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Master Thesis

The cost-effectiveness of a hybrid closed-loop system compared to continuous subcutaneous insulin infusion and sensor-augmented pump therapy for type 1 diabetes patients with high glucose levels in Norway

Sophie Schildbach, Student number: 607539

Supervisor: Eline Aas

Co-supervisors: Gunhild Hagen, Dr. Sven Carlsen

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DECLARATION OF OATH

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Abstract

Background: Only 22% of Norwegian type 1 diabetes mellitus (T1DM) patients achieve recommended blood glucose levels with current treatment options. Poor glucose control may lead to serious complications in the long-term. Hybrid closed-loop systems (HCLS) combine continuous subcutaneous insulin infusion (CSII) with continuous glucose monitoring (CGM). The system is able to automatically adjust insulin doses based on CGM reading. HCLS is associated with improved glycaemic control but also with high costs. The aim of this analysis was to assess the cost-effectiveness of the MiniMed 670G HCLS compared to CSII and sensor-augmented pump (SAP) therapy for T1DM patients with high glucose levels in Norway.

Methods: Cost-effectiveness analysis was performed from a healthcare payer perspective. A markov cohort model was developed to assess lifetime costs and benefits of the treatments. The cost of the treatment technologies was derived from the Norwegian purchasing organization. All other model inputs were derived from published literature. Costs and effects were discounted at 4% per year. Uncertainty was assessed by a series of one-way sensitivity analyses and probabilistic sensitivity analysis (PSA).

Results: The MiniMed 670G was associated with a gain of quality-adjusted life-years (QALY) compared to SAP and CSII (61.21 and 143.51 respectively). However, it was also associated with higher costs. The incremental cost-effectiveness ratio (ICER) of HCLS compared to SAP was NOK 4,018,422 per QALY gained. Compared to CSII, the ICER was NOK 4,761,669. The results were most sensitive to changes in baseline HbA1c, treatment effect and the cost of HCLS. PSA outcomes were higher than in the base-case analysis and indicated large uncertainty.

Conclusion: At a willingness-to-pay threshold of NOK 385,000, HCLS was not found to be cost-effective compared to SAP or CSII for this patient population.

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List of Abbreviations

CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CGM	Continuous Glucose Monitor
CI	Confidence Interval
CPI	Consumer Price Index
CSII	Continuous Subcutaneous Insulin Infusion
DCCT	The Diabetes Control and Complication Trial
DRG	Diagnosis-Related Group
EMA	European Medicines Agency
EQ-5D	EuroQol Five Dimension Scale
ESRD	End-Stage Renal Disease
GP	General Practitioner
HbA1c	Glycated Hemoglobin
HCLS	Hybrid Closed-Loop System
HrQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
INMB	Incremental Net Monetary Benefit
LEA	Lower Extremity Amputation
LY	Life Year
NMB	Net Monetary Benefit
NoMA	Norwegian Medicines Agency
PPP	Purchasing Power Parity
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year

RCT	Randomized Controlled Trial
SAP	Sensor-Augmented Pump
T1DM	Type 1 Diabetes Mellitus
WESDR	The Wisconsin Epidemiologic Study of Diabetic Retinopathy
WTP	Willingness-to-Pay

1. Introduction

In Norway, Type 1 Diabetes Mellitus (T1DM) accounts for around 7.5% of all diabetes cases (1). The incidence in 2012 was estimated to be 32.5 per 100,000 patient-years (2). Further, Norway has one of the highest prevalence of T1DM among children in the world (3). Data from the Norwegian prescription database suggest that in 2013, a total of approximately 28.000 patients suffered from the disease (1).

T1DM is a chronic condition characterized by an inability of the body to produce the hormone insulin, which absorbs sugar (glucose) into the cells. If absorption is not possible, the glucose accumulates in the blood. If blood glucose levels remain high, it may lead to serious long-term complications including heart and blood vessel disease, nerve damage, kidney damage and others which in turn lead to a higher risk of mortality (4). T1DM patients experience a reduced health-related quality of life (HrQoL) compared to people without the disease (5). In addition to that, T1DM is associated with considerable costs for the healthcare system (6). T1DM is not curable and patients need life-long treatment. Treatment consist of artificial delivery of insulin, requiring careful monitoring of glucose levels in order to deliver the right dose of insulin. If insulin is not administrated in the right way, it may lead to adverse events like hypoglycaemia or ketoacidosis. Patients experiencing adverse events often need clinical assistance and untreated they can even be lethal (7),(8). Monitoring of blood glucose is generally performed by finger-prick blood tests multiple times a day (9). As glucose levels fluctuate continuously, glycosylated hemoglobin (HbA1c) measures are frequently used in clinical practice to inform about glycaemic control. HbA1c indicates long-term blood glucose. High HbA1c levels indicate more time spent with high blood glucose and vice versa. HbA1c is measured either in mmol/mol or in percentage. The Norwegian Ministry of Health recommends patients and professionals to aim at an HbA1c of ≤7.0% (8).

For T1DM patients, there are several options how insulin can be delivered to the body. Traditionally, patients deliver it to the body manually through multiple daily injections (MDI). However, automated insulin infusion systems are becoming more and more common. These systems aim at achieving better glycaemic control and at reducing adverse events (9). The first generation of automated systems were subcutaneous insulin infusion systems (CSII), known as standard insulin pumps. In the second generation, CSII were coupled with continuous glucose monitors (CGM). CGM systems continuously display blood glucose levels on a monitor and thereby reduce the need for finger-prick blood testing (10). CSII together with CGM is also referred to as sensor-augmented pump system (SAP). In 2017, approximately 36% of Norwegian T1DM patients used CSII treatment and 25% out of these used CGM (SAP) (11). Regardless of the improvement in treatment technology, most patients still struggle to achieve normal glucose levels with the available options. According to the annual report of the

Norwegian Diabetes Register, only 22% of Norwegian T1DM patients achieved glucose levels as recommended by the Ministry of Health in 2017 (11),(12). This indicates that existing treatment technologies are not sufficient to manage the disease. As a result, new generations of automated infusion systems are on the rise. The most recent of these are hybrid closed-loop insulin infusion systems (HCLS). These devices are able to continuously adjust insulin doses based on CGM data. They are associated with even better glycaemic control, a further reduction in adverse events and a reduced need for patient action (13),(14). In 2018, Medtronic obtained EMA market approval for their MiniMed 670G system, which is the first HCLS on the market up until now (15). The new technology seems promising to patients but is also associated with high acquisition costs. Cost-effectiveness analysis (CEA) is frequently used to inform about new interventions in healthcare decision contexts (16). Jendle et al. published a CEA on HCLS compared to CSII earlier this year from a Swedish perspective. In their analysis, HCLS was found to be a cost-effective alternative and it was suggested that HCLS offers good value for money (17). The study was based on the commercially available diabetes CORE model. This patient-level simulation model was developed by the centre for outcomes research in Basel in 2004 and can be used for Type 1 and Type 2 diabetes interventions (18).

To my knowledge, there has been no evaluation of HCLS against SAP or from a Norwegian perspective. Even though the MiniMed 670G is not yet available in Norway, it is expected that the system will be marketed there soon. There has already been a call for evaluation of the system, indicating great interest in the technology (19). Assessing the cost-effectiveness of the device early can provide benefits as the time gap between market access and reimbursement decision can be shortened. The primary objective of the present study was therefore to inform about the cost-effectiveness of the MiniMed 670G system from a Norwegian perspective by means of the following research question: “Is HCLS a cost-effective alternative to SAP or CSII for Norwegian T1DM patients with elevated blood glucose levels?” By doing so, it should provide decision makers with information relevant for the recommendation and reimbursement of the MiniMed 670G. A further aim was to be fully transparent in the analysis so that others would be able to replicate the study.

2. Methods

This chapter describes the data sources and methods that were used as basis for the analysis. First, it will be described from which perspective the analysis was conducted and how long-term outcomes were modelled. Secondly, the data sources used to drive and populate the model will be elaborated before describing methods undertaken to reduce uncertainty surrounding the outcomes.

2.1 Model Structure

A Markov cohort model was developed in Microsoft Excel (Version 1905) to assess the lifetime costs and effects of the different treatment technologies. The model had an annual cycle length and a lifetime horizon, following patients until death or age 95. All costs were reported in Norwegian Kroner and inflated to 2019 values when necessary, using the consumer price index (CPI) (20) and the purchasing power parity (PPP) (21). Details are available in Appendix 1.

2.1.1 Patient population

The model was populated by a cohort of 1000 hypothetical T1DM patients. They were assumed to be identical in terms of patient characteristics. The patients were assigned a starting age of 20 years. That age was considered appropriate since T1DM develops early and young people are more like to have high HbA1c levels (22). It was assumed that patients did not have any pre-existing diabetes-related complications. In accordance with expert opinion, high HbA1c was defined as levels >8%. In the base-case analysis, baseline HbA1c was set at 10%. Regarding the treatment, it was assumed that patients could not switch between treatments and used the technology until death or the end of the model.

2.1.2 Perspective

A healthcare payer perspective was adopted for the analysis. Therefore, only direct costs falling on the healthcare system and direct benefits to the patients were included. As suggested by the Norwegian Ministry of Finance, a discount rate of 4% was applied to both, costs and effects, in order to represent differences in time-preference (23). Moreover, costs and health outcomes were corrected for continuity. The number of patients in each health state and associated costs and effects were calculated as the average of two subsequent cycles. The willingness-to-pay (WTP) threshold in Norway is dependent on severity of the disease. Severity if classified into six groups and the threshold ranges from NOK 275,000 to NOK 825,000 (24). As T1DM is associated with a reduced HrQoL and a higher mortality, it was assumed that T1DM is classified into the second group (shortfall of 4-7.9 QALYs)

(4),(5). The corresponding threshold used in this analysis was NOK 385,000 (25). A table of the six categories can be found in the Appendix.

2.1.3 Intervention and Comparator

HCLS was used as the intervention in the analysis. As the MiniMed 670G was the only available device at the time of the study, it was the HCLS that was assessed. HCLS is composed of an insulin pump, a glucose sensor and a transmitter. The device continuously measures blood glucose and can adjust insulin dosage accordingly every 5 minutes. Moreover, the device can automatically stop insulin delivery if glucose levels are low or predicted to be low in a 30 minutes time span ("threshold suspend" feature). Nonetheless, patients still need to perform finger-prick blood tests in order to calibrate the device and test blood glucose before meals or exercise. Medtronic states that at least two tests per day are necessary (26).

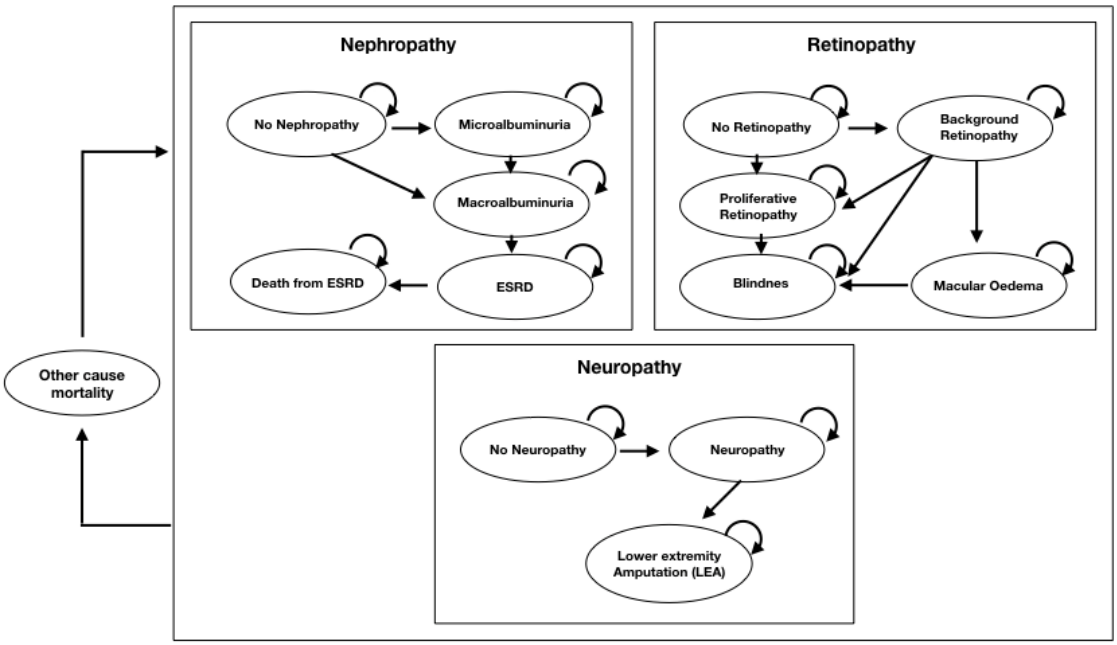
SAP and CSII were both assessed as comparators. CSII is most commonly used in Norway. However, SAP is a likely treatment for patients that have problems with glycaemic control according to expert judgement. Like HCLS, SAP is composed an insulin pump, a glucose sensor and a transmitter. Several devices are available on the market. Some of these are integrated and some combine stand-alone CGM with CSII. Newer SAP are also augmented by the threshold suspend feature. However, SAP devices are not able to adjust insulin dosage based on CGM data. Blood testing is still needed with SAP treatment before meals or exercise or to calibrate the device. CSII consists only of an insulin pump that delivers a continuous amount of insulin to the body. Blood testing is needed multiple times a day in order to control blood glucose levels and to adjust insulin dosage (27). Even though there are several devices available, the Accu Check Insight is the only one reimbursed in Norway (Norwegian Purchasing Organization). Illustrations of the devices are shown in Appendix 3.

2.1.4 The Markov Model

The overall model was composed of three Markov sub-models, simulating the progression of different long-term complications. The complications included in the model were nephropathy, retinopathy, and neuropathy. Nephropathy describes medical condition related to damage to the renal and urinary system. Retinopathy describes damage to the eyes and neuropathy includes conditions caused by damage to the nerves. Macrovascular complications were not considered as they were assumed not be influenced by the treatment. In each sub-model, patients could experience several different health states. For nephropathy these were: no nephropathy, microalbuminuria, macroalbuminuria, end-stage

renal disease (ESRD) and death from ESRD. For retinopathy: no retinopathy, background retinopathy, proliferative retinopathy, macular edema and blindness. In the neuropathy sub-model, patients could experience no neuropathy, peripheral neuropathy or lower extremity amputation (LEA). Clinical definitions of all health states are available in Appendix 4. ESRD was the only disease-related cause of death in the model but patients could also die from other causes, represented in an "other-cause mortality" health state.

FIGURE 1: STRUCTURE OF THE MARKOV MODEL



The three boxes represent diebatetes-related complications. Circles represent health states in the model and arrows indicate possible patient movements; ESRD = end-stage renal disease; LEA = lower extremity amputation

Progression was modelled based on annual transition probabilities. In each cycle, patients could either remain in their present health state or progress to more severe states. In the nephropathy sub model, patients who had no nephropathy could stay within that state or develop microalbuminuria or macroalbuminuria. Patients who had already developed microalbuminuria, could either remain in that state or progress to macroalbuminuria. Similarly, patients with macroalbuminuria could remain in that state or progress to ESRD. Patients with ESRD could remain in that state or die from the condition. Patients moved through retinopathy and neuropathy the same way. All living patients were subject to other-cause mortality before each new cycle. Possible movements within the model are indicated as arrows in Figure 1. Death, blindness and LEA were absorbing states, where the patients stayed until the end of the model.

In principle, the sub-models were assumed to run independent from each other. Patients started simultaneously in all three sub-models, in the no nephropathy/retinopathy/neuropathy states and progressed through them accordingly. Thus, it was possible for patients to develop more than one complication at the same time. However, progression within one sub-model was not influenced by the presence of another complication. The sub-models were connected through the number of deaths from ESRD and other-cause mortality, as to ensure that the same number of patients were alive in each of the sub-models every cycle.

2.1.5 Model Outcomes

The main outcomes of the model were estimated lifetime costs and benefits of the different treatment options. Benefits were measured as life years and then converted into QALYs for each intervention. QALYs take into account the duration of a health state as well as its HrQoL. One QALY equals one life year in perfect health. Cost-effectiveness was expressed as the incremental cost-effectiveness ratio (ICER). The ICER is computed by dividing the incremental lifetime cost of two interventions by the incremental lifetime benefits and describes the cost per QALY gained (28).

$$\frac{Cost\ of\ intervention\ A - Cost\ of\ intervention\ B}{QALYs\ of\ intervention\ A - QALYs\ of\ intervention\ B} \quad \text{I}$$

Another way to express cost-effectiveness is the incremental net-monetary benefit (INMB):

$$(\Delta QALYs * Threshold\ ) - \Delta Costs \quad \text{II}$$

$\Delta QALYs$ = incremental QALYs; $\Delta Costs$ = incremental costs

A new intervention is cost-effective, if the ICER lies below the WTP threshold or if the INMB is positive. Net monetary benefit (NMB) is computed the same way as in equation II but uses the absolute costs and effects of an intervention. The interventions in this analysis were compared pairwise: HCLS compared to SAP and HCLS compared to CSII. For both cases, the ICER and the INMB were calculated.

2.2 Model Inputs

2.2.1 Transition probabilities

Annual transition probabilities were adopted from the literature or estimated from reported incidence rates. Norwegian data was preferred but other sources were used if no country-specific information was available. Probabilities for the progression from background retinopathy/proliferative retinopathy/macular edema to blindness as well as for neuropathy were adopted from the Sheffield type 1 diabetes policy model. The authors of the Sheffield model combined several large studies on the development of long-term complication in order to arrive at annual transition probabilities. Details on that process have been reported in their original publication (29). The remaining transition probabilities were estimated from incidence rates, using formulas suggested by Briggs (28).

In the first step, the instantaneous event rate (r) was calculated from cumulative incidence (q) and follow-up time (t), assuming a constant rate:

$$r = -[\ln(1-q)]/t \quad \textbf{III}$$

In a second step, the annual probability (p) was calculated from the instantaneous event rate (r) as follows:

$$p = 1 - \exp(-r * 1) \quad \textbf{IV}$$

The final transition probabilities were summarized in Table 1. The distribution assigned for sensitivity analysis as well as corresponding alpha and beta values, derived from standard errors are also indicated in the table. For those probabilities which were estimated from the literature, cumulative incidence and follow up time are indicated as footnotes.

TABLE 1: FIXED ANNUAL TRANSITION PROBABILITIES

Parameter	transition probability	Distribution	alpha	beta	Source
Nephropathy					
Macroalbuminuria to ESRD	0.00164	Beta	100	60775	Gagnum 2017(30) [a]
ESRD to death from ESRD	0.06885	Beta	93	1258	
Retinopathy					
Background retinopathy to blindness	0.00010	Beta	25	249949	Thokala 2013 (29)
Proliferative retinopathy to blindness	0.00380	Beta	25	6528	
Macular edema to blindness	0.00160	Beta	25	15574	

Neuropathy					
No neuropathy to peripheral neuropathy	0.03540	Beta	24	656	Thokala 2013 (29)

[a] cumulative incidence of ESRD = 4.8% after 30 years follow-up, cumulative incidence of death from ESRD = 51% after 10 years follow-up

Some probabilities, represented in Table 2, were assumed to be dependent on HbA1c levels. They were continuously updated to match the patients HbA1c levels. In order to adjust baseline probabilities (p) as reported in Table 1, an exponential function based on the Sheffield model and Eastman et al. was used (29),(31):

$$p_s = p_i * (\alpha_s/\alpha_i)\hat{}\beta_i \quad \text{V}$$

s = 0,1,2,…,75
i = no nephropathy to microalbuminuria, no nephropathy to macroalbuminuria,,.no neuropathy to peripheral neuropathy

Where p_s is the adjusted transition probability for a given cycle s, p_i is the baseline probability for the transition pathway reported in table 2, α_s is the HbA1c level in cycle s and α_i is the baseline HbA1c level for which p_i was estimated. The ß-coefficient indicates the increasing risk of developing a complication with higher HbA1c levels. Baseline HbA1c α as well as the ß-coefficients are shown in Table 2.

TABLE 2: HBA1C-DEPENDENT TRANSITION INPUTS

Parameter	baseline probability (p)	Distribution	Alpha	Beta	baseline HbA1c (α)	ß-coefficient	Source
Nephropathy							
No nephropathy to microalbuminuria	0.00333	Beta	25	7457	8.8%	3.25	Skrivarhaug 2006 (32)[a]
No nephropathy to macroalbuminuria	0.00131	Beta	25	19033		7.95	
Microalbuminuria to macroalbuminuria	0.03232	Beta	24	723	9.4%		de Boer 2011 (33) [b]
Retinopathy							
No retinopathy to background retinopathy	0.06197	Beta	23	354	8.5%	10.10	Skrivarhaug 2006 (34) [c]
No retinopathy to proliferative retinopathy	0.00195	Beta	25	12770		6.30	
Background retinopathy to proliferative retinopathy	0.00922	Beta	25	2661			
Background retinopathy to macular edema	0.01338	Beta	25	1818	10.5%	1.20	Klein 2009 (35)[d]

Neuropathy							
No neuropathy to peripheral neuropathy	0.03540	Beta	24	656	10.0%	5.30	Thokala 2013 (29)

[a] follow-up time = 24 years, cumulative incidence of microalbuminuria = 7.7%, cumulative incidence of macroalbuminuria = 3.1%; [b] cumulative incidence of macroalbuminuria = 28% after 10 years follow-up; [c] follow-up time = 24.1 years, cumulative incidence of background retinopathy = 78.6%, cumulative incidence of proliferative retinopathy (from no retinopathy) = 4.6%, cumulative incidence of proliferative retinopathy (from background retinopathy) = 20%; [d] cumulative incidence of macular edema = 28.6% after 25 years follow-up

Example for calculating the transition probability from no nephropathy to microalbuminuria for cycle 0, with HbA1c of 10%: pc = 0.00333*(10/8.8)^3.25 = 0.005; In cycle 1 HbA1c = 8.92% for HCLS, so the transition probability would be: 0.00333*(8.92/8.8)^3.25 = 0.0035

2.2.2 Other-cause mortality

Apart from ESRD, patients could also die from causes unrelated to T1DM. This other-cause mortality is modelled based on Norwegian life tables from 2018 (36). As those life tables already incorporate the number of disease-related deaths, other-cause mortality needed to be adjusted accordingly as not to overestimate overall deaths. The different treatment technologies were expected to influence the number of overall deaths by leading to more or less deaths from ESRD. Of the three technologies, CSII is most commonly used in Norway. For that reason, the probability of dying from ESRD with CSII was used to adjust other-cause mortality from the life table. In order to normalize numbers from the life table, the probability of death from ESRD with CSII was calculated for each cycle and subtracted from the probability of other-cause death in each cycle.

Patients first progressed through the model before other-cause mortality was applied. The number of patients in each health state after progression was multiplied with the normalized probability of other-cause death in every cycle. This number was then subtracted from the total number of patients in the corresponding health states. As individual patients could not be tracked in the model, it was unknown whether patients that died from other causes had more than one complication. As a result, other-cause mortality was applied to all health states in every sub-model.

2.2.3 Treatment effect

The effect of the different treatment technologies was defined as a percentage reduction in HbA1c. Through those HbA1c levels, the development of long-term complications was influenced, as described in the previous sections. It was assumed that rates of adverse events were zero in all treatment arms. For HCLS, data was obtained from a 12-week, multicentre RCT by Tauschmann et al. (13). This trial looked at the effect of HCLS on glycaemic control of patients aged 6 years and older with high baseline HbA1c. A modified MiniMed 640G insulin pump, having the same features as the MiniMed 670G, was used in the trial. After the 12-week period, HbA1c values were reduced by 10.84% from baseline values

with HCLS. Data for the treatment effect of SAP and CSII was obtained from a 6-month, randomized, multicentre, treat-to-target study by Hirsch et al. (37). Baseline HbA1c was reduced by 8.48% with SAP and by 6.56% with CSII treatment as indicated in Table 3.

It was assumed that the effect reported by the two studies was equal to the effect of using the technologies for a whole year. The treatment effect was applied until HbA1c levels of the patients in the model reached 7.0%. After that, HbA1c was kept constant at 7.0% until death or the end of the model. This was the case for all three interventions. It was further assumed that patients using a sensor-augmented device wear this sensor over enough time to uphold the effect of the CGM system.

TABLE 3: TREATMENT EFFECTIVENESS

Parameter	baseline value	Distribution	alpha	beta	Source
Treatment effect HCLS	-10.84%	Beta	93	1330	Tauschmann 2018 (13)
Treatment effect SAP	-8.48%	Beta	91	987	
Treatment effect CSII	-6.56%	Beta	89	732	Hirsch 2008 (37)

2.2.4 Costs

Costs applied in the model were divided into four categories: Technology-related costs, costs of consumables, costs of the management of diabetes and costs of complications. Each category was composed of several cost components. Resource use was estimated separately and multiplied with the unit cost of the different components.

The costs for the different treatment technologies were obtained from the Norwegian Purchasing Organisation and are shown in Table 4. Tender prices were confidential and could therefore not be used for this analysis. The costs obtained from the Norwegian Purchasing Organizations were non-confidential, annual costs including the different insulin pumps as well as sensors and transmitters. There was only one evaluated device for HCLS and CSII whereas several SAP devices were available in Norway. The mean cost of these was applied in the model as the cost of SAP technology. Details are available in the Appendix. In the following tables, the distribution chosen for sensitivity analysis and corresponding alpha and beta values derived from the standard error are also indicated.

TABLE 4: TECHNOLOGY COSTS

Technology costs	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*

HCLS						
Annual cost of the MiniMed 670G	**NOK 50,480**					Norwegian Purchasing Organization*
SAP						
Annual mean cost of SAP	**NOK 39,136**	Gamma	25	1565		
CSII						
Annual cost of the Accu Check Insight	**NOK 13,268**					

*costs were obtained upon personal request

The costs of consumables as well as resource use were based on a 2016 NICE report about SAP and were converted into 2019 NOK values using the PPP. Patients using HCLS and SAP were assumed to need the same amount of finger-prick calibration tests per day. Patients using CSII were assumed to need double that amount in the base-case analysis. The aggregated, annual cost of consumables in the base-case analysis were NOK 24,910 for HCLS and SAP and NOK 29,325 for CSII.

TABLE 5: COST AND RESOURCE USE OF CONSUMABLES

Cost of consumables	*Price*	*Distribution*	*Alpha*	*Beta*	*Remarks*	*Source*
capillary glucometer	NOK 47*	Gamma	25	2		
test strips	NOK 312	Gamma	25	12	pack of 50	
lancets	NOK 156	Gamma	25	6	pack of 100	(38)
Insulin reservoirs	NOK 460	Gamma	25	18	pack of 10	
Infusion sets	NOK 1,708	Gamma	25	68	pack of 10	
Resource use	*Amount*	*Distribution*	*Alpha*	*Beta*	*Remarks*	*Source*
test strips & lancets HCLS/SAP	2	Gamma	25	0.08	daily amount needed with HCLS/SAP	(38), Assumption
test strips & lancets CSII	4	Gamma	25	0.16	daily amount needed with CSII	
Insulin reservoir & infusion sets interval	3	Gamma	25	0.12	Interval in which insulin reservoirs and infusion sets need to be exchanged (in days)	
Annual cost for HCLS/SAP	**NOK 24,910**					
Annual cost for CSII	**NOK 29,325**					

*annual cost for a use of 5 years

Unit costs for GP consultations, specialist visits and tests performed at their office were sourced from the Norwegian fee schedule for physician services 2018/19 (39). As recommended by Norwegian guidelines for economic evaluation, the costs reported in the fee schedule were multiplied times two in order to estimate the true cost to the healthcare system (40). Costs for surgical interventions and

outpatient clinic visits were estimated per DRG using the 2019 DRG price list. In the DRG system, patients are grouped by diagnosis. Each group is given a cost weight which is multiplied by a base-price in order to determine the reimbursement price for the hospitals. The 2019 base-price was NOK 44,654 (41). For the management of diabetes, the Norwegian ministry of health recommends two GP visits per year. It was assumed that patients with poorly controlled diabetes (HbA1c >8%) needed two more visits per year and one additional outpatient hospital visit. Details are available in Table 6. Annual management costs in the base-case analysis were NOK 1,600 for well controlled diabetes and NOK 4,852 for poorly controlled diabetes.

TABLE 6: MANAGEMENT-RELATED COSTS AND RESOURCE USE

Management-related costs	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*
GP visit	NOK 310	Gamma	25	12	(39)
HbA1c test at GPs office*	NOK 260	Gamma	25	10	
Measurement of microalbuminuria*	NOK 230	Gamma	25	9	
Outpatient hospital visit for Diabetes	NOK 1,652	Gamma	25	66	DRG 910A
Resource Use	*Amount*	*Distribution*	*Alpha*	*Beta*	*Source*
GP visit good control (<8%)	2	Gamma	25	0.08	(12)
GP visit poor control (≥8%)	4	Gamma	25	0.16	Assumption
Outpatient hospital visit	1	Gamma	25	0.04	Assumption
Annual cost for good control (≤8%)	**NOK 1,600**				
Annual cost for poor control (>8%)	**NOK 4,852**				

*assumed to be performed at every GP visit

The costs of diabetes-related complications were calculated as annual cost for each health state. Death from ESRD, blindness and LEA were also associated with a one-off cost that was incurred in the transition year. Unit costs and dosages for concomitant medication were obtained from the Norwegian Medicines Agency (NoMA). Resource use was mostly obtained from recommendations of the Norwegian ministry of health for the management of diabetes (12). However, much of it had to be estimated by the authors choice and expert opinion as available information was meagre. The estimated annual cost of microalbuminuria was NOK 1,180 and of macroalbuminuria NOK 3,190. ESRD was related to annual costs of NOK 710,534 while fatal ESRD incurred a one-off cost of NOK 71,625. Details are available in table 7.

TABLE 7: COSTS AND RESOURCE USE OF NEPHROPATHY HEALTH STATES

Microalbuminuria	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*

Specialist consultation	NOK 702	Gamma	100	7	(39)
ACE inhibitors	NOK 478*	Gamma	25	19	NoMA
Resource Use	*Amount*	*Distribution*	*Alpha*	*Beta*	*Source*
specialist consultations	1	Gamma	25	0.04	(12)
Annual cost of microalbuminuria	**NOK 1,180.15**				
Macroalbuminuria	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*
Specialist consultation	NOK 702	Gamma	100	7	(39)
Outpatient hospital visit	NOK 1,786	Gamma	100	18	DRG 911O
Resource Use	*Amount*	*Distribution*	*Alpha*	*Beta*	*Source*
specialist consultations	2	Gamma	25	0.08	(12)
Outpatient hospital visits	1	Gamma	25	0.04	Assumption
Annual cost of macroalbuminuria	**NOK 3,190.16**				
ESRD	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*
Cost of ESRD (fatal)	**NOK 71,625****	Gamma	25	2865	DRG 613
Annual cost of ESRD	**NOK 710,534*****	Gamma	25	28421	DRG 617, (42)

*annual cost, based on a dosage of 1 tablet per day and a cost of NOK 1.31 per tablet; **one-off cost incurred if the patient dies from ESRD; *** calculated as DRG 617*52*3

In the retinopathy sub-model, costs were also incurred by a screening programme. The Norwegian ministry of health recommends diabetes patients to perform eye screening through retinal imaging at five years after diagnosis and every other year after that (12). In this analysis, screening was performed at the start of the model and every other year after that for patients with no retinopathy. Costs for retinopathy health states are shown in table 8 and costs for neuropathy states in table 9.

TABLE 8: COSTS AND RESOURCE USE OF RETINOPATHY HEALTH STATES

Retinopathy screening	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*
Specialist consultation	NOK 702	Gamma	100	7	(39)
Taking of retinal image	NOK 172	Gamma	100	2	
Cost of screening procedure	**NOK 874***				
Background retinopathy	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*
Specialist consultation	NOK 702	Gamma	100	7	(39)
Resource Use	*Amount*	*Distribution*	*Alpha*	*Beta*	*Source*
specialist consultations	1	Gamma	25	0.04	Assumption
Annual cost of background retinopathy	**NOK 702**				

Proliferative retinopathy	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*
Laser treatment at Opthamologist	NOK 1,830	Gamma	100	18	(39)
Outpatient hospital visit for eye diasease	NOK 1,206	Gamma	100	12	DRG 902O
Resource Use	*Amount*	*Distribution*	*Alpha*	*Beta*	*Source*
Laser treatments	1	Gamma	25	0.04	Assumption
Outpatient hospital visits	1	Gamma	25	0.04	
Annual cost of proliferative retinopathy	**NOK 3,036**				
Macular edema	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*
Macular edema	**NOK 3,036**	Gamma	25	121	Assumption**
Blindness (first year)	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*
Specialist consultation	NOK 702	Gamma	100	7	(39)
Hospital admission for eye disease	NOK 39,653	Gamma	100	397	DRG 46/47
Information course for patients with blindness	NOK 48,300***	Gamma	25	1932	(42)
Resource Use	*Amount*	*Distribution*	*Alpha*	*Beta*	*Source*
Specialist consultations	2	Gamma	25	0.08	(42)
Hospital admissions	1	Gamma	25	0.04	
Total cost of blindness (first year)	**NOK 89,357****				
Blindness (subsequent years)	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*
Specialist consultation	NOK 702	Gamma	100	7	(39)
Resource Use	*Amount*	*Distribution*	*Alpha*	*Beta*	*Source*
specialist consultations	1	Gamma	25	0.04	(42)
Annual cost of blindness	**NOK 702**				

* cost per screening procedure per patient, needs to be performed every other year; **assumed to be the same as the cost for proliferative retinopathy; ***assumption based on Solli 2013: NOK 2300 per course day at a length of 21 days ; ****one-off cost incurred in the transition year

TABLE 9: COSTS AND RESOURCE USE OF NEUROPATHY HEALTH STATES

Peripheral neuropathy	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*
Specialist consultation	NOK 702	Gamma	100	7	(39)
Outpatient hospital visit	NOK 2,233	Gamma	100	22	DRG 901C
Amitriptyline treatment	NOK 742*	Gamma	25	30	NoMA
Resource Use	*Amount*	*Distribution*	*Alpha*	*Beta*	*Source*
Specialist consultations	1	Gamma	25	0.04	Assumption

Outpatient hospital visits	2	Gamma	25	0.08	
Annual cost of peripheral neuropathy	**NOK 5,909.81**				

LEA	*Price*	*Distribution*	*Alpha*	*Beta*	*Source*
Cost of LEA (first year)	**NOK 224,208****	Gamma	25	8968	DRG 113
Annual cost of LEA	**NOK 116,452**	Gamma	25	4658	(42)

* annual cost, based on a dosage of two tablets per day and a cost of NOK 1.017 per tablet; **one-off cost incurred in the transition year

2.2.5 Health-related quality of life

Utility values for the different health states were sourced from the literature, as reported in Table 10. Microalbuminuria and background retinopathy were assumed not to influence HrQoL. Death was associated with a utility of 0. The baseline utility value for patients without complication was 0.9 as reported in a Norwegian study by Solli et al. (5). Complications were associated with a (negative) disutility. Utilities that were generated using the EQ-5D instrument and specified to Norwegian T1DM patients were preferred. However, such measures were available only for the baseline utility and peripheral neuropathy. Values for LEA were based on a UK sample and the disutility for blindness was generated for T2DM patients. Disutilities for macroalbuminuria and proliferative retinopathy were obtained by a Finnish study on T1DM patients, using a more sensitive 15D questionnaire. Values for ESRD were based on the EQ-5D but not specified to diabetes patients at all.

The total number of QALYs in each cycle was calculated by multiplying the number of patients alive with the baseline utility and subtracting the number of patients in the different complications multiplied with the corresponding disutility.

TABLE 10: UTILITY VALUES ASSOCIATED WITH HEALTH STATES

Baseline utility value	**utility**	**Distribution**	**Alpha**	**Beta**	**Source**
Type 1 Diabetes and no complication	0.9	Beta	9	1	Solli 2010 (5)

Utility Decrements	**Disutility**	**Distribution**	**alpha**	**beta**	
macroalbuminuria	0.04	Beta	96	2580	Ahola 2010 (43)
ESRD	0.11	Beta	89	719	Wyld 2012 (44)
Proliferative retinopathy	0.03	Beta	97	2744	Hannula 2014 (45)
Macular Edema	0.03	Beta	97	2744	Assumption
Blindness	0.07	Beta	93	1158	Clarke 2002 (46)
Peripheral neuropathy	0.36	Beta	16	28	Solli 2010 (5)
LEA	0.12	Beta	22	165	Peasgood 2016 (47)

2.3 Sensitivity analysis

2.3.1 One-way sensitivity analysis

A series of one-way sensitivity analyses were performed in order to explore how sensitive the outcomes were to different parameters. In these analyses, only one parameter was varied at a time while all others stayed constant (16). The effect of baseline HbA1c was explored by setting values to 8.5% and 12.5% respectively. Further sensitivity analyses were conducted on the treatment effects and the annual cost of all three interventions. Upper and lower bounds of +/- 25% of the base-case values were applied. Discount rates for costs and effects were set to 3% and 5% respectively. As the disutility of neuropathy reported by Solli (5) was very high, changes in that value were assessed using the 95%-confidence interval (CI) reported in the study. In addition, the effect of changes in some transition probabilities and other disutilities were explored. In total, 26 one-way sensitivity analyses were performed. A table with all parameters and their corresponding upper and lower bounds is available in Appendix 5. 95%- CIs were preferred as upper and lower bounds but in the absence of these, the author judged on plausible bounds. In order to provide more detailed information on the effect of price changes of HCLS, the relationship between price reductions and the ICERs was explored separately. The annual price of HCLS was reduced up to 50% in 10% steps in this sub-analysis.

3.3.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) addressed the overall parameter uncertainty in the model. In contrast to one-way analysis, all parameters were varied simultaneously. For each parameter, the standard error was estimated and a distribution was assigned (16). Distribution parameters alpha and beta were estimated based on those inputs. For the PSA, 1000 simulations of model outcomes were run with random draws for each parameter. Each time the lifetime costs and QALYs for each intervention as well as the ICER and INMB were calculated. From these outcomes it was possible to determine the probability that an intervention is cost-effective. The number of positive INMB is counted and divided by the number of simulations. Repeated for different threshold values, the probability can be illustrated as a cost-effectiveness acceptability curve (CEAC) (28).

In this analysis, a beta distribution was assigned to baseline utility, disutilities, treatment effect and baseline probabilities. The cost of HCLS and CSII was fixed and not varied. Other costs and resource use were assigned a gamma distribution. Alpha and beta parameters estimated by the standard error are given in the corresponding tables in the previous sections. Standard errors were estimated to be

either 10% or 20%, based on the authors judgement. No distribution was assigned to baseline HbA1c since it was assumed that values were confined in the interval between 8.0% and 13%. Instead, Excel was instructed to draw random numbers from that interval in the PSA. From the outcomes, a joint CEAC was computed, comparing all three treatment options at the same time. In order to do so, the INMB was computed by subtracting the maximum NMB of SAP or CSII from the NMB of HCLS. SAP was identified as cost-effective if the INMB of HCLS vs. SAP and CSII was negative and the INMB of SAP vs. CSII was positive. If the INMB was negative in both cases, CSII was selected as the cost-effective intervention. Threshold values from NOK 0 to NOK 2,500,000 were explored.

4. Results

4.1 Base-case results

Lifetime use of HCLS for the 1000 T1DM patients was associated with a lifetime benefit of 61.61 and 143.51 QALYs compared to SAP and CSII respectively (Table 11). However, it was also associated with higher lifetime costs. CSII had the lowest lifetime costs of the three interventions (NOK 1,305,833,664) while HCLS had the highest (NOK NOK 1,989,189,585). Weighting these lifetime outcomes against each other, resulted in an ICER of NOK 4,018,422 for HCLS compared to SAP and NOK 4,761,669 for HCLS compared to CSII. Both ICERs are clearly above the WTP threshold of NOK 385,000. Hence the MiniMed 670G was not found to be a cost-effectiveness alternative to SAP or CSII in the base-case analysis.

TABLE 11: BASE-CASE RESULTS

Strategy	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER	INMB
HCLS	NOK 1,989,189,585	19427.20				
SAP	NOK 1,743,209,325	19365.98	NOK 245,980,260	61.21	**NOK 4,018,422***	-NOK 227,616,314
CSII	NOK 1,305,833,664	19283.69	NOK 683,355,921	143.51	**NOK 4,761,669****	-NOK 640,302,366

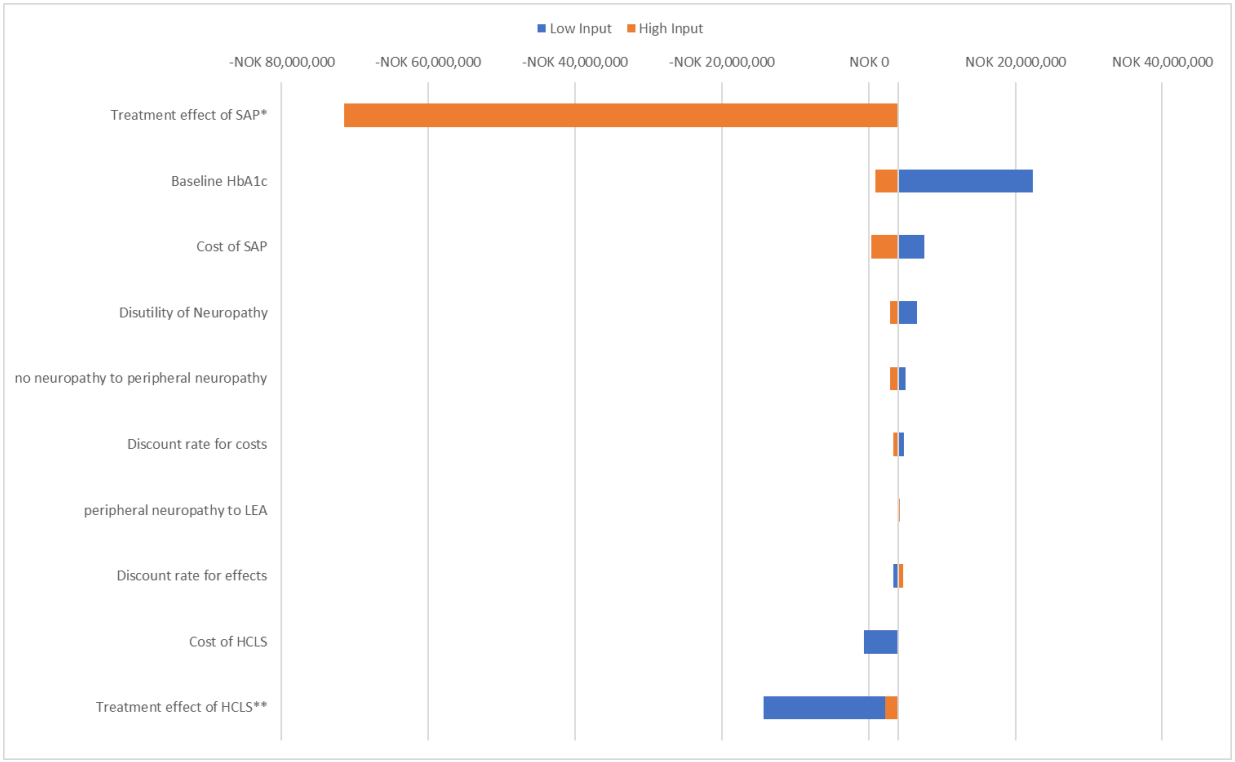
*HCLS compared to SAP; **HCLS compared to CSII

4.2 Results from sensitivity analyses

4.2.1 One-way sensitivity analysis

The main drivers of the cost-effectiveness of HCLS compared to SAP were the treatment effect of both interventions, baseline HbA1, and the cost of each intervention (Figure 2). When the treatment effect of SAP was increased by 25%, SAP was dominant over HCLS. This was also the case when the treatment effect of HCLS was reduced by 25%. If the treatment effect was reduced for SAP and increased for HCLS, it resulted in lower ICERs than in the base-case (NOK 1,309,044 and NOK 2,203,071 respectively) even though they were still well above the WTP threshold. Setting baseline HbA1c to 8.5% increased the ICER by more than five times from the base-case to NOK 22,353,643. Choosing patients with a baseline HbA1c of 12.5% on the other hand reduced the ICER to NOK 870,935. A change in cost-effectiveness could be observed when the annual cost of HCLS was reduced by 25%. In this case HCLS was dominating SAP and yielded an ICER of -NOK 626,943. Increasing the price of SAP also reduced the ICER considerably but did not fall below the WTP threshold (NOK 416,967).

FIGURE 2: ONE-WAY SENSITIVITY ANALYSES OUTCOMES FOR HCLS VS. SAP

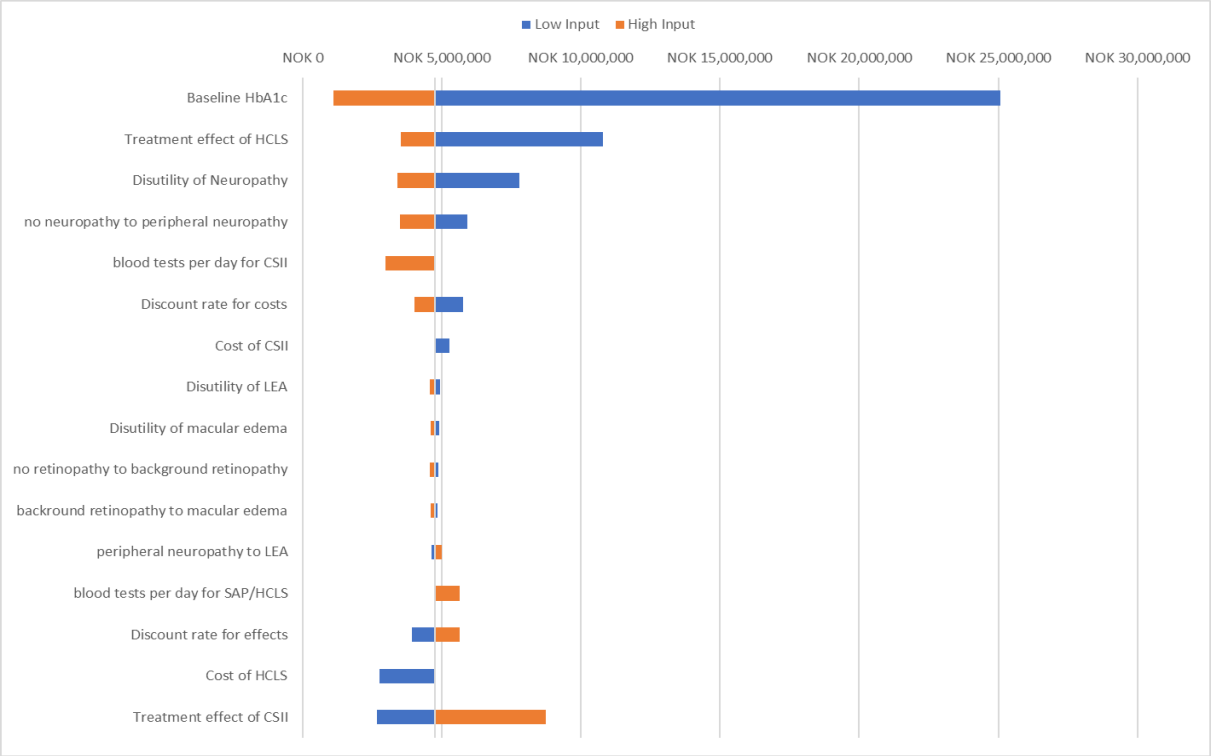


*negative ICER because of a loss in QALYs with the high input; **negative ICER because of a loss in QALYs with the low input

The outcomes for HCLS compared to CSII were similar as main drivers were also the treatment effect of both interventions, baseline HbA1, and the cost of HCLS (Figure 3). Choosing a baseline HbA1c of

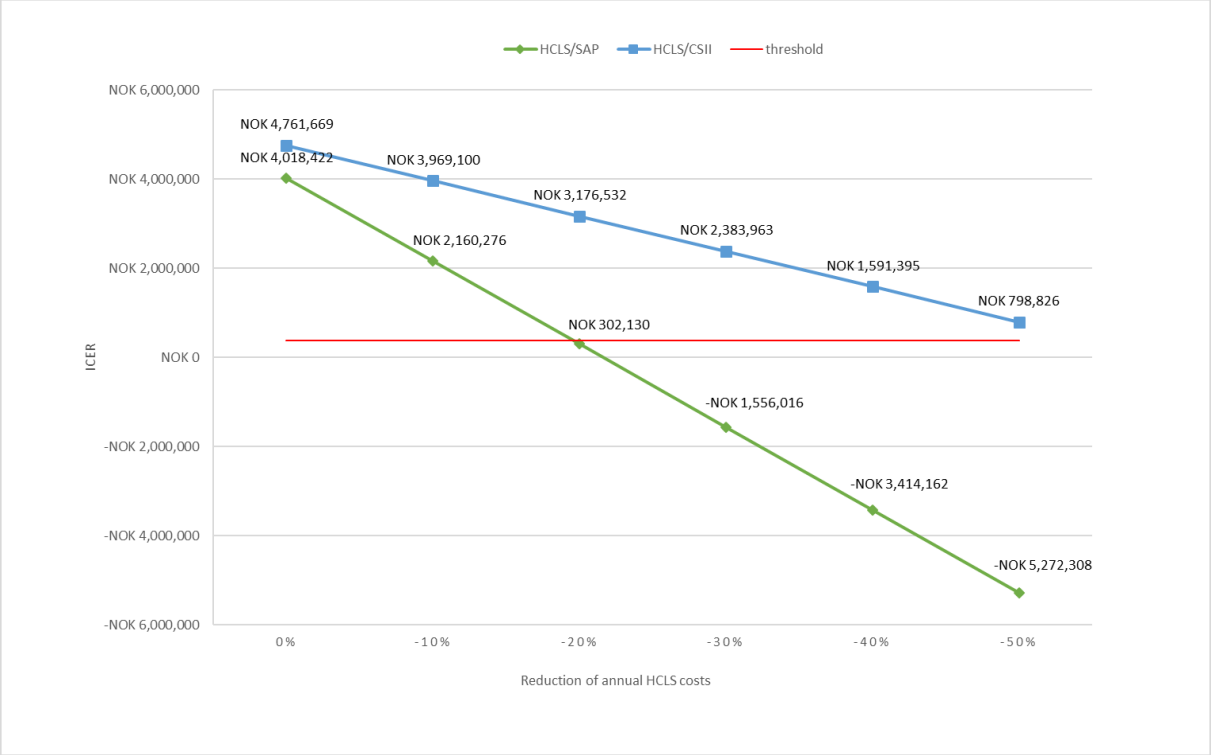
8.5% and reducing the treatment effect of HCLS by 25% lead to the highest ICERs (NOK 25,065,161 and NOK 10,807,125). In contrast to that, increasing baseline HbA1c to 12.5% and decreasing the treatment effect of CSII lead to the lowest ICERs (NOK 1,117,073 and NOK 2,671,886). However, no change in cost-effectiveness could be observed with any parameter variation.

FIGURE 3: ONE-WAY SENSITIVITY ANALYSES OUTCOMES FOR HCLS VS. CSII



A more detailed investigation of the effect of price changes of HCLS is illustrated in figure 4. If the annual cost was reduced by 20%, HCLS was a cost-effective alternative to SAP and from reductions of 30% on, HCLS was dominant over SAP. The cost-effectiveness of HCLS compared to CSII was not influenced as stongly by HCLS costs. At a price reduction of 50%, the ICER was still NOK 798,826 and above the WTP threshold.

FIGURE 4: THE RELATIONSHIP BETWEEN HCLS COST AND ICERS

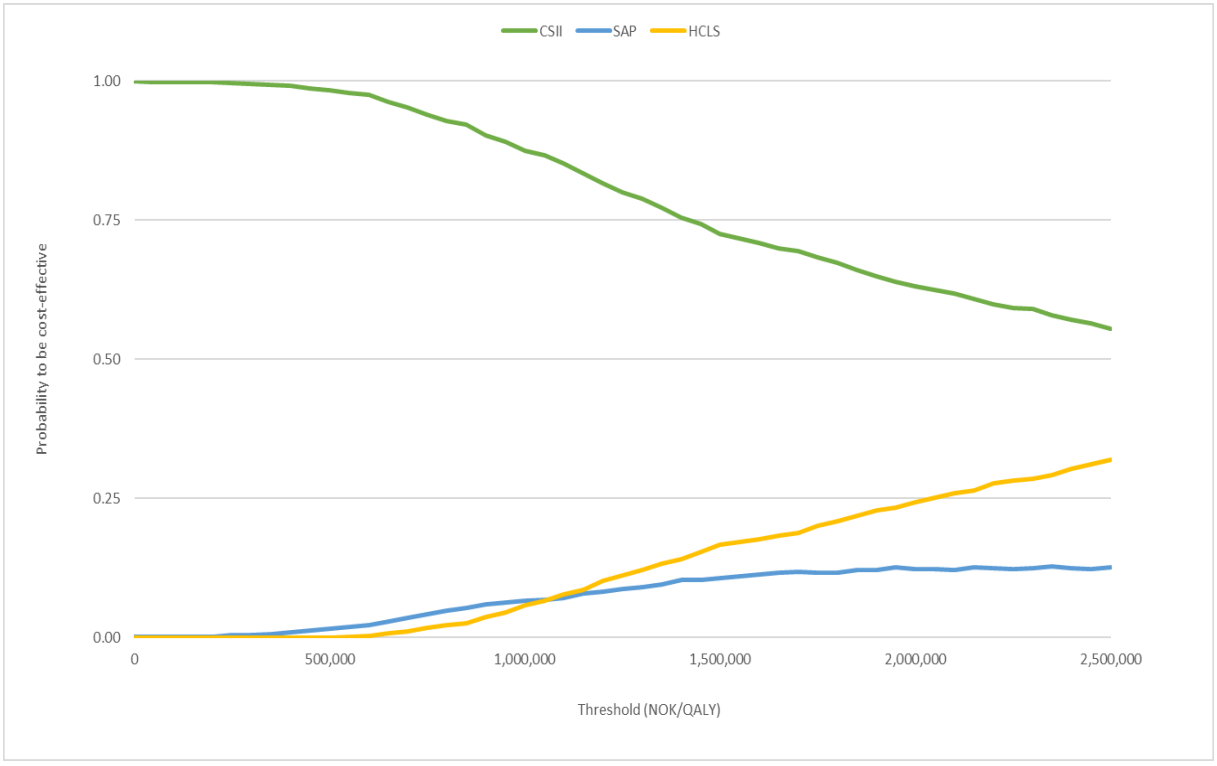


4.2.2 Probabilistic sensitivity analysis

Statistical uncertainty was investigated in the PSA. Lifetime cost and QALY outcomes of the 1000 probabilistic simulations are depicted in figure 5. While QALY outcomes were similar for the different treatment arms, they differed greatly in costs. The mean outcomes were higher than in the base-case analysis. HCLS compared to SAP resulted in a mean ICER of NOK 8,073,903 (95%-CI: [-NOK 5,117,436; NOK 68,849,618]. The mean ICER of HCLS compared to CSII was even higher at NOK 10,120,292 [NOK 742,256; NOK 51,873,664]. When jointly compared to SAP and CSII, the probability of HCLS being cost-effective was zero at the WTP threshold of NOK 385,000 per QALY gained. Compared to that, SAP had a chance of 0.9% and CSII of 99.1% to be cost-effective. Figure 4 shows that even if the threshold would be increased to as much as NOK 2,500,000, HCLS would only have a probability of 32% to be cost-effective compared to the other technologies. CEACs for pairwise comparison of the treatment technologies are available in Appendix 6.

FIGURE 5: SCATTERPLOT OF LIFETIME COST AND QALY OUTCOMES FROM THE PSA

FIGURE 6: CEAC OF HCLS COMPARED TO SAP AND CSII



5. Discussion

5.1 Strengths and limitations

Type 1 diabetes is a very complex disease and modelling its natural progression is challenging. Working on this analysis has illustrated that much about T1DM and about the treatment technologies is unknown. The aim of this study was to provide decision makers with information to be used in a reimbursement decision. However, the uncertainty surrounding the outcomes is great. Likely, more information is needed before a decision can be made. Nonetheless, this analysis has several strengths. One of them is that number and assumptions used in this analysis were thoroughly reported. That is important as previous analysis have been lacking in that[1]. Others should be able to reproduce the outcomes reported in this paper. Another great strength of this analysis is that it is at least partly based on current data. Previous T1DM models were often based on large, popular trials on diabetes progression like the DCCT (9) or WESDR (48). But as these studies were conducted in the 1980s, treatment standard was substantially different from today. For that reason, data obtained from these sources is like to overestimate long-term complications. In contrast to that, the studies by Skrivarhaug (32),(34), which were used a lot in this analysis, reported a very low incidence of diabetes-related complications. Model outcomes were specified to Norway by using Norwegian cost and utility inputs as well as by calculating transition probabilities based on Norwegian data. Unfortunately, country-specific data was not available for all input parameters. Nonetheless, it is an advantage to other T1DM models.

On the other hand, there are several limitations to this analysis. The first category is related to the model construction. Macrovascular complications were excluded in this paper because they were assumed not to be affected by the treatment. However, there has been evidence that HbA1c is related to macro- as well as microvascular complications (49). Excluding these from the analysis results in less costs to the healthcare system and more QALYs then what might be the case including macrovascular diseases. Moreover, it was assumed that there is no time-dependence and no interdependence of progression probabilities. That was a great simplification as in reality, there are clearly such things. As a result, the number of people with complications will be underestimated. In addition, the choice of a cohort model could be questioned as it does not account for heterogeneity of patients. Nonetheless, some characteristics have been shown to influence the progression of T1DM. Primarily duration of diabetes and age at diabetes onset are related to the development of long-term complications (50). Apart from that, sex might also be related to different risks of progression or mortality (28). Moreover,

[1] This was explored during my internship at the Norwegian Institute of Public Health (Folkehelseinstituttet) when I was working on a systematic review on cost-effectiveness analyses of insulin infusion systems. Specifically the cost of the interventions and distributions used in a PSA were often missing.

the treatment effect could be different in different patient groups while it was assumed to be uniform in this model.

The second category of limitations is related to inputs used in the model. Due to a lack of information, some transition probabilities were still based on historic data and might overestimate the progression to these health states. Aside from that, treatment effects should preferably be sourced from meta-analysis, however, none such were available. The effects used in this model were taken directly from clinical studies. In addition, there was no RCT available that directly compared HCLS and SAP or CSII. Therefore, the absolute values of HbA1c reduction from different clinical studies were used. This will likely overestimate the treatment effect. Even more so by keeping the treatment effect constant and keeping HbA1c levels at 7% once patients achieved that goal. By this assumption the difference between the different technologies was projected only into the first 3-5 cycles which is not enough to capture the full differences. This is most likely the reason why neither HCLS nor SAP were found to be cost-effective in this analysis compared to CSII. Another difference between the treatments could have been the incidence of hypoglycaemia. SAP and HCLS are both reducing the incidence of such (13),(51). As the condition was excluded from the analysis however, it leads to more favourable outcomes of CSII treatment. Moreover, some disutilities for complications were sourced from 15D instruments as the EQ-5D was not sensitive enough to capture effects. That indicates that the EQ-5D might not be optimal in capturing the burden of chronic diseases. The outcomes regarding cost-effectiveness in this study were very different from those of Jendle et al. (17). While in their analysis, HCLS compared to CSII was found to be cost-effective at an ICER of SEK 164,236 (≈ NOK 150,921), the ICER in this study was NOK 4,761,669. The difference might be due to several causes. At first, the patient population in their model had very low HbA1c levels (mean 7.5%). That indicates that the treatment effect was based more on a reduction in adverse events than in reduction of HbA1c. HCLS was assumed to completely prevent adverse events, while CSII was associated with such. Moreover, they used a societal perspective, including indirect costs and benefits as well as direct ones. Both would lead to a more favourable outcome of HCLS than it was the case in this study.

5.2 Implications

More information is needed before it can be determined if HCLS should be reimbursed for patients in Norway. The great range of ICERs in the sensitivity analysis show just how great the uncertainty regarding that decision is. Even with a threshold value of 6.5-times as much as the commonly used value, the probability that HCLS is cost-effective is only 32%. As the costs of the different technologies were applied as annual costs including sensors and transmitters, no sensitivity analysis regarding the

life of these technologies could be made. However, as technology costs were the main costs in the model, it might be worth to include this in another analysis. Even so, it was shown that with a reduction of 20% of annual HCLS costs, SAP would be dominated by the new technology. That indicates that HCLS is still a promising technology. It also emphasizes the importance of price negotiations. Results from this analysis could be used as an informative basis in such. In order to decide on the cost-effectiveness of HCLS compared to CSII, adverse events should be included in another analysis. Apart from that, more information about the long-term effect of HCLS compared to other devices would be necessary. The use of a patient-level model could lead to outcomes that are closer to reality but would need much more input factors. It would be interesting to compare outcomes from this study to outcomes from a patient-level model like the CORE diabetes model to see if there is a great difference. At last, the low incidence of complications in current studies on T1DM compared to historic data indicates that that the development of diabetes-related complications is well controlled today. Instead, the benefits of new treatments might be in different areas. It is likely, that a reduction in patient action or greater freedom of lifestyle are benefits of new technologies. However, these will not be captured by conventional CEA.

6. Conclusion

HCLS treatment with the MiniMed 670G for Norwegian T1DM patients with high glucose levels was associated with additional QALYs but also with higher costs compared to SAP and CSII. At a WTP threshold of NOK 385,000 per QALY gained, HCLS was not found to be cost-effective for these patients. The deterministic ICER for HCLS compared to SAP and CSII was NOK 4,018,422 and NOK 4,761,669 respectively. Outcomes from the PSA were even higher at NOK 8,073,903 and NOK 10,120,292. Main drivers of the cost-effectiveness were baseline HbA1c levels of the patients, the treatment effect of the interventions and the cost of HCLS. HCLS may be cost-effective compared to SAP if the annual cost was reduced by at least 20%. Uncertainty surrounding model outcomes in this analysis was high. The goal of full transparency was reached by reporting all model inputs and assumptions that were used in the analysis.

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Appendix 1: Indexation of costs

	price base year in original currency	base year	PPP (£/$)	PPP (NOK/$)	price/base year in NOK	(indexed) cost in NOK 2019 (02/19)
Cost of consumables						
capllary glucometer	£15.00	2016	0.699	10.25	NOK 219.96	NOK 233.97
test strips	£20.00	2016	0.699	10.25	NOK 293.28	NOK 311.96
lancets	£10.00	2016	0.699	10.25	NOK 146.64	NOK 155.98
Insulin reservoirs	£29.50	2016	0.699	10.25	NOK 432.58	NOK 460.14
Infusion sets	£109.50	2016	0.699	10.25	NOK 1,605.69	NOK 1,707.98
Cost of LEA						
LEA subsequent years		2009			NOK 95,000.00	NOK 116,451.61

Appendix 2: Severity-based threshold values in Norway

Tabell 3. Forholdet mellom absolutt prognosetap og øvre betalingsvillighet for et godt leveår

Gruppe	1	2	3	4	5	6
Absolutt prognosetap	0-3,9	4-7,9	8-11,9	12-15,9	16-19,9	20+
Vekt	1	1,4	1,80	2,2	2,6	3
Øvre grense (1000 kr) for betalingsvillighet per godt leveår	275	385	495	605	715	825

(obtained from: Helsedirektoratet (Norwegian Ministry of Health). severity of disease and priority 2015 [Available from: https://www.regjeringen.no/contentassets/d5da48ca5d1a4b128c72fc5daa3b4fd8/paa_ramme_alvor.pdf].

Appendix 3: Different insulin infusion systems

HCLS, SAP and CSII look much the same. The Accu Check Insight consists of the insulin pump and a remote control:

(Picture downloaded from: http://www.accu-chek.de/produkte/de/insulinpumpentherapie/insight/index.jsp#insulinpumpentherapie/diskret/tragemoeglichkeiten; 03.06.19

The following picture is an example of a sensor-augmented pump. In addition to the pump, it is composed of a CGM. The pump illustrated in the picture is the t:slim insulin pump together with the Dexcom G5 sensor.

(Picture downloaded from: https://amsldiabetes.com.au/item/tslim-x2-insulin-pump/; 03.06.19)

The last picture illustrates the MiniMed 670G device.

(Picture downloaded from: https://www.medtronicdiabetes.com/products/minimed-670g-insulin-pump-system; 03.06.19)

The following table was obtained from the Norwegian purchasing organization. It includes all SAP devices that are available in Norway together with estimated annual costs.

SAP	**Estimated annual cost**
MiniMed 640G	NOK 41,302.00
OmniPod	NOK 22,916.00
t:slim with Dexcom G5	NOK 58,602.00
Pump+Freestyle Libre2	NOK 25,654.00
Pump+ Dexcom G6	NOK 41,613.00
pump+Guardian connect	NOK 35,599.00
pump+eversense XL	NOK 48,265.00
MEAN COST	NOK 39,135.86

Appendix 4: Clinical definition of health states

Microalbuminuria	Albumin excretion rate 15-200 µ/min	Skrivarhaug 2006 (32)
Macroalbuminuria	Albumin excretion rate >200 µ/min	Skrivarhaug 2006 (32)
ESRD	Introduction of renal replacement therapy	Gagnum (30)
Background retinopathy	Any of the following: Microaneurysms, more than 20 intraretinal haemorrhages in each of four quadrants, definitive venous beading in two or more quadrants, prominent intraretinal microvascular abnormalities in one or more quadrant and no signs of PDR	Skrivarhaug 2006 (34)
Proliferative retinopathy	At least one of the following: neovascularisation, vitreous haemorrhage, photocoagulation scars	Skrivarhaug 2006 (34)
Macular edema	retinal thickening in the macular area	Klein 2009 (35)
Blindness	blindness in at least one eye	Thokala 2013 (29)
Peripheral neuropathy	abnormal neurologic examination with the presence of peripheral sensormonitor neuropathy plus either abnormal nerve conduction in at least two peripheral nerves or unequivocally abnormal autonomic-nerve testing, or painful neuropathy	DCCT 1993 (9), Assumption
LEA	Amputation of toes or leg	Moss 1992 (52)

Appendix 5: Parameters assessed in one-way sensitivity analysis

HCLS vs. SAP

Parameters included in the Tornado Diagram

Parameter	base-case value	Low value	High value	Low Input Outcome (HCLS/SAP)	High Input Outcome (HCLS/SAP)	Difference
Treatment effect of SAP	0.0848	0.06	0.11	NOK 1,309,044	-NOK 71,431,492	NOK 72,740,537
Baseline HbA1c	10.0000	8.50	12.50	NOK 22,353,643	NOK 870,935	NOK 21,482,708
Cost of SAP	NOK 39,136	NOK 29,352	NOK 48,920	NOK 7,619,771	NOK 416,967	NOK 7,202,804
Disutility of Neuropathy	0.3580	0.1800	0.5350	NOK 6,571,807	NOK 2,875,915	NOK 3,695,892
no neuropathy to peripheral neuropathy	0.0354	0.0266	0.0531	NOK 5,013,374	NOK 2,930,786	NOK 2,082,588
Discount rate for costs	4.0%	3.0%	5.0%	NOK 4,860,162	NOK 3,395,481	NOK 1,464,681
peripheral neuropathy to LEA	0.0154	0.0116	0.0231	NOK 3,907,989	NOK 4,229,591	-NOK 321,602
Discount rate for effects	4.0%	3.0%	5.0%	NOK 3,337,522	NOK 4,745,131	-NOK 1,407,609
Cost of HCLS	NOK 50,480	NOK 37,860	NOK 50,480	-NOK 626,943	NOK 4,018,422	-NOK 4,645,365
Treatment effect of HCLS	10.8%	8.1%	13.6%	-NOK 14,310,639	NOK 2,203,071	-NOK 16,513,710

Parameters not included in the Tornado Diagram

Parameter	base-case vaue	Low value	High value	Low Input Outcome (HCLS/SAP)	High Input Outcome (HCLS/SAP)	Difference
Disutility of LEA	0.1172	0.0586	0.1758	NOK 4,170,988	NOK 3,863,276	NOK 307,712
Disutility of macular edema	0.0340	0.0170	0.0510	NOK 4,150,145	NOK 3,877,761	NOK 272,384
no retinopathy to background retinopathy	0.0620	0.0465	0.0930	NOK 4,117,358	NOK 3,860,028	NOK 257,329
backround retinopathy to macular edema	0.0134	0.0100	0.0201	NOK 4,093,097	NOK 3,888,646	NOK 204,451
Disutility of proliferative retinopathy	0.0340	0.02	0.05	NOK 4,083,952	NOK 3,946,059	NOK 137,892
no nephropathy to macroalbuminuria	0.00131	0.0010	0.0020	NOK 4,032,849	NOK 3,986,771	NOK 46,079

Disutility of Macroalbuminuria	0.0360	0.02	0.05	NOK 4,038,651	NOK 4,000,887	NOK 37,764
microalbuminuria to macroalbuminuria	0.03232	0.0242	0.0485	NOK 4,020,184	NOK 4,014,917	NOK 5,266
no nephropathy to microalbuminuria	0.00333	0.0025	0.0050	NOK 4,020,120	NOK 4,015,093	NOK 5,027
Disutility of ESRD	0.1100	0.06	0.17	NOK 4,019,294	NOK 4,017,376	NOK 1,917
baseline utility for T1DM patients	0.9000	0.88	0.93	NOK 4,018,805	NOK 4,017,847	NOK 958
blood tests per day for CSII	4	4	8	NOK 4,018,447	NOK 4,018,422	NOK 25
Cost of CSII	NOK 13,268	NOK 9,951	NOK 13,268	NOK 4,018,422	NOK 4,018,422	NOK 0
Treatment effect of CSII	6.56%	4.92%	8.20%	NOK 4,018,422	NOK 4,018,422	NOK 0
blood tests per day for SAP/HCLS	2	2	4	NOK 4,018,422	NOK 4,018,447	-NOK 25
peripheral neuropathy to LEA	0.0154	0.0116	0.0231	NOK 3,907,989	NOK 4,229,591	-NOK 321,602

HCLS vs. CSII

Parameters included in the Tornado Diagram

Parameter	**base-case value**	**Low value**	**High value**	**Low Input Outcome HCLS/CSII**	**High Input Outcome HCLS/CSII**	**Difference**
Baseline HbA1c	10.0000	8.50	12.50	NOK 25,065,161	NOK 1,117,073	NOK 23,948,088
Treatment effect of HCLS	0.1084	0.08	0.14	NOK 10,807,125	NOK 3,539,646	NOK 7,267,479
Disutility of Neuropathy	0.3580	0.1800	0.5350	NOK 7,784,484	NOK 3,408,401	NOK 4,376,082
no neuropathy to peripheral neuropathy	0.0354	0.0266	0.0531	NOK 5,925,050	NOK 3,491,472	NOK 2,433,578
blood tests per day for CSII	4.0000	4.00	8.00	NOK 4,761,669	NOK 2,973,961	NOK 1,787,708
Discount rate for costs	4.0	3.0	5.0	NOK 5,763,511	NOK 4,020,720	NOK 1,742,791
Cost of CSII	NOK 13,268	NOK 9,951	NOK 13,268	NOK 5,282,444	NOK 4,761,669	NOK 520,775
Disutility of LEA	0.1172	0.06	0.18	NOK 4,941,717	NOK 4,578,522	NOK 363,196
Disutility of macular edema	0.0340	0.02	0.05	NOK 4,914,243	NOK 4,598,502	NOK 315,740
no retinopathy to background retinopathy	0.06197	0.0465	0.0930	NOK 4,874,586	NOK 4,586,988	NOK 287,598

backround retinopathy to macular edema	0.0134	0.0100	0.0201	NOK 4,847,891	NOK 4,611,684	NOK 236,207
peripheral neuropathy to LEA	0.0154	0.0116	0.0231	NOK 4,628,468	NOK 5,016,439	-NOK 387,972
blood tests per day for SAP/HCLS	2.0000	2.00	4.00	NOK 4,761,669	NOK 5,655,549	-NOK 893,880
Discount rate for effects	4.0	3.0	5.0	NOK 3,945,537	NOK 5,636,794	-NOK 1,691,257
Cost of HCLS	NOK 50,480	NOK 37,860	NOK 50,480	NOK 2,780,248	NOK 4,761,669	-NOK 1,981,421
Treatment effect of CSII	0.0656	0.05	0.08	NOK 2,671,886	NOK 8,748,254	-NOK 6,076,367

Parameters not included in the Tornado Diagram

Parameter	**base-case vaue**	**Low value**	**High value**	**Low Input Outcome (HCLS/SAP)**	**High Input Outcome (HCLS/SAP)**	**Difference**
Disutility of proliferative retinopathy	0.0340	0.02	0.05	NOK 4,843,274	NOK 4,671,709	NOK 171,565
no nephropathy to macroalbuminuria	0.00131	0.0010	0.0020	NOK 4,778,755	NOK 4,724,204	NOK 54,551
Disutility of Macroalbuminuria	0.0360	0.02	0.05	NOK 4,786,199	NOK 4,740,411	NOK 45,788
microalbuminuria to macroalbuminuria	0.03232	0.0242	0.0485	NOK 4,764,046	NOK 4,756,943	NOK 7,103
no nephropathy to microalbuminuria	0.00333	0.0025	0.0050	NOK 4,763,925	NOK 4,757,242	NOK 6,683
Disutility of ESRD	0.1100	0.06	0.17	NOK 4,762,725	NOK 4,760,402	NOK 2,323
baseline utility for T1DM patients	0.9000	0.88	0.93	NOK 4,762,131	NOK 4,760,976	NOK 1,156
Cost of SAP	NOK 39,136	NOK 29,352	NOK 48,920	NOK 4,761,669	NOK 4,761,669	NOK 0
Treatment effect of SAP	0.0848	0.06	0.11	NOK 4,761,669	NOK 4,761,669	NOK 0

Appendix 6: CEACs for pairwise comparison of HCLS vs. SAP and CSII