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A Cost-Effectiveness Analysis of Continuous Subcutaneous Insulin Injection versus Multiple Daily Injections in Type 1 Diabetes Patients: A Third-Party US Payer Perspective

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ABSTRACT

Objective: To estimate the long-term cost-effectiveness of using continuous subcutaneous insulin infusion (CSII) compared with multiple daily injections (MDI) of insulin in adult and child/young adult type 1 diabetes mellitus (T1DM) patients from a third-party payer perspective in the United States.

Method: A previously validated health economic model was used to determine the incremental cost-effectiveness ratio (ICER) of CSII compared with MDI using published clinical and cost data. The primary input variable was change in HbA_{1c}, and was assumed to be an improvement of −0.9% to −1.2% for CSII compared with MDI for child/young adult and adults, respectively. A series of Markov constructs simulated the progression of diabetes-related complications.

Results: CSII was associated with an improvement in quality-adjusted life-years (QALYs) gained of 1.061 versus MDI for adults and 0.799 versus MDI for children/young adults. ICERs were $16,992 and $27,195 per QALY gained for CSII versus MDI in adults and children/young adults, respectively. Improved glycemic control from CSII led to a lower incidence of diabetes complications, with the most significant reduction in proliferative diabetic retinopathy (PDR), end stage renal disease (ESRD), and peripheral vascular disease (PVD). The number needed to treat (NNT) for PDR was nine patients, suggesting that only nine patients need to be treated with CSII to avoid one case of PDR. The NNT for ESRD and PVD was 19 and 41, respectively.

Conclusions: Setting the willingness to pay at $50,000/QALY, the analysis demonstrated that CSII is a cost-effective option for patients with T1DM in the United States.

Keywords: cost-effectiveness analysis, continuous subcutaneous insulin injection, multiple daily injections, type 1 diabetes mellitus.

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease where the insulin-secreting beta cells from the pancreas are destroyed and the person is unable to produce insulin [1]. The current standard of care for patients with T1DM includes intensive multiple daily injections (MDI) of insulin or administration of insulin through medical device technologies referred to as continuous subcutaneous insulin infusion (CSII), with some T1DM patients still treated with conventional insulin therapy. More specifically, MDI requires at least three premeal injections of rapid-acting insulin per day, whereas CSII offers continuous or intermittent delivery of subcutaneous infusions of insulin in very small amounts, with adjustments in the delivery rate or dose size when necessary.

The goal of diabetes treatments is to regulate circulating blood glucose levels and achieve a near normal glycemia. Hypoglycemia, or less than adequate levels of glucose in the blood, can occur as a complication of treatment of diabetes with insulin and can range from moderate (headache) to severe (coma). In cases of moderate to severe hypoglycemia, hospitalization may be necessary, in which costs can accrue. Reducing the risk of such complications from diabetes both in the near and distant future is essential for improving the patient's health-related quality of life (HRQOL).

Evidence from comprehensive reviews and meta-analyses has shown that CSII is associated with improved glycemic control and fewer hypoglycemic events compared with MDI. The improved glycemic control found with CSII may be because of a "more physiological" means of insulin delivery using rapid-acting insulin analogs accurately administered at rates specifically tailored to patient lifestyles and needs [2,3]. Nevertheless, CSII requires more equipment and training at initiation than MDI and thus tends to be more expensive on a short-term basis.

Because of health-care constraints in the United States and multiple effective treatment options, it is becoming more important that decision-makers identify cost-effective interventions for use in treating T1DM. A recent study by Cohen and colleagues examined the cost-effectiveness of CSII with MDI in adults and in children/young adults with T1DM in Australia [4]. Their findings suggest that CSII represents good value for money in Australia. A similar study performed by Roze et al. in the United Kingdom also found that CSII was a cost-effective treatment option for patients with T1DM [5]. The objective of this study was to project long-term cost-effectiveness of CSII compared with MDI of insulin in adults and in children/young adults with T1DM using published clinical and cost data from the United States. A modeling analysis using the previously published and validated CORE Diabetes Model was the method for evaluation.

Methods

CORE Diabetes Model

A brief overview of the CORE Diabetes Model (CDM) is provided below; however, previous articles have outlined more specifically the structure, data inputs, and validation studies for the CDM [6,7]. The CDM is a computer simulation model that was developed to estimate the long-term clinical and economic

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Table 1 Baseline characteristics of the US adult and child/young adult type 1 diabetes patient cohorts

Characteristic	Adult cohort baseline value (reference)	Child/young adult cohort baseline value* (reference)
Patient demographics		
Mean age (Years)	27.0 [32]	13.0 [10]
Duration of diabetes (Years)	9.0 [32]	5.6 [10]
Proportion male (%)	53.5% [32]	50.0% [10]
Risk factors		
HbA_{1c} (%)	8.95% [32]	8.2% [10]
Systolic blood pressure (mmHg)	115 [32]	115 [32]
Body mass index (kg/m^2)	23.75 [32]	23.75 [32]
Total cholesterol (mg/dl)	178.5 [32]	178.5 [32]
High-density lipoprotein cholesterol (mg/dl)	49.0 [32]	49.0 [32]
Low-density lipoprotein cholesterol (mg/dl)	112.0 [32]	112.0 [32]
Triglycerides (mg/dl)	87.0 [32]	87.0 [32]
Ethnic group		
Caucasian	90% [32]	81.25% [10]
African American	5% [32]	6.25% [10]
Other	5% [32]	12.5% [10]
Cardiovascular disease (CVD)		
Angina pectoris	1.9% [32]	1.9% [32]
Stroke	0.0%	0.0%
Myocardial infarction	0.0%	0.0%
Congestive heart failure	0.0%	0.0%
Atrial fibrillation	3.0% [32]	3.0% [32]
Left ventricular hypertrophy detected by ECG	3.0% [32]	3.0% [32]
Peripheral vascular disease	0.0%	0.0%
Renal disease		
Microalbuminuria	10.0% [32]	10.0% [32]
Retinopathy		
Background diabetic retinopathy	100% [32]	100% [32]
Patient management of type 1 diabetes		
Taking ACE-I/ARB: primary prevention	43.0% [32]	
Taking statins: primary prevention	33.0% [32]	
Taking aspirin: primary prevention	40.0% [32]	
Screened for retinopathy (assumed to be treated with laser if detected)	74.0% [32]	
Screened for renal disease (assumed to be treated with ACE-I or ARB if detected)	55.0% [32]	
Screened for foot disease	87.0% [32]	

*The parameter values for the children/young adult cohort are a combination of values from Doyle et al. [10] and assumptions made from applying the DCCT secondary (intensive) treatment cohort.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; DCCT, Diabetes Control and Complications Trial; ECG, electrocardiogram.

consequences of interventions for T1DM and type 2 diabetes mellitus (T2DM). The model is a nonproduct-specific diabetes policy analysis tool that performs real time simulations while taking into account intensive or conventional insulin therapy, oral hypoglycemic medications, screening and treatment strategies for microvascular complications, treatment strategies for end-stage complications, and multifactorial interventions. The model is based on a series of submodels that simulate the major complications of diabetes (angina, myocardial infarction [MI], congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular edema, cataract, hypoglycemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcers, amputation, and nonspecific mortality). Each submodel is Markov-based and utilizes Monte Carlo simulation with tracker variables, which uses time, state, and diabetes type-dependent probabilities derived from published sources such as the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study [8,9].

The CDM was designed and programmed by experienced diabetes disease modelers from IMS-Health along with clinicians and endocrinologists with superior knowledge of the published clinical and epidemiological research. For additional details on CDM, please see Palmer et al. [6].

Adult Cohort Description

Theoretical cohorts of 1000 adult T1DM patients were defined with baseline demographics, risk factors, and preexisting complications taken predominantly from the DCCT secondary intervention cohort and are completely summarized and referenced in Table 1 [3,9]. Briefly, the adult cohort had a mean age of 27.0 years, mean duration of diabetes was 9.0 years, 53.5% were male, 90% were Caucasian, 5% African American, 5% Hispanic, mean body mass index (BMI) was 23.75 kg/m^2, and mean HbA_{1c} was 8.95%. Patient management data for adults were taken from published epidemiological data in a variety of settings (Table 1).

Child/Young Adult Cohort Description

The child/young adult cohort was defined with baseline demographics, risk factors, and preexisting complications taken from Doyle (2004) and the DCCT secondary intervention cohort (summarized in Table 1) [3,9,10]. The child/young adult cohort was defined with baseline characteristics of a mean age of 13.0 years (range of 8–21 years) and mean duration of diabetes equal to 5.6 years, 50% were male, 81.25% were Caucasian, 6.25% were African-American, 12.5% Hispanic, mean BMI was 23.75 kg/m^2, and mean HbA_{1c} was 8.2% [10]. Patient management data for children/young adults were taken from published epidemiological data in a variety of settings (Table 1).

Intervention: CSII versus MDI (Adults)

Weissberg-Benchell et al. published a meta-analysis of insulin pump therapy in 2003 [3]. The meta-analysis took into account 52 studies with over 1500 patients and was able to quantify and

highlight key differences between CSII and MDI therapies in a comprehensive manner. CSII treatment was associated with improved HbA_{1c} levels and increased body weight. Based on the meta-analysis, treatment with CSII for 1 year or greater was associated with a mean decrease in baseline HbA_{1c} of 1.2% ± 0.2%, and a mean increase in BMI of 1.03 kg/m^2 compared with MDI therapy. These data were used as the base case comparison for the adult population in the present study with two other HbA_{1c} values used in the sensitivity analysis (see Sensitivity Analysis).

Data from an observational study published by Linkeschova et al., reviews of outpatient insulin therapy in T1DM by DeWitt and Hirsh, and Bode et al., along with a study by Bruttomesso, all suggest that hypoglycemia rates are not the same for CSII and MDI [11–14]. Bruttomesso et al. suggested that CSII reduces hypoglycemia rates by as much as 74% compared with MDI, and a similar reduction was observed in an observational study reported by Linkeschova et al. [11,12]. Therefore, for the adult base case analysis, we assumed that hypoglycemia event rates were 50% lower in the CSII group than in the MDI group (CSII event rate [age < 18] = 42.8657/100 patient-years; CSII event rate [age > 18] = 28.4492/100 patient years; MDI event rate [age < 18] = 85.7315/100 patient-years; MDI event rate [age > 18] = 56.8985). To test this assumption, additional sensitivity analyses were performed, assuming no difference in hypoglycemia rates between CSII and MDI and also a 75% reduction in hypoglycemia for the CSII treatment arm compared with MDI.

Intervention: CSII versus MDI (Children/Young Adults)

Doyle and colleagues performed a randomized, prospective trial in children and young adults with T1DM, comparing the efficacy of CSII with MDI using insulin glargine [10]. Patients were assigned to receive either MDI treatment with once-daily glargine and premeal/snack insulin aspart or CSII with insulin aspart [10]. This study was the first direct evaluation of CSII and glargine-based analogue MDI therapy in youth with T1DM using a randomized, prospective study design and a short time frame. The study found that lower HbA1c and premeal glucose levels were more achievable with CSII than with glargine-based analogue MDI treatment, and that CSII is an efficacious treatment to improve metabolic control in children/young adults with T1DM. Specifically, over a 16-week period, the study found a mean decrease in HbA_{1c} of 0.9% ± 0.2% ($P < 0.01$) for patients treated with CSII and a mean decrease in HbA_{1c} of 0.1% ± 0.1% for patients treated with MDI. These data were used as the base case comparison for the child/young adult population in the present study, with two other HbA_{1c} values used in the sensitivity analysis (see Sensitivity Analysis).

Similar to the adult base case analysis, in the child/young adult base case analysis, we assumed that hypoglycemia event rates were 50% lower in the CSII group than in the MDI group (see rates above for adults) [11–14]. In addition, sensitivity analysis were run using the same hypoglycemia event rates in both groups and reducing hypoglycemia event rates even further (75%) (see Sensitivity Analysis) [9].

Costs, Perspective, and Utility Values

The perspective for our analyses was that of a third-party US payer. All costs were expressed in 2007 US dollars. Costs of concomitant medications and diabetes-related complications were taken from published sources and inflated to 2007 US dollars and summarized in Table 2 [15]. The cost for diabetic complications largely arise from studies in T2DM populations. This is because of the number of studies in complications that come from T2DM populations compared with almost no analogous studies in T1DM populations. Therefore, our study utilized diabetes complication costs largely from T2DM populations, which are a potential limitation of our study.

Table 2 Cost per diabetes complication or event, adjusted to $US 2007 [15]

Description of event or state	Adjusted diabetes complication costs ($US 2007)*	Reference
Myocardial infarction, year of event	$38,783.33	[25]
Myocardial infarction, each subsequent year	$2,143.85	[25]
Angina, year of onset	$7,694.28	[25]
Angina, each subsequent year	$1,987.16	[25]
Congestive heart failure, year of onset	$3,331.62	[25]
Congestive heart failure, each subsequent year	$3,331.62	[25]
Stroke, year of event	$51,359.50	[25]
Stroke, each subsequent year	$17,140.63	[25]
Peripheral vascular disease, onset	$4,878.19	[33]
End-stage renal disease	$47,298.92	[25]
Laser treatment	$864.13	[25]
Severe vision loss/blindness, first year	$4,185.53	[25]
Severe vision loss/blindness, each subsequent year	$4,184.49	[25]
Cataract extraction	$2,751.35	[33]
Neuropathy, onset	$422.41	[25]
Uninfected ulcer (monthly based)	$1,833.87	[34]
Infected ulcer (monthly based)	$3,314.58	[34]
Gangrene (monthly based)	$6,466.78	[34]
Amputation, year of event	$34,204.23	[25]
Amputation, each subsequent year	$1,229.04	[25]
Major hypoglycemic event	$1,234.31	[21]
Ketoacidosis	$13,891.96	[25]
Annual cost aspirin	$23.85	[35]
Annual cost statins (assume simvastatin 10 mg at 238/100 tablets, inflated to $US 2007)	$982.23	[35]
Annual costs angiotensin converting enzyme inhibitor (based on 25-mg captopril *tris in diem*)	$441.72	[36]
Costs of screening for retinopathy	$85.17	[22]
Costs of screening for microalbuminuria	$19.30	[22]
Costs of screening for gross proteinuria	$28.40	[22]
Costs (monthly) nonstandard ulcer treatment (Regranex, Ethicon, Somerville, NJ, USA)	$173.74	[37]

*Diabetes complication costs largely arise from T2DM populations and not T1DM populations as there are few if any diabetes complication cost data available for T1DM populations. T1DM, type 1 diabetes mellitus; T1DM, type 2 diabetes mellitus.

Annual costs of CSII and MDI were based on pump costs (assuming 7-year pump life before replacement is needed in the base case), insulin costs, consumable supplies, self-monitoring of blood glucose, and outpatient costs. We assumed that 28% of MDI users in the United States use pen devices and inject four times per day (Medtronic data on file). We also assumed that CSII users change the reservoirs and infusion sets every 3 days (defined as Consumables in Table 3). These costs are fully itemized for US T1DM adult and child/young adult patients in Table 3.

The health state utilities and disutilities used in the analyses were taken from previously published studies as described in Table 4 [16–19]. In cases where no published state-specific health utilities were identified, it was conservatively assumed that the utility value was equivalent to a T1DM patient with no diabetes complications. This assumption was applied to the following health states: microalbuminuria, gross proteinuria, background diabetic retinopathy, and healed foot ulcer.

Time Horizon and Discounting

The time horizon for the simulation was set to 60 years to capture the remainder of a T1DM patient's lifetime consistent

Table 3 Annual costs of CSII and MDI in the United States ($US 2007) [15]

	Adult patients (reference)		Child/young adult patients (reference)	
	CSII	MDI	CSII	MDI
Pump	$677.14*	—	$677.14*	—
Insulin (CSII patients were assumed to use 0.53 u/kg/day and MDI patients use 0.71 u/kg/day) [38]	$1224.10	$1762.71	$1033.14	$1487.73
Consumables (pump supplies, syringes, and needles)	$1410.12	$395.17	$1410.12	$395.17
Self-monitoring blood glucose (lancets and glucose strips)	$1726.45 (assumed to be 5.5/day)	$1349.77 (assumed to be 4.3/day)	$1726.45 (assumed to be 5.5/day)	$1349.77 (assumed to be 4.3/day)
Outpatient	$320.61 (assumed 5 visits)	$268.68 (assumed 4 visits)	$320.61 (assumed 5 visits)	$268.68 (assumed 4 visits)
TOTAL	$5358.42	$3776.33	$5167.46	$3501.35

*Annual cost calculated based on pump lifespan of 7 years. Pump initiation included in pump cost.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

Table 4 Utility/disutility values used in the comparison between CSII and MDI for United States

Event/state	Utility/disutility†	Reference
Diabetes, no complications	0.814	[16]
Angina	0.682	[16]
Congestive heart failure	0.633	[16]
Myocardial infarction, year of event	−0.129	[16]
Myocardial infarction, years 2+ following event	0.736	[16]
Stroke, year of event	−0.181	[16]
Stroke, years 2+ following event	0.545	[16]
Peripheral vascular disease	0.570	[17]
Microalbuminuria	0.814	*
Gross proteinuria	0.814	*
Hemodialysis	0.49	[17]
Peritoneal dialysis	0.56	[17]
Kidney transplant	0.762	[17]
Background diabetic retinopathy	0.814	*
Cataract	0.794	
Macular edema	0.794	
Proliferative diabetic retinopathy	0.794	
Severe vision loss/blindness	0.734	[16]
Neuropathy	0.624	
Active ulcer	0.600	[18]
Healed diabetic ulcer	0.814	*
Amputation, year of event	−0.109	[16]
Amputation, years 2+ following event	0.68	[16]
All hypoglycemic events	−0.0052	[19]

*No state-specific health utility identified—conservatively assumed to be equivalent to complication-free utility, 0.020 = disutility for mild vision loss, 0.190 = disutility for neuropathy.
†Diabetes health state utilities largely arise from T2DM populations and not T1DM populations, as there are few, if any, diabetes health state utility data available for T1DM populations.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; T1DM, type 1 diabetes mellitus; T1DM, type 2 diabetes mellitus.

with diabetes modeling guidelines that recommend time horizons be sufficient to include the development of all relevant complications [20]. In the base case analysis, a discount rate of 3.0% per annum was applied to both costs and clinical outcomes in line with current recommendations in the US setting [20]. Discounting is a standard economic principle based on the hypothesis that future costs and events are worth less than current costs and events.

Sensitivity Analysis

Sensitivity analyses were performed to test the robustness of our results in adult and child/young adult US patients with T1DM. The first sensitivity analysis for adults varied the treatment effects on HbA_{1c} by using the overall HbA_{1c} lowering effects of (−0.95% ± 0.15%) from the Weissberg-Benchell meta-analysis for all CSII users, regardless of treatment duration [3]. The second sensitivity analysis for adults varied the treatment effects on HbA_{1c} by (−0.51% ± 0.24%) because of findings from an earlier meta-analysis by Pickup et al. [2]. In child/young adult patients, a sensitivity analysis was performed in which the base case treatment effect for HbA_{1c} for the CSII treatment arm was increased and decreased by 25% from the base case of 0.9% (i.e., −1.125% and −0.675%).

Next, based on new data from published reviews, an observational study, and meta-analyses, we assumed for the base case analysis for adults and children/young adults that hypoglycemia event rates were 50% lower in CSII than in MDI [11–14]. To test these assumptions, we performed additional sensitivity analyses reducing the hypoglycemia event rates by 0% and 75% in the CSII treatment arm to show the results for no difference between groups and a larger difference between groups. We also performed a sensitivity analysis on the cost of severe hypoglycemia. For the base case, we assumed the costs to be $1234.31 [21], but

Table 5 Summary results for adult type 1 diabetes patients in the United States: CSII versus MDI base case

	CSII	MDI	Difference between CSII and MDI
Life expectancy (years)	18.874 ± 0.231	17.888 ± 0.169	0.987
Quality-adjusted life expectancy (years)	12.848 ± 0.197	11.788 ± 0.107	1.061
Total direct costs ($US 2007)	$204,192 ± 2,950	$186,170 ± 3,159	$18,023
Costs/life expectancy ($US 2007 per life-year gained)			$18,268
Costs/QALY ($US 2007 per QALY gained)			$16,992

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; QALY, quality-adjusted life-year.

because of the uncertainty surrounding this value and findings from O'Brien and colleagues, which suggest a much lower value, we performed a sensitivity analysis utilizing the cost of $273.89 as well [22].

Additional sensitivity analyses included varying the discount rates on costs and clinical outcomes using 0% and 6% in adult and child/young adult US patients with T1DM and a change in BMI equal to 0 and 1.59 in adults. Further, we considered replacement of an insulin pump every 4, 6 and 8 years instead of the base case assumption of a 7-year pump life to make our analyses more comprehensive. It was assumed that payers would not replace a pump any earlier than 4 years because the warranty is only 4 years; thus exploring the cost-effectiveness for less than 4 years was not performed.

We performed a sensitivity analysis on the fear of hypoglycemia in adult and children/young adult patients with T1DM based on a study by Currie and colleagues, which addressed a disutility because of a fear of hypoglycemia associated with hypoglycemic events [23]. In our analysis, a lower number of episodes of severe hypoglycemia were assumed in patients taking CSII. Therefore, there may be an annual improvement in quality of life (QOL) compared with those taking MDI because of an annual reduction in the fear of hypoglycemia (fear of hypo disutility per event × number of hypo events). A sensitivity analysis was run using the QOL disutility rate associated with a severe hypoglycemic event (4.7%; Currie et al.), and was adjusted based on the annual number of severe hypoglycemia events in the two treatment groups, (14 events/100 patients/year in the CSII group and 62 events/100 patients/year in the MDI group), providing an overall annual reduction in utility of –0.00658 (4.7% × 0.14) in the CSII arm and –0.02914 (4.7% × 0.62) in the MDI group. Thus, an annual difference in QOL of 0.023 (–0.00658 – [–0.02914]) was compared between the two groups to determine whether QOL was affected.

Finally, in the base case analysis for both adults and children/young adults, the QOL utilities for major hypoglycemia event and for all hypoglycemia event were based on findings from the National Institute for Clinical Excellence study (QOL for major event = –0.0121 and QOL for all events = –0.0052) [19]. Nevertheless, based on more recent findings from Currie and colleagues, these values may differ slightly. Therefore, sensitivity analyses were run using QOL utilities from the Currie study to determine how these differences may affect the study outcomes. The Currie values were as follows: (QOL for major event = –0.0118 and QOL for all events = –0.0035) [23].

Statistical Analysis

To evaluate the uncertainty in the estimated cost-effectiveness and clinical outcomes from this analysis, nonparametric resampling methods, incorporating the updated methodology from Halpern et al., were used [24]. All of the probabilities that were used in the CDM were initially sampled using a first-order Monte Carlo simulation approach, which provided a point estimate for each parameter. These point estimates were then used in a second-order Monte Carlo simulation approach. The resampling method was then applied to each parameter from the first-order Monte Carlo results with costs and outcomes accumulated for 1000 theoretical patients, each going through the model 1000 times, resulting in a joint distribution of mean incremental costs and effectiveness gained. The percentages of joint distributions falling within a cost-effective range were calculated with these data and used to plot a cost-effectiveness acceptability curve and scatter plots. This type of statistical approach can be considered equivalent to repeating the same clinical trial multiple times. Therefore, this method is intended to provide information on the uncertainty surrounding outcomes data simulated through the CDM [7].

Results: Adult T1DM Patients in the United States

Life Expectancy (LE) and Quality-Adjusted Life Expectancy

In the base case analysis, T1DM treatment with CSII was projected to improve discounted LE and quality-adjusted life-years gained (QALYs) by 0.987 and 1.061 years, respectively, compared with MDI. Mean (±SD) discounted LE was 18.874 ± 0.231 years for CSII and 17.888 ± 0.169 years with MDI. Mean (±SD) discounted QALYs were 12.848 ± 0.197 years for CSII and 11.788 ± 0.107 years with MDI (see Table 5). Calculation of undiscounted LE produced values of 30.753 ± 0.231 years in the CSII group and 28.287 ± 0.169 years in the MDI arm (a difference of 2.466 years). Calculation of undiscounted QALYs produced values of 20.318 ± 0.197 years in the CSII group and 18.153 ± 0.107 years in the MDI arm (a difference of 2.165 QALY).

Incidence of Complications

Improved glycemic control associated with CSII treatment compared with MDI led to a lower incidence of several key complications from diabetes over patients' lifetimes. In regard to eye disease, the cumulative incidence of proliferative diabetic retinopathy was reduced by 29% compared with MDI over the 60-year simulation period (relative risk [RR] = 0.71). The corresponding number needed to treat (NNT) for proliferative diabetic retinopathy was nine patients, suggesting that only nine patients need to be treated with CSII to avoid one case of proliferative diabetic retinopathy. In regard to end-stage renal disease (ESRD), the cumulative incidence of ESRD was reduced by 20% compared with MDI over the 60-year simulation period (RR = 0.80). Similarly, the cumulative incidence of neuropathy death was reduced by 22% compared with MDI (RR = 0.78). Corresponding NNT for ESRD and neuropathy death was 19

Table 6 Diabetes complications for adult type 1 diabetes patients in the United States: CSII versus MDI

Body system	Complication	Incidence ± SD (%)		Relative risk (CSII vs. MDI)	Number needed to treat (CSII vs. MDI)
		CSII	MDI		
Eyes	Proliferative diabetic retinopathy	24.489 ± 1.951	34.558 ± 1.382	0.708	9
	Cataract	19.911 ± 1.329	18.446 ± 1.284	1.079	—
	Macular edema	53.127 ± 1.534	54.314 ± 1.562	0.978	84
	Severe vision loss	40.163 ± 1.566	41.061 ± 1.530	0.977	111
Renal	Microalbuminuria	70.978 ± 2.101	78.518 ± 1.345	0.904	13
	Gross proteinuria	53.605 ± 2.637	65.775 ± 1.475	0.815	8
	End-stage renal disease	21.037 ± 1.579	26.238 ± 1.424	0.802	19
	Nephropathy death	15.851 ± 1.422	20.613 ± 1.395	0.783	21
Cardiovascular	Myocardial infarction	26.098 ± 1.416	27.481 ± 1.361	0.950	72
	Myocardial infarction death	14.825 ± 1.153	15.481 ± 1.193	0.957	152
	Stroke event	9.203 ± 0.957	7.862 ± 0.835	1.170	—
	Stroke death	3.359 ± 0.603	2.814 ± 0.508	1.194	—
	Congestive heart failure	25.146 ± 1.364	22.659 ± 1.264	1.109	—
	Congestive heart failure death	11.939 ± 1.045	10.205 ± 0.995	1.170	—
	Peripheral vascular disease	13.158 ± 1.121	15.552 ± 1.089	0.839	41
	Angina	11.918 ± 1.069	9.935 ± 0.998	1.199	—
Extremities	Peripheral neuropathy	94.368 ± 0.868	96.635 ± 0.565	0.976	44
	Foot ulcer	58.562 ± 1.160	59.537 ± 1.555	0.984	102
	Recurring foot ulcer	87.894 ± 4.983	88.325 ± 4.991	0.995	232
	Amputation from foot ulcer	19.014 ± 1.465	19.378 ± 1.407	0.981	274
	Amputation from recurring foot ulcer	7.901 ± 1.167	7.951 ± 1.143	0.994	2000

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

and 21, respectively. Finally, the findings for cardiovascular complications showed that the cumulative incidence of peripheral vascular disease was reduced by 16% compared with MDI over the 60-year simulation period (RR = 0.84), with a NNT of 41 patients. Additional observations for diabetes complications are shown in Table 6.

Costs and Cost-Effectiveness

The mean discounted lifetime direct medical costs associated for T1DM with CSII in US adults was projected to be $US204,192 ± 2,950 compared with $US186,170 ± 3,159 for MDI treatment (see Table 5). The incremental difference in costs of $US18,023 translates into a cost per life-year gained (LYG) of $US18,268 with CSII therapy versus MDI. The cost per QALY gained was $US16,992. The resampling simulation data were placed on a scatter plot based on QALYs gained and included as Figure 1. The data were then plotted on an acceptability curve to assess the likelihood of cost-effectiveness according to willingness to pay in the United States. Setting the willingness to pay at $US50,000/QALY, the analysis demonstrated that CSII had a 100% probability of being cost-effective for adult T1DM using QALYs gained as the outcome measure (see Fig. 2).

The breakdown of total direct medical costs showed that treatment costs were the greatest component. Mean lifetime treatment costs were $US103,386 in the CSII group compared with $US69,247 for MDI. Complication and other management costs were $US16,117 lower for CSII compared with MDI ($US100,806 vs. $US116,923, respectively). Therefore, the extra treatment costs associated with CSII were partially offset by the reduction in diabetes complications compared with MDI, even when taking into account the survival paradox (that patients live longer with CSII treatment, and therefore should experience more complications and incur greater complication costs compared with MDI) (see Table 7).

Sensitivity Analysis

Sensitivity analyses showed that the findings in US adults with T1DM were most sensitive to changes in HbA_{1c}, hypoglycemia rates, fear of hypoglycemia, cost of severe hypoglycemia, and a 4-year pump life (See Table 8). Altering the improvement in HbA_{1c} levels associated with CSII compared with MDI from 1.2% in the base case to 0.95% (reported by Weissberg-Benchell et al. [3]), and to 0.51% (as reported by Pickup et al. [2]), increased the incremental cost-effectiveness ratios (ICERs) to $US21,493/QALY and $US39,384/QALY, respectively. Recent publications have suggested that CSII may be associated with lower rates of hypoglycemia than MDI, with a 50% to 74% reduced incidence of hypoglycemia [9,11–14]. Keeping the hypoglycemia rates the same in both groups (0% increase) resulted in an ICER of $US27,721/QALY, while reducing the hypoglycemia rate in the CSII treatment arm by 75% led to an improvement in the ICER to $US11,189/QALY compared with MDI. Adding a disutility for fear of hypoglycemia provided an ICER of $US11,647. Altering the cost of severe hypoglycemia to that reported by O'Brien and colleagues led to an ICER of $US23,225/QALY [25]. Replacement of an insulin pump every 4 years led to an ICER of $US26,230/QALY. Although this was significantly higher than the base case of 7 years, this still is well within the acceptable range for cost-effectiveness in the United States.

Exploratory Analysis: Child/Young Adult T1DM Patients in the United States

LE and Quality-Adjusted Life Expectancy

In the base case analysis, T1DM treatment with CSII was projected to improve discounted LE and QALY gained by 0.695 and 0.799 years, respectively, compared with MDI. Mean (±SD) discounted LE was 20.827 ± 0.238 years for CSII and 20.132 ± 0.194 years with MDI. Mean (±SD) discounted QALYs were 14.418 ± 0.199 years for CSII and 13.618 ± 0.143 years with MDI (see Table 9). Calculation of undiscounted LE produced values of 36.495 ± 0.238 years in the CSII group and 34.480 ± 0.194 years in the MDI arm (a difference of 2.02 years). Calculation of undiscounted QALYs produced values of 24.392 ± 0.199 years in the CSII group and 22.564 ± 0.143 years in the MDI arm (a difference of 1.83 QALY).

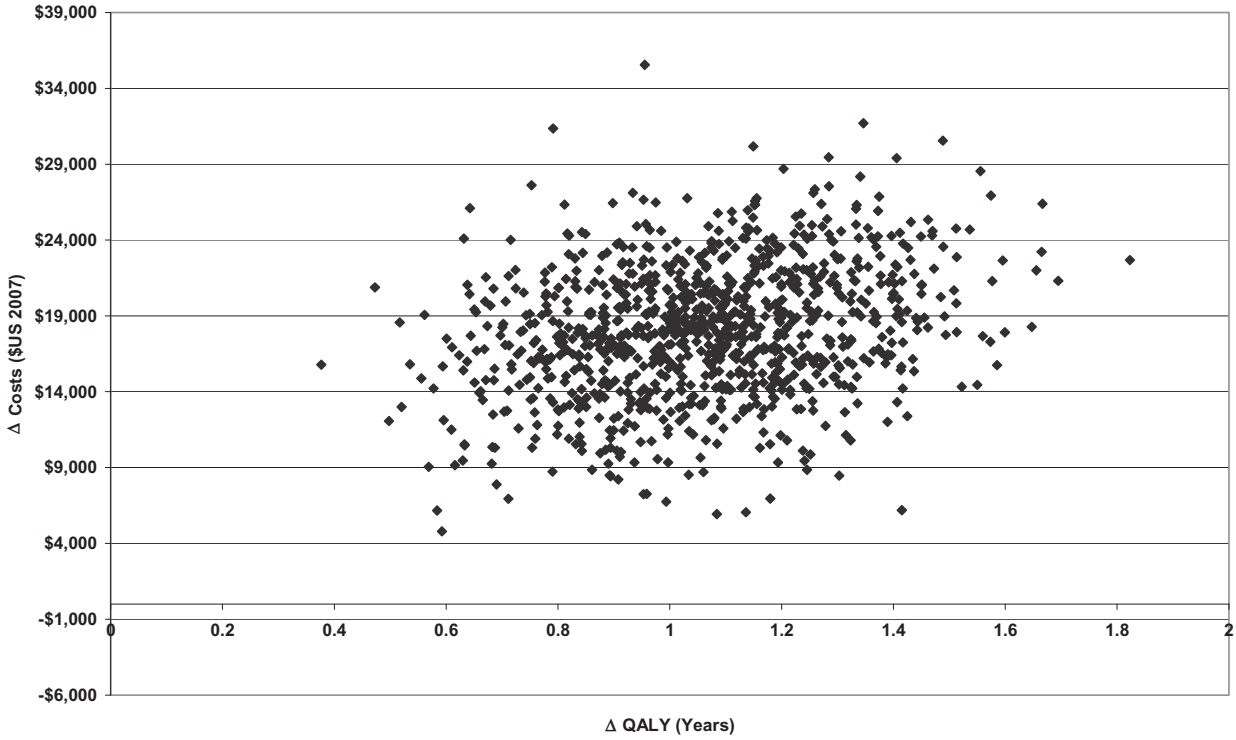

Figure 1 Scatterplot for QALY comparing CSII versus MDI in adult type 1 diabetes patients in the United States. CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; QALY, quality-adjusted life-year.

Incidence of Complications

Improved glycemic control associated with CSII treatment compared with MDI led to a lower incidence of several key complications from diabetes over patients' lifetimes. In regards to eye disease, the cumulative incidence of proliferative diabetic retinopathy was reduced by 21% compared with MDI over the 60-year simulation period (RR = 0.79). The corresponding NNT for proliferative diabetic retinopathy was 18 patients; suggesting that only 18 patients need to be treated with CSII to avoid one

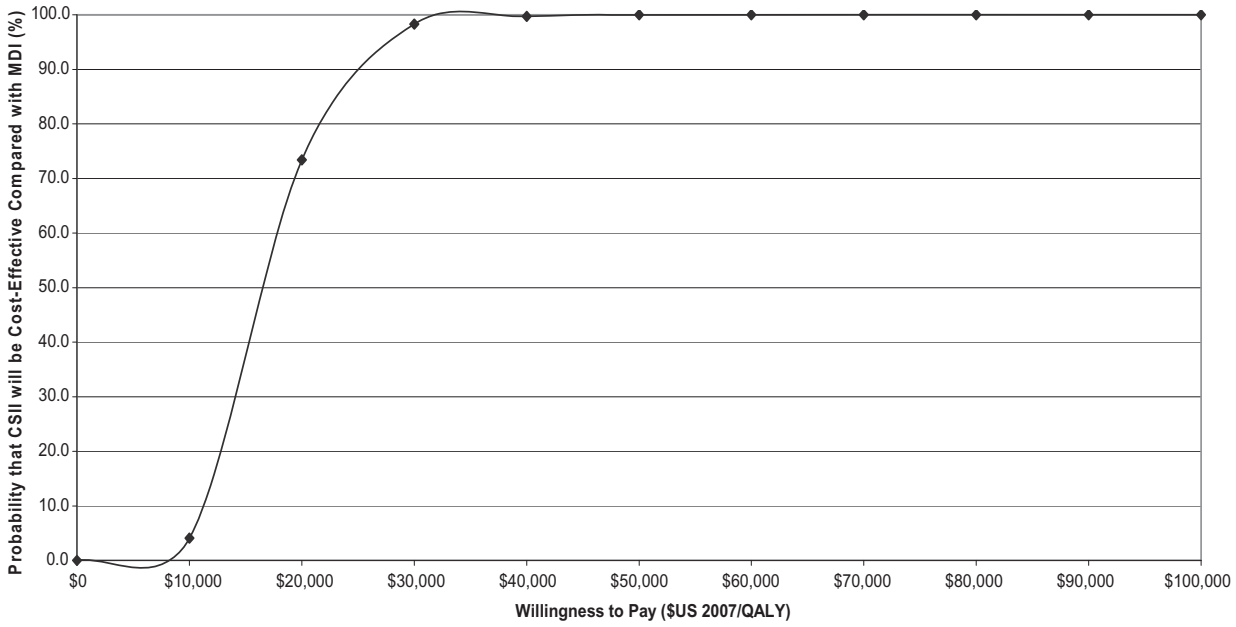

Figure 2 Cost-effectiveness acceptability curve for adult type 1 diabetes patients in the United States.

Table 7 Breakdown of direct medical costs over patients' lifetimes (adults)

Cost (per patient)	CSII	MDI	Difference
Total direct medical costs ($US)	204,192 (2,950)	186,170 (3,159)	18,023
Treatment costs (index medication) ($US)	103,386	69,247	34,139
Management costs (concomitant medications and screening) ($US)	12,895	12,503	392
Complication costs ($US)	87,911	104,420	−16,509
CVD	14,776	14,446	330
Renal	19,939	26,689	−6,750
Ulcer/amp/neuropathy	22,853	24,540	−1,687
Eye	13,189	13,406	−217
Hypoglycemia	11,844	20,297	−8,453
Keto/lactic acidosis	5,310	5,042	268

Values shown are means with SDs in parentheses.
CSII, continuous subcutaneous insulin infusion; CVD, cardiovascular disease; MDI, multiple daily injections.

case of proliferative diabetic retinopathy. In regard to ESRD, the cumulative incidence of ESRD was reduced by 15% compared with MDI over the 60-year simulation period (RR = 0.85). Similarly, the cumulative incidence of neuropathy death was reduced by 18% compared with MDI (RR = 0.82). Corresponding NNT for ESRD and neuropathy death were 24 and 27, respectively. Finally, the findings for cardiovascular complications showed that the cumulative incidence of peripheral vascular disease was reduced by 13% compared with MDI over the 60-year simulation period (RR = 0.87), with a NNT of 78 patients. Additional observations for diabetes complications are shown in Table 10.

Costs and Cost-Effectiveness

The mean discounted lifetime direct medical costs associated with CSII for T1DM in US children/young adults was projected to be $US212,597 ± 2,915 compared with $US190,862 ± 2,891 for MDI treatment (see Table 9). The incremental difference in costs of $US21,734 translates into a cost per LYG of $US31,259 with CSII therapy versus MDI. The cost per QALY gained was $US27,195.

The resampling simulation data were placed on a scatter plot based on QALYs gained and included as Figure 3. The data were then plotted on an acceptability curve to assess the likelihood of cost-effectiveness according to willingness to pay in the United States. Setting the willingness to pay at $US50,000/QALY, the analysis demonstrated that CSII had a 93.8% probability of being cost-effective for child/young adult T1DM patients using QALYs gained as the outcome measure. (See Fig. 4)

The breakdown of total direct medical costs showed that treatment costs were the greatest component. Mean lifetime treatment costs were $US109,440 in the CSII group compared

Table 8 Summary of sensitivity analysis results for adult patients with type 1 diabetes in the United States

	QALY (years)		Total lifetime costs ($US 2007)		
Analysis	CSII	MDI	CSII	MDI	ICER
Base case (−1.2% ± 0.2% HbA_{1c} for CSII compared with MDI) [3]	12.848 ± 0.197	11.788 ± 0.107	204,192 ± 2,950	186,170 ± 3,159	$16,992
HbA_{1c} setting no. 2 (−0.95% ± 0.15% HbA_{1c} for CSII compared with MDI) [3]	12.647 ± 0.152	11.788 ± 0.107	204,645 ± 3,041	186,170 ± 3,159	$21,493
HbA_{1c} setting no. 3 (−0.51% ± 0.24% HbA_{1c} for CSII compared with MDI) [2]	12.273 ± 0.207	11.788 ± 0.107	205,305 ± 2,982	186,170 ± 3,159	$39,384
No difference in hypoglycemia rates	12.753 ± 0.200	11.788 ± 0.107	212,942 ± 3,009	186,170 ± 3,159	$27,721
Hypoglycemia rates reduced by 75%	12.899 ± 0.203	11.788 ± 0.107	198,603 ± 2,929	186,170 ± 3,159	$11,189
Fear of hypoglycemia	11.448 ± 0.171	10.433 ± 0.101	198,790 ± 2,972	186,967 ± 2,858	$11,647
Conservative rate for cost of severe hypoglycemia ($273.89) [25]	12.830 ± 0.199	11.773 ± 0.110	194,989 ± 2,897	170,440 ± 3,059	$23,225
0% discount rate	20.318 ± 0.425	18.153 ± 0.225	380,120 ± 7,300	339,173 ± 7,272	$18,910
6% discount rate	9.060 ± 0.108	8.454 ± 0.060	126,840 ± 1,613	116,475 ± 1,706	$17,085
No effect on BMI	12.854 ± 0.198	11.788 ± 0.107	204,243 ± 3,034	186,170 ± 3,159	$16,943
Change in BMI = +1.59	12.828 ± 0.205	11.773 ± 0.110	204,217 ± 3,085	186,170 ± 3,159	$17,106
QOL for major hypo event and for all hypo event (Currie et al.) [23]	12.851 ± 0.197	11.792 ± 0.107	204,192 ± 2,950	186,170 ± 3,159	$17,023
4-year pump life	12.848 ± 0.197	11.788 ± 0.107	213,991 ± 2,994	186,170 ± 3,159	$26,230
6-year pump life	12.848 ± 0.197	11.788 ± 0.107	206,370 ± 2,960	186,170 ± 3,159	$19,045
8-year pump life	12.848 ± 0.197	11.788 ± 0.107	202,560 ± 2,943	186,170 ± 3,159	$15,452

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; ICER, incremental cost-effectiveness ratio for CSII versus MDI, expressed in cost ($US 2007) per QALY saved; MDI, multiple daily injections; QALY, quality-adjusted life-year; QOL, quality of life.

Table 9 Summary results for child/young adult type 1 diabetes patients in the United States: CSII versus MDI base case

	CSII	MDI	Difference between CSII and MDI
Life expectancy (years)	20.827 ± 0.238	20.132 ± 0.194	0.695
Quality-adjusted life expectancy (years)	14.418 ± 0.199	13.618 ± 0.143	0.799
Total direct costs ($US 2007)	$212,597 ± 2,915	$190,862 ± 2,891	$21,734
Costs/life expectancy ($US 2007 per life-year gained)			$31,259
Costs/QALY ($US 2007 per QALY gained)			$27,195

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; QALY, quality-adjusted life-year.

Table 10 Diabetes complications for child/young adult type 1 diabetes patients in the United States: CSII versus MDI

Body system	Complication	Incidence ± SD (%)		Relative risk (CSII vs. MDI)	Number needed to treat (CSII vs. MDI)
		CSII	MDI		
Eyes	Proliferative diabetic retinopathy	21.154 ± 1.665	26.652 ± 1.469	0.794	18
	Cataract	23.415 ± 1.329	22.291 ± 1.358	1.050	—
	Macular edema	52.565 ± 1.518	53.247 ± 1.595	0.987	146
	Severe vision loss	42.961 ± 1.504	43.063 ± 1.552	0.997	980
Renal	Microalbuminuria	72.426 ± 1.939	77.793 ± 1.427	0.931	18
	Gross proteinuria	55.021 ± 2.458	63.404 ± 1.659	0.867	11
	End-stage renal disease	22.573 ± 1.570	26.682 ± 1.477	0.846	24
	Nephropathy death	17.102 ± 1.377	20.800 ± 1.384	0.822	27
Cardiovascular	Myocardial infarction	19.244 ± 1.274	19.799 ± 1.185	0.971	180
	Myocardial infarction death	10.767 ± 0.995	11.097 ± 0.952	0.970	303
	Stroke event	5.603 ± 0.734	5.038 ± 0.702	1.112	—
	Stroke death	2.069 ± 0.447	1.823 ± 0.428	1.135	—
	Congestive heart failure	19.032 ± 1.279	17.741 ± 1.201	1.073	—
	Congestive heart failure death	8.018 ± 0.853	7.301 ± 0.826	1.098	—
	Peripheral vascular disease	8.841 ± 0.926	10.129 ± 0.926	0.873	78
	Angina	8.158 ± 0.897	7.220 ± 0.795	1.130	—
Extremities	Peripheral neuropathy	94.471 ± 0.811	95.965 ± 0.618	0.984	66
	Foot ulcer	63.763 ± 1.605	64.473 ± 1.529	0.988	140
	Recurring foot ulcer	102.224 ± 5.534	102.914 ± 5.539	0.993	144
	Amputation from foot ulcer	21.827 ± 1.429	22.039 ± 1.573	0.990	471
	Amputation from recurring foot ulcer	10.060 ± 1.329	10.209 ± 1.353	0.985	671

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

with $US71,804 for MDI. Complication and other management costs were $US15,901 lower for CSII compared with MDI ($US103,157 vs. $US119,058, respectively). Therefore, the extra treatment costs associated with CSII were partially offset by the reduction in diabetes complications compared with MDI, even when taking into account the survival paradox (that patients live longer with CSII treatment, and therefore should experience more complications and incur greater complication costs compared with MDI) (see Table 11).

Sensitivity Analysis

Sensitivity analyses showed that the findings in US child/young adult patients with T1DM were most sensitive to changes in

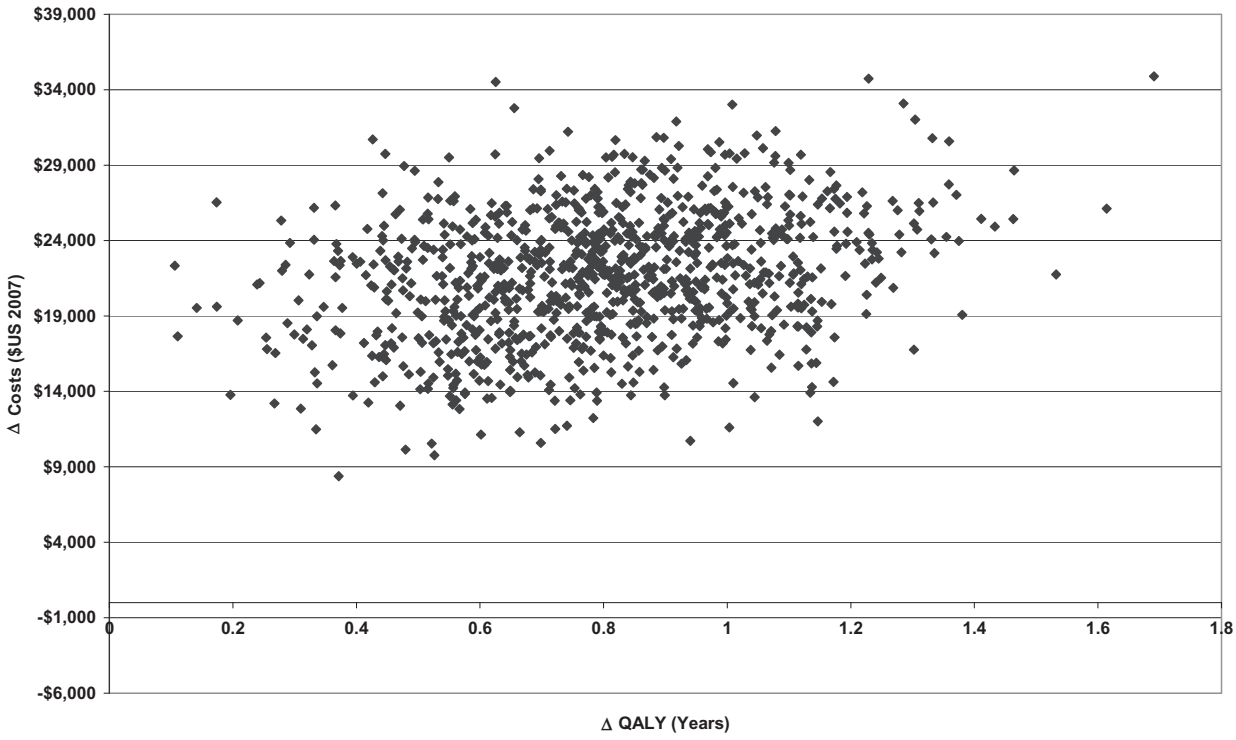

Figure 3 Scatterplot for QALY comparing CSII versus MDI in child/young adult type 1 diabetes patients in the United States. CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; QALY, quality-adjusted life-year.

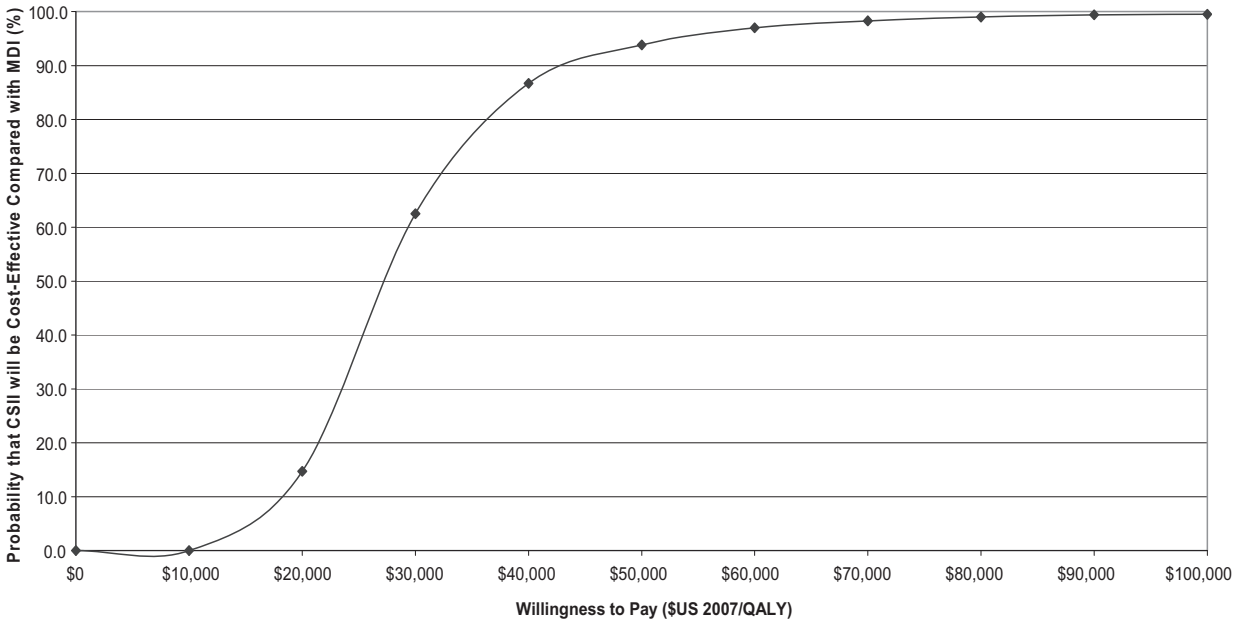

Figure 4 Cost-effectiveness acceptability curve for child/young adult type 1 diabetes patients in the United States.

HbA_{1c}, hypoglycemia rates, fear of hypoglycemia, and a 4-year pump life (See Table 12). Altering the improvement in HbA_{1c} levels associated with CSII compared with MDI from –0.9% in the base case to –1.125% and to –0.675% altered the ICERs to $US20,997/QALY and $US37,326/QALY, respectively. Recent publications have suggested that CSII may be associated with lower rates of hypoglycemia than MDI, with a 50% to 74% reduced incidence of hypoglycemia [9,11–14]. To test this uncertainty, hypoglycemia rates were assumed to be equivalent between CSII and MDI and also assumed a 75% reduction in the CSII treatment arm. Keeping the hypoglycemia rates the same in both groups resulted in an ICER of $US45,595/QALY, while reducing the hypoglycemia rate in the CSII treatment arm by 75% led to an improvement in the ICER to $US17,673/QALY compared with MDI. Adding a disutility for fear of hypoglycemia provided an ICER of $US19,300. Reducing the pump life to 4 years from 7 years in child/young adult with T1DM led to an ICER of $40,652/QALY, suggesting that even if the insulin pump is replaced more frequently, CSII is still cost-effective for child/young adult T1DM patients in the United States.

Discussion

This study represents the first cost-effectiveness analysis comparing CSII with MDI in adult and child/young adult patients with T1DM in the United States. Our study findings suggest that CSII improves both mortality and morbidity for adult and child/young adult patients with T1DM in the United States. Further, our analysis suggests that CSII is a cost-effective medical intervention for patients with T1DM. The study findings are important in that the cost-effectiveness of CSII was compared with the use of MDI with a newer insulin analogue and revealed ICERs well under the $50,000 threshold often cited in studies using a US perspective [26].

Treatment with CSII in adult patients with T1DM was associated with improvements of 0.987 and 1.061 years in discounted life-years gained and QALYs, respectively, compared with MDI. Additionally, treatment with CSII in child/young adult patients with T1DM was associated with improvements of 0.695 and 0.799 years in discounted life-years gained and QALY, respectively, compared with MDI. Total lifetime costs were

Table 11 Breakdown of direct medical costs over patients' lifetimes (child/young adult)

Cost (per patient)	CSII	MDI	Difference
Total direct medical costs ($US)	212,597 (2,915)	190,862 (2,891)	21,734
Treatment costs (index medication) ($US)	109,440	71,804	37,636
Management costs (concomitant medications and screening) ($US)	14,016	13,745	271
Complication costs ($US)	89,141	105,313	–16,172
CVD	9,216	9,036	180
Renal	22,566	27,865	–5,299
Ulcer/amp/neuropathy	23,381	24,716	–1,335
Eye	13,881	13,839	42
Hypoglycemia	14,252	24,208	–9,956
Keto/lactic acidosis	5,845	5,649	196

Values shown are means with SDs in parentheses.
CSII, continuous subcutaneous insulin infusion; CVD, cardiovascular disease; MDI, multiple daily injections.

Table 12 Summary of sensitivity analysis results for child/young adult patients with type 1 diabetes in the United States

Analysis	QALY (years)		Total lifetime costs ($US 2007)		ICER
	CSII	MDI	CSII	MDI	
Base-case (–0.9% ± 0.2% HbA_{1c} for CSII compared with MDI). Hypoglycemia rates reduced by 50%.	14.418 ± 0.199	13.618 ± 0.143	212,597 ± 2,915	190,862 ± 2,891	$27,195
HbA_{1c} setting no. 2 (–1.125% ± 0.2% HbA_{1c} for CSII compared with MDI)	14.614 ± 0.201	13.618 ± 0.143	211,766 ± 2,814	190,862 ± 2,891	$20,997
HbA_{1c} setting no. 3 (–0.675% ± 0.2% HbA_{1c} for CSII compared with MDI)	14.218 ± 0.200	13.618 ± 0.143	213,227 ± 2,991	190,862 ± 2,891	$37,326
Hypoglycemia rates reduced by 0%	14.316 ± 0.200	13.618 ± 0.143	222,677 ± 2,933	190,862 ± 2,891	$45,595
Hypoglycemia rates reduced by 75%	14.472 ± 0.187	13.618 ± 0.143	205,952 ± 2,935	190,862 ± 2,891	$17,673
Fear of hypoglycemia	12.773 ± 0.167	11.999 ± 0.119	205,221 ± 2,811	190,289 ± 3,058	$19,300
0% discount rate	24.392 ± 0.483	22.564 ± 0.339	429,931 ± 7,990	382,735 ± 7,364	$25,820
6% discount rate	9.802 ± 0.100	9.378 ± 0.074	126,342 ± 1,494	113,234 ± 1,541	$30,935
No effect on BMI	14.417 ± 0.199	13.618 ± 0.143	212,521 ± 2,826	190,682 ± 2,891	$27,103
QOL for major hypo event and for all hypo event (Currie et al.) [23]	14.421 ± 0.199	13.618 ± 0.143	212,597 ± 2,915	190,862 ± 2,891	$27,273
4-year pump life	14.418 ± 0.199	13.618 ± 0.143	223,353 ± 2,960	190,862 ± 2,891	$40,652
6-year pump life	14.418 ± 0.199	13.618 ± 0.143	214,987 ± 2,924	190,862 ± 2,891	$30,185
8-year pump life	14.418 ± 0.199	13.618 ± 0.143	210,804 ± 2,901	190,862 ± 2,891	$24,952

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; ICER, incremental cost-effectiveness ratio for CSII versus MDI, expressed in cost ($US 2007) per QALY saved; MDI, multiple daily injections; QALY, quality-adjusted life-year; QOL, quality of life.

greater for CSII in patients with T1DM in the United States when compared with MDI for both adults and children/young adults. Examining direct costs only, treatment costs were always greater with CSII therapy, but these were partially offset by reduced costs of complications from diabetes compared with MDI. Our findings led to ICERs of $US18,268/LYG for adult patients with T1DM and $US31,259/LYG for child/young adult patients with T1DM, which are within the range of <$US50,000 often cited in the literature representing good value for money in the United States [26].

The use of CSII compared with MDI led to a reduction in many diabetes-related complications. The majority of diabetes-related complications that were part of this analysis favored the use of CSII over MDI, with RR reductions ranging from 0.5% to 29.2% for adults and 0.2% to 20.6% for children/young adults. Renal complications and eye complications showed the greatest reductions for patients receiving CSII.

Several other studies have examined the cost-effectiveness of insulin pump therapy. Scuffham and Carr performed a cost-effectiveness study on insulin pump therapy within the United Kingdom [27]. They focused solely on hypoglycemia and ketoacidosis over an 8-year period. Their study found that CSII is cost-effective in patients with severe and/or unpredictable hypoglycemia requiring hospitalization more than twice a year. A study performed by Colquitt and colleagues that used semi-quantitative methods reached similar conclusions [28]. Roze et al. evaluated adult patients using insulin pump therapy within the UK using the CDM [5]. They reported ICERs of £27,477/LYG and £25,648/QALY, demonstrating that insulin pump therapy represents good value for money in the United Kingdom. Findings from Cohen and colleagues in Australia also supported the cost-effectiveness of CSII when compared with MDI in both adults and children/young adults with T1DM, resulting in ICERs of $A74,147QALY and $A74,661/QALY respectively (threshold = $A76,000) [4].

The key assumptions within the CDM were thoroughly tested by performing multiple sensitivity analyses. In our analysis, cost-effectiveness was highly sensitive to HbA_{1c} changes, hypoglycemia rates, and fear of hypoglycemia. Specifically, in adults with T1DM, an HbA_{1c} decrease of only 0.51% for CSII compared with MDI was less cost-effective, with an ICER of $US 39,384, but still well below the generally accepted threshold. There are several publications showing a marked reduction in hypoglycemia rates (50% to 75%) with CSII compared with MDI, and recurrent hypoglycemia is one of the most common clinical indications for insulin pump therapy [9,11–14]. A 75% reduction in hypoglycemic events resulted in an ICER of $US11,189/QALY for adults and $US17,693/QALY ICER for children/young adults. Further improvements in ICERs may also result with newer insulin pump technologies becoming available with continuous glucose monitoring systems designed to further reduce hypoglycemia events. These devices can help identify fluctuations that may otherwise be unrecognizable with standard HbA_{1c} tests and intermittent finger stick measurements. Finally, adding a disutility for fear of hypoglycemia resulted in a 31% ICER improvement to $US11,647 for adults and a 29% ICER improvement to $19,300 for children/young adults. Lastly, our results were somewhat sensitive to shorter lifespan of the insulin pump; however, each ICER remained below the $50,000 threshold value many deem cost-effective in the USA.

Research has found that a disutility may exist because of a fear of injection, thus making CSII more attractive than MDI [29,30]. Although this disutility could not be included in our modeling analysis, this variable may have led to a more substantial effect for patients receiving CSII versus MDI if it was part of the analysis. Reducing this barrier for patients may help to improve compliance and in turn patient outcomes, supporting the use of CSII over MDI. In addition, there are new values for HRQOL, suggesting improved patient-reported outcomes with CSII over glargine or NPH-based MDI regimens [31]. Nevertheless, most of these new values for HRQOL have not been directly linked with utilities or disutilities. Therefore, in the absence of these updated utility inputs, our model outcomes may have underestimated the impact of improved patient utilities for CSII compared with MDI.

Although some limitations exist, the Weissberg-Benchell meta-analysis is an excellent source for data on insulin pump therapy [3]. One limitation involves the time frame in which many of studies were published, as a majority of the 52 studies included in the meta-analysis were published before 1987, with relatively few studies published following the DCCT in 1993. Therefore, many studies that were part of this meta-analysis represent data on older insulin device technology, including nonbuffered insulin used in pumps that were less accurate and reliable than modern devices or newer insulins. A growing body of evidence and our clinical experience suggests that newer insulin pump devices available today lead to lower rates of hypoglycemia than MDI.

One limitation of our study was that the base case analysis only takes into account *direct* medical costs from a third-party US payer perspective. The base case study does not include nonmedical costs, such as lost productivity, transport costs, resi-

dential aged or nursing care, and intangible costs, and therefore is likely to underestimate total costs from a complete societal perspective. A further limitation of modeling studies is that the data used to design most models are primarily from clinical trials. As a result, many real-life factors, such as compliance, effectiveness, and treatment drop-out rates may not be taken into consideration, as clinical trials often represent a "best-case scenario." HRQOL estimates provided by most studies reflect changes associated with long-term complications rather than with the treatment modality, per se. A further limitation of our study was the lack of applicability to certain key patient subgroups (e.g., hypoglycemia-prone T1DM patients) that could be a subject for future analyses and study.

An additional limitation of this study surrounds the exploratory analysis that compared the cost-effectiveness of MDI versus CSII in children and young adults with T1DM. The methods for this analysis included the use of findings from Doyle and colleagues, which included only 32 patients ranging in age from 8 to 21 years. Thus, the small number of patients provided little for extrapolation of the data or reliability of the findings. Nevertheless, this study was the first direct evaluation comparing the use of glargine-based analogue MDI versus CSII therapy in youth, with T1DM using a randomized, prospective study design and a short time frame, making it of interest to payers to get some guidance on the cost-effectiveness in this age group. In addition to the weaknesses in the Doyle study, many of the inputs for the CDM for this child/young adult analysis were taken from the adult cohort as they were unknown. These inputs (costs of complications, rates of complication, etc.), which were extrapolated from the adult cohort to the child/young adult cohort, may not accurately represent this population. Thus, the findings for this population should be considered speculative.

Modeling is a useful mathematical tool that allows for the projection of long-term clinical outcomes and costs using the best, often shorter-term, published clinical and epidemiological data currently available. Every effort has been made to utilize the most accurate and reproducible data sources in the present analysis to provide a real-world simulation of adult T1DM in the United States [7]. Moreover, during development of the CDM, preference was given to epidemiological data sources to attempt to overcome, when possible, the potential drawback of relying on clinical studies only as data sources in a modeling analysis.

Our modeling analysis of CSII versus MDI for T1DM in the United States has demonstrated that improvements in glycemic control attributed to CSII leads to improvements in LE and QALYs because of the reduced incidence of diabetes-related complications and side effects of therapy. CSII is associated with ICERs for adult and child/young adult patients with T1DM of $US 16,992 and $US27,195, respectively, representing good value for money in the United States [26].

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