an ICER threshold λ, which is often assumed to be a fixed reference number (e.g., $20,000 per QALY [78]). In theory, a technology is deemed cost effective when the calculated ICER is less than λ. This case study baseline ICER for CSII compared to MDI were $123,041 and $122,115, from health payer and societal perspectives, respectively. At an ICER threshold (λ) of $100,000 per QALY, CSII would have been considered cost-ineffective.

It is assumed that a technology that meets a certain ICER threshold will result in an efficient allocation of scarce resources. However, this is generally not the case, as specific requirements need to be met. Theoretically, the ICER threshold represents the opportunity cost of the resources at the margin, which depends on full knowledge of (1) the health care budget, (2) the program costs and benefits (which are uncertain), and (3) the range of programs available for funding (distribution is dynamic and changing) [72]. The last two properties are stochastic, as the cost and effects of programs are uncertain (unknown) and the range of programs (or distribution of programs) is unknown and always changing. These properties of the ICER threshold are not (and cannot be) recognized in a cost analysis, and the assumed ICER thresholds

do not represent the opportunity cost of health care resources. Thus, utilization of an ICER does not meet the policy maker's goal of efficient resource allocation. The ICER threshold deviates from its theoretical foundations and the concepts of health care budgets and assumes an "indeterminate stream of additional resources at a constant marginal opportunity cost," resulting in increasing health care expenditures [71, 72, 79, 80].

2.6 Conclusions

Existing evidence has shown that CSII is associated with a reduction in HbA1c and reduced insulin dosage [10, 13, 14] and systematic reviews and meta-analyses comparing CSII with MDI have shown ambiguous evidence on frequency of hypoglycemic events [7, 9, 10, 12]. The only conclusive evidence in favor of CSII over MDI is CSII's ability to reduce the mean level of glycated hemoglobin and reduced insulin usage in adolescents and adults, however, the long term health benefits of such a small reduction in glycated hemoglobin is unknown. The management of T1DM is often challenging in different ages groups (infants, children, adolescents and adults), and requires patient discipline, skill and adherence and requires continuing education, dietary management, instruction on insulin delivery and blood glucose monitoring, emotion and behavioral support and access to expertise in diabetes care.

The cost analysis comparing CSII to MDI calculated an ICER of $123,041 and $122,155, from the health payer and societal perspectives, respectively. The major drivers of the ICER are the cost of CSII consumables, which account for 85% of the total cost of providing CSII (over the lifetime of the technology) in Alberta. This study shows that CSII therapy is cost effective at an ICER threshold of $125,000 and is a conservative estimate due to the strict eligibility criteria, where individuals with T1DM admitted to the program were very well managed. The use of

these inputs may produce a higher ICER than would be calculated for a general T1DM population because of reduced effectiveness of the technology in well managed patients.

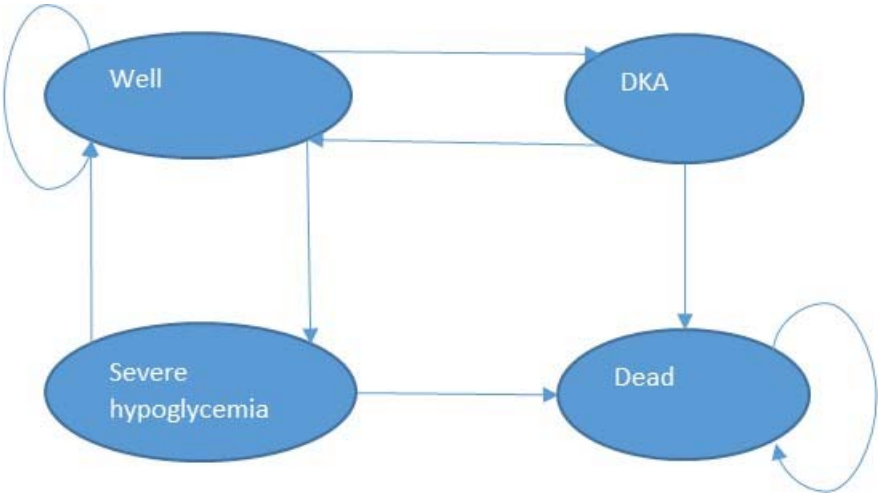

Figure 2-1: Markov model comparing cost effectiveness acceptability of CSII and MDI from the health payer perspective.

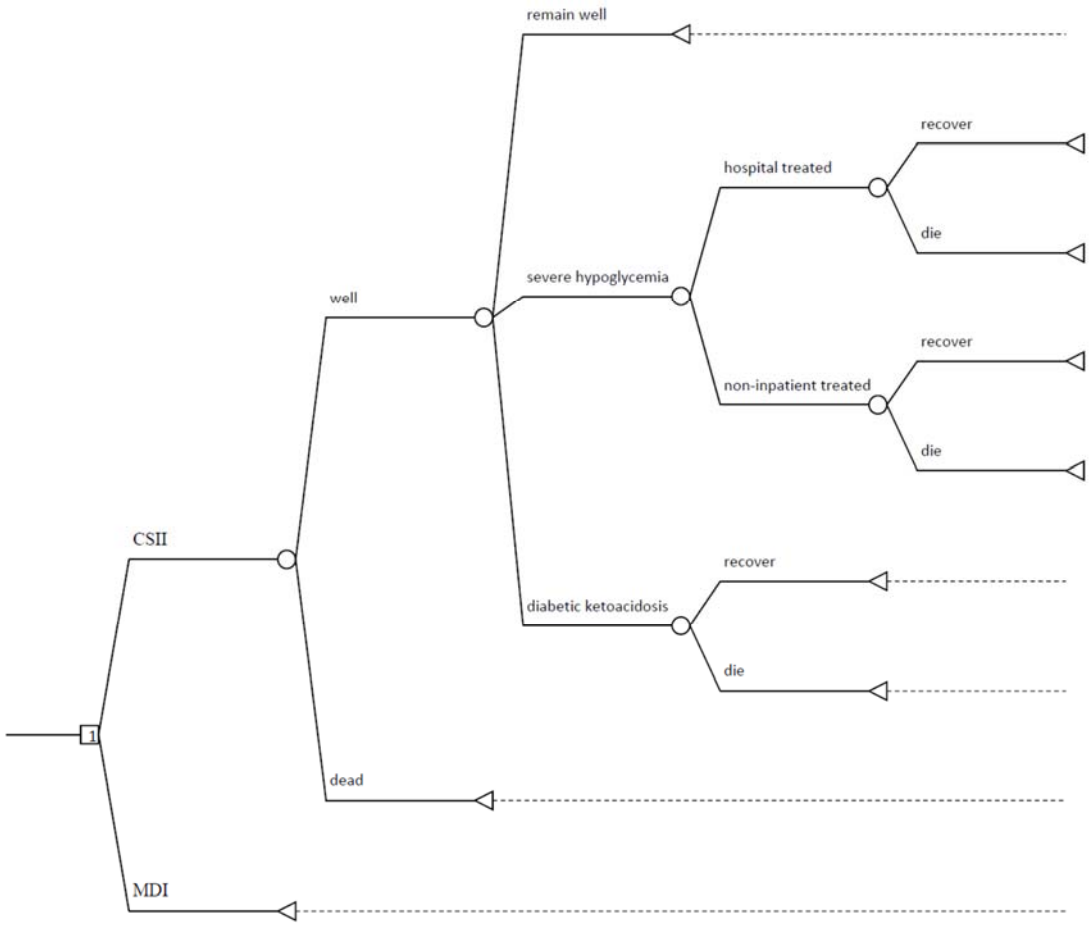

Figure 2-2: Decision tree comparing continuous subcutaneous insulin infusion (CSII) with multiple daily injections (MDI) from the health payer perspective. The MDI branch is not shown for clarity, but it is identical to the CSII branch; however, the event probabilities of CSII and MDI differ.

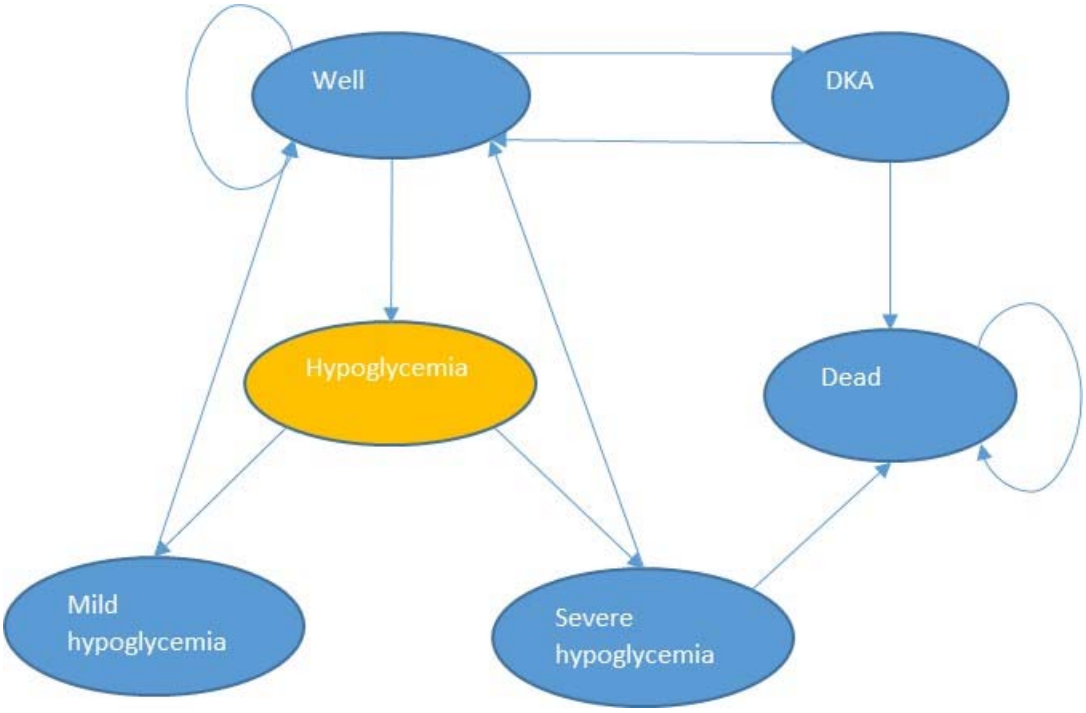

Figure 2-3: Markov model comparing the cost effectiveness acceptability of CSII and MDI from the societal perspective.

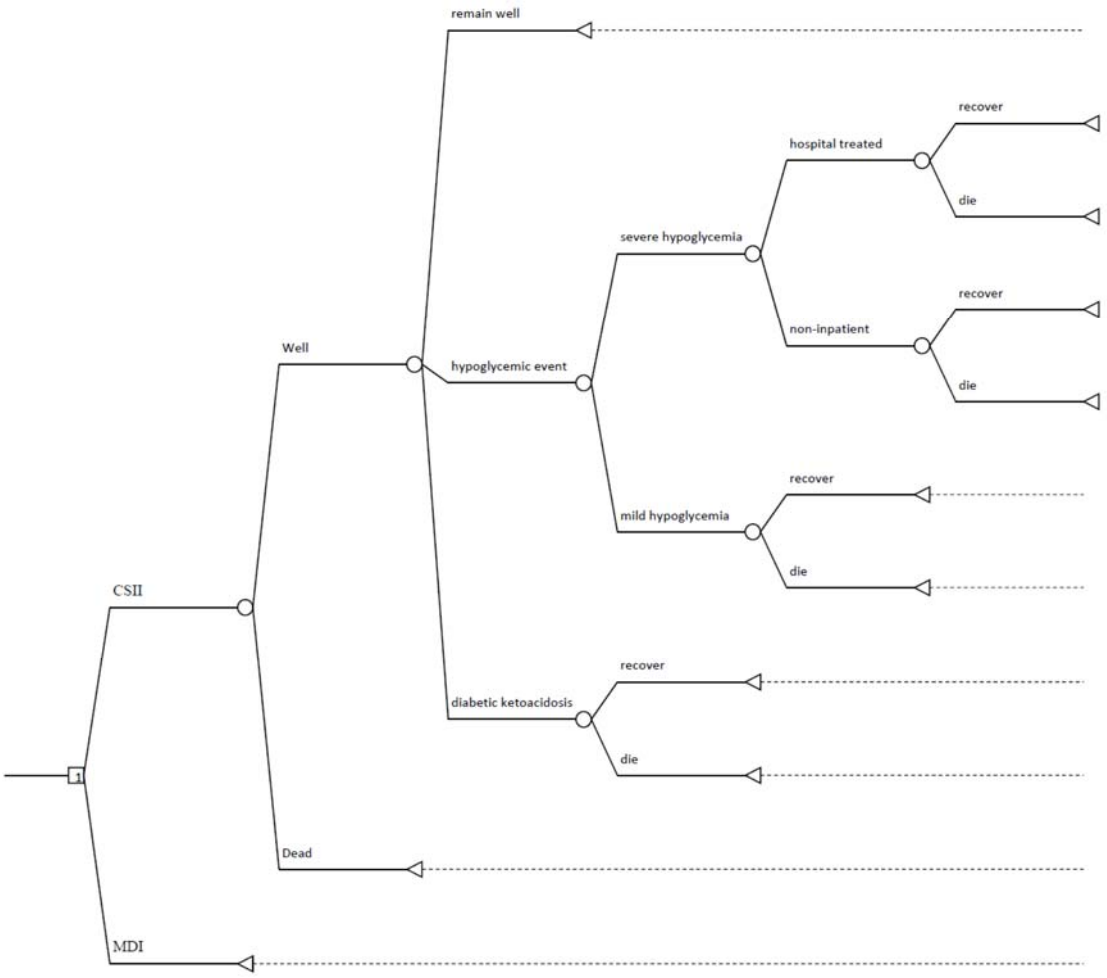

Figure 2-4: Decision tree comparing continuous subcutaneous insulin infusion (CSII) with multiple daily injections (MDI) from the societal perspective. The MDI branch is not shown for clarity, but it is identical to the CSII branch; however, the event probabilities of CSII and MDI differ.

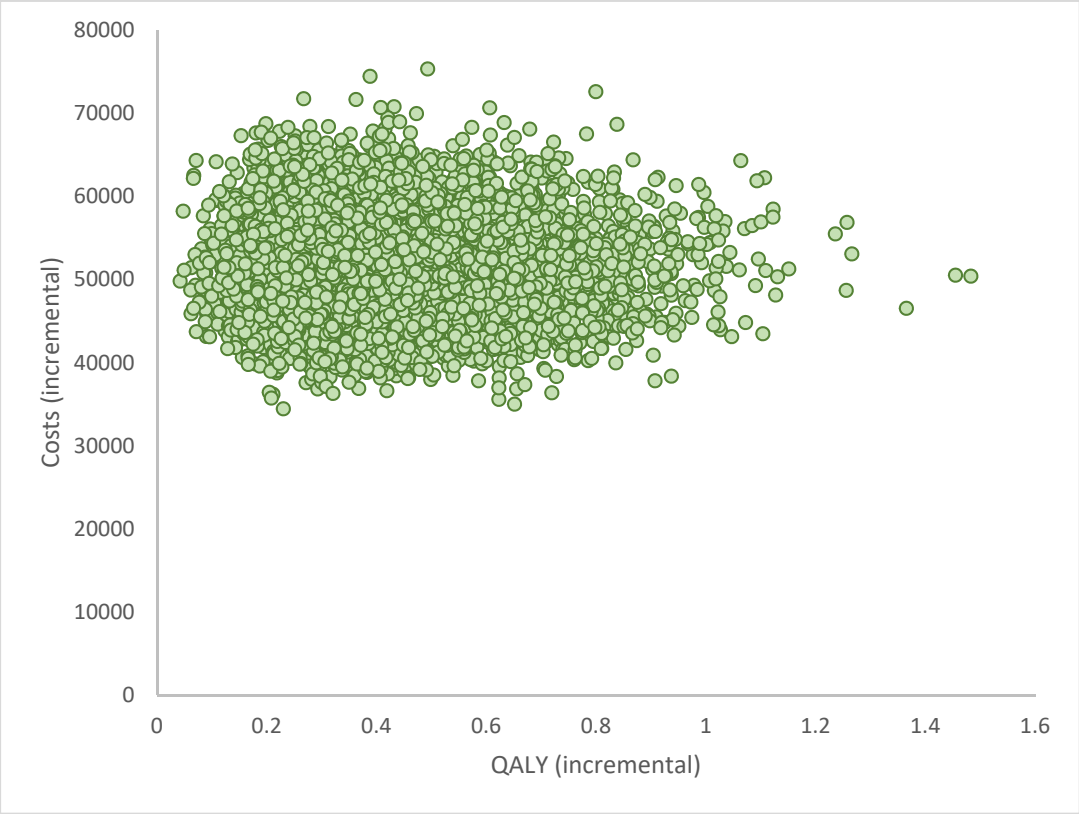

Figure 2-5: Incremental costs versus incremental QALYs from the health payer perspective.

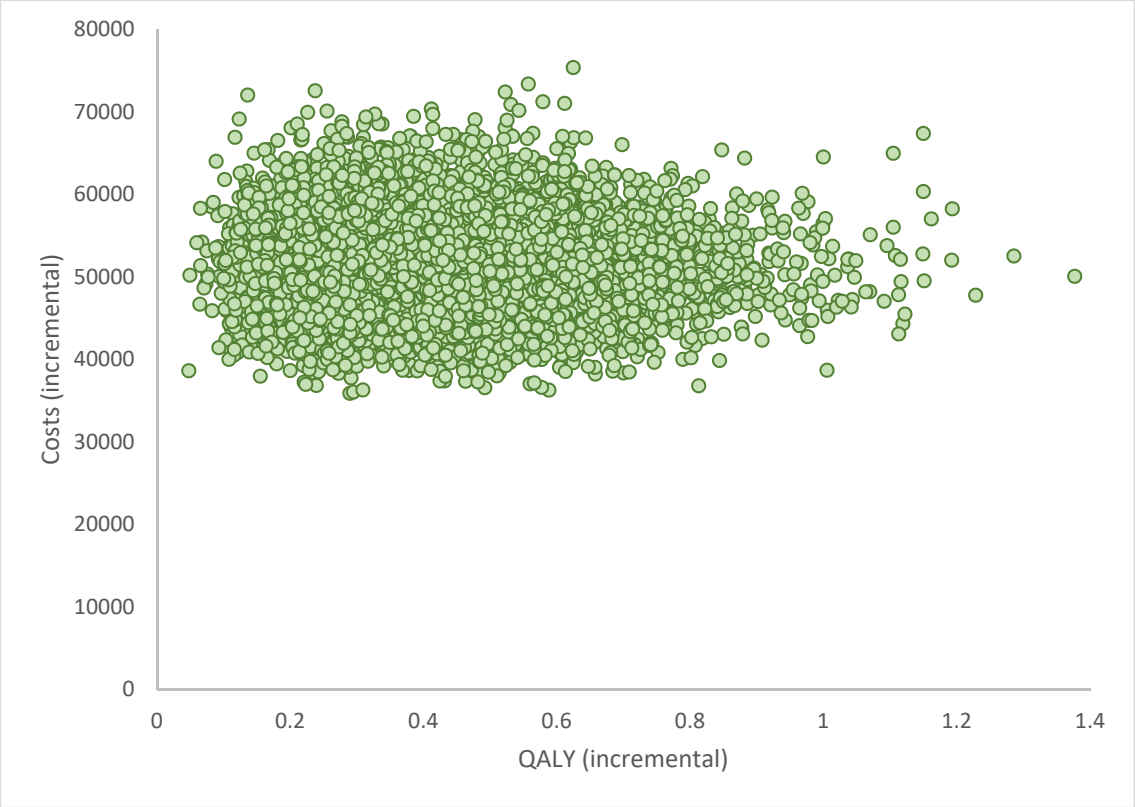

Figure 2-6: Incremental costs versus incremental QALYs from the societal perspective.

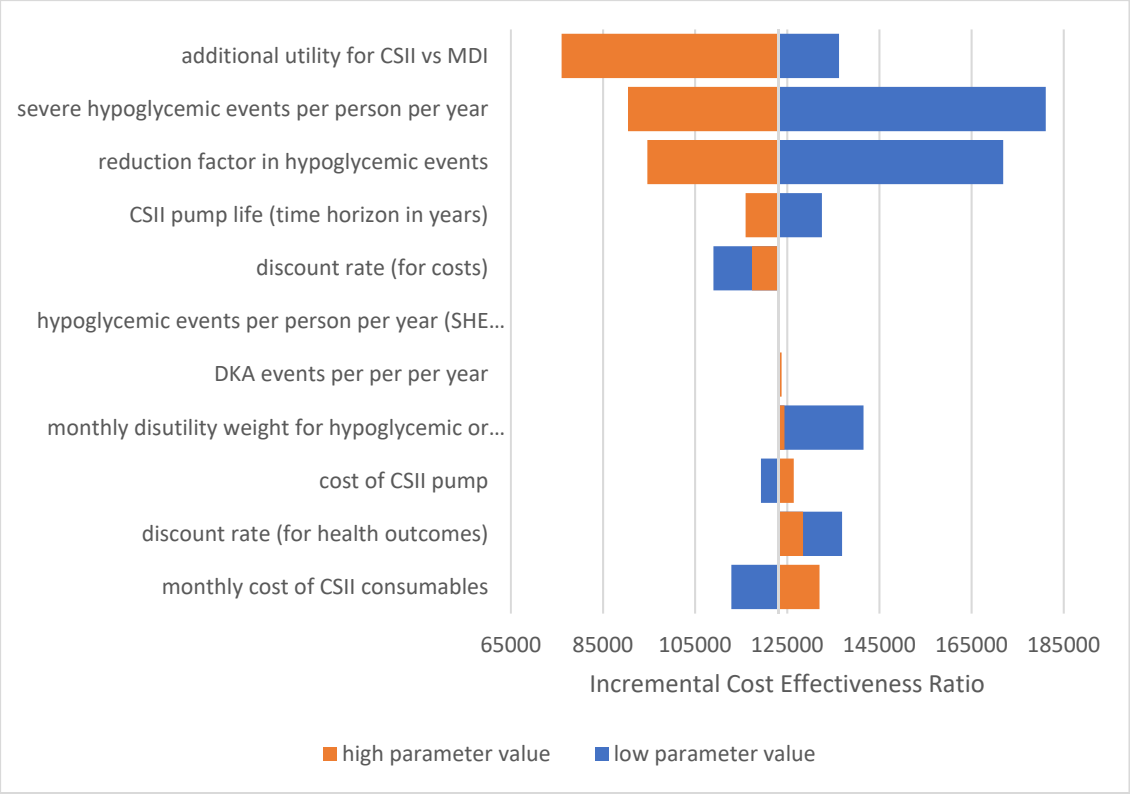

Figure 2-7: One-way sensitivity analysis results from the health payer perspective.

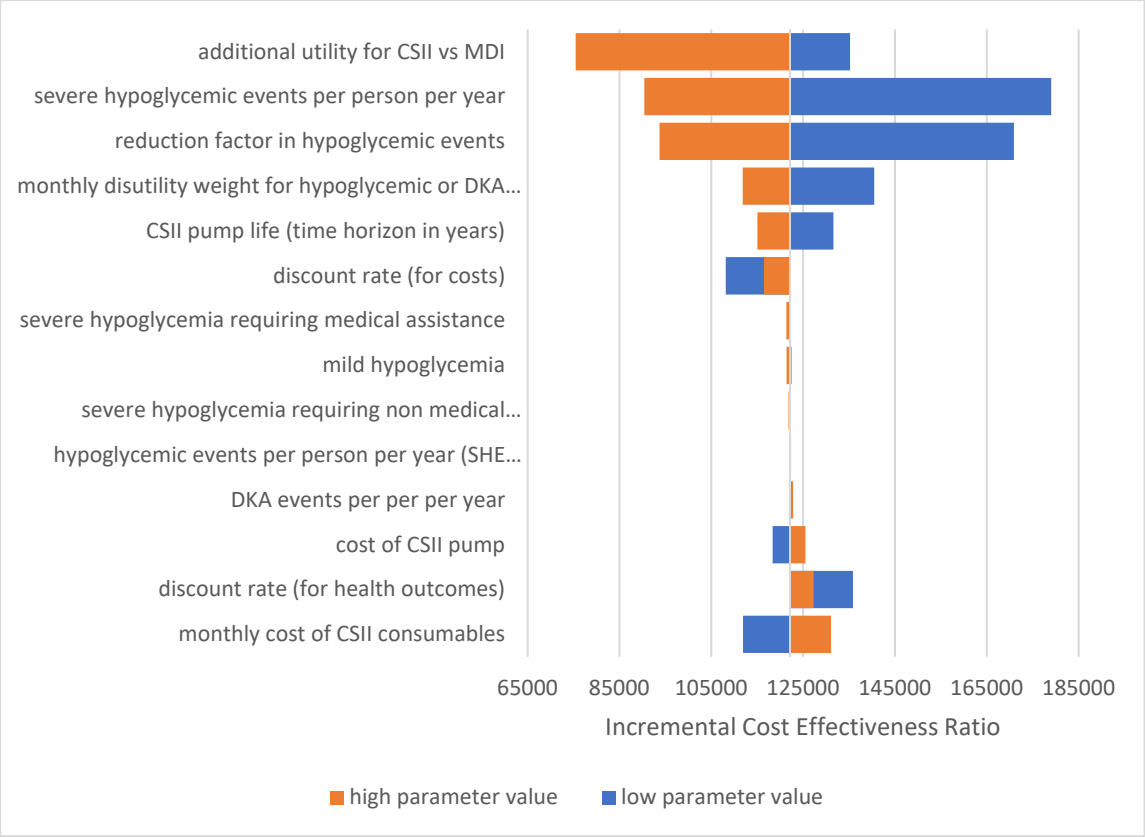

Figure 2-8: One-way sensitivity analysis results from the societal perspective.

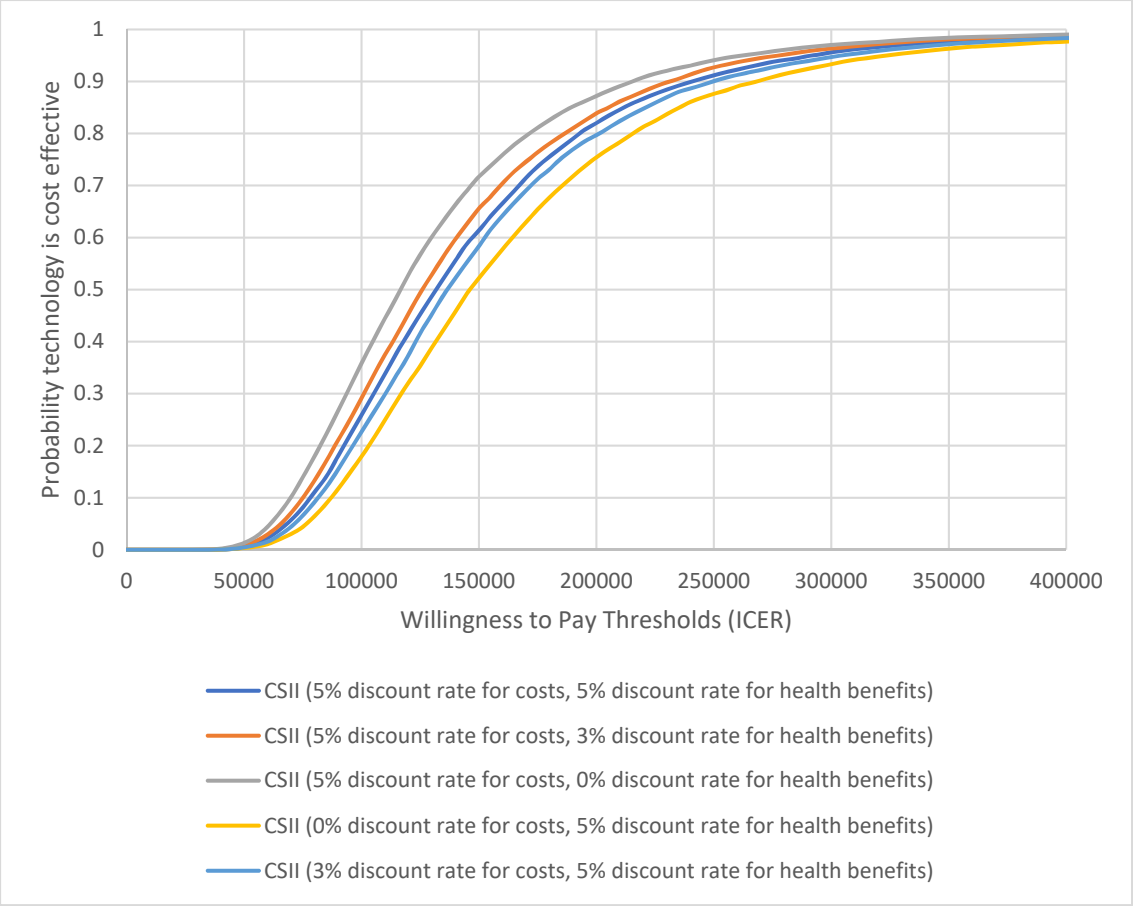

Figure 2-9: Cost effectiveness acceptability curves for various combinations of discount rates.

Table 2-1: Summary of systematic reviews and meta-analyses comparing CSII and MDI

Review	Type of Review	Type of studies included	Population	Outcomes	Conclusion for adults, adolescents and children with type 1 diabetes
Churchill et al. 2009 [7]	Systematic Review (1996-March 2008)	3 RCT and 4 quasi-experimental studies)	• children (aged 6 and younger)	• glycemic control • hypoglycemic events • quality of life (QOL)	• most studies showed significant improvements in HbA1c and showed a decreasing trend of hypoglycemia • parental satisfaction with therapy was observed with continuation of CSII treatment
Fatourechi et al. 2009 [8]	meta-analysis (2002-2008)	15 RCTs	• type 1 and type 2 • adults • adolescents	• glycemic control • hypoglycemic events	• patients using CSII had a slightly lower HbA1c (WMD -0.2%, 95%CI: -0.3,-0.1) • no significant impact on severe hypoglycemia or nocturnal hypoglycemia, however, the point estimates favoured CSII • unclear impact on hypoglycemia
Jeitler et al. 2008 [9]	meta-analysis (up to march 2007)	17 RCTs[22]	• type 1 and type 2 • adults • children	• glycemic control (HbA1 or HbA1c) • insulin requirements • hypoglycemic events • adverse events	• statistically significant difference in HbA1c between treatment effects difference of -0.4% (95%CI: -0.65, -0.20) in favour of CSII compared to MDI • no difference in hypoglycemic events was found between treatment groups • statistically significant reduction in insulin requirements in CSII compared to MDI
Monami et al. 2010 [10]	meta-analysis (up to July 2008)	11 RCTs	• type 1 • all ages	• glycemic control • hypoglycemic events (mild,	• CSII associated with a significant improvement in HbA1c compared to MDI (SMD: -0.3, 95%CI: -0.4, -0.1) • no significant differences observed in the rate of severe hypoglycemic events

[22] 6 RCTs were used in the meta-analysis of HbA1c.

				severe, nocturnal)	
Mukhopadhyay et al. 2007 [11]	meta-analysis[23]	6 RCTs	• type 1 and type 2 • pregnant diabetic women	• glycemic control • insulin dose • hypoglycemic events • ketoacidosis	• no significant difference in glycemic control (HbA1c) between the two treatments • no significant difference in insulin requirements between the two treatment groups • no significant difference in the number of hypoglycemic events • no significant difference in the number of ketoacidosis events
Pankowska et al. 2009 [12]	meta-analysis (up to October 2007)	6 RCTs[24]	• children • adolescents • young adults	• glycemic control (HbA1c) • insulin requirements • hypoglycemic events • diabetic ketoacidosis therapy • discontinuation rates	• significant lower HbA1c value in group treated with CSII (WMD -0.24, 95%CI: -0.41, -0.07) compared to MDI group • significant decrease in insulin dose recorded in CSII group compared to MDI group (-0.22IU/kg/d, 95%CI: -0.31, -0.14) • no difference in incidence of hypoglycemia or ketoacidosis
Pickup et al. 2002 [13]	meta-analysis[25]	13 RCTs	• type 1 • all ages	• glycemic control • insulin dose	• mean blood glucose concentration was lower in CSII group compared to MDI group (SMD 0.56, 95%CI: 0.35, 0.77) • HbA1c was lower in CSII group compared to MDI group (0.44, 95%CI: 0.20, 0.69)

[23] Medline: 1955–April 2006; CENTRAL, CINAHL, EMBASE: 1974–April 2006.
[24] 5 RCTs were used for meta-analysis of glycemic control.
[25] Medline: 1975–2002; Embase: 1980–2000.

					• less variation in blood glucose concentration • lower insulin dose (14% reduction, difference in dose 0.58, 95%CI: 0.34, 0.83)
Pickup et al. 2008 [14]	meta-analysis[26]	26 studies (6 RCTs, 20 before/after studies)	• type 1 • all ages	• glycemic control (HbA1c) • severe hypoglycemia	• CSII associated with improvement in HbA1c, with the greatest improvement in those with the highest baseline HbA1c • CSII associated with improvement in severe hypoglycemic events (RCT-rate ratio 2.89) with the greatest reductions in those with the most severe hypoglycemia rates
Retnakaran et al. 2004 [15]	meta-analysis (1982-2002)	3 RCTs	• Type 1 • Adults	• glycemic control • insulin dose • hypoglycemia adverse events	• no significant overall difference in HbA1c reduction with CSII compared to MDI • no significant differences in hypoglycemic risk between CSII and MDI • reduction in total daily insulin dose in CSII compared to MDI • treatment effect (reduction in HbA1c) more apparent in patients with higher baseline HbA1c

[26] Medline/Embase 1996–2006.

Table 2-2: Literature review of incidence and mortality rates of hypoglycemic and diabetic ketoacidosis events

Parameter	Rate	Rate (person-year)	Rate (person-months)	95%CI	Notes	Reference
Hypoglycemic events (all)						
Hypoglycemic events (all)	42.89 events per patient year	42.89	3.5742	95%CI (34.08, 51.70)	No SD reported	Donnelly et al. 2003. Frequency and predictors of hypoglycemia in type 1 and insulin treated type 2 diabetes: a population based study. Diabetic Medicine 22: 749-755.
Mild hypoglycemic events						
Mild self-reported hypoglycemic events	29.0 episodes per patient-year (mean)	29.00	2.4167	95%CI (16.4, 41.8)	Diabetes duration for > 15 years (17-75 years of age)	UK Hypoglycemia Study Group. 2007. Risk of hypoglycemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 50: 1140-1147.
Mild self-reported hypoglycemic events	35.5 episodes per patient-year (mean)	35.50	2.9583	95%CI (22.8, 48.2)	Diabetes duration for < 5 years (17-75 years of age)	UK Hypoglycemia Study Group. 2007. Risk of hypoglycemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 50: 1140-1147.
Mild hypoglycemia	(42.89-1.15)=41.74 events per patient year	41.74	3.4783	N/A	Deduced from Donnelly et al., NO SD reported	Donnelly et al. 2003. Frequency and predictors of hypoglycemia in type 1 and insulin treated type 2 diabetes: a population based

						study. Diabetic Medicine 22: 749-755.
Mild hypoglycemia	2.0 episodes/patient week		8.0000	N/A	Adults (>= 18 years of age), Danish and British populations	Pedersen-Bjergaard et al. 2004. Severe hypoglycemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes/Metabolism Research and Reviews 20: 479-486.
Symptomatic hypoglycemia	2 episodes per week		8.0000	N/A		Cryer PE. 2010. Hypoglycemia in Type 1 Diabetes Mellitus. Endocrinology Metabolism Clin North Am 39: 641-654.
Severe hypoglycemia						
Severe hypoglycemia (CSII)	0.98 per 100 person months	0.12	0.0098	N/A	Adolescent study (10-17 years of age)	Cherubini et al. 2014. Health-related quality of life and treatment preferences in adolescents with type 1 diabetes. The VIPKIDS study. Acta Diabetol 51:43-51.
Severe hypoglycemia	1.11 per 100 person months	0.13	0.0111	N/A	Adolescent study (10-17 years of age)	Cherubini et al. 2014. Health-related quality of life and treatment preferences in adolescents with type 1 diabetes. The VIPKIDS study. Acta Diabetol 51:43-51.
Severe hypoglycemia	0.2 events per person	0.20	0.0167	N/A	Danish population study	Marmolin et al. 2012. Better treatment of outpatients with T1DM after introduction of CSII. Danish Medical Journal 59(6): A4445.

Severe hypoglycemia with coma or seizures	0.35 (0.04) episodes/patient year	0.35	0.0292	N/A	Adults (>= 18 years of age), Danish and British populations	Pedersen-Bjergaard et al. 2004. Severe hypoglycemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes/Metabolism Research and Reviews 20: 479-486.
Severe hypoglycemia	People with T1DM suffer an average of approximately 1 severe hypoglycemia per year	1.00	0.0833	N/A		Cryer PE. 2010. Hypoglycemia in type 1 diabetes mellitus. Endocrinology Metabolism Clin North Am 39: 641-654.
Severe self-reported hypoglycemic events	1.1 episodes per patient-year (mean)	1.10	0.0917	95%CI (0.0, 2.3)	Diabetes duration > 15 years (17-75 years of age)	UK Hypoglycemia Study Group. 2007. Risk of hypoglycemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 50: 1140-1147.
Severe hypoglycemia	1.15 events per patient per year	1.15	0.0958	95%CI (0.10, 2.19)	No SD reported	Donnelly et al. 2003. Frequency and predictors of hypoglycemia in type 1 and insulin treated type 2 diabetes: a population based study. Diabetic Medicine 22: 749-755.
Severe hypoglycemia	1.3 events per person	1.30	0.1083	N/A	Unselected Danish material on T1DM	Marmolin et al. 2012. Better treatment of outpatients with T1DM after introduction of CSII. Danish Medical Journal 59(6):A4445, Pedersen-Bjergaard U et al. 2004. Severe hypoglycemia in 1076 adult

						patients with type 1 diabetes: influence of risk markers and selection. Diabetes Metab Res Rev 20: 479-486.
Severe hypoglycemia	1.3 (0.10) (mean (SEM)) episode/patient year	1.30	0.1083	N/A	Adults (>= 18 years of age), Danish and British populations	Pedersen-Bjergaard et al. 2004. Severe hypoglycemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes/Metabolism Research and Reviews 20: 479-486.
Severe hypoglycemia	3.2 episodes per patient year (mean)	3.20	0.2667	95%CI (1.6, 4.9)	Diabetes duration > 15 years (17-75 years of age)	UK Hypoglycemia Study Group. 2007. Risk of hypoglycemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 50: 1140-1147.
Severe hypoglycemia	19 episodes per 100 patient years	0.19	0.0158		Pediatric clinic	Rewers et al. 2002. Predictors of acute complications in children with type 1 diabetes. JAMA 287:2511-2518.
Ketoacidosis						
Ketoacidosis (CSII)	0.33 per 100 person months	0.03960	0.0033	N/A	Adolescent study (10-17 years of age)	Cherubini et al. 2014. Health-related quality of life and treatment preferences in adolescents with type 1 diabetes. The VIPKIDS study. Acta Diabetol 51:43-51.
Ketoacidosis (MDI)	0.37 per 100 person months	0.04440	0.0037	N/A	Adolescent study (10-17 years of age)	Cherubini et al. 2014. Health-related quality of life and treatment preferences in adolescents with type 1 diabetes.

						The VIPKIDS study. Acta Diabetol 51:43-51.
Ketoacidosis (all)	4.8-8 per 1000 patients			N/A		Kitabachi et al. 2001. Management of hyperglycemic crisis in patients with diabetes. Diabetes Care 24(1):131-153.
Ketoacidosis	2.7-9 episodes per 100 patient years			N/A		Realson et al. 2012. Morbidity and mortality of diabetic ketoacidosis with and without insulin pump care. Diabetes Technology and Therapeutics 14(12):1-6.
Ketoacidosis	8 episodes per 100 patient years	0.08000	0.0067	N/A		Rewers et al. 2002. Predictors of acute complications in children with type 1 diabetes. JAMA 287:2511-2518.
Deaths						
Diabetes related treatment deaths (hypogycemia, DKA, etc.)	18 deaths (3452 patients followed up for 10.3 years)	0.00051	4.21752E-05	N/A		Muhlhauser et al. 2000. Prognosis of person with type 1 diabetes on intensified insulin thearpy in relation to nephropathy. Journal of Internal Medicine 248: 333-341.
hypoglycemia death	5 deaths in 219061 person years	0.00002	1.90206E-06	N/A	followed 28887 children for an average of 7 years, including children diagnosed with diabetes under	Patterson et al. 2007. Early mortality in EURODIAB population based cohorts of type 1 diabetes diagnosed in childhood since 1989. Diabetologia 50:2439-2442.

					15 years of age (cohort)	
Hypoglycemia death	8 deaths in 50471 person years	0.00016				Feltbrower et al. 2008. Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes. Diabetes Care 31(5): 922-926.
Hypoglycemia death	10 deaths in 46147 person years	0.00022				Skrivarhaug et al. 2006. Long term mortality in a nationwide cohort of childhood onset type 1 diabetic patients in Norway. Diabetologia 49: 298-305
DKA death	14 deaths in 81600 person years	0.00017	1.42974E-05	N/A	followed children diagnosed with diabetes at age 0-14 (cohort)	Dahlquist et al. 2005. Mortality in childhood-onset type 1 diabetes. Diabetes Care 28(10): 2384-2387.
DKA death	27 deaths in 219061 person years	0.00012	1.02711E-05	N/A	followed 28887 children for an average of 7 years, including children diagnosed with diabetes under 15 years of age (cohort)	Patterson et al. 2007. Early mortality in EURODIAB population based cohorts of type 1 diabetes diagnosed in childhood since 1989. Diabetologia 50:2439-2442.
DKA death	13 deaths in 46147 person years	0.00028				Skrivarhaug et al. 2006. Long term mortality in a nationwide cohort of childhood onset type 1

						diabetic patients in Norway. Diabetologia 49: 298-305
DKA death	14 deaths in 50471 person years	0.00028				Feltbower et al. 2008. Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes. Diabetes care 31(5): 922-926.

Table 2-3: Direct costs of CSII pump and CSII consumables

	no pump	new pump	existing pump	Total
One time cost				
Insulin pump	-	6,577.88	0.00	6,577.88
Monthly costs of consumables				
Blood glucose test strips	-	188.82	165.42	179.44
Blood ketone test strips	-	28.43	26.51	27.92
Infusion sets	-	558.62	437.12	499.60
Insulin syringe	-	26.23	26.68	26.41
Lancets	-	23.33	20.68	22.42
Pen tip needle	-	28.09	29.65	28.67
Serters	-	34.68	33.15	33.71
Skin preparation	-	27.83	25.98	27.25
Total	-	916.02	765.18	845.43

Table 2-4: Health related quality of life

Adult	EQ-5D		HUI3	
	no pump	pump	no pump	pump
baseline	0.85	0.85	0.70	0.75
3 months	0.84	0.89	0.69	0.83
6 months	0.84	0.89	0.73	0.85
9 months	0.84	0.91	0.69	0.84
12 months	0.82	0.88	0.68	0.80
	0.8388	0.8888	0.7000	0.8238
EQ-5D incremental health benefit (pump vs. no pump	0.0500			
HUI incremental health benefit (pump vs. no pump)	0.1238			

Table 2-5: Health care utilization costs

Direct costs	Cost	Standard Error
Emergency room | severe hypoglycemia	392.68	50
Outpatient | severe hypoglycemia	179.89	50
Inpatient | severe hypoglycemia	4995.81	150
Treatment costs of DKA	4995.81	150
Cost of CSII pump	6577.88	100
Cost of CSII consumables (monthly)	845.43	100
Cost of education session (one time cost -CSII)	241.26	25

Table 2-6: Epidemiologic parameters used in the Markov model

Parameter	Rate	SE	Notes	Reference
Hypoglycemic events per person per year (all)	42.89	4.4949	15-74 years of age	Donnelly et al. 2003. Frequency and predictors of hypoglycemia in type 1 and insulin treated type 2 diabetes: a population based study. Diabetic Medicine 22: 749-755.
Severe hypoglycemic events per person per year	1.15	0.5967	Diabetes Duration > 15 years, 17-75 years of age)	UK Hypoglycemia Study Group. 2007. Risk of hypoglycemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 50: 1140-1147.
Diabetic ketoacidosis per person per year	0.04	0.022	No SE reported: SE author's assumption: Adolescent study (10-17 years of age)	Cherubini et al. 2014. Health-related quality of life and treatment preferences in adolescents with type 1 diabetes. The VIPKIDS study. Acta Diabetol 51:43-51.
Mortality rate severe hypoglycemia	0.00016	0.00001	No SE reported: SE	Patterson et al. 2007. Early mortality in EURODIAB population based cohorts of type 1 diabetes diagnosed

			author's assumption. Cohort study, diabetes diagnosis < 15 years of age, follow up	in childhood since 1989. Diabetologia 50:2439-2442.
Mortality rate diabetic ketoacidosis	0.00028	0.00002	No SE reported: SE author's assumption. Cohort study, diabetes diagnosis < 15 years of age, follow up	Patterson et al. 2007. Early mortality in EURODIAB population based cohorts of type 1 diabetes diagnosed in childhood since 1989. Diabetologia 50:2439-2442.

Table 2-7: Severe hypoglycemic events that resulted in paramedic services, emergency or hospital admission, and nonmedical assistance

Event	Proportion	Standard Error
Outpatient | severe hypoglycemia	0.760	0.050
Emergency room | severe hypoglycemia	0.030	0.030
Inpatient | severe hypoglycemia	0.005	0.005
Assisted by family/colleagues | severe hypoglycemia	0.205	0.050

Table 2-8: Direct and indirect costs, health related quality of life, and incremental costs and benefits of CSII and MDI from 10,000 Monte Carlo simulations over a 5 year time horizon

	Mean	Std. Dev.	Min.	Max.
Direct Costs				
CSII pump costs	6,551.59	99.78	6,175.19	6,955.74
CSII consumables costs	44,953.45	5,261.25	27,786.35	68,460.12
CSII therapy health care utilization	1,349.70	537.78	112.72	4,300.23
CSII education	240.48	19.95	172.45	317.19
CSII therapy direct costs (total)	53,095.21	5,292.12	36,361.91	76,135.96
MDI therapy direct costs (total)	1,528.96	574.48	173.94	4,580.89
Incremental costs (CSII vs. MDI)	51,566.25	5,264.72	34,449.47	75,313.27
Indirect Costs				
MDI therapy indirect costs	3,989.47	1,332.75	880.30	11,085.49
CSII therapy indirect costs	3,695.74	1,310.10	531.17	10,611.48
Difference	-293.73	273.28	-3,481.14	516.27
HRQL				
CSII QALYs	3.95	0.25	2.30	4.38
MDI QALYs	3.53	0.32	1.81	4.25
Incremental QALYs (CSII vs. MDI)	0.41	0.17	0.04	1.48

Table 2-9: One-way sensitivity analysis – best and worst case scenarios

	Low parameter value	Health payer low ICER	Societal low ICER	High parameter value	Health payer high ICER	Societal high ICER
additional utility for CSII vs. MDI	0.05	136,243	135,218	.1238	76,034	75,462
monthly disutility weight for hypoglycemic or DKA event	0.02	141,566	140,501	0.10	124,396	111,839
Epidemiologic Factors						
hypoglycemic events per person per year (SHE and NSHE)	34.08	123,041	122,380	51.70	123,041	121,987
severe hypoglycemic events per person per year	0.12	181,103	179,024	3.20	90,449	90,407
DKA events per person per year	0.027	122,853	121,928	0.09	123,761	122,832
CSII Effectiveness						
reduction factor in hypoglycemic events	0.10	171,892	170,908	0.50	94,627	93,735
CSII pump life (time horizon in years)	3 years	132,526	131,594	10 years	115,970	115,046
Indirect Costs						
mild hypoglycemia	11	-	122483	200	-	121395
severe hypoglycemia requiring medical assistance	100	-	122248	500	-	121360
severe hypoglycemia requiring nonmedical assistance	100	-	122196	750	-	121824
Cost Factors						
cost of CSII pump	5,000.00	119,288	118,362	8,000.00	126,423	125,497
monthly cost of CSII consumables	765.18	112,859	111,933	916.02	131,997	131,071

discount rate (for costs)	0.00%	136,911	135,866	3.00%	128,424	127,272
discount rate (for health outcomes)	0.00%	108,973	108,153	3.00%	117,360	116,477

Chapter 3: Value of Information Analysis of Continuous Subcutaneous Insulin Infusion (CSII) compared with Multiple Daily Injections (MDI)

3.1 Introduction

Economic evaluations are used increasingly to (1) consciously frame decision(s), (2) recognize that uncertainty is the primary cause of difficulty in decision making, (3) describe uncertainty using probabilities, (4) calculate the value of information[27], and (5) recognize and create options. However, economic evaluations may not communicate or resolve the level of uncertainty to decision makers. In situations where a new health technology is neither clearly inferior nor clearly superior to current practice, economic evaluations may exacerbate uncertainty by not addressing issues relevant to stakeholders (health care providers, health care decision makers, patients) affected by a definitive funding decision. A cost effectiveness analysis (CEA) might be insufficient to estimate the results of a decision, resulting in a decision having to be made about the adoption and diffusion of a technology without sufficient evidence.

Sensitivity analyses and CEACs aid in the communication of uncertainty, however, they omit important information needed to make a definitive funding decision. A decision maker would be interested in knowing, based on the current level of information (and uncertainty), (1) the probability of not selecting the "true" preferred alternative and (2) the consequences of not selecting the true preferred alternative. Conveying the level of uncertainty in model parameters and model outputs provides important information and expands available options to decision makers – for example, would delaying a decision to collect more evidence improve the implementation and outcomes of a health technology? Value of information (VOI) analysis is another method of analyzing and communicating uncertainty, and introduces the concept of time in decision making – would delaying a decision and collecting more information resolve decision uncertainty?

[27] Which have not been consistently presented with cost effectiveness analyses.

VOI analysis can identify strategies to improve the prospective outcomes of a chosen course of action [81] and helps to answer two related questions: (1) whether to adopt a technology given the existing evidence (and uncertainty) and (2) whether more information is required to support the decision to adopt or to not adopt the technology or treatment [82]. If more information is required to support the decision, what type of evidence would have the greatest impact? Conducting additional research may resolve decision uncertainty and generate better health outcomes from available resources by enabling more knowledgeable decisions. However, the current policy environment does not consistently address whether it is worthwhile to invest in the generation of further evidence before a definitive funding decision is made [83]. This study presents a VOI analysis using a CSII case study (see chapter 2 for an in-depth description of the case study) to describe decision uncertainty and to indicate whether further research would inform a plan to implement CSII for patients with type 1 diabetes mellitus (T1DM).

Objective of Study

The objectives of this study are to:

1) Perform a value of information analysis for the use of continuous subcutaneous insulin infusion (CSII) to treat T1DM, including:
    a. Expected value of perfect information (EVPI)
    b. Expected value of partial perfect information (EVPPI)
    c. Expected value of sample information (EVSI)
    d. Expected net benefit of sampling (ENBS)
2) Discuss the value of VOI analysis and its application in decision making and access with evidence development (AED) schemes

3.2 Background

Incremental Cost Effectiveness Ratio (ICER)

When faced with a competing choice, where alternatives are mutually exclusive, cost effectiveness analysis requires the calculation of incremental cost effectiveness ratios (ICERs), which allow the decision maker to determine the average incremental cost for an additional unit of health benefit. The ICER is calculated as follows:

$$\text{ICER} = (C_1 - C_0)/(E_1 - E_0), \quad (1)$$

where C_1 and E_1 are the cost and health benefit in treatment group (in this case CSII) and C_0 and E_0 are the cost and effectiveness of the comparator group (in this case MDI). Confidence intervals may be calculated to represent uncertainty in the ICER (see Appendix A for a discussion of confidence intervals; see Appendix B for a discussion of uncertainty of cost and effects and the ICER). In theory, the ICER is compared to a threshold ICER, λ; if the ICER is less than λ, then the technology is deemed to be cost effective for the treatment group and provides satisfactory value for the money spent.

ICER Thresholds (λ)

The optimum health policy is established by estimating the maximum health benefits that can be obtained in a constrained budget. Therefore, specification of the threshold ratio λ is the opportunity cost of resources at the margin [84]. The theoretical foundations of the threshold ratio λ require assumptions of perfect divisibility and constant returns to scale, which rarely hold true in decision making settings [84, 85]. To determine λ, information on all incremental costs and effects of all current and potential interventions must be identified and known; total health benefits are maximized with the implementation of interventions that have ICERs of less than λ [84]. Three strategies have been identified to set the ICER threshold: (1) the threshold should be

inferred from previous funding decisions, (2) the threshold should be set to determine the optimal health care budget, and (3) the threshold should be set to exhaust an exogenously determined budget [86]. However, each strategy has limitations. The size of λ depends on the size of the budget (or available resources) and changes in the health budget change the value of λ; healthcare budgets are uncertain and dynamic. In the real world, complete rankings of all interventions cannot be produced, and therefore λ cannot be determined [84]; therefore, implementing health technologies that have ICERs less than λ does not necessarily result in an efficient allocation of resources.

The determination and use of an ICER threshold have been contentious in Canada. It was proposed some years ago that an arbitrary value of $20,000 be assigned to λ [7,8]. This was deemed to be independent of the budget. It has been reported that the use of such a threshold would escalate medical expenditures in Canada and elsewhere [4,9]. The ICER threshold should not be viewed as a firm line where technologies falling under the threshold should be funded and technologies above the threshold should be rejected; the threshold should be viewed as a point where additional criteria are taken into consideration to inform funding decisions [86]. A cost effectiveness analysis and an ICER threshold are not sufficient evidence to inform complex policy questions of decision uncertainty and efficient resource allocation.

NICE Guidelines and Recommendations for the ICER Threshold

The National Institute for Health and Care Excellence (NICE) Methods Guide addresses and acknowledges the uncertainty around ICERs and its influence on decision uncertainty. The proposed solution is to seek out additional information and decision criteria. The 2013 NICE Methods Guide [87] suggests that the ICER threshold is an indicator of whether more information is required to inform a definitive funding decision:

> The Appraisal Committee does not use a precise maximum acceptable ICER above which a technology would automatically be defined as not cost effective or below which it would. Given the fixed budget of the NHS, the appropriate maximum acceptable ICER to be considered is that of the opportunity cost of programmes displaced by new, more costly technologies. NICE does not have complete information about the costs and QALYs from all competing healthcare programmes in order to define a precise maximum acceptable ICER. However, NICE considers that it is most appropriate to use a range … furthermore, consideration of the cost effectiveness of a technology is a necessary, but is not the sole, basis of decision making. Consequently, the Institute considers technologies in relation to this range of maximum acceptable ICERs, such that the influence of other factors upon the decision to recommend a technology is greater when the ICER is closer to the top of the range. [87]

The NICE guidelines go on to suggest that

> below the most plausible ICER of £20,000 per QALY gained, the decision to recommend the use of a technology is normally based on the cost effectiveness estimate and the acceptability of a technology as an effective use of NHS resources. When the estimated ICERs presented are less than £20,000 per QALY gained and the Committee judges that particular interventions should not be provided by the NHS, the recommendations will make specific reference to the Committee's view on the plausibility of the inputs to the economic modelling and/or the certainty around the estimated ICER. This might be affected, for

example, by sensitivity analysis or limitations to the generalizability of findings regarding effectiveness. [87]

Above the ICER threshold of £20,000,

judgement about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors:

- The degree of uncertainty around the ICER
- Whether there are strong reasons to indicate that the assessment of the change in health related quality of life has been inadequately captured and therefore the health utility gained is misrepresented
- The innovative nature of the technology, especially if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure
- Where appropriate, the wider societal costs and benefits. [86, 87]

Canadian Agency for Drugs and Technologies in Health (CADTH) Guidelines and Recommendations on Uncertainty

CADTH distinguishes the difference between variability and uncertainty [46].

> Variability reflects the unknown differences in parameter values that are associated with identifiable differences in circumstances. It is represented by frequency distributions, and cannot be reduced. Uncertainty occurs when the true value of a parameter is unknown, thus reflecting the fact that knowledge or measurement is imperfect. It can relate to parameter values in a model and model design features. [46]

It is recommended to analyze uncertainty around the model[28] and parameters, using a probabilistic[29] and a deterministic sensitivity analysis (SA)[30]. The CADTH guidelines go on and suggest an extension to the SA—a value of information (VOI) analysis to assess the value of gathering more information through additional research [46].

> A probabilistic sensitivity analysis can be extended to Bayesian analysis. A Bayesian framework can be used to assess the value of gathering additional information, based on comparing the costs of conducting more research and the benefits from reducing uncertainty. The framework recognizes the binary nature of the decision facing a decision-maker (accept or reject), and quantifies all forms of parameter and model uncertainty in a PSA. It focuses on identifying parameters for which it is worth obtaining more sample information to reduce risk. This information[31] can be used to prioritize research, or increase the efficiency of study design. [46].

The CADTH guidelines recognize the impact of uncertainty on decisions and decision makers and acknowledge that a VOI analysis can aid in optimizing a decision by reducing risk through further research where applicable.

Sensitivity Analysis (SA)

A sensitivity analysis acknowledges the underlying uncertainty around model parameters and outputs and determines how sensitive the outputs are to changes in parameters [88]. If the model outputs do not vary greatly with some reasonable change in model parameters, the results can be considered robust and the decision maker can have greater confidence in them [88]. Two

[28] Analytical methods, model structure, model assumptions, and choice of data sources.
[29] Monte Carlo simulations.
[30] Alternative assumptions, one-way SA, multiway SA, threshold SA, worst-best case SA.
[31] Value of information analysis.

general approaches to sensitivity analyses are deterministic SA and probabilistic SA. A deterministic SA has two major limitations: (1) it may not take into account all the available information about the assumed values of parameters and (2) it does not provide information about the variance or spread of the distribution of model outputs, costs, and health benefits [88]. If the new health technology is indistinguishable from an existing technology in costs and health benefit, then information on variances would be informative to decision makers; the decision maker would be interested in the health technology with the smaller variance, or less uncertainty [88].

Ideally, a sensitivity analysis should communicate information about the range of possible outcomes of key parameters in the analysis and the probability of each possible outcome being realized, information that is absent from univariate and multivariate analyses [89]. This would incorporate information on the joint probability distributions of variables [89]. Monte Carlo (MC) simulations overcome these problems.

The Monte Carlo simulation approach starts by assigning probability distributions (e.g., gamma, beta, normal, binomial, uniform, etc.) to model parameters. The simulation is accomplished by drawing a random sample from the predetermined probability distributions and recording the outputs from the model, cost, and health benefit [29]. By providing a random sample consisting of a range of estimates, the information can be used to assess how likely the estimates are. The results of the Monte Carlo simulation are plotted on a cost effectiveness plane (incremental costs and incremental benefits) (Figure 1).

Cost Effectiveness Acceptability Curves (CEACs)

Cost effectiveness acceptability curves (CEACs) were introduced as an alternative to confidence intervals [90-92] to convey uncertainty in the ICER estimates; however CEACs are

limited in their ability to present decision uncertainty. CEACs are derived from the joint density of incremental costs and incremental benefits, typically from MC simulations or bootstrapping, and represent the proportion of the density where the intervention is cost effective for a range of values of the ICER threshold (λ)[32] [90]. A CEAC presents the probability that the ICER falls below the ICER threshold (λ) and presents uncertainty as the probability that an intervention is more cost effective than its comparator, or in a study comparing more than two interventions, the CEAC presents uncertainty as the probability that a given intervention is the most cost effective given the observed data [93]. In theory, the CEAC shows decision makers the probability that funding or reimbursement of the intervention would be the "right" decision [93].

However, CEACs are insensitive to the amount of uncertainty present in the joint distribution of incremental expected costs and health outcomes. Since CEACs are a measure of the proportion of cost effectiveness ratios that lie below a specified ICER threshold, information on the spread and variance of the points are ignored [91, 94]; points lying, on the cost effectiveness plane, on the same ray that passes through the origin will have the same cost effectiveness ratio and the same cost effectiveness outcome (e.g., either cost effective or not) [91]. Any shift of the incremental joint distribution away or toward the origin will produce identical cost effectiveness acceptability curves [91, 95]. Cost effectiveness acceptability curves therefore omit important information on uncertainty that policy makers would find valuable [91].

Policy makers can appraise uncertainty only when both the probability and the consequences of not selecting the true alternative are present [91]. They tend to be risk averse and when faced with uncertainty they attempt to reduce it. Ideally, policy makers should consider two main aspects of uncertainty: (1) the probability of not selecting the "true" preferred

[32] On an incremental cost effectiveness plane, this is the proportion that falls to the southeast of a ray through the origin with a slope equal to λ.

alternative and (2) the possible consequences of not selecting the true preferred alternative [91]. CEACs do not allow the analysis of the probability or the consequences of making a wrong decision [91]. Informed policy decision requires an unambiguous presentation of uncertainty.

Net-Health and Net-Monetary Benefit Framework

Net-Health Benefit

To address problems associated with inference stemming from uncertainty around ICER estimates, ICER confidence intervals, and the threshold value λ, the net benefit framework analyzes the uncertainty in economic evaluations. The net benefit framework transforms cost and effects into a linear function and is useful in conveying information and performing sensitivity analyses. The average net health benefit (NHB) of an intervention T_i is defined as:

$$\mu_{Ei} - \mu_{Ci}/\lambda, \qquad (2)$$

where μ_{Ci} and μ_{Ei} represent the mean cost and mean health effect, respectively, of treatment T_i, and λ is interpreted as society's willingness to pay for an incremental gain in health benefit. μ_{Ei}, is the health effect associated with intervention T_i, and μ_{Ci}/λ is the minimum level of health benefit that society would demand for an investment μ_{Ci}. [89].

The incremental NHB of T_1 (intervention) compared to T_0 (comparator) is calculated by the following formula

$$(\mu_{E1} - \mu_{C1}/\lambda) - (\mu_{E0} - \mu_{C0}/\lambda) = (\mu_{E1} - \mu_{E0}) - (\mu_{C1} - \mu_{C0})/\lambda. \qquad (3)$$

If net health benefit (NHB) > 0, T_1 is deemed cost effective at the specified threshold value λ. If NHB < 0, T_1 is deemed cost ineffective and T_0 is deemed cost effective at the

specified threshold value λ. A new intervention grows more favorable as the NHB moves from negative numbers to infinity[33] [89].

Net-Monetary Benefit

The average net monetary benefit (NMB) of an intervention (T_i) is defined as:

$$\mu_{Ei}*\lambda - \mu_{Ci}, \quad (4)$$

where μ_{Ci} and μ_{Ei} represent the mean cost and the mean health effect, respectively, of treatment T_i, and λ is interpreted as society's willingness to pay for an incremental gain in health benefit. $\mu_{Ei}*\lambda_i$ is the maximum level of monetary benefit society would demand for a health improvement of μ_{Ei}, and μ_{Ci} is the cost associated with intervention T_i.

The incremental NMB of T_1 compared to T_0 is

$$(\mu_{E1}*\lambda - \mu_{C1}) - (\mu_{E0}*\lambda - \mu_{C0}) = (\mu_{E1} - \mu_{E0})*\lambda - (\mu_{C1} - \mu_{C0}). \quad (5)$$

If the net monetary benefit (NMB) is > 0, T_1 is deemed cost effective at the specified threshold value λ. If NMB is < 0, T_1 is deemed cost ineffective and T_0 is deemed cost effective at the specified threshold value λ a positive NMB value is favorable for the new intervention, while a negative NMB value is unfavorable for the new intervention. The new intervention grows more favorable as the NMB moves from negative values to infinity.

Statistical Inference

There are three advantages to using a net benefits framework rather than ICER confidence intervals for statistical inference. Due to its linearity in cost and health effect, the net benefits framework (1) is asymptotically normal, (2) is an unbiased estimator of the true NMB, and (3) has a mean distribution evaluated at the mean estimates of cost and health effect [89].

[33] Calculation of NHB is not bounded mathematically

These qualities have advantages over the use of an ICER for statistical inference because the ICER (1) is not linear in its cost and effects, (2) is a biased estimator of the true ICER, and (3) is uncertain with respect to its parametric distribution assumption; the magnitude and sign of the ICER has no meaningful interpretation without reference to the cost effectiveness quadrant or to λ [89].

3.3 Value of Information (VOI)

In "classic" decision analysis, the optimal choice between two or more strategies is the one with the highest expected value and is almost always based on existing information that is incomplete or imprecise [96]. A decision based on existing information will be therefore be uncertain and there is a chance that a wrong decision will be made [97]. VOI is a tool to estimate expected gains from reducing uncertainty through data collection; it can be used to assess the cost effectiveness of alternative research projects [98]. The expected value of research undertaken to reduce uncertainty in a given decision is a reduction in the probability of making a "wrong" decision multiplied by the average consequences of being wrong [98]. If the value of the research exceeds the expected cost of the research, the research should be undertaken.

Expected Value of Perfect Information (EVPI)

The EVPI (see Appendix D for an EVPI example calculation) is the difference between the benefit derived from optimal treatment with full information (no uncertainty) and the benefit derived from treatment at the current level of information (uncertainty). This difference is known as the opportunity loss or the expected cost of uncertainty [97, 99]. With current information, a decision must be made before uncertainties can be resolved [97]. With perfect information, decisions can be made with the knowledge of how the uncertainties will be resolved and based on the net benefits of alternatives. Perfect information enables decision makers to select an

intervention that maximizes net benefit [97]. The difference between the "expected value given perfect information" and the "expected value given current information" on the net benefit of alternatives is interpreted as the maximum a health care system should pay for additional information to inform a future decision [96]. The EVPI is also the upper bound of the value of further research. It can be described as:

$$EVPI = E_{\theta}\max_t B(t,\theta) - \max_t E_{\theta} B(t,\theta), \quad (7)$$

where θ represents a list of unknown parameters, t represents the treatments available, B is the health benefit provided by the technology, and E_{θ} refers to the expected value over the joint distribution of θ.

The net monetary benefit (NMB) is:

$$NMB = (\lambda E_t) - C_t \text{ [89, 99]}, \quad (8)$$

where λ is the incremental cost effectiveness ratio (or the willingness to pay), E_t is the health benefit of the technology, and C_t is the cost of the technology [89].

The current value of a technology is the EVPI per patient and a population EVPI (PEVPI) can be calculated by multiplying the EVPI by the expected number of patients. The PEVPI represents the upper bound of what would be needed to reduce uncertainty through further research and has two major applications as (1) a "go/no go" threshold for deciding whether further research is worthwhile and (2) a way to compare the "cost effectiveness" of research across interventions, clinical problems, and therapeutic areas [96]. For example, the PEVPI for the CSII case study could be interpreted as the upper bound of the amount that should be spent to reduce uncertainty through further research.

Expected Value of Partial Perfect Information (EVPPI)

The magnitude of the PEVPI indicates whether further research can be worthwhile, however, the PEVPI cannot tell which type of additional information will be the most useful. EVPPI is the value of reducing uncertainty around a certain unknown subset of parameters in the decision model, and can be calculated for a partial set of input parameters [100, 101]. It is the difference between the "expected net benefit given perfect information" (about a parameter or a subset of parameters) and the "expected value given current information."

$$EVPPI = E_{\theta i} max_t E_{\theta|\theta i} B(t,\theta) - max_t E_{\theta} B(t,\theta), \quad (9)$$

where θ_i is a subgroup of parameters within θ. Such decision analysis can be used to focus on evidence that will be most valuable to decision makers for further research. For example, the EVPPI for the CSII case study could be interpreted as the value of information required to reduce uncertainty around specific CSII parameters or parameter groups (e.g., hypoglycemic events, health related quality of life, costs). The population EVPPI can be calculated in the same manner as the PEVPI (section 2.8.1).

Expected Value of Sample Information (EVSI)

The EVPPI represents the parameters of interest for which it would be cost effective to obtain more information when the calculated EVPPI exceeds the cost of conducting further research [101]. The EVSI represents the value of gaining access to a sample of information before making a decision. The EVSI estimates the potential benefit of what the improvement would be if sample data were collected. The EVSI is the difference between the expected value of a decision after data has been collected and the expected value of a decision made without the sample data information [101].

$$EVSI = E_D max_t E_{\theta IC,(\theta|D)} B(t,\theta_I,\theta_{IC}) - max_t E_{\theta} B(t,\theta_I,\theta_{IC}), \quad (10)$$

where D is the statistics of the parameters of interest after sampling, θ_I is a subgroup of parameters within θ, and θ_{IC} is the complement set. For example, the EVSI for the CSII case study is the benefit of collecting data from a sample of T1DM patients. The population EVSI can be calculated in the same manner as the PEVPI (section 2.8.1).

Expected Net Benefit of Sampling (ENBS)

The EVSI estimates the potential information on the value of collecting additional data through sampling, and can aid in determining optimal sample size. The ENBS can be interpreted as the payoff for research involving various sample sizes and study designs [102]. By incorporating the expected value of sample information (EVSI), the ENBS finds the sample size (*n*) that maximizes the expected net benefit of sampling (ENBS). The ENBS is the difference between the EVSI and the expected cost of sampling [102].

$$\text{ENBS}(n) = \text{Population EVSI}(n) - \text{Cost}(n) \text{ [101]}, \quad (11)$$

where *n* is the sample size that maximizes the ENBS(*n*). For example, the ENBS for the CSII case study is the societal benefit of collecting information from a sample of *n* T1DM patients.

3.4 Research Design and Methods

Case Study: Continuous Subcutaneous Insulin Infusion (CSII) compared with Multiple Daily Injections (MDI)

A CEA of CSII compared to MDI produced ICERs of $123,041 and $122,015 per QALY from the health payer and societal perspectives, respectively. A sensitivity analysis found that the ICER was influenced by (1) the cost of CSII pump consumables, (2) the additional utility of CSII, (3) the rate of SHEs and (4) the effectiveness of CSII (in reducing the number of severe hypoglycemic events). At the current level of uncertainty, decision makers would be interested in knowing whether to adopt CSII given the existing evidence or whether more information is

required before a decision is made, and if more information is needed – how much value would there be in reducing the level of uncertainty around these variables? A VOI analysis was performed using the decision model of CSII versus the decision model of MDI (see chapter 2 for an in-depth discussion of the rationale, the decision model description, and the relevant variables).

Expected Value of Information (EVPI) for CSII compared with MDI

To estimate the EVPI for CSII compared to MDI, a Monte Carlo simulation was used. Ten thousand (10,000) cycles were run and the net monetary benefit (NMB) of each iteration was calculated, using equation 8 (Eq. 8), for CSII and for MDI at a specific ICER threshold. The first term in the EVPI equation (Eq. 7), $E_{\theta}max_{t}B(t,\theta)$, represents perfect information and is the average of the highest NMB across treatment groups (CSII and MDI). For example, if a decision maker knew the parameters with certainty, he/she would be able to choose the treatment (CSII or MDI) with the highest NMB for every situation and for every patient, thus maximizing the NMBF.

The second term of the EVPI equation (Eq. 7), $max_{t}E_{\theta}B(t,\theta)$, represents current information, and is the average NMB of each treatment group (CSII or MDI). For example, based on current information, a decision maker knows only which treatment has the highest NMB and would choose the treatment that maximizes the NMB. The EVPI is the difference between the average NMB with perfect information and the average NMB with current information and represents the upper bound of the cost of additional research. This calculation was performed over numerous ICER thresholds ($0 to $300,000 per QALY).

The population EVPI (PEVPI) was calculated by multiplying the EVPI by the number of patients that would potentially use CSII over the time horizon (five years) of the analysis. Since

this is not known with certainty, the PEVPI was calculated over potential T1DM populations of 100, 250, and 500 patients per year over the lifetime (five years) of the technology. A 5% discount rate was applied[34].

Expected Value of Partial Perfect Information (EVPPI) for CSII versus MDI

To estimate the EVPPI for CSII compared to MDI, a two loop (outer and inner) MC simulation (Figure 2) was used. The outer loop sampled a value from the target parameter of interest (e.g. QALYs gained from CSII) and the sampled value was considered to be one possible realization, or full knowledge of the parameter or parameter group. This "known" value was entered into the inner loop of the MC simulation. The remaining unknown variables in the inner loop were sampled from their respective distributions to represent the uncertainty that exists around CSII and MDI. The inner loop MC simulation was repeated 1000 times and the NMB (Eq. 8) of each treatment was calculated and recorded. When 1000 cycles of the inner loop were completed, the outer loop sampled another value of the parameter of interest and the value was entered into the inner loop of the MC simulation and the inner loop cycles were repeated. The outer sampling of the parameter of interest was performed 100 times, that is, 100 NMBs were recorded for CSII and MDI.

The first term of the EVPPI equation (Eq. 9), $E_{\theta i}max_t E_{\theta|\theta i}B(t,\theta)$, represents a perfect knowledge parameter (or parameter group), and is the average of the highest NMB (Eq. 8) over the treatment groups CSII and MDI. For example, if a decision maker knew the health related quality of life with certainty, the decision maker would be able to choose the treatment (CSII or MDI) with the highest NMB, given the level of uncertainty around other parameters, for each situation and for each patient, thus maximizing the NMB.

[34] $\Sigma n/((1-r)^{(t-1)})$, where n is the number of eligible patients per year, r is the discount rate, and t is the year (1,…, 5).

The second term of the EVPPI equation (Eq. 9), $\max_t E_\theta B(t,\theta)$, represents current information, and is the average NMB of each treatment group (CSII or MDI). For example, based on current information, a decision maker knows only which treatment has the highest NMB and would choose the treatment that maximizes the NMB. The EVPPI is the difference between the NMB expected with perfect information and the NMB expected with current information and represents the upper bound of additional research to investigate the uncertainty around QALYs.

The EVPPI was performed at numerous ICER thresholds for different parameters of interest. The variables were drawn from the CEA of the CSII versus MDI (see chapter 2). The sensitivity analysis identified three variables that had an impact on the ICER and were therefore considered uncertain: (1) epidemiologic parameters[35], (2) the cost of CSII consumables, and (3) the QALYs associated with CSII.

The population EVPPI (PEVPPI) was calculated by multiplying the EVPPI by the number of patients that would potentially use CSII over the time horizon (five years) of the analysis. Since the population size that would qualify for CSII technology is unknown, the PEVPPI were calculated over the potential T1DM populations of 100, 250, and 500 per year.

Expected Value of Sample information for CSII Parameters versus MDI Parameters

To estimate the EVSI of uncertain parameters (e.g., cost of consumables, rate of SHEs, QALYs associated with CSII, reduction of SHEs associated with CSII) a two loop MC simulation was used (Figure 3). The outer loop of the EVSI calculation requires a randomly simulated sample (of size n). The simulated sample is used to compute a preposterior distribution – a combination of the current information and the potential information from collecting a

[35] Rate of SHEs, rate of diabetic ketoacidosis (DKA), mortality rate of SHEs, mortality rate of DKA, effectiveness of CSII in reducing SHEs, proportion of SHEs utilizing outpatient, inpatient, and emergency services.

sample (for a discussion of Bayesian analysis see Appendix C). This preposterior distribution was input into the inner loop of the MC simulation to calculate the EVSI. The outer loop was run for 100 cycles to calculate a preposterior distribution. The inner loop or MC simulation was run for 1000 cycles. This analysis was run for numerous sample sizes and the NMB of each cycle was recorded. The calculation of the EVSI was the same as the calculation of the EVPPI (section 3.1.2).

3.5 Results

Expected Value of Perfect Information

Health Payer Perspective

From the health payer perspective, the EVPI for a decision between CSII and MDI was calculated to be $8523 per patient at a cost effectiveness threshold of $125,000/QALY, where uncertainty is the highest (Figure 4; Table 1); the population EVPI (PEVPI) for 100, 250, and 500 patients (per year) over five years who would eligible to receive CSII instead of MDI was calculated to be $3.93, $9.82, and $19.6 million, respectively (Figure 4: Table 1).

Societal Perspective

From the societal perspective, the per patient EVPI was calculated to be $8351; the population EVPI (PEVPI) for 100, 150, and 500 patients per year who would eligible to receive CSII instead of MDI was calculated to be $3.80, $9.49, and $19.0 million, respectively (Figure 5; Table 1).

At a cost effectiveness threshold of $125,000/QALY, the EVPI was calculated to be upwards of $19.6 million. Additional evidence would be potentially worthwhile if the research costs less than the PEVPI for the respective potential populations.

Expected Value of Partial Perfect Information

Health Payer Perspective

- ***QALYS Associated with CSII***

The EVPPI per patient for the QALYs associated with CSII was calculated to be $5,779; the population EVPPI for 100, 250, and 500 eligible patients per year over five years who would be eligible to receive CSII instead of MDI was calculated to be $2.6, $6.6, and $13.1 million dollars, respectively (Figure 6; Table 2).

- ***Cost of CSII consumables***

The EVPPI per patient for the cost of consumables was calculated to be $1,949; the population EVPPI for 100, 250, and 500 eligible patients per year over five years who would be eligible to receive CSII instead of MDI was calculated to be $0.88, $2.2, and $4.4 million dollars, respectively (Figure 6; Table 3).

- ***Epidemiologic parameters***

The per patient EVPPI for the epidemiological parameters was calculated to be $4,479; the population EVPPI for 100, 250, and 500 eligible patients each year over five years who would be eligible to receive CSII instead of MDI was calculated to be $2.0, $5.1, and $10.1 million, respectively (Figure 6; Table 4).

Societal Perspective

- ***QALY s associated with CSII***

The EVPPI per patient for the QALY associated with CSII was calculated to be $5,954; the population EVPPI for 100, 250, and 500 eligible patients per year over five years who would be eligible to receive CSII instead of MDI was calculated to be $2.7, $6.8, and $13.5 million dollars, respectively (Figure 7; Table 2).

- ***Cost of CSII consumables***

The EVPPI per patient for the cost of consumables was calculated to be $2,206; the population EVPPI for 100, 250, and 500 eligible patients each year over five years who would be eligible to receive CSII instead of MDI was calculated to be $ 1.0, $2.5, and $5.0 million dollars, respectively (Figure 7; Table 3).

- ***Epidemiologic parameters***

The per patient EVPPI for epidemiological parameters was calculated to be $4,883, the population EVPPI for 100, 250, and 500 eligible patients per year over five years who would be eligible to received CSII over MDI was calculated to be $2.2, $5.5, and $11.1 million dollars, respectively (Figure 7; Table 4).

At a threshold of $125,000/QALY, conducting additional research into specific parameters would be potentially worthwhile if the research costs less than the PEVPPI for the respective population sizes.

Expected Value of Sample Information and the Expected Net Gain of Sampling

- ***QALYs Associated with CSII***

For a potential sample of 300 patients, from the health payer perspective, the per patient EVSI for QALYs associated with CSII was calculated to be $4,485 and the population EVSI was calculated to be 10.2 million for the potential population (n = 500 per year) of eligible patients over five years (Figure 8; Table 5). Comparing the EVSI with the cost of research at ($600,000), the expected net benefit of collecting more information on the QALYs associated with CSII was $9.6 million.

- ***Effectiveness of CSII***

For a sample of 300 patients, the per patient EVSI for the effectiveness of CSII in reducing SHEs was calculated to be $206 and for the population EVSI was calculated to be $468,656 (Figure 9; Table 6). Comparing the EVSI with the cost of research at $600,000, the expected net benefit of collecting more information on the effectiveness of CSII is -$131,344; the cost of the research is more expensive than the EVSI for the effectiveness of CSII at reducing SHEs.

- ***Rate of SHEs***

The per patient and population EVSI for the rate of SHEs was calculated to be $0 for all sample sizes. Therefore, there is no benefit in collecting information on the rate of SHEs or the effectiveness of CSII at reducing SHEs in the population.

EVSI from the Societal Perspective

The EVSI results from the societal perspective were similar to the EVSI results from the health payer perspective (Table 5; Table 6; Figure 10; Figure 11). Given the uncertainty in QALYs associated with CSII compared to QALYs associated with MDI, the EVSI results indicate that research into the QALYs associated with CSII is worthwhile.

3.6 Discussion

The results of a VOI analysis can be used as an additional sensitivity analysis to measure the level of uncertainty around a decision model's parameters. The VOI analysis result may aid in additional understanding of model uncertainty attributed to parameters or parameter groups. For example, the CSII case study, from the societal perspective, calculated an EVPI of $19.0 million and an EVPPI of $11.1, $5.0, and $13.5 million dollars for epidemiologic parameters, cost of CSII consumables, and QALYs associated with CSII, respectively. The ENBS found that a sample of 300 patients at a cost of $600,000 would provide an ENBS of $9.6 million. The case study suggests that investing in a study to investigate the QALYs associated with CSII may be

potentially worthwhile, however, the ability of additional research to reduce uncertainty depends on the feasibility, quality, sample sizes, and time horizons of the studies [103].

Value of information analyses have often been advocated to inform priority setting decisions, aid in clinical decision making [104], and support research recommendations [105, 106]. However, evidence for its application in decision making is scarce, despite being promoted by NICE [105, 106] and CADTH [46]. Keisler et al. (2014) [81] reviewed the prevalence of VOI applications reported in peer reviewed literature between the years 1990 and 2011, and found an increase in the application of VOI analysis over this period, especially in the medical field. The increased application of VOI analysis in the medical field is due to a greater concern around treatment costs, the increased availability of new health technologies, an increased push for more centralized decision making, and a desire to address patient risk [81]. These medical applications tend to focus on loss avoidance[36] as a criterion and on single attribute cost benefit value measures such as information cost, sensitivity analysis, decision trees, and discrete uncertainties [81]. VOI was found to be applied to generic situations with no specific identifiable individual decisions and decision makers [81]. VOI analyses are attempts to produce insight into a decision problem and they increase in complexity as they move from problems that dominate individual decision makers to problems of health care institutions or organizations [81].

VOI is a powerful sensitivity analysis measure that addresses the limitations of CEA research by communicating the level of uncertainty around a decision (or decision model). In the case study of CSII compared to MDI, the ability of research to reduce uncertainty will depend on the feasibility of studies targeting the uncertain parameters and their sample sizes, which need to be clearly defined and agreed upon by stakeholders. For example, capturing more information on

[36] Loss avoidance – decision focused primarily on avoiding potential negative consequences rather than on positive results from improvements in the status quo.

the QALYs of CSII compared with the QALYs of MDI would require stakeholder consultation to answer the following questions: (1) where does uncertainty lie in the QALYs? and (2) how should such uncertainty be resolved? Two questions would be: what specific information on QALYs would reduce decision risk? and what methods should be used to gather additional evidence? VOI analysis can suggest where the potential uncertainty lies. However, how to resolve such uncertainty is less clear.

Strengths and Limitations

The present study applied VOI analysis to compare CSII with MDI. Strengths of this study are: (1) the study adds a VOI analysis to the CEA analysis, as recommended by CADTH [46] and (2) the EVPI, the EVPPI, and the EVSI were calculated using nonparametric methods [98]. The fact that the VOI analysis focused on a small subset of parameters is a limitation of the study. However, the parameters used are assumed to be the main parameters influencing CSII in Alberta[37]. They are quantifiable and are assumed to be important in the management of T1DM – uncertainty with respect to other unquantifiable parameters such as well-being, productivity, the role of diabetes education, the benefits of health care support networks, and effective implementation of CSII in the target population should be analyzed and incorporated into the decision making process. A second limitation involved the number of cycles for the inner (1000 iterations) and outer (100 iterations) loops in estimations of the EVPPI and the EVSI; the number of iterations was fewer than the number recommended in literature[38] [98]. The reliability and validity of the results were thus somewhat compromised.

The case study found that designing a study to collect additional information on the health outcomes of CSII was potentially worthwhile. Performing VOI analysis alongside CEA

[37] Defined in the decision model (see chapter 2).
[38] Over 1000 cycles for both inner and outer loops are recommended.

improves the communication of uncertainty to decision makers. The study demonstrates a real world application of VOI analysis and the challenges that remain for its widespread application.

Policy Implications

Currently, the value of information analysis in health policy is limited, due to (1) heavy computational time, (2) the complexity involved in interpreting and applying the relevant information to social, economic, and political environments where health policy decisions are made, and (3) a limited knowledge of decision maker preferences on which to base the interpretation of VOI analyses. First, computing the minimum recommended number of cycles [98] (1000 inner and 1000 outer) for EVPPI and EVSI at one threshold value (λ) is estimated to require over five hours for EVPPI and over four days for EVSI[39]. Computation of EVPPI and EVSI at various ICER thresholds (λ) would take substantially longer, for instance, computation over five threshold values with a minimum of 1000 inner and outer loops (Figure 2, Figure 3) would require 25 hours for EVPPI and over 20 days for EVSI. New methods have been developed to shorten the time required to calculate EVPPI [107-110] and EVSI [111-113], but such methods require specific assumptions to be applied to a specific analysis.

Second, the results of a VOI analysis need to be interpreted and applied to current social, economic, and political environments where decisions involving numerous stakeholders are being made. For example, the VOI analysis found an EVPI of $19.6 million for CSII compared to MDI, which represents the upper bound to the funding needed for the comparative CSII-MDI research. The decision to fund research depends on (1) the health care budget, (2) the program's costs and benefits, and (3) the range of programs available for funding. None of this information is known or communicated through the VOI analysis. In addition, the VOI analysis brings into

[39] The EVSI was calculated over 20 sample sizes (1, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 750, 1000, 1500, 2000).

question the nature of uncertainty. The German physicist Werner Heisenberg's Uncertainty Principle states that, "the more precisely the position is determined, the less precisely the momentum is known in this instant, and vice versa." In other words, "absolutely perfect knowledge is impossible and therefore absolutely perfect prediction is impossible" [114]. Prediction is not guaranteed by the amount of information one has or the level of measurement one has determined, it is a matter of statistics and probability [114].

It is possible to reduce uncertainty through the collection of more data with more research and observation, by analyzing data with the increasing computational capabilities, and through applying more logic to solve a problem. However, this avoids the real nature of uncertainty. The "fuzziness" in nature referred to in Heisenberg's Uncertainty Principle implies that there is a fundamental limit to what can be known and points to the impossibility of perfect prediction [114]. Policy makers must function in an environment where the social, economic, and political environments are constantly influencing the way decision variables unfold. In the case of CSII, the data can suggest but not predict how effective this health technology will be in improving population health, particularly when population needs change over time.

Third, the calculation of a net monetary benefit (NMB), which must be included in a VOI analysis, requires the utility function of a decision maker to be established [115]; in this case study, the utility function is in the form of an ICER threshold, or the willingness to pay for an additional QALY. The analysis assumes a single decision maker, but in reality, the decision making process involves multiple decision makers (and stakeholders), and to establish a utility function for multiple decision makers with unknown preferences is challenging [115]. In the case study, uncertainty regarding the benefits of CSII is the highest at the ICER threshold of $125,000/QALY, and due to the unknown preferences of decision makers, the VOI analysis was

calculated over a range of ICER threshold values. Based on the analysis, decision makers must choose a relevant ICER threshold and draw conclusions regarding the adoption of CSII.

3.7 Conclusions

The EVPI and EVPPI was calculated for varaious ICER thresholds and potential population sizes. At an ICER threshold of $125,000 for a potential T1DM population of 500, the EVPI was calculated to be $19.6 million and $19.0 million from the health payer and the societal perspectives, respectively. The EVPPI was calculated to be $13.1, $4.4, $10.1 and $13.5, $5.0 and $11.1 million for QALYs associated with CSII, costs of CSII consumables, and epidemilogic parameters[40] from the health payer and societal perspectives, respeectively.

The EVSI was calculated, from the health payer perspective, for a potential study sample of 300 T1DM patients at an ICER threshold of $125,000. The EVSI was calculated to be $10.2, $0.5 and $0 million for QALYs associated with CSII, costs of CSII consumables and epidemilogic parameters. Comparing the EVSI with the cost of research at ($600,000), the expected net benefit of collecting more information on the QALYs associated with CSII was $9.6 million.

Some experts describe CEA and VOI analysis in the context of the decision making process – a process that incorporates all stakeholders whose interests can be then used to direct scarce resources. Others restrict CEA and VOI analysis as quantitative assessments of the level of uncertainty in a decision. CEA and VOI analysis should be viewed as decision support tools that do not encompass the entire decision making process. Current decision analysis tools and thinking are needed to avoid the streetlight effect, which is a type of observational bias that occurs when people are searching for something and only look where it is the easiest to find.

[40] Rate of SHEs, rate of diabetic ketoacidosis (DKA), mortality rate of SHEs, mortality rate of DKA, effectiveness of CSII in reducing SHEs, proportion of SHEs utilizing outpatient, inpatient, and emergency services.

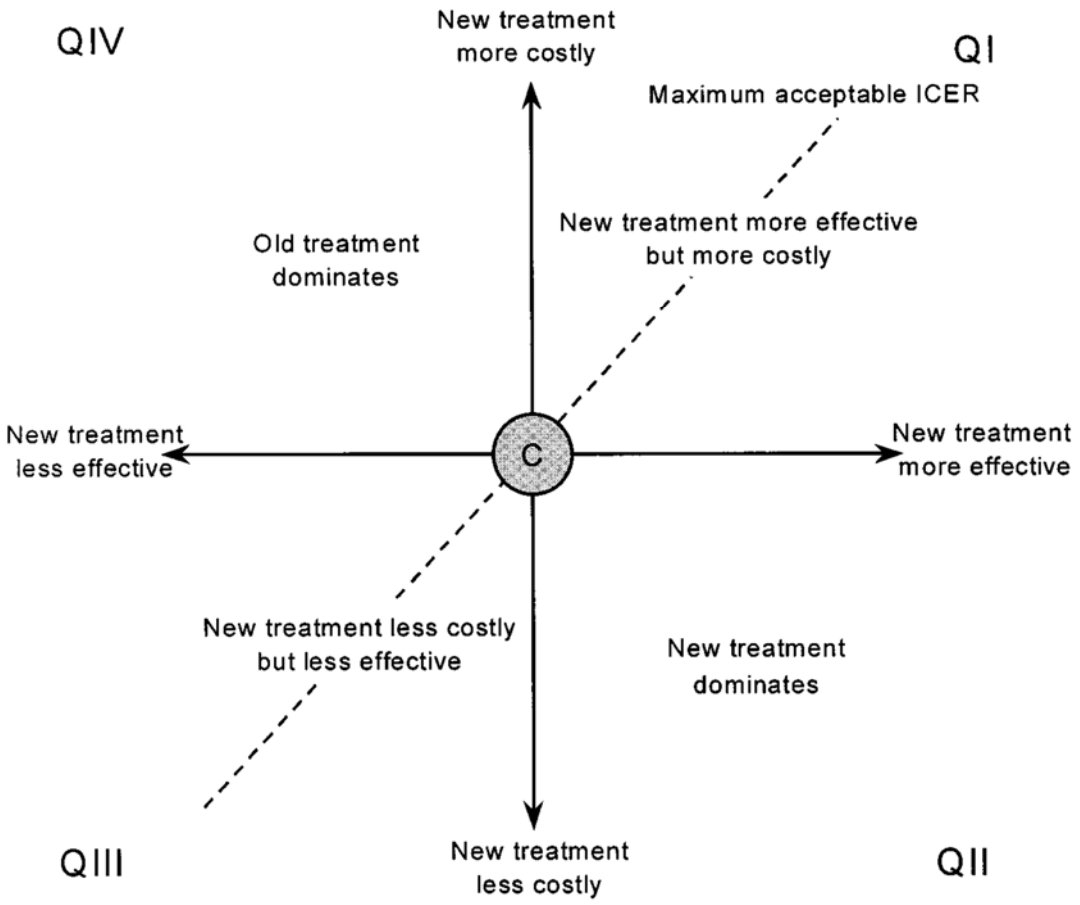

Figure 3-1: The cost effectiveness plane comparing a new health technology to a currently provided treatment (from Briggs and Fenn, 1998 [116]).

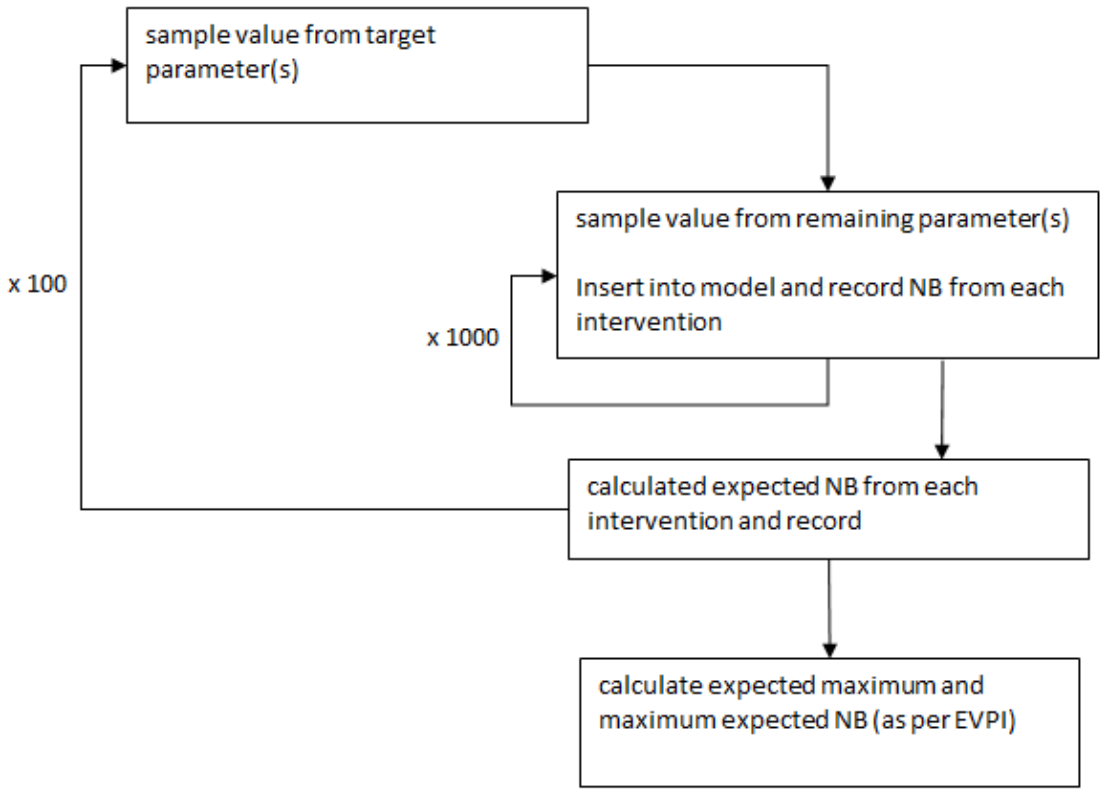

Figure 3-2: Calculation process for EVPPI (from Wilson, 2015 [98]).

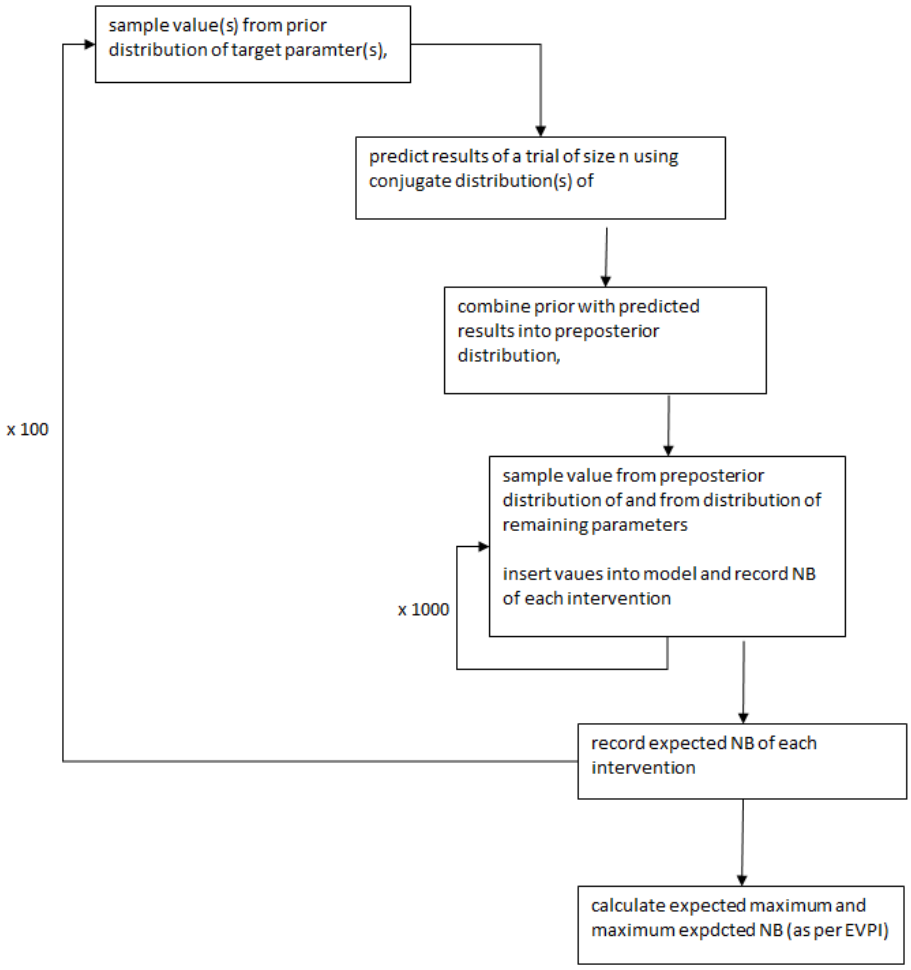

Figure 3-3: Calculation process for EVSI (from Wilson, 2015 [98]).

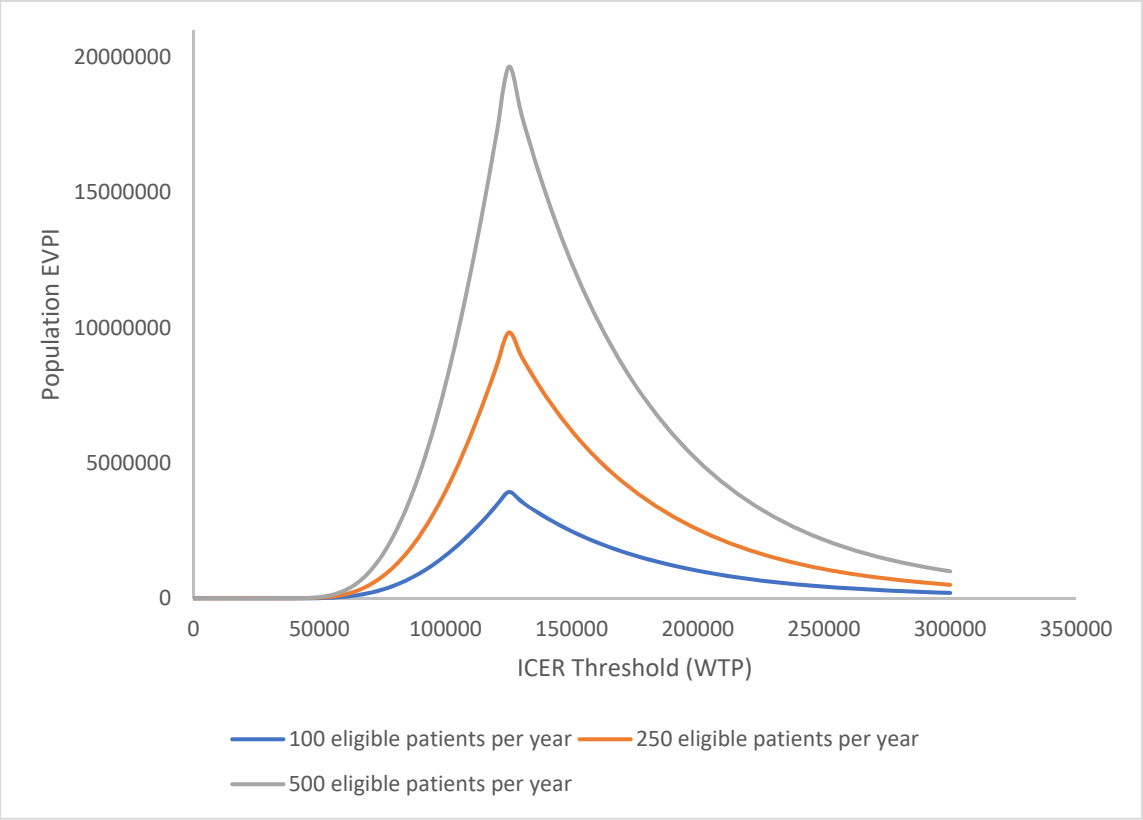

Figure 3-4: Population EVPI of CSII vs. MDI for various potential T1DM populations from the health payer perspective.

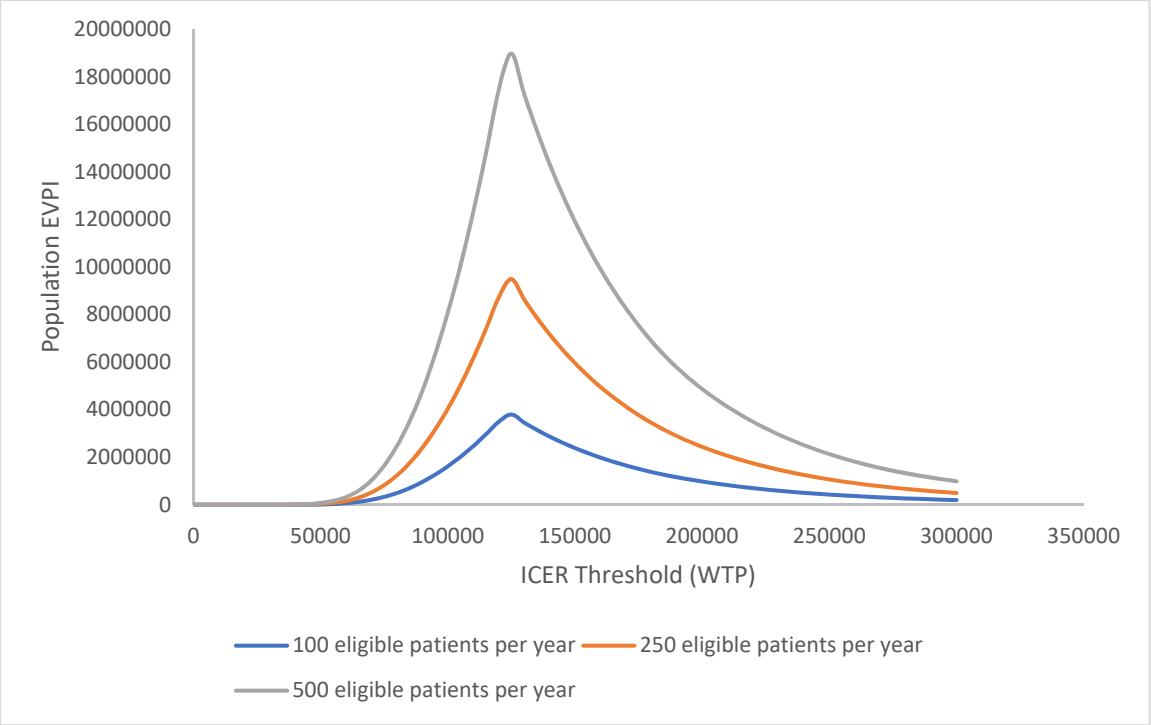

Figure 3-5: Population EVPI of CSII vs. MDI for various potential T1DM populations from the societal perspective.

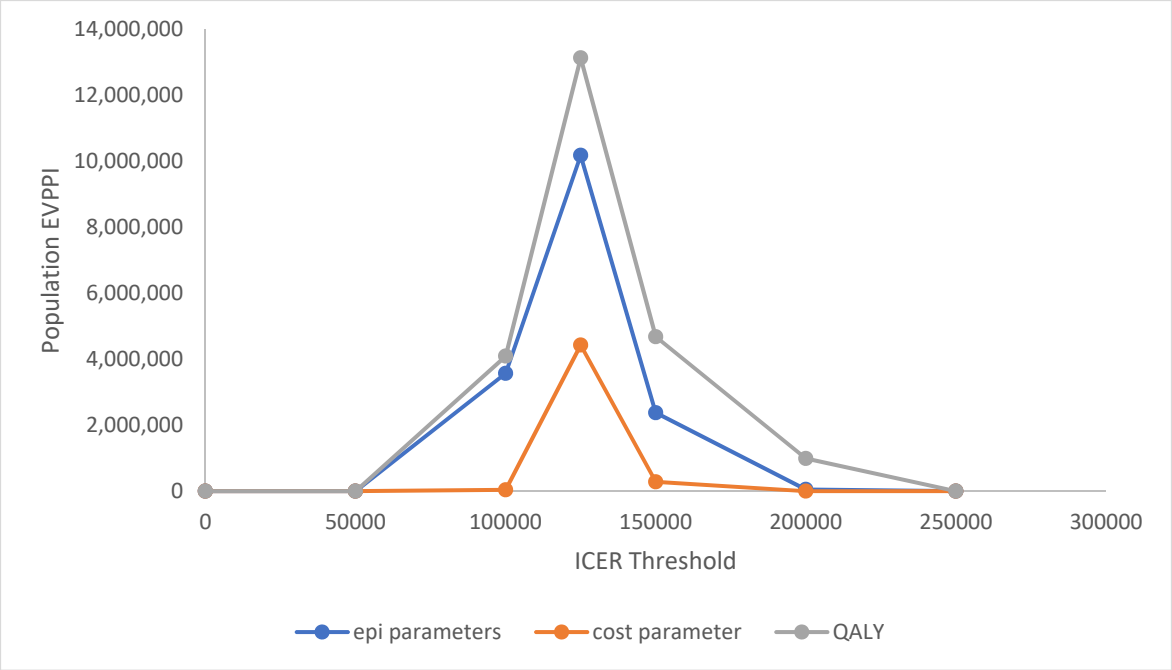

Figure 3-6: Population EVPI of CSII vs. MDI for (1) QALYs associated with CSII, (2) CSII consumables, and (3) epidemiologic parameters associated with T1DM from the health payer perspective.

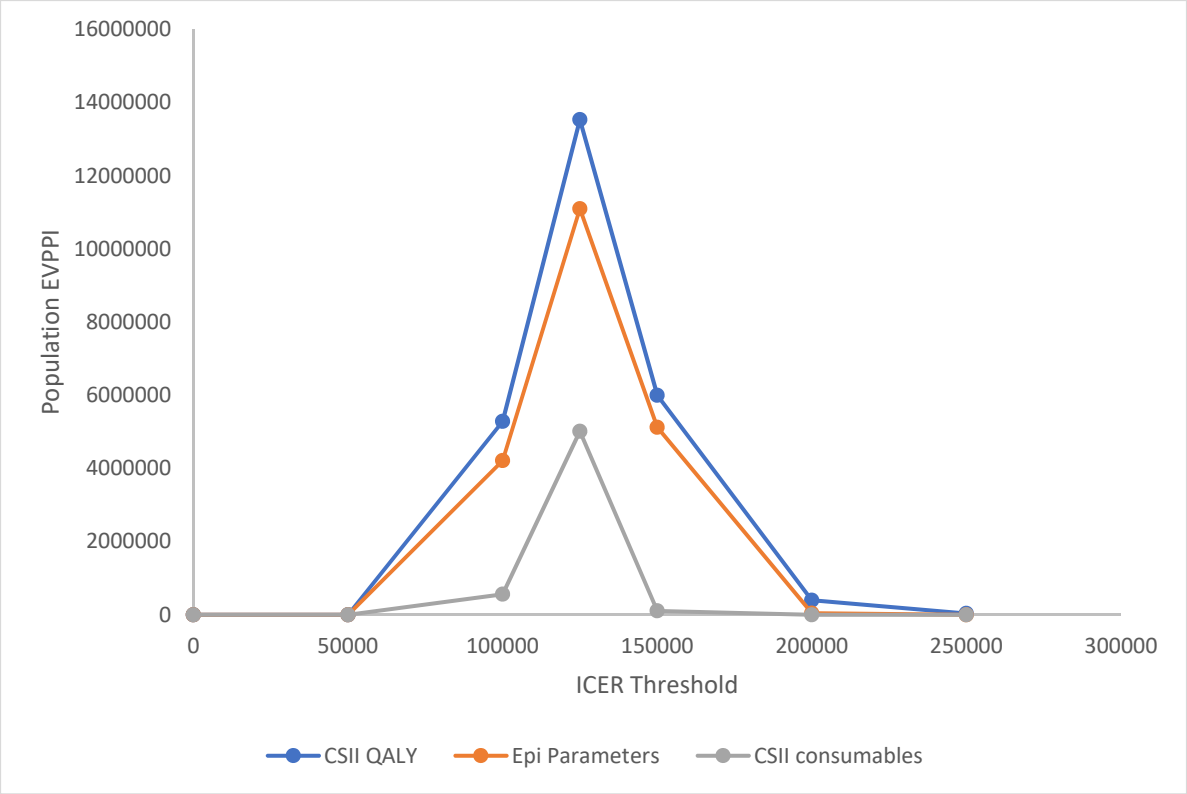

Figure 3-7: Population EVPI of CSII vs. MDI for (1) QALYs associated with CSII, (2) CSII consumables, and (3) epidemiologic parameters associated with T1DM from the societal perspective.

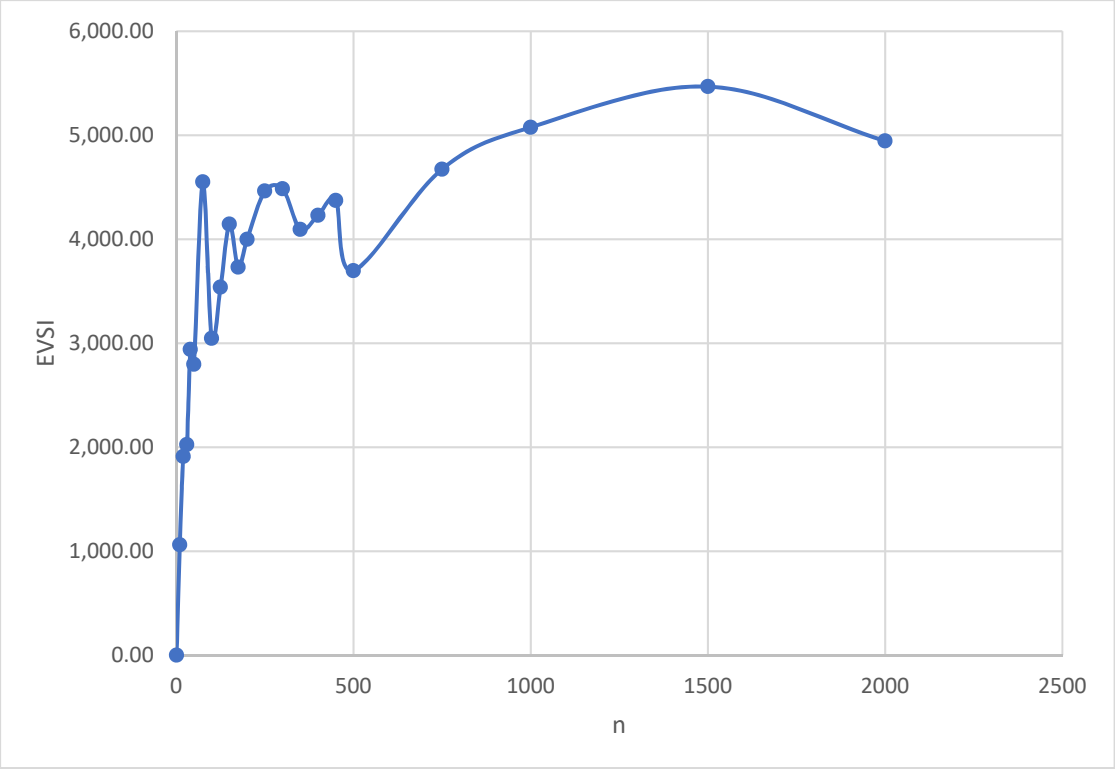

Figure 3-8: EVSI per patient for QALYs associated with CSII from the health payer perspective for various sample sizes.

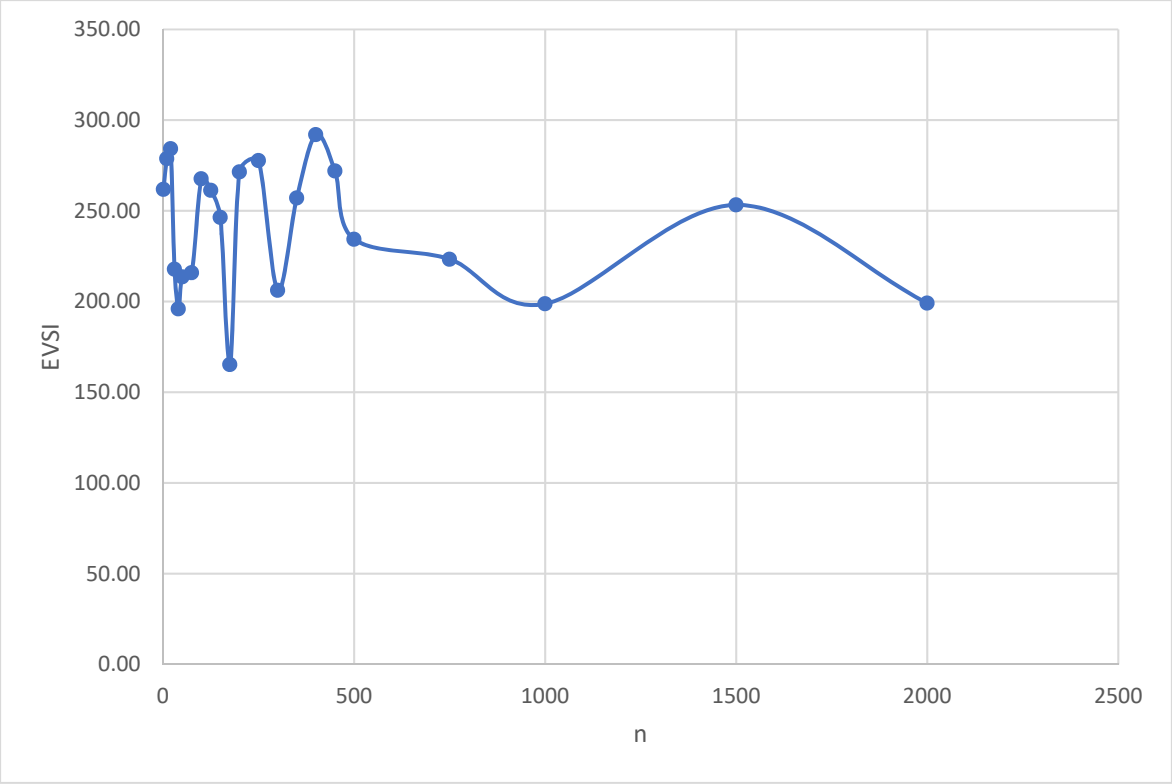

Figure 3-9: EVSI per patient for effectiveness of CSII compared to MDI from the health payer perspective for various sample sizes.

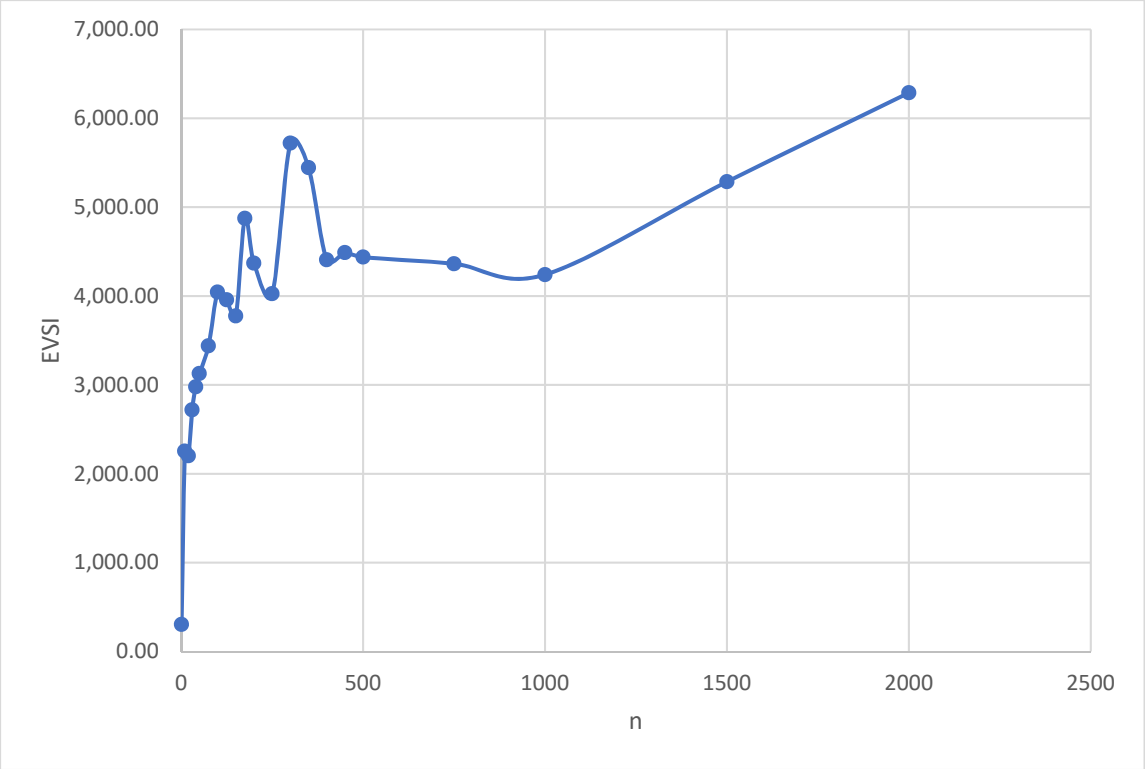

Figure 3-10: EVSI per patient for QALYs associated with CSII from the societal perspective for various sample sizes.

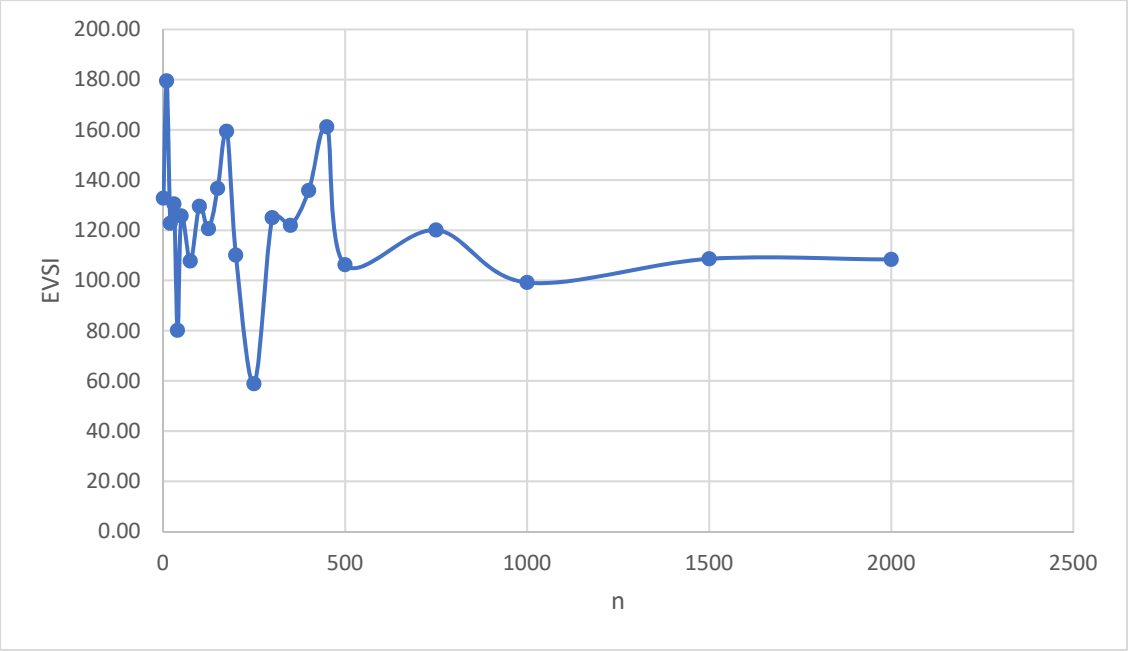

Figure 3-11: EVSI per patient for effectiveness of CSII compared to MDI from the societal perspective for various sample sizes.

Table 3-1: Expected value of perfect information (EVPI) for various ICER thresholds

	Health Payer				Societal			
ICER Threshold or WTP	individual	n=100	n=250	n=500	individual	n=100	n=250	n=500
0	0	0	0	0	0	0	0	0
1,000	0	0	0	0	0	0	0	0
10,000	0	0	0	0	0	0	0	0
20,000	0	0	0	0	0	0	0	0
30,000	0	0	0	0	0	0	0	0
35,000	0	0	0	0	0	205	513	1,025
40,000	1	354	885	1,769	3	1,319	3,297	6,593
45,000	5	2,056	5,140	10,280	12	5,438	13,595	27,190
50,000	21	9,467	23,668	47,337	34	15,409	38,523	77,046
55,000	57	25,809	64,524	129,047	73	33,108	82,770	165,541
60,000	126	57,310	143,275	286,551	141	64,122	160,306	320,611
65,000	251	113,920	284,801	569,602	262	119,064	297,660	595,319
70,000	444	201,933	504,833	1,009,665	454	206,534	516,335	1,032,670
75,000	712	323,627	809,068	1,618,135	726	330,175	825,437	1,650,874
80,000	1,070	486,552	1,216,379	2,432,758	1,087	494,352	1,235,881	2,471,762
85,000	1,522	692,010	1,730,025	3,460,051	1,547	703,317	1,758,293	3,516,587
90,000	2,074	942,919	2,357,296	4,714,593	2,112	960,225	2,400,562	4,801,123
95,000	2,726	1,239,236	3,098,089	6,196,178	2,782	1,264,731	3,161,828	6,323,656
100,000	3,489	1,586,246	3,965,614	7,931,228	3,557	1,616,810	4,042,025	8,084,050
105,000	4,355	1,979,671	4,949,177	9,898,355	4,434	2,015,781	5,039,452	10,078,903
110,000	5,319	2,418,164	6,045,410	12,090,819	5,420	2,463,731	6,159,328	12,318,656
115,000	6,371	2,896,148	7,240,370	14,480,740	6,507	2,958,121	7,395,302	14,790,604
120,000	7,514	3,415,683	8,539,208	17,078,416	7,679	3,490,972	8,727,431	17,454,862
125,000	8,643	3,929,180	9,822,950	19,645,899	8,351	3,796,445	9,491,113	18,982,226
130,000	7,875	3,579,734	8,949,335	17,898,670	7,604	3,456,590	8,641,474	17,282,948

135,000	7,176	3,262,084	8,155,209	16,310,419	6,926	3,148,585	7,871,463	15,742,926
140,000	6,541	2,973,609	7,434,022	14,868,043	6,308	2,867,762	7,169,405	14,338,810
145,000	5,966	2,712,051	6,780,126	13,560,253	5,750	2,614,049	6,535,122	13,070,245
150,000	5,444	2,474,982	6,187,455	12,374,910	5,240	2,382,088	5,955,220	11,910,439
155,000	4,973	2,260,554	5,651,386	11,302,772	4,778	2,172,051	5,430,129	10,860,257
160,000	4,542	2,064,946	5,162,365	10,324,730	4,360	1,981,897	4,954,743	9,909,486
165,000	4,153	1,888,157	4,720,393	9,440,787	3,981	1,809,766	4,524,414	9,048,828
170,000	3,800	1,727,438	4,318,595	8,637,190	3,635	1,652,369	4,130,922	8,261,844
175,000	3,476	1,580,286	3,950,715	7,901,430	3,319	1,508,814	3,772,034	7,544,068
180,000	3,182	1,446,733	3,616,832	7,233,665	3,033	1,378,842	3,447,104	6,894,208
185,000	2,915	1,325,290	3,313,225	6,626,450	2,774	1,260,859	3,152,146	6,304,293
190,000	2,671	1,214,040	3,035,099	6,070,198	2,540	1,154,691	2,886,729	5,773,457
195,000	2,446	1,111,943	2,779,856	5,559,713	2,330	1,059,251	2,648,128	5,296,256
200,000	2,239	1,017,798	2,544,495	5,088,989	2,141	973,166	2,432,914	4,865,828
205,000	2,050	931,914	2,329,784	4,659,568	1,969	895,252	2,238,131	4,476,262
210,000	1,878	853,512	2,133,780	4,267,561	1,812	823,733	2,059,331	4,118,663
215,000	1,719	781,475	1,953,688	3,907,376	1,667	757,787	1,894,468	3,788,935
220,000	1,575	715,903	1,789,758	3,579,517	1,534	697,370	1,743,425	3,486,850
225,000	1,445	656,974	1,642,434	3,284,868	1,412	641,873	1,604,682	3,209,365
230,000	1,328	603,481	1,508,703	3,017,406	1,300	590,806	1,477,016	2,954,032
235,000	1,221	554,855	1,387,136	2,774,273	1,196	543,778	1,359,445	2,718,890
240,000	1,122	510,062	1,275,155	2,550,310	1,101	500,587	1,251,467	2,502,935
245,000	1,033	469,403	1,173,507	2,347,014	1,015	461,337	1,153,342	2,306,683
250,000	951	432,315	1,080,789	2,161,577	935	425,045	1,062,613	2,125,226
255,000	876	398,207	995,518	1,991,035	863	392,326	980,815	1,961,631
260,000	808	367,359	918,398	1,836,796	796	362,054	905,135	1,810,269
265,000	746	339,243	848,107	1,696,214	736	334,358	835,896	1,671,792
270,000	690	313,616	784,039	1,568,078	680	309,286	773,215	1,546,430
275,000	638	289,971	724,928	1,449,855	631	286,824	717,060	1,434,121
280,000	591	268,571	671,427	1,342,853	586	266,240	665,600	1,331,201

285,000	548	249,161	622,903	1,245,805	543	246,923	617,307	1,234,614
290,000	509	231,370	578,424	1,156,849	503	228,865	572,163	1,144,327
295,000	473	214,865	537,162	1,074,324	467	212,271	530,677	1,061,354
300,000	439	199,750	499,375	998,750	434	197,115	492,788	985,576

Table 3-2: Expected value of partial perfect information for QALYs associated with CSII

	Health Payer				Societal			
ICER threshold	Individual	n=100	n=250	n=500	Individual	n=100	n=250	n=500
0	0	0	0	0	0	0	0	0
50,000	0	0	0	0	0	0	0	0
100,000	1,801	818,533	2,046,332	4,092,664	2,325	1,056,904	2,642,261	5,284,522
125,000	5,779	2,627,244	6,568,110	13,136,220	5,954	2,706,533	6,766,333	13,532,666
150,000	2,060	936,301	2,340,753	4,681,505	2,639	1,199,694	2,999,234	5,998,469
200,000	436	197,981	494,953	989,906	174	79,203	198,007	396,014
250,000	0	0	0	0	16	7,281	18,201	36,403

Table 3-3: Expected value of partial perfect information for CSII consumables

	Health Payer				Societal			
ICER threshold	Individual	n=100	n=250	n=500	individual	n=100	n=250	n=500
0	0	0	0	0	0	0	0	0
50,000	0	0	0	0	0	0	0	0
100,000	18	8,201	20,501	41,003	247	112,243	280,606	561,213
125,000	1,949	886,142	2,215,354	4,430,708	2,206	1,003,001	2,507,502	5,015,005
150,000	125	56,630	141,576	283,152	46	21,051	52,627	105,253
200,000	0	0	0	0	0	0	0	0
250,000	0	0	0	0	0	0	0	0

Table 3-4: Expected value of partial perfect information for epidemilogic parameters associated with T1DM

	Health Payer				Societal			
ICER threshold	Individual	n=100	n=250	n=500	Individual	n=100	n=250	n=500
0	0	0	0	0	0	0	0	0
50,000	0	0	0	0	0	0	0	0
100,000	1,572	714,527	1,786,317	3,572,635	1,853	842,591	2,106,478	4,212,956
125,000	4,479	2,036,131	5,090,329	10,180,657	4,883	2,219,748	5,549,371	11,098,742
150,000	1,046	475,580	1,188,950	2,377,899	2,253	1,024,415	2,561,038	5,122,076
200,000	23	10,627	26,566	53,133	19	8,655	21,637	43,275
250,000	0	0	0	0	0	0	0	0

Table 3-5: Health Payer EVSI

QALY					CSII Effectiveness				
n	EVSI	n=100	n=250	n=500	n	EVSI	n=100	n=250	n=500
1	0	0	0	0	1	262	119,016	297,540	595,080
10	1,062	482,724	1,206,810	2,413,620	10	279	126,698	316,745	633,490
20	1,912	869,161	2,172,903	4,345,807	20	284	129,181	322,954	645,907
30	2,025	920,456	2,301,139	4,602,278	30	218	99,015	247,538	495,076
40	2,941	1,336,881	3,342,203	6,684,406	40	196	89,086	222,716	445,432
50	2,798	1,271,753	3,179,382	6,358,764	50	214	97,106	242,764	485,528
75	4,552	2,069,347	5,173,368	10,346,737	75	216	98,144	245,359	490,718
100	3,046	1,384,860	3,462,149	6,924,298	100	268	121,665	304,163	608,325
125	3,539	1,608,853	4,022,134	8,044,267	125	261	118,764	296,911	593,822
150	4,145	1,884,379	4,710,948	9,421,896	150	246	111,981	279,951	559,903
175	3,731	1,695,982	4,239,955	8,479,909	175	165	75,126	187,814	375,628
200	4,000	1,818,185	4,545,462	9,090,925	200	271	123,386	308,466	616,931
250	4,464	2,029,524	5,073,809	10,147,618	250	278	126,220	315,549	631,099
300	4,485	2,038,799	5,096,999	10,193,997	300	206	93,731	234,328	468,656
350	4,095	1,861,645	4,654,113	9,308,226	350	257	116,849	292,123	584,246
400	4,230	1,922,717	4,806,794	9,613,587	400	292	132,720	331,799	663,598
450	4,373	1,988,161	4,970,403	9,940,806	450	272	123,615	309,037	618,075
500	3,698	1,681,233	4,203,082	8,406,164	500	234	106,515	266,288	532,576
750	4,674	2,124,648	5,311,621	10,623,241	750	223	101,510	253,776	507,551
1000	5,077	2,307,768	5,769,420	11,538,841	1000	199	90,362	225,905	451,809
1500	5,468	2,485,941	6,214,852	12,429,703	1500	253	115,134	287,835	575,670
2000	4,945	2,247,776	5,619,440	11,238,881	2000	199	90,509	226,272	452,545

Table 3-6: Societal EVSI

QALY					CSII Effectiveness				
n	EVSI	n=100	n=250	n=500	n	EVSI	n=100	n=250	n=500
1	305	138,654	346,635	693,269	1	133	60,348	150,870	301,741
10	2,255	1,024,984	2,562,461	5,124,922	10	179	81,573	203,934	407,867
20	2,202	1,001,069	2,502,672	5,005,343	20	123	55,807	139,518	279,036
30	2,718	1,235,540	3,088,849	6,177,698	30	130	59,313	148,282	296,563
40	2,977	1,353,422	3,383,556	6,767,112	40	80	36,411	91,026	182,053
50	3,127	1,421,392	3,553,481	7,106,962	50	126	57,141	142,852	285,703
75	3,438	1,562,885	3,907,213	7,814,426	75	108	48,977	122,442	244,883
100	4,043	1,837,913	4,594,782	9,189,564	100	130	58,884	147,210	294,420
125	3,958	1,799,250	4,498,124	8,996,248	125	121	54,822	137,055	274,110
150	3,775	1,715,963	4,289,909	8,579,817	150	137	62,111	155,277	310,555
175	4,874	2,215,778	5,539,446	11,078,891	175	159	72,471	181,178	362,356
200	4,370	1,986,620	4,966,551	9,933,101	200	110	50,043	125,108	250,215
250	4,025	1,829,796	4,574,489	9,148,978	250	59	26,742	66,856	133,712
300	5,720	2,600,080	6,500,201	13,000,401	300	125	56,824	142,060	284,119
350	5,444	2,474,759	6,186,897	12,373,794	350	122	55,429	138,571	277,143
400	4,407	2,003,316	5,008,289	10,016,578	400	136	61,748	154,371	308,742
450	4,489	2,040,760	5,101,900	10,203,800	450	161	73,277	183,192	366,384
500	4,438	2,017,313	5,043,282	10,086,564	500	106	48,288	120,719	241,439
750	4,363	1,983,451	4,958,628	9,917,256	750	120	54,579	136,446	272,893
1000	4,241	1,927,765	4,819,412	9,638,825	1000	99	45,074	112,685	225,370
1500	5,285	2,402,699	6,006,748	12,013,496	1500	109	49,374	123,434	246,868
2000	6,287	2,858,011	7,145,027	14,290,053	2000	108	49,256	123,139	246,278

Chapter 4: SWOT Analysis of the Continuous Subcutaneous Insulin Infusion Access with Evidence Development Study in Alberta, Canada

4.1 Introduction

At the launch of a new health technology, its manufacturer is expected to provide evidence of the quality, safety, and efficacy of the technology to regulatory authorities for licensing purposes [1]. However, this information may be inadequate or incomplete for decision makers dealing with the potential funding of the technology. Health technology assessment (HTA) systems have been put in place in many jurisdictions to generate information for reimbursement decisions. Even so, the HTA may not provide adequate information for payers, as there may still be uncertainties that are beyond the control of HTA bodies [2]. Access with evidence development (AED) schemes were devised to bridge this evidence gap. In Alberta, continuous subcutaneous insulin infusion (CSII), also known as insulin pump therapy (IPT), is the first health technology to be funded under an AED scheme.

An existing HTA of CSII [2] identified three main areas of uncertainty: (1) safety and health effectiveness[41], (2) cost effectiveness[42], and (3) system/resource requirements[43]. Given these uncertainties, Alberta Health, the provincial ministry of health, agreed to fund research to determine the real world effectiveness of CSII. The results of this research, which took the form of an AED, have been reported in earlier chapters of this thesis (see chapter 2 for an in-depth description of the case study; see chapter 3 for a value of information analysis). This chapter considers future AED applications, based on the experience with the CSII-AED.

[41] Diabetes malfunction, diabetes related emergency room visits, and other adverse events decreased compared to treatment with multiple insulin injections.
[42] Costs and health benefit from CSII compared with MDI in terms of health related quality of life and glycemic control.
[43] Health care utilization, cost per patient utilizing CSII.

Objectives

1. To conduct a strengths, weaknesses, opportunities, and threats (SWOT) analysis of the CSII-AED.
2. To present considerations for the establishment of AED as an ongoing policy option for introducing new health technologies.

4.2 Background

Case Study: Continuous Subcutaneous Insulin Infusion

On May 30, 2013, Alberta Health (AH) announced the availability of IPT (CSII) for Alberta residents with type 1 diabetes mellitus (T1DM) who meet eligibility and clinical requirements. The program provides funding for the cost of insulin pump supplies, less amounts covered through government sponsored agencies or through patient employer-sponsored or private insurance programs. Research has indicated that CSII is neither clearly inferior nor clearly superior to multiple daily insulin injections (MDI). For example, CSII was associated with a reduction in glycated hemoglobin tests (HbA1c) and a reduction in the total insulin dose; however, the long term consequences of treating T1DM with CSII are unknown [7-15]. The effect of CSII on the rate of hypoglycemic events is inconclusive. CSII has been shown to be effective in patients who have uncontrolled diabetes and who experience high rates of hypoglycemic events, but in patients who have well managed T1DM, the findings were ambiguous. [7-15]. The inconsistency in the literature could be due to inconsistent definitions of hypoglycemia [7, 9], short trial durations [12], inconsistent reports of hypoglycemia [10], and/or missing data [9], all of which result in an inability to capture long term health outcomes of CSII.

Nonetheless, CSII has been associated with a better health related quality of life than MDI [66], and patients using CSII appear to have higher levels of treatment satisfaction, higher

levels of autonomy in diabetes management, and lower levels of daily activity interference than patients using MDI [51, 67]. CSII is resource intensive, requiring ongoing insulin pump maintenance, the purchase of equipment and supplies, and care teams that include doctors, nurses, pharmacists, dietitians, and diabetes educators. While there are health benefits to CSII, the costs are greater than costs associated with MDI [29, 30]. In Alberta, the state of CSII technology diffusion is not known, neither is the amount of system resources required to implement CSII known.

Access With Evidence Development: CSII Therapy in Alberta

The planning and implementation of the AED study were overseen by a working group comprising representatives from Alberta Health (AH), Alberta Health Services (AHS), the Nutrition, Diabetes and Obesity Strategic Clinical Network, and academic researchers. Separate recruitment processes were developed for each of 11 clinics in the province with input from clinic staff to align available clinic resources for the study. Adult and pediatric patients with an interest in receiving insulin pump therapy through the provincial program were recruited to participate in the AED study. Interviews during enrollment (baseline) and follow up surveys (by mail, Internet, or in person, depending on preference) were conducted every three months. Several validated questionnaires were administered at each interview to measure the health-related quality of life of the patient, the caregiver burden, and patient satisfaction[44]. Additional information regarding how diabetes impacted patients, their experience with CSII, and their opinion of CSII was also collected. Patient-specific information was recorded in a registry. On a quarterly basis, AHS provided information on relevant laboratory results and diabetes related

[44] Health Utilities Index Mark 2 and Mark 3 (HUI2 and HUI3), EuroQol-5D-5L, EuroQol-5D-Youth, Diabetes Treatment Satisfaction Questionnaire (DTSQ), Child Health Utilities Index (CHU9D), Caregiver Burden Inventory (CBI).

encounters[45] with the health system. Alberta Health (AH) provided data on costs associated with these encounters and the cost of insulin pump-related supplies[46].

Information was collected from 340 patients (242 adults, 98 children) with type 1 diabetes mellitus in the CSII-AED study.

Presentations of the final CSII-AED report were given to multistakeholder groups: the Alberta Health IPT multistakeholder steering committee, comprising AH, AHS, diabetes patient organizations, and the device industry (established by the Alberta government), and to the Alberta Advisory Committee on Health Technologies (which oversees the HTA process in Alberta).

4.3 Methods

A SWOT analysis of the CSII-AED study was conducted using peer reviewed literature and stakeholder interviews. Health care organizations must continually adapt and adjust to maintain optimal function and require tools and techniques to identifying where improvements can be made [117]. By listing favorable and unfavorable internal and external factors in the SWOT analysis grid [118], policy makers can identify (1) how strengths can be leveraged to realize new opportunities, (2) how threats and weaknesses can be overcome and (3) future strategies [118]. There are four inputs to a SWOT analysis, internal strengths (S) and weaknesses (W) and external opportunities (O) and threats (T). Internal factors can be categorized into management and organizational, operations, finance, and others factors and external factors can be categorized into economic factors, social political factors, products and technology, demographics factors, markets and competition and others factors [119].

[45] Emergency room visits, out patient visits, inpatient stays.
[46] Blood glucose test strips, lancets, glucagon tablets, syringes, alcohol wipes, blood ketone test strips, urine ketone test trips, pin tip needle, infusion sets (tubing, insertion device, needle/cannula, adhesive, syringe, reservoir cartridge).

Literature review: A literature search of the electronic bibliographic databases PubMed, Embase, Web of Science, Econlit, CINAHL, and CRD DARE was conducted using the keywords: “coverage with evidence development,” access with evidence development,” “field evaluations,” “conditional listing,” “only in research,” “approval with research,” and “only with research.” Publication dates ranged from 2007 to 2017. Articles were selected for review if they provided information on challenges that AED studies have faced in various jurisdictions, or issues that have come up in their implementation. This information was then used to populate the external opportunities and threats parts of the SWOT table.

Stakeholder interviews: Individual administrators and health care professionals (from AH, AHS, and the Nutrition, Diabetes and Obesity Strategic Clinical Network) who were involved in the CSII-AED study were interviewed by telephone. Questions during the interviews were related to four broad categories: uncertainties, information, stakeholders, and implementation (see Appendix A). In addition, transcripts of interviews conducted by the AED research nurses with clinical staff of the 11 IPT clinics in the province were reviewed for relevant information. This information was incorporated into the SWOT analysis in Table 3. Based on the literature, responses from interviewees, and interview transcripts with clinic staff, a “global” SWOT analysis of the CSII-AED study was conducted. Interviews were analyzed using an inductive approach, that is, the data were analyzed without the use of a predetermined theory or structure. Thematic content analysis was used to identify characteristics of the CSII-AED scheme that affect its operational efficiency. For example, the internal factors for this study address questions like “What did the CSII-AED study do well?” and “What can the CSII-AED study improve on?” The external factors addressed questions like “What opportunities are available for a CSII-AED study?” and “What threats would harm a CSII-AED study?”

By matching strengths and weaknesses with opportunities and threats [119, 120], potential future applications of AED schemes were identified. These strategies were developed based on the CSII-AED study. The results of the SWOT analysis (Table 3) and the strategies developed to address the threats to CSII implementation were provided to AH and AHS stakeholders for comment and validation.

4.4 Results

Literature review

The peer reviewed papers presented information on experiences with and challenges facing AED studies that have been conducted in different countries. The information search of electronic bibliographic databases identified 145 citations of which 21 were selected for review (Table 1). Escalating health care cost, increasing number of health technology reimbursement requests and scarce health care resources [121, 122] have influenced decision making bodies to seek new evidence base platforms for decision making around medical devices, procedures and programs [121, 122]. Often the evidentiary base is incomplete, poor quality, conflicting, not based on "real world" effectiveness or there are concerns of implementation, uptake and diffusion of the new technology [121]. Inadequate evidence may result in a failure to make a policy decision and lead to passive diffusion, no diffusion or intuitive policy decision making [123].

AED schemes have been used to address an inadequate evidence based for decision making [124]. For example, economic evaluations may provide information on the value of a health technology through the calculation of an ICER, however, their specific model assumptions regarding unit costs, practice patterns or patient preferences may affect the transferability of economic evaluations to other jurisdictions [121]. Clinical evidence may have limited

transferability to other jurisdictions because of differences in (1) patient characteristics, (2) rates of compliance with therapies (3) human resource characteristics (level of expertise or training) and (4) health care system characteristics (available infrastructure, payment incentives) [121].

An AED scheme might provide a recommendation for coverage for a new product with associated limitations that may relate to the eligibility of specified patient groups or to a specific dose or dose duration requirement [4, 125]. Two examples that could profit from an AED scheme are: (1) a reimbursement situation where the new health technology could be reasonable and necessary for patients but adequate evidence and standards are lacking and (2) the collection of data is necessary to confirm that a new technology is being used as described by the coverage decision documentation [125].

The literature demonstrates that there is a general lack of evidence for the practicality of new technologies at the time of reimbursement decisions [126-128], and as a result, there has been growing demand for such evidence across health systems [125, 128, 129]. The use of AED schemes around the world reflect pressures for increasing accountability, transparency, and timeliness of decision making [127, 129-135]. This trend toward conditional coverage suggest a growing need for conditional approval and the integration of data collection into coverage and reimbursement schemes [123, 136, 137].

AED schemes have the potential to alter the reimbursement landscape for health technologies [136] but significant barriers and threats exist. These barriers and threats include an absence of established and credible research infrastructure [128, 138] and a lack of a stable source of funds needed to carry out the research at a reasonable cost and in a reasonable time frame [121, 128, 133]. The early detection of valuable technologies and the timing of relevant evidence for decision making are crucial [128, 133]. Research takes time before results are

available and this leads to a tension between the timing of the research and the needs of senior management [121]. The rigors of research methodology and the timing of evidence need to be balanced through timely AED scheme decisions and through stakeholder agreements about data requirements, data privacy and confidentiality issues, study designs, follow up time, and when and what evidence is needed to resolve decision uncertainty [121, 126, 134, 135, 139-142].

Stakeholder Interviews

Interviews with administrators and health care professionals from AH, AHS, and the strategic clinical network provided insights into how the CSII-AED study addressed uncertainties regarding safety and effectiveness, cost effectiveness, and system/resource requirements. Administrator and health care professionals felt that the study worked with the current health care environment and addressed uncertainties relevant to decision makers. For example, the study assessed the impact of the technology on patients with type 1 diabetes mellitus, health care providers, and funders by (1) asking patients for their reasons for starting the insulin pump therapy, (2) collecting additional information on quality of life and clinical outcomes for IPT, and (3) collecting insulin pump supplies and health care utilization data. The study collected qualitative and quantitative information that allowed the generation of evidence in the current decision making environment and provided insights on how insulin pump implementation impacted patients, health care providers, and funders.

Administrators and health care professionals felt that the data collection could have been broader, but barriers to increased data collection included privacy and data ownership issues, organizational barriers (e.g., organizational rules and policies and complex organizational structures), and resource limitations.

Nine (out of 11) clinic interviews (Table 2) indicated that operating the insulin pump program in Alberta is resource intensive. There are five phases to the insulin pump program in Alberta: (1) information sessions about insulin pump therapy, (2) insulin pump referral, (3) patient assessment (by appointment), (4) insulin pump approval and start, and (5) follow up and reassessment of IPT. In terms of patients who were already on the insulin pump or waiting to start pump therapy, clinics in the Edmonton area (Grey Nuns, Stollery Children's Hospital, Kaye Edmonton Clinic) saw 40 to 100 per month, clinics in the Calgary area (Calgary Metabolic Centre, Alberta Children's Hospital) saw up to 204 per month, and clinics outside of the Edmonton and Calgary areas (Red Deer Clinic, Lethbridge Clinic, Medicine Hat Clinic, Grande Prairie Clinic) saw two to 12 per month. Teams consisting of physicians, registered dietitians, registered nurses, and social workers were involved in developing recruitment for their respective clinics for the publicly funded IPT program, which involved training staff, reviewing objectives of the program, generating eligibility requirements and insulin pump suitability decision making tools, designing patient flow processes, and creating material for patient education.

During each phase of the program, members of the care team were responsible for reviewing material and/or collecting data for the CSII-AED program. For example, during the referral and insulin pre-pump information session phase, members of the care team (registered nurses, registered dietitians) reviewed online insulin pre-pump information tests, patient charts, laboratory results (HbA1c), food diaries, blood glucose testing practices, discussed insulin pump therapy with the family, and prepared and delivered insulin pre-pump information sessions.

The assessment phase for insulin pump therapy ranged from two to 24+ months depending on readiness and patient skill, which required ongoing support and assessment from

the care team. During the assessment phase, patients were followed up in person or by telephone two to 12 times a year to assess (1) whether the patient met the starting criteria, (2) patient interest, (3) patient readiness for IPT, and (4) patient goals for type 1 diabetes management. After insulin pump approval, IPT start and follow up required nurses and insulin trainers to prepare and conduct insulin pump and saline pump classes, and to follow up with patients who had started insulin pump therapy. Implementation of CSII in Alberta required substantial upfront and continued time and resource commitment to ensure the success of the program. Preparation and delivery of insulin pump and saline pump classes for new patients each took 90 to 420 minutes of staff time. Sessions were offered six to 12 times per year. Smaller clinics provided sessions on a one on one basis. Follow up appointments (in person, by telephone) during assessment, insulin pump therapy start, and reassessment phases ranged from 10 to 90 minutes per patient.

Clinics voiced an increased burden from the added responsibility of collecting data (in terms of additional paperwork) for the CSII-AED study, and suggested that additional resources be provided. The number of follow up sessions and insulin pump therapy starts for patients and the number of clinic appointments and follow ups needed for insulin pump implementation could have been increased with additional resources for nurses, dietitians, and administrative support staff.

SWOT Analysis

The SWOT analysis of the CSII-AED study is shown in Table 3. The study provided valuable local information about the health outcomes, the utilization, the implementation, and the clinical impact of insulin pump therapy from clinics, patients, and families. The information obtained from the CSII-AED study linked clinical indicators to health outcomes and

contextualized the evidence for decision makers. For example, patient interviews allowed patients to voice their reasons for starting insulin pump therapy, their expectations for insulin pump therapy, and the quality of life improvements they experienced that may not be captured by standard health related quality of life questionnaires. The CSII-AED study determined that patients began insulin pump therapy because, compared to multiple daily injections, they valued the improved glycemic control, the improved flexibility with lifestyle factors, the reduced number of injections, and the improved accuracy and precision of insulin delivery. The broad engagement with CSII of health system administrators and strategic clinical networks allowed for their concerns and values to be uncovered; for example, we learned how clinics selected patients for CSII and how data were collected and analysed.

A larger sample size would have reduced the risk of ascertainment bias; however, privacy concerns, organizational barriers, and resource limitations were impediments to full data collection. The study discovered that the burden on clinics varied due to different clinical structures, staffing levels, practice patterns, and geographical location. Some larger clinics had research capacity built into their organization and were able to collect data without interference with daily activities, while additional data collection was a burden that interfered with the daily activities in smaller clinics. Lack of funding to clinics resulted in resistance to the CSII-AED data collection. The perception was that research is not in the job description of clinic staff.

A well implemented AED scheme can be used effectively to reduce the uncertainty in reimbursement of a health technology. The CSII-AED study collected data that allowed decision makers to judge whether the health benefits of CSII were worth the financial impact of implementing CSII. The information collected allowed clinics to tell patients who considered switching from multiple insulin injections to CSII what health outcomes they could expect from

CSII. Internal weaknesses and threats can prevent AED schemes from fully taking advantage of opportunities. Privacy concerns and data ownership, resources limitations, and organizational barriers (i.e., rules and policies, complex organizational structure) were serious threats to the CSII-AED study. To counter these threats, stakeholders were engaged early in the AED study planning stage to resolve privacy concerns and data ownership. Resource constraints can be resolved through the engagement of senior officials in Alberta Health and Alberta Health Services for additional resources for data collection. A long term solution would be to develop research capacity throughout the organization by engaging clinical researchers (nurses, physicians) who can bridge the gap between clinical practice and research.

4.5 Discussion

Access with evidence development (AED) is a scheme that allows patients provisional access to a new health technology while evidence for its advantages and disadvantages is still being collected. Early use of the technology enables a faster accrual of such evidence [4]. AED schemes create a middle ground between coverage and no coverage [136] and have been found to influence the final funding decision [122, 123, 132, 140]. The evidence from an AED project can be interpreted either positively or negatively, and a range of possible changes to the reimbursement status may result [125]. Studies [122, 132] have found that the time between the funding an AED scheme to a final administrative decision to reimburse the users of the technology ranged from 0.75 years to 11 years, with a median time to final decision of 4.5 years. The absence of scientific criteria for decisions [122] may contribute to such delays.

In Alberta, an AED scheme was used to study the implementation of continuous subcutaneous insulin infusion (CSII) with a plan to reimburse users for the cost of the technology. The CSII-AED scheme was implemented after sufficient evidence had been obtained

to ratify the safety of the CSII procedure, but when the cost effectiveness of user reimbursement was still uncertain.

Implementation of a health technology under an AED scheme allows decision makers to meet patient demand through managed entry of a promising health technology, improving patient safety and control of public funds. The controlled entry of health technologies enables effective evidence generation and ensures that new evidence is shared with the decision makers. Health systems benefit from an increased accumulation of evidence and a reduced risk of reimbursing ineffective or harmful technologies [143]. Health care providers gain access to a new technology early in the life cycle, improving the number of treatment options available to patients [143]. The involvement of health care providers improves the generation of evidence surrounding clinical uncertainties, which improves patient care and best practices [143]. Manufacturers benefit from early adoption of the technology and an opportunity for the rapid generation of evidence about the cost effectiveness and safety of the technology in real life applications [143]. Patients gain access to a health technology that otherwise would not be available, and the AED scheme allows patients to be involved in decision making and evidence generation [143]. Researchers benefit through rapid recruitment of patients into trials, increasing the chance that the results will improve clinical practice and health policy [143].

The CSII-AED scheme encouraged collaboration between Alberta Health, Alberta Health Services, the Strategic Clinical Networks, and health researchers. Developing consensus on which CSII uncertainties to resolve and what data would be collected resulted in evidence that strengthened policy. Increased engagement and communication of the goals and objectives of key stakeholders and frontline staff at the planning stage of an AED project can minimize privacy issues, resource limitations, and organizational barriers. To increase the consistency and

timeliness of evidence generation, clear data agreements and resource commitments should be secured from senior government officials during the AED planning stage.

The establishment of AED schemes as a policy option in Alberta requires certain actions. These will include (1) acknowledging that a degree of uncertainty will always exist around evidence and decision making [125], (2) negotiating clear criteria for a final decision and (3) negotiating clear stakeholder agreements about data requirements, available resources, the type of evidence, data privacy and confidentiality issues, study designs, and follow up time [121, 122, 126, 134, 135, 139-142]. To be accepted as a policy option, Alberta Health will have to take the leadership role to make this happen and early stakeholder involvement and agreements will also be paramount.

4.6 Conclusions

Evaluating health care technologies, through an AED scheme, in a real world setting provides a greater understanding of the impact and contribution the health technology makes to health care system, health care providers and patients. Local data collection around CSII provided evidence on costs, patient health outcomes, and health systems resources required for successful implementation and carries significant weight to decision makers and senior management. Increased engagement and dialogue earlier in the AED process to secure funding and to negotiate clear criteria about criteria for final decision would aid in the operational efficiency of AED schemes. AED schemes before long term funding decisions for widespread adoption aids in the creation, management and dissemination of evidence to stakeholders and should be funded by health systems.

Table 4-1: Selected articles from the literature search of "coverage with evidence development," "access with evidence development," "field evaluations," "conditional listing," "only in research," and "approval with research"

Article	Rationale/Objective	Methods	Findings
Bishop and Lexchin, 2013 [138]	Examines how power relations shape knowledge and how that knowledge from coverage with evidence development (CED) is interpreted into decisions.	Stakeholder interviews with researchers, decision makers, and policy makers from Australia, Canada, the United Kingdom and the United States.	- Questions about the usefulness and operation of CED will remain unresolved until the underlying political nature of the CED is recognized.
Briggs et al., 2010 [134]	Discusses the potential of access with evidence development (AED) schemes in the United Kingdom.	Discussion paper.	- The greatest challenge is making reliable decisions concerning new health technologies in the absence of a mature evidence base. - The development of health informatics and routine collection of data could drastically reduce the cost of future data collection initiatives.
Brugger et al., 2014 [132]	Assesses the incidence, time frame, and outcome of a coverage with evidence development (CED) decision in the Swiss Basic Health Insurance Scheme.	A retrospective analysis of technologies submitted for decisions by the Department of Home Affairs.	- CED provides early access to promising new therapies and allows better final decisions for funding. - The study showed a long time span to arrive at a final decision. This favors CED in the early introduction of nondrug technologies. - No information could be obtained on factors associated with the final outcome.
Brugger et al., 2015 [122]	Identifies factors associated with decisions concerning CED schemes for novel technologies in Switzerland.	A quantitative, retrospective, descriptive analysis of publicly available materials and prospective qualitative interviews with stakeholders.	- Absence of scientific criteria for decisions were reported by stakeholders. - CED increases the complexity of the decision making process: CED recommendations should be put forward with care. - CED recommendations should follow internationally agreed principles and be integrated into a clear and structured process and consistent decisions.
Carlson et al., 2010 [136]	Identifies, categorizes, and examines performance based health outcomes; reimbursement schemes for medical technologies.	Literature review (1998-2009) to develop a taxonomy of scheme types.	- There is potential to alter the reimbursement and pricing landscape for medical technologies, however, significant challenges remain, including high transaction costs and insufficient information systems. - There is a shift from a postmarket research environment focused on safety to one that seeks to resolve and mitigate the impact of uncertainty related to transitioning from efficacy to effectiveness in real world applications.

Dhalla et al., 2009 [135]	Investigates the view of United Kingdom stakeholders of current arrangements for implementing only in research (OIR) decisions, and suggests how improvements can be made.	Stakeholder interviews with individuals from academia, industry, government, and the National Health Service (NHS).	The key challenges to only in research (OIR) are practical in nature and include: - When and how should OIR be issued? - Who should design studies? - How can OIR research be designed to maximize legitimacy and public acceptance? - How can the process be developed so that relevant research findings are fed back into the HTA process in a timely manner? - Which data are required to reduce uncertainty? - Hot to engage stakeholders earlier in the process?
Goeree et al., 2010 [121]	Describes the conditionally funded field evaluation (CFFE) used by the Programs for Assessment of Technology in Health (PATH) Research Institute.	Discussion paper.	- CFFEs may result in cost savings generated by controlled diffusion of a technology. - The biggest challenge is finding the resources to fund the infrastructure associated with an evidence based decision making platform and process. - Research conduct may be compromised because of time pressures and restrictions, however, CFFEs have to be rigorous, conclusive, and defensible.
Hutton et al., 2007 [141]	Explores conceptual and policy issues related to coverage with evidence development (CED).	Discussion paper.	- There should be standards and agreement for data requirements and study design, the time horizon of the study, funding and management of CED studies, data collection and analysis (all should be independent of the decision maker and manufacturer).
Levin et al., 2011 [123]	Analyzes and reports results from Ontario's conditionally funded field evaluations (CFFEs).	Multiple case study.	- Assessment of 12 interventions and 1 subgroup; CFFEs were responsible for widespread access to and adoption of technologies in 6 instances, limited access in 3, and withdrawal of the technology in 4 instances.
Longworth et al., 2013 [137]	Identifies and examines key considerations in only in research (OIR) or approval with research (AWR) recommendations.	Systematic review of National Institute for Health and Care Excellence (NICE) technology appraisal documents.	- Only in research (OIR) has been used for technologies that have been found to be cost ineffective and more information on effectiveness was deemed necessary. - Some OIR recommendations included further research on long term outcomes and adverse effects of treatment.
Martelli and van den Brink, 2014 [133]	Assesses two different approaches to temporary funding for innovative devices: coverage with evidence development (CED) and National Programs for Hospital Based Research in France.	Discussion paper.	- CED transparency needs to be enhanced by clearly stating the selection criteria for devices that may benefit from a CED. - CED decisions need to be made more quickly. - Effective collaboration is the cornerstone to success of a CED. - A stable source of funding for CED is needed.

Martelli et al., 2016 [127]	Describes recent modifications to the French coverage with evidence development (CED) scheme for innovative medical devices.	Discussion paper.	- Recent modifications to the CED process increased its transparency.
Mckenna et al., 2015 [131]	Demonstrates how the principles of only in research (OIR), approve with research (AWR), and approve and reject can be applied in practice.	Case study.	- Cost effectiveness is a necessary but not a sufficient condition for approval. Lack of coverage with evidence development (CED) is not a necessary or sufficient condition for rejection. - OIR may be appropriate when the technology is expected to be cost effective
Mohr and Tunis, 2010 [142]	Examines 10 years of experience with access with evidence development (AED) in the U.S.	Case study/discussion paper.	Barriers to implementing AED include: - Increase in patient care costs, - Conflicts of interest, - Coercion/therapeutic misconception issues, - Data security/patient confidentiality issues, - Investment in expensive, lengthy trials.
Mohseninejad et al., 2015 [126]	Develops a model for regular evaluation of patient registries during an access with evidence development process.	Case study of oxaliplatin for treatment of stage III colon cancer.	- Patient registries can be an efficient method of collecting data, however, they need to be carefully designed and evaluated, specifically with regard to follow up time. - Optimally, decision making should be taken once sufficient data are available.
O'Malley et al. 2009 [140]	A case study of PillCam capsule endoscopy registry in Australia.	Case study.	- If coverage with evidence development (CED) is to become an effective mechanism for bridging the evidence gap of new health technologies, guidance needs to be developed on the design of registers to be able to cater to the unique characteristic of individual procedures (health technologies).
Trueman et al., 2010 [125]	Describes current issues surrounding coverage with evidence development (CED).	Summary and interpretations from presentations and discussions at the 2008 Health Technology Assessment International (HTAi) meeting and material in the medical literature.	- Payers could interpret evidence from a CED either positively or negatively, and a range of possible changes to reimbursement status of a health technology may result. - CED strikes a balance between demands for prompt access to new technologies and acknowledging that uncertainty will exist around decisions - CED requires well developed and well designed studies. - Timing of key technology results is critically important.

			- Choosing appropriate health technologies for CED is critical for CED success. - The evidence gap must be defined prior to data collection. - CED should not be used to delay access to a new health technology.
Tunis and Whicher, 2009 [139]	Provides empirical evidence on how CED (coverage with evidence development) works and how policy design and implementation for CED might be improved.	Case study of the National Oncologic PET Registry. The registry was the first attempt of the Centers for Medicare & Medicaid Services (CMS) to apply coverage with evidence development.	- Timing of CED schemes is crucial for the success of the CED approach. - Early detection of potentially valuable emerging technologies will be crucial to the successful implementation of CED. - Identifying reliable funding sources to cover research costs would remove a barrier to CED. - A process for stakeholder agreements about what evidence is sufficiently robust is needed. - More efficient methods for conducting real world evaluations are needed.
Turner et al., 2010 [129]	Reports results from a prospective cohort study evaluating spinal cord stimulation for chronic back and leg pain after spine injury.	Prospective cohort study.	- Coverage with evidence development studies uncover important information concerning the long term risks and benefits of a therapy in clinical practice for specific subpopulations that may not be apparent from a randomized controlled trial (RCT) and may be met with criticism from interested parties.
Walker et al., 2012 [130]	Describes a conceptual framework allowing a wider set of decision options available to technology purchasers to be understood.	Discussion paper.	- The decision option needs to be matched with a technology purchaser's authority over access, research, and price, and the characteristics of the technology regarding reversibility and evidence.
Wallner and Konski, 2008 [128]	Evaluates the role of various stakeholders' interests in contributing to the increasing costs of care.	Literature review and analysis.	- Lack of decision relevant evidence has increased interest in finding solutions that generate and use evidence. - One challenge to access with evidence development (AED) is the lack of an established and credible research infrastructure necessary to carry out research in a reasonable time frame at an acceptable cost.

Table 4-2: Clinic Interviews

	Grande Prairie Clinic	Medicine Hat Clinic	Lethbridge Clinic	Red Deer Clinic	Alberta Children's Hospital	Kaye Clinic	Calgary Metabolic Clinic	Grey Nuns Clinic	Stollery
How many patients do you see at the clinic in a month for an insulin pump related visit?	6 to 12	2	2 to 10	n/a	n/a	100	204	39	64
Preparation for the public IPT program									
Who was involved in preparing for the start of the IPT program?	RN (registered nurse), dietitians, administration support, insulin pump trainers, internists	RNs	clinical coordinator and diabetes educator	clinic manager, RN, administration support, dietitians	RN, RD (registered dietitian), endocrinologists	RN and a dietitian	general educator, RN, dietitians, endocrinologists, education consultants, administration. staff, medical director, pump companies, social workers, pharmacists, psychologists	clinic manager, RN, administration support, dietitians	RN, dietitians, administration support, pump trainers, nurse practitioners and physicians
Initial Referral to the Public IPT program									
How much time is spent reviewing referrals?	n/a	20 to 30 min	n/a	n/a	5 to 15 min	30 min	no	n/a	n/a
Who is responsible for reviewing referrals?	n/a	RNs	n/a	n/a	RN, RD, or endocrinologist	RN	n/a	n/a	n/a
How much time is spent reviewing	45 to 60 min	30 min	15 to 30 min	n/a	5 to 15 min	30 min	15 to 20 min	45 to 60 min	60 to 75 min

referrals to the program?									
Who reviews referral information?	RN and dietitians	RNs	diabetes educator	n/a	RN, RD, or endocrinologist	RN	clinician	RN or dietitians	RD
How much time is spent discussing IPT with the family?	pre-pump session = 150 min	30 to 45 min	90 min	n/a	10 to 120 min	15 min	n/a	IPT is discussed as it proceeds	30 to 45 min
Who discusses the IPT program with the family?	RN	RN	diabetes educator	n/a	RN, RD, or endocrinologist	RN	clinician	RN or dietitians	RN, RD, physician or NP (nurse practitioner)
Pre-pump information session									
How many completed tests from online pre-pump information sessions does the clinic receive in a month?	1 to 2	2 to 5	2 to 10	5 to 10	10 to 15/month	15 to 18	n/a	0 to 10/month	8 to 12
How much time is spent reviewing these tests?	60 mins with patient	30 min	5 min	n/a	20 to 35 min	2 min/patient	n/a	n/a	30 min
Who reviews these tests?	RN	RN	diabetes educator	RN	RN, RD	NA	clinician	RN or dietitian	RD
How much time is spent preparing for the in person pre-pump information session?	30 to 45 min	n/a	n/a	30 min	120 min	30 min	180 min	45 to 60 min	n/a

Who is involved in the preparation?	RNs and clerical/administration staff	n/a	n/a	RN and clerical/admin staff	RN, pump vendors' clerks	RN and dietitian	clinicians, dietitians, pump trainers, RN, educators, administration staff	RN or dietitian	n/a
How much time is spent delivering the pre-pump information session?	150 min	n/a	n/a	150 min	150 min	210 min	120 to 180 min	170 min	n/a
Who is involved in its delivery?	RN	n/a	n/a	RN	RN	RN and dietitian	RN and dietitian	RN, dietitian, and pump companies	n/a
Is follow up required after the pre-pump education session prior to the assessment process?	yes	n/a	n/a	no	no	yes	n/a	yes	n/a
How much time is spent on follow up?	60 to 90 min	n/a	n/a	n/a	n/a	25 min	n/a	15 min	n/a
Who is involved?	RN and dietitians	n/a	n/a	n/a	n/a	RN and dietitian	n/a	RN or dietitian	n/a
Assessment Phase									
How many appointments related to assessing patients for IPT eligibility does the clinic conduct in a month?	2 to 6	1	1 to 8	n/a	n/a	25	70/month	3/month	n/a
How many appointments does an average patient have during the assessment phase?	3 to 4	1 to 2	5 to 6	12	n/a	4	n/a	3+	2 to 6

How long is each appointment?	60 mins	60 min	60 to 90 min	75 min	30 min	10 to 15 min	45 to 90 min	45 to 60 min	30 min
Who is involved in each appointment?	RN or dietitian	RN	RN and educator	RN or dietitian or physician	RN, RD, endocrinologist	RN	RN, RD, pharmacist, psychologist, social worker	RN and dietitian	RN, RD physician, social worker
How many appointments does a “short” patient have during the assessment phase?	2 to 3	n/a	2 to 3	5	1	2	13 to 17	1 to 2	10
How long is each appointment?	30 to 60 min	n/a	60 to 90 min	75 min	90 min	10 to 15 min	n/a	45 min	120 to 240 min
How many appointments does a "long" patient have during the assessment phase?	6 or more	n/a	10 to 12	39 to 52	2 to 3	7	n/a	7 to 27	n/a
How long is each appointment?	60 to 90 min	n/a	60 to 90 min	75 min	120 min	10 to 15 min	n/a	20 min	n/a
How long does it take an “average” patient to go through the qualification process?	6 months to 1 year	n/a	5 to 6 months	6 to 9 months	12 to 18 months	3 months	n/a	3 to 6 months	13 to 14 months
How long does it take a "short" patient to go through the qualification process?	6 to 9 months	n/a	2 to 3 months	2 to 4 months	8 to 9 months	2 months	n/a	2 months	2 to 4 months

How long does it take a "long" patient to go through the qualification process?	1 year at least; "long" patients might never qualify, some have been waiting for 2 years.	2 to 3 appointments (45 to 60 min each) for qualification	10 to 12 months	12+ months	24+ months	6 months	n/a	6+ months	n/a
Pump Start									
How many pump start classes are conducted at the clinic in a month?	staff shortages have limited the number of pump start classes	no classes; one on one with patient	1/month	3/month	6–7/year	2/month	6 every 4–6 weeks	2/month	1/ three months
How much time is spent preparing for the saline pump start class?	90 to 120 min	60 to 90 min	10 to 15 min	165 min	330 to 360 min	n/a	180 min	120 to 240 min	420 min
Who is involved in the preparation?	RN and pump trainers	RN	RN and educator	RN	RN	n/a	clinicians, pump companies, admin support	RN, dietitians and pump trainers	RD, RN, physician
How much time is spent delivering the saline pump class?	180 min	60 to 90 min	90 to 120 min	90 min	240 min	n/a	120 to 180 min	240 min	420 min
Who is involved?	RN and pump trainers	RN	RN and educator	RN	RN	n/a	clinicians	RN	RN, pump company
How much time is spent following up with patients after the saline pump class?	30 to 60 min	180 min	15 min	15 min	30 min/patient	n/a	180 to 240 min	n/a	part of class
Who is involved?	RN and pump trainers	n/a	RN and educator	RN	RN	n/a	clinicians	RN and dietitian	educators who taught class

How much time is spent preparing the insulin pump start class?	60 mins	30 to 60 min	10 min	15 min	120 min	30 min	240 to 360 min	n/a	600+ min
Who is involved in the insulin pump start class?	RN and pump trainers	RN	RN and educator	RN	RN	RN	clinicians	n/a	RN, RD, clerk and physician
How much time is spent delivering the insulin pump start class?	n/a	120 to 180 min	90 to 120 min	90 min	420 min	240 min	180 to 360 min	180 min	1110 min
Who is involved in deivering the insulin pump start class?	RN, pump trainers	RN	RN and educator	RN	RN	RN	clinicians	RN and dietitian	RN, RD, clerk, physician
How much time is spent following up patients within the first 48 hours after the insulin pump class?	48 to 72 hours follow up through phone, email, or in person by RN; 3 to 5 hours spent with each patient.	3 to 5 hours depending on patient	30 to 45 min	120 min	360 min	15 to 20 min	2 to 6 hours	10 to 20 min	480 min
Who is involved in the class follow up?	RN and pump trainers and sometimes internists	RN	RN and educator	RN	RN	RN	RN and pump trainers	RN and dietitian	RN, physician, RD
When is the first post pump start follow up session scheduled for?	within 1–2 weeks	within 1–2 weeks	within the first month but can range between 1 and 3 months; patient is closely followed during the first few days of starting pump	within 72 hours	within 2 weeks	6 months	first week	48 to 72 hours	within 3 to 4 months

How long is each post pump start follow up session appointment?	60 min	60 min	60 to 90 min	60 min	90 min	30 min	60 to 75 min	120 min	45 to 240 min
Who is present at the post pump start follow up session?	RN, pump trainers, family	RN	RN and educator	RN	RN	RN	clinician	RN and dietitian	RN, RD, physician
Follow up and annual reassessment									
How many follow ups does an "average" patient have after starting pump and before the annual reassessment?	2 to 3	1 to 2	2 to 3	4 to 5	3/year	8 to 12	n/a	10 to 12	4
How long is each follow up appointment?	60 min	60 min	60 min	90 min	45 to 60 min	15 to 20 min	n/a	30 to 60 min	45 to 240 min
Who is involved in the follow up appointment?	RN, patient, and family	RN	RN and educator	RN	RN, RD, endocrinologist	RN	n/a	RN/RD or MD	RN, RD, physician, social worker
How many follow ups does a "short" patient have within the first year after starting the pump?	1 to 2	n/a	2	2 to 3	3/year	n/a	n/a	n/a	n/a
How long is each follow up appointment?	60 min	n/a	60 min	90 min	45 to 60 min	n/a	n/a	n/a	n/a

How many follow ups does a "long" patient have within the first year of starting the pump?	4 to 6	n/a	4 to 6	8 to 12	3+/year	n/a	n/a	n/a	n/a
How long is each follow up appointment?	60 min	n/a	60 min	90 min	45 to 60 min	n/a	n/a	n/a	n/a
Does the clinic conduct annual reassessments?	yes	yes	yes, at the clinic with an endocrinologist	yes	yes	yes	yes	yes	yes
How many reassessments does a clinic conduct in a month?	fewer than 1	2	5 to 8 on average	n/a	n/a	20	12.8	8 to 10	4 reassessments
How many appointments are required to complete a reassessment?	1 to 2 (if required)	1	1 to 2	3 to 5	n/a	1	n/a	1 required	n/a
How long is each appointment?	30 to 60 min	60 min	30 to 60 min	90 min	n/a	30 min	60 to 90 min	60 min	60 min

Table 4-3: SWOT analysis of a CSII-AED study

Internal		External	
Strengths	Weaknesses	Opportunities	Threats
(1) Evidence is contextualized to the current environment (2) Engaged stakeholders (3) Provides evidence for CSII implementation (4) Provides evidence linking clinical indicators to outcomes	(1) Not enough patients enrolled to ascertain results (ascertainment bias) (2) Data collected at venues with various levels of ability to address data collection	(1) Lack of relevant evidence for decision making [125, 128, 129] (2) Growing demand for relevant evidence [125, 128, 129] (3) Increasing pressures for accountability, transparency and timeliness of decision [127, 129-135] (4) Trend toward conditional approval of technologies [123, 136, 137]	(1) Data security and privacy issues [142] (2) Resource limitations [121, 128, 133, 139] (3) Organizational barriers [128, 138] (4) Data ownership [121, 126, 134, 135, 139-141]

Chapter 5: Thesis Rationale and Research Purpose

5.1 A CSII-AED Study of Insulin Pump Therapy

Access with evidence development (AED) schemes are an innovative decision option that allows decision makers considering the introduction of a new health technology to actively reduce uncertainty. AED schemes allow decision makers to (1) meet patient demand through managed entry of a health technology, (2) improve patient safety, and (3) control public funds. In Alberta, Canada, continuous subcutaneous insulin infusion (CSII) is the first health technology to be funded under an AED scheme.

An AED study was performed to address uncertainties surrounding the government funded implementation of CSII in Alberta. CSII allows for more flexibility and precision in glycemic control than multiple daily insulin injections in patients with type 1 diabetes mellitus (T1DM). However, CSII is neither clearly inferior nor clearly superior to multiple daily injections (MDI) in respect to three factors: (1) safety and health effectiveness, (2) cost effectiveness, and (3) system/resources required for widespread implementation [2, 7-15]. These uncertainties must be reduced before a definitive funding decision can be made.

The CSII-AED study provided valuable local information regarding health outcomes, health care utilization, CSII implementation, and the impact of CSII on clinics and patients. The information linked clinical indicators to health outcomes and contextualized the evidence for decision making. It was found that AED schemes could be improved if external threats were mitigated through additional resources for clinics for data collection and by engaging relevant stakeholders during the planning stages to ensure their interests and concerns were addressed.

Decision makers must weigh evidence and consider uncertainties in the formulation of policy that affects population health. Numerous tools exist to aid in such policy formulation. A cost effectiveness analysis (CEA) is one example, it is commonly used to communicate the value

of a health technology; however, the presentation of outcome uncertainty is usually incomplete. The decision maker may not know how relevant the cost analysis results will be because of existing uncertainty in the long range effects of the technology. Although a CEA has limits, it is a starting point when a decision must be made. A value of information (VOI) analysis expands on a CEA and, in theory, provides an unambiguous presentation of the uncertainty surrounding the implementation of a technology. Therefore, in theory, a decision-maker will know what the uncertainties are and allow for the development of policy options that include the collection of data.

This thesis reports the findings of an AED scheme that was initiated to perform (1) a CEA (2) a VOI, and (3) a strengths, weaknesses, opportunities, and threats (SWOT) analysis concerning the implementation of CSII for T1DM patients in Alberta, Canada.

5.2 Cost Effectiveness Analysis of CSII

Chapter 2 examined how a CEA of CSII compared to a CEA of MDI could reduce uncertainties in the "value for money" in a CSII implementation. The CEA of CSII calculated incremental cost effectiveness ratios (ICERs) of $123,041 and $122,155 from health payer and societal perspectives, respectively. Therefore, a conservative estimate indicates that the CSII will be cost effective at an ICER threshold of $125,000. The cost of the CSII pump and pump consumables account for over 85% of the total cost of providing CSII in Alberta. Over the lifetime of the technologies, indirect costs due to lost productivity from nonsevere hypoglycemic events and severe hypoglycemic events requiring medical and nonmedical assistance were calculated to be $3,695.74 for CSII and $3,989.47 for MDI. Therefore, CSII is predicted to save on average $293.73 of lost productivity compared with MDI over the lifetime of the technologies.

The CEA study may not have captured the full indirect costs of the T1DM disease. The CSII-AED study indicated that patients valued the improved glycemic control, the improved flexibility of lifestyle factors, the reduced number of injections, and the improved accuracy and precision of insulin delivery that CSII offered compared to MDI. The ICER of CSII would be more favorable if it could incorporate the intangible benefits of CSII.

5.3 Value of Information Analysis of CSII

Chapter 3 explored the role of a value of information (VOI) analysis in technology acquisition decision making. The VOI had three goals: (1) to calculate the value of research regarding insulin pump therapy, (2) to determine which uncertainties should be pursued as research priorities, and (3) to understand the benefits of conducting a CSII-AED study. The expected value of perfect information (EVPI) was calculated at an ICER threshold of $125,000 to be $19.6 million dollars from the health payer perspective. The analysis found it would be potentially worthwhile to collect more information on (1) the quality adjusted life years (QALYs) associated with CSII and (2) the effectiveness of CSII in reducing severe hypoglycemic events. The VOI analysis found that with a study cost of $600,000, collecting more information would be potentially worthwhile. The expected net benefit of sampling (ENBS) was calculated to be $9.6 million dollars.

5.4 SWOT Analysis of the CSII-AED Study

Chapter 4 examined the CSII-AED study using a strengths, weaknesses, opportunities, and threats (SWOT) analysis. The SWOT analysis found a well implemented AED scheme is an effective way to reduce the uncertainty in reimbursement of a health technology. The CSII-AED scheme worked with the environment to address uncertainties regarding safety and effectiveness, cost effectiveness and system/resource requirements. The results of the study allowed for

insights on how insulin pump implementation impacted patients, health care providers and funders. The study discovered an increased burden on clinics and resource limitations which resulted in resistance to the CSII-AED study data collection.

AED schemes have been found to be influenced and shaped by the power relations between researchers, decision makers and policy makers [137] and has been found to increase the complexity of the decision making process [122]. Acknowledging a degree of uncertainty will always exist and engaging and communicating the goals and objectives during the planning stage may minimize privacy issues, resources limitations and organizational barriers and increase operational efficiency.

5.5 Recommendations for Future Research

Three areas for future research emerged from this thesis. The limited number of economic studies on the indirect costs of type 1 diabetes mellitus was surprising given the burden of type 1 diabetes on patients (chapter 2). Therefore, further evaluations of indirect costs (e.g., productivity loss) of type 1 diabetes mellitus are needed to capture societal cost that could be alleviated with future health technologies.

The value of information (VOI) analysis communicates the level of uncertainty surrounding a decision to implement a specific health technology (chapter 3). The limitations of the VOI tool, the heavy computational time, and the complexity involved in the interpretation and application of the VOI analysis, need to be adapted to increase the relevance of this tool to decision makers. Studies of VOI applications to decision making are scarce and further research is needed to determine how the VOI can be transformed from a theoretical tool to an applied decision making tool.

The SWOT analysis uncovered factors that affect the operational efficiency of AED schemes in Alberta. Negotiating clear criteria for a final decision and clear stakeholder agreements about data requirements, available resources, the type of evidence, data privacy and confidentiality issues, study designs, and follow up time [121, 122, 126, 134, 135, 139-142] can help to increase the operational efficiency of AED schemes. Additional AED schemes will allow for operational experience required to develop the AED scheme.

5.6 Research Contribution

This thesis evaluates the first AED scheme in Alberta using a cost analysis, value of information analysis and SWOT analysis. This thesis analyzes the strengths and weaknesses of the decision tools available to decision makers using the CSII-AED case study.

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Appendices

Appendix 2-A: Criteria for children and adolescents eligible to be started on CSII under the Provincial Coverage Program

- The patient must have adequate blood sugar control (at least 2 consecutive HbA1c < 9% at least 3 months apart).
- The patient must demonstrate the ability to do a minimum of 4 blood glucose tests per day and must be willing to do 6 to 8 tests per day while on an insulin pump.
- The patient must have appropriate carbohydrate counting skills as assessed by a pediatric pump trained diabetes educator dietitian.
- The patient must exhibit regular attendance at the Pediatric Diabetes Education Centre with the pediatric endocrinologist or pediatrician, nurse, and dietitian (minimum to 2 visits in the past 12 months).
- The patient and his/her family must express willingness to start insulin pump therapy.
- The patient must have on-going family support.
- The patient's family must have completed pump therapy information sessions.
- The patient's family must have prepared a plan for pump management at school.
- Children and adolescents with atypical circumstances (e.g., they do not meet the above criteria) may be started on an insulin pump if recommended by a pediatric endocrinologist and a Pediatric Diabetes Education Centre team after full assessment of such individuals.
- The patient's family must sign the "pump contract."

Criteria for pediatric CSII maintenance

- The patient must be seen regularly by his/her pediatric diabetes team (minimum 2 visits/year with at least 3 months between visits).
- The patients must have at least 3 HbA1c measurements within 12 months, each at least 60 days apart.
- Of the required 3 HbA1c measurements within 12 months, the patient must have no more than 1 HbA1c level above 9%.
- The patient must not have had more than 1 hospitalization with diabetic ketoacidosis (DKA).

Criteria for pediatric pump therapy discontinuation

- More than 1 HbA1c above 9% in the past 12 months.
- More than 1 admission with DKA in the past 12 months.
- Failure to have regular medical follow-up with the pediatric diabetes team (a minimum of 2 visits in the past 12 months).
- Failure to have 3 HbA1c measurements in the past 12 months with at least 60 days between measurements.

Appendix 2-B: Indications for continuous subcutaneous insulin infusion (CSII) for adults with type 1 diabetes mellitus

- A desire to use insulin pump therapy (after appropriate education).
- The ability to describe clear goals for IPT and expectations of what difference(s) IPT will make to the patient's diabetes management.

- Consent to participate in a provincial pump program and registry.
- Recurrence of severe hypoglycemia (2 or more episodes in 12 months).
- Impaired hypoglycemia awareness, i.e., hypoglycemia unawareness (Clarke ≥ 4/7).
- Preconception planning or pregnancy where hypoglycemia is a barrier to tighter glycemic control.
- Suboptimal glycemic control (including glycemic variability, excessive hypoglycemia, or undesirable HbA1c) with multiple dose injections (MDI) in patients with optimal support, including assistance from a specialized interdisciplinary diabetes team, if necessary.
- Variable lifestyle factors – exercise, variation in the timing of meals, shift work, safety risk from hypoglycemia, etc.

Criteria for maintenance/justification for continuing reimbursement of IPT equipment and supplies

- HbA1c > 9%
- Admission/ER visit/paramedic call for hypoglycemia
- Admission/ER visit/paramedic call for DKA
    - > 2/year
- Recurrent hypoglycemia
    - No reduction in hypoglycemia frequency since pump initiation
- Persistent, inappropriate use of pump
    - No boluses
    - Excessive basal rates
    - Inadequate self-monitoring
- No meetings with the specialist diabetes care team
- No longer able to use the insulin pump technology

Appendix 2-C: Clinical results that support insulin pump therapy (CSII) in Alberta
In order of importance:

- decreased hypoglycemic episodes,
- improvement in hypoglycemia awareness,
- preconception planning for pregnancy where hypoglycemia is a barrier to tighter glycemic control,
- improvement in glycemic control that has been unsuccessful with multiple daily injections, and support from the diabetes team,
- improvement in the flexibility of lifestyle factors such as intensive exercise, frequent variation in meal times, shift work, safety risk of hypoglycemia, and
- improvement in glycemic control as a result of increased HbAlc testing frequency; such improvement is related to full diabetes supply coverage.

The priority of the Alberta government is to reduce the frequency of hypoglycemic events because they are a barrier to tight glycemic control.

Appendix 3-A: Use of Confidence Intervals and ICERs

There are two main theoretical problems with the ICER and its confidence intervals. Assume an analysis comparing two treatments (T_0 and T_1). First, the ICER is unable to communicate information on the quadrant of the cost effectiveness plane (Figure 1). For example, a negative ICER would correspond to quadrants II and IV, however, both have different decision rules (Figure 1). In quadrant II, T_1 is preferred over T_0 and in quadrant IV, T_0 is preferred over T_1. A positive ICER would correspond to quadrants I and III; a ICER less than λ is favorable to T_1 in quadrant I but unfavorable in quadrant III [89].

Second, an incremental cost effectiveness ratio (ICER) does not communicate the magnitude of incremental effects. For the following ICERs, the decision to fund a \$30,000/QALY[47] gained or \$25,000/QALY[48] gained may depend on the magnitude of incremental cost savings and the magnitude of the incremental health effects. From the ICER, decision makers are unable to draw information about the magnitudes of the incremental cost and incremental effects. More information needs to be presented to decision makers.

Appendix 3-B: Uncertainty about Costs and Effects, the Cost Effectiveness Plane and Decision Rules

In an analysis comparing two treatments (T_0 and T_1), the cost effectiveness plane is divided into four quadrants (Figure 1). Four possible combinations of incremental cost and incremental effects are plotted on the y-axis and incremental health effects are plotted on the x-axis of T_1 compared to T_0 (Figure 1) [116]. In quadrants II and IV, the decision rule states that T_1 and T_0 will be the preferred treatment. In quadrants I and III, a judgement must be made [116]. In quadrant I, T_1 is more costly and more effective than T_0 and in quadrant III, T_1 is less costly and less effective than T_0; the correct treatment choice is not clear. Does the increase in cost justify the increase in effectiveness? Does the decrease in cost justify the decrease in effectiveness?

The decision rules are as follows [89]:

Quadrant	Decision Rule
I	$T_1 >^* T_0$ if and only if $\Delta C/\Delta E < \lambda^{**}$
II	$T_1 > T_0$
III	$T_1 > T_0$ if and only if $\Delta C/\Delta E < \lambda$
IV	$T_0 > T_1$

* "is preferred to."
** Threshold ICER.

In Figure 1, λ is the threshold ICER indicated by the slope of the dashed line [89]. The threshold ICER, λ, can be interpreted as the maximum amount society is willing to pay for an incremental gain in health or, the minimum amount society would be willing to accept to forego an incremental gain in health [89]. In Figure 1, T_1 is preferred to T_0 for all points under the dashed line and T_0 is preferred to T_1 for all points above the dashed line [89]. Central to this analysis is the value of λ, which is not known.

[47] \$120,000/4QALY = \$30,000/QALY.
[48] \$25,000/1QALY = \$25,000/QALY.

Appendix 3-C: Value of Information Analysis and the Bayesian Statistical Framework

Value of information analysis (VOI) is based on the Bayesian statistical framework, where the probability represents a "degree of belief" about the plausible values of an unknown but potentially observable quantity rather than the long run frequency of an event (the frequentist approach) [98, 144]. The Bayesian approach requires specification of a probabilistic model of prior beliefs about unknown parameters, it is also known as the prior distribution; this subjectively expresses the uncertainty about a true unknown parameter in the language of probability. Bayesian analysis involves the updating of a prior belief about possible values of a parameter with likely values of that parameter drawn from sample data (also known as the likelihood function[49]), to form a posterior distribution [98]. In VOI analysis, a likelihood function is predicted to be conditional on a prior belief to generate an expected posterior distribution [98]. For example, a VOI analysis uses the current state of knowledge to predict the results of a knowledge generating exercise; the results will be combined with the prior belief to predict the state of knowledge after the data are collected [98].

Rules of Probability and Bayes' Theorem

Three basic rules of probability [145]

1. Bounds: $0 \leq p(a|H) \leq 1$, where $p(a|H) = 0$ if a is impossible and $p(a|H) = 1$ if a is certain in the context of H.
2. Addition rule: If a and b are mutually exclusive (i.e., one at most can occur), $p(a \text{ or } b|H) = p(a|H) + p(b|H)$.
3. Multiplication rule: for events a and b, $p(a \text{ and } b|H) = p(a|b,H)p(b|H)$. We say that a and b are independent if $p(a \text{ and } b|H) = p(a|H)p(b|H)$ or equivalent $p(a|b,H) = p(a|H)$; thus the fact that b has occurred does not alter the probability of a. Therefore $p(a|b,H) = p(a \text{ and } b|H) / p(b|H)$ if $p(b|H) \neq 0$.

Bayes' Theorem for simple events [145]

$p(b|a) = p(a|b)/p(a)*p(b)$.

Appendix 3-D: Example of Value of Information Analysis

Expected Value of a Perfect Information Calculation

Consider a case in which a health decision maker is faced with two alternatives (Treatment A and Treatment B) for a specified group of patients, with Treatment A being current practice and Treatment B being a new technology or innovation. Assume the treatments have the following parameters, mean life expectancy, and mean cost.

Table 1. Expected values of outcomes of interest for Treatment A and Treatment B

Outcome	Treatment A	Treatment B
Mean life expectancy (Et)	18	18.5
Mean cost (Ct)	$9350	$9550

[49] The likelihood function is a function of the parameters and it measures the support provided by the data for each possible value of each parameter.

Willingness to pay for 1 additional year of life (λ)	$750	$750
Net monetary benefit (NMB)	4150	4325

In a setting where the optimal decision is based on the incremental cost effectiveness ratio (ICER) Treatment B would be preferred if the decision maker were willing to pay $400[50] for a life year saved. An alternative decision criterion to ICER is a net monetary benefit (NMB),

Net monetary benefit (NMB) = $(\lambda \cdot E_t) - C_t$ [89, 99],

where λ is the willingness to pay for a health benefit (or outcome), E_t is the health benefit of the technology, and C_t is the cost of the technology [89].

At a given willingness to pay, the treatment that provides the highest NMB will be the optimal treatment.

Based on the information in Table 1 (i.e., current information), Treatment B with a NMB of $4325 will be preferred over Treatment A with an NMB of $4150. However, the uncertainty in the parameters mean life expectancy (Et) and mean cost (Ct) of treatments A and B results in wide confidence intervals for both parameters, leading to uncertain NMBs.

To analyze the uncertainty of Treatment A and Treatment B, NMBs, a probabilistic sensitivity analysis (PSA) of mean life expectancy and mean cost involved in each treatment will be performed. Table 2 shows the results of 10 simulations of the use of Treatment A and Treatment B drawn from their respective parameter distributions. NMBs for Treatment A and Treatment B were calculated based on a willingness to pay (WTP) threshold of $750. If the decision is based on the highest NMB and Treatment B is adopted, there is a five out of 10 chance the decision would be wrong.

Table 2. Results of 10 Simulations of Treatment A and Treatment B (WTP = $750)

Simulation Number	Net Benefits of Treatment A ($)	Net Benefits of Treatment B ($)	Maximum Net Benefits ($)	Preferred Strategy	Opportunity Cost ($)
1	5976	3744	5976	A	2232
2	3761	1009	3761	A	2752
3	1968	4074	4074	B	0
4	1128	5545	5545	B	0
5	7533	4999	7533	A	2534
6	2367	4245	4245	B	0
7	4379	5963	5963	B	0
8	6319	1739	6319	A	4580
9	5509	6297	6297	B	0

[50] ICER = $(cost_A - cost_B)/(QALY_A - QALY_B)$=($9550-$9350)/(18.5-18.0 life years saved) = $400/life year saved.

10	2401	5538	5538	B	0
Expected value (mean of simulations 1–10)	4134	4315	5525		1210

The mean NMB across the 10 simulations in Table 2 is the expected value (or expected NMB). The expected NMB for Treatment A is $4134 and the expected NMB for Treatment B is $4315. Based on the highest expected NMB, Treatment B is the preferred option. Given the current information (and uncertainty) the "expected value given current information" is the optimal treatment with the maximum expected NMB.

Expected value given current information[51] = $\max_t E_\theta B(t,\theta)$ = $4315 = Treatment B,

where θ represents a list of unknown parameters, t represents the treatments available, B is the health benefit provided by the technology, and E_θ refers to the expected value over the joint distribution of θ (life expectancy and costs).

In 5 of the 10 simulations, Treatment A had a higher NMB. If decision makers possessed perfect information regarding which treatment would be optimal, over all the unknown parameters, a decision maker would choose the treatment with the highest NMB in each situation. The "expected value given perfect information" is calculated by averaging the maximum net benefit by selecting, in each situation, the treatment with the highest NMB (over the joint distribution of θ [life expectancy and costs]).

Expected value given perfect information[52] = $E_\theta \max_t B(t,\theta)$ = $5525.

The expected value of perfect information (EVPI) is the difference between the "expected value given perfect" information minus the "expected value given current information."

Expected value of perfect information (EVPI) = $E_\theta \max_t B(t,\theta) - \max_t E_\theta B(t,\theta)$ = $5525-$4315 = $1210.

The EVPI can be considered the opportunity loss of making a wrong decision; in the example, the EVPI is opportunity loss of choosing Treatment B when Treatment A provides a higher net monetary benefit.

The expected value of partial perfect information (EVPPI) and the expected value of sample information (EVSI) are calculated in the same way as the EVPI. The EVPPI is calculated for a specific variable or a subset of variables (e.g., life expectancy), holding the other group of variables (e.g., mean costs) constant, and performing a PSA [96]. The expected value of sample information (EVSI) calculation has the same logic as the EVPPI; rather than having perfect information about a subset of parameters (EVPPI), the EVSI is calculated knowing in advance

[51] $B(t,\theta)$ is the net monetary benefit of treatment t if the parameters take the value θ, $E_\theta B(t,\theta)$ is the mean net monetary benefit of treatment t (over the values of θ), $\max_t E_\theta B(t,\theta)$ is the treatment with the highest expected net monetary benefit.

[52] $B(t,\theta)$ is the net monetary benefit of treatment t if the parameters take the value θ, $\max_t B(t,\theta)$ is the treatment with the highest NMB (over the values of θ), therefore, $E_\theta \max_t B(t,\theta)$ is the mean of the treatments with the highest NMB over the values of θ.

the benefit of additional information acquired by collecting information from a sample of individuals.

Appendix 4-A: Stakeholder Questionnaire

Uncertainties

1. In your view, did the CSII-AED study address the right uncertainties?

Information

2. Did we collect the right kinds of information?
3. Did the fact that the roll-out of the program involved a study conducted alongside it affect any of the program's parameters (e.g., eligibility for starting and continuing on the insulin pump)?
4. Did the study measure the right outcomes in the right way?
5. Did the results of the study have any impact on the program parameters?
6. Were the findings of the study valued appropriately during subsequent decision making?
7. Were the findings of the study available when you needed them?

Stakeholders

8. Were the right people involved in the study's oversight?
9. If the insulin pump was half the price, do you think the decision would have been different?
10. What would you do the same and what would you do differently in a subsequent AED study?
11. Have you received feedback from nongovernmental stakeholders (e.g., Canadian Diabetes Association, insulin pump manufacturers, Juvenile Diabetes Association)?

Implementation

12. Were the right people involved in CSII implementation?
13. In your view, how did the CSII-AED study affect the roll out of the insulin pump program? (Did it get in the way of the program or did it help to facilitate the program?)
14. How did the CSII-AED study affect clinics?
15. Was a burden placed on clinics (e.g., resources)? If yes, was it a manageable one?
16. Did the study cause you to deviate from normal practice?
17. Has anything changed in the IPT program and its funding?
18. How did the study influence any decision (for example, the funding decision) regarding the IPT program?
19. Did the study affect how insulin pumps are funded?