The improved survival rate and cost-effectiveness of a 7-day continuous subcutaneous insulin infusion set

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ABSTRACT

**Aims:** The purpose of this article is to compare the insulin cost-savings of the Medtronic Extended Infusion Set (or EIS, a.k.a. Extended Wear Infusion Set) designed and labeled for up to 7-day use with rapid-acting insulins to the current standard of care, 2- to 3-day infusion sets.

**Methods:** There are three major improvements (reducing insulin waste, plastic waste, and adverse events) with the extended duration of infusion set wear. This analysis focuses on cost savings from reduced insulin wastage during set changes. Studies published on insulin infusion set survival and EIS clinical trial data (NCT04113694) were used to estimate device lifetime performance using a Markov chain Monte Carlo model, including the assessment of adverse effects and device failure. Total costs associated with infusion set change or failure were systematically found in published literature or estimated based on physical usage, and the direct impact on insulin costs was calculated.

**Results:** Based on the model and clinical data, EIS users can expect to change their infusion sets about 75 fewer times than standard set users each year. The costs related to unrecoverable insulin during an infusion set and reservoir change in the US were estimated to range from $19.79 to $22.48, resulting in approximately $1324 to $1677 in annual cost-savings for the typical user from minimizing insulin wastage.

**Limitations:** The study only assessed devices used within a monitored setting, that is, clinical trials. In addition, the variability associated with healthcare standards and costs and individual treatment variability including insulin dosages, contribute to the uncertainties with the calculations.

**Conclusions:** Our analysis demonstrates that by extending the duration of infusion set wear, there may be substantial cost savings by reducing insulin wastage.

Introduction

Globally, type 1 diabetes prevalence is rapidly rising, approaching 22.9 million (21.1–25.4, 95% UI) in 2017, more than double the 11.3 million (10.6–12.1, 95% UI) from 1990, and this number is expected to grow to 26.6 million by 2025. Notably, these increases are localized within high-income regions, for example, Europe and the United States, with reported annual incidence rate increases of 2.7–4%.

The rising cost of insulin has become an increasing burden on payers and patients and this number is expected to grow to 26.6 million by 2025. Notably, these increases are localized within high-income regions, for example, Europe and the United States, with reported annual incidence rate increases of 2.7–4%

The effectiveness and advantages of continuous subcutaneous insulin infusion (CSII) are well-established. Studies performed on the economic value of CSIIIs compared to multiple daily injections (MDI) have demonstrated cost-effectiveness at varying willingness-to-pay thresholds across a broad set of geographies.

Although the therapeutic and economic benefits of CSII are well known, there are still significant opportunities for
technological growth and improvement. The infusion set has long been touted as the “Achilles heel” of subcutaneous insulin infusion. Current on-the-market infusion sets for CSII users have developed dermatologic conditions, infection, and bleeding. The most cited reason for the cessation of CSII therapy is blistering; however, it has been observed at low frequencies: 134 cases of blistering over 518 patient-years of care for people with diabetes to demonstrate the incremental benefit of the EIS.

The reason that current infusion sets have an indication for 2 to 3 days of use is that failures occur frequently, which can lead to serious adverse events. Studies done to assess infusion set failure have identified the most common failure mode as unexplained hyperglycemia, where BG levels are elevated beyond 250 mg/dL and corrective insulin doses are ineffective at reducing the BG. As noted in the clinical study methods, the typical remedy for an infusion set failure is an infusion set/site change.

Because the device contains a cannula that penetrates and remains within the subcutaneous tissue for insulin delivery, inflammatory responses may occur; in rare instances, users have developed dermatologic conditions, infection, and bleeding. The most cited reason for the cessation of CSII therapy is blistering; however, it has been observed at low frequencies: 134 cases of blistering over 518 patient-years from 116 individuals. Additional low-frequency complications regarding infusion sets include discomfort, skin irritation, and inflammation. By changing the infusion set, and in extreme circumstances with the use of antibiotics, users recover uneventfully in all cases reported in literature. Other failure modes include adhesive failures, mechanical failures, and tubing occlusions that impede insulin delivery.

To address these failure modes, the Extended Infusion Set (EIS) was recently developed by Medtronic scientists. In addition to increased robustness, the use of EIS enables three major cost-savings opportunities: (a) savings from reducing insulin wastage during set changes, (b) savings from a reduction in adverse effects associated with device failure, and (c) savings from the reduction of plastic waste due to the use of a reduced number of infusion sets per year. The assessment in this article only focuses on the savings from reducing insulin wastage during infusion set changes.

**Increased insulin usability with extended infusion sets**

When an infusion set reaches its end of life, residual, unusable insulin within the infusion set and reservoir must be discarded with the fluid-path components. For each set change, the insulin solution is transferred from a storage vial to the reservoir through a transfer guard, and then the tubing is filled before the infusion set insertion as shown in Figure 1. Removing bubbles and priming the fluid path in each transfer step results in additional unrecoverable insulin. The reservoir is then placed into an insulin pump. Due to varying needs and behaviors, residual, unusable, insulin (e.g. dead volume) will be localized in three key areas: (A) Reservoir and H-Cap connector, (B) Tubing, 23”, 32”, or 43”, and (C) Cannula connection to the subcutaneous tissue.

Figure 1. The Extended Infusion Set (EIS) connecting the insulin pump to the body. (1) A reservoir attached to a transfer guard (blue) and incorporated plunger can only be filled once. (2) Insulin stored in 10 mL (1000 U) vials is used to fill the insulin reservoir (maximum volume 1.8 mL or 3 mL), generating essential insulin waste with each reservoir fill (3) The reservoir is connected to the EIS through the H-Cap connector. (4) The reservoir is placed into an insulin pump. Due to varying needs and behaviors, residual, unusable, insulin (e.g. dead volume) will be localized in three key areas: (A) Reservoir and H-Cap connector, (B) Tubing, 23”, 32”, or 43”, and (C) Cannula connection to the subcutaneous tissue.

Initial calculations were performed to assess the potential for the EIS to save insulin, summarized in (Table 1), and show that the EIS could save from $1401 to $2335 per user per year, as a result of minimizing insulin loss due to set changes. The purpose of this analysis is to systematically quantify the total insulin-related cost-savings when using a robust infusion set, the EIS, that is designed and labeled for up to 7-day use compared to the current standard of care infusion sets, labeled for 2- to 3-day wear. A Markov chain Monte Carlo model constructed from clinical data was used to determine expected device lifetimes and failure mode frequencies over 100,000,000 h among 7-day and 2- to 3-day infusion sets. These cost-savings were then directly applied to previously reported annual costs of insulin and total cost of care for people with diabetes to demonstrate the incremental benefit of the EIS.
Methods

Calculating the unrecoverable insulin loss

A wide range of insulin and device usage patterns were incorporated in the model to determine insulin wastage associated with each infusion set change, as described previously. Briefly, the amount of insulin remaining within the fluid path components (see Figure 1) was calculated based on physical dimensions in conjunction with eight combinations of user profiles to cover a broad range of user needs: reservoir size (1.8- or 3.0-mL), tubing length (long-43” or short-23” as the maximum and minimum lengths available on the market for the typical user), the total daily dose (TDD) of insulin (35 U, 46 U, or 62 U per day, representing the median and upper and lower quartiles of insulin dosages) and 3-day or 7-day set/reservoir changes.

The insulin wastage calculations also included a few constraints. Both the reservoir and infusion set are sterile, single-use devices. For the current 2- to 3-day infusion sets, due to design limitations, the reservoir and the infusion set have to be changed simultaneously (i.e. users have an equal number of the infusion set and reservoir changes each year). For the 7-day EIS, the reservoir may be changed independently of the infusion set change. Therefore, while the number of 7-day EIS changes is not impacted by TDD of insulin, individuals in the upper quartile of TDD will require more frequent reservoir changes with 7-day EIS than those in the lower quartile of TDD. Additional waste, based on experimental findings, was generated through reservoir fills. A 10 mL insulin vial was able to fully supply a 3 mL reservoir 3 times, or a 1.8 mL reservoir 5 times, without compromising the integrity of the insulin filling process. There was about 10% insulin wastage associated with the process of filling the reservoir from the insulin vial, which contributed to the essential insulin waste calculations presented in the results.

Model inputs

In addition to estimating the amount of insulin lost per infusion set and reservoir change, a device-level Markov Chain Monte Carlo model was constructed to determine device lifetimes, which would provide estimates of the annual total amount of unusable insulin when using the standard 2- to 3-day set compared to the EIS. Data from published clinical trials were used to estimate device lifetime probabilities of the standard infusion sets currently available on the market. The goal of these studies was to assess the effect of device reliability based on certain parameters: Patel et al. assessed the robustness of steel (Sure-T™) compared to Teflon (Quick-Set™) cannulas; and Karlin et al., investigated infusion set failure rates in subjects experiencing lipohypertrophy, a complication where adipocytes grow and proliferate in response to repeated same-site injections. In both studies, there was no statistically significant difference in device performance across any of the groups (p < .45), so all the available data were pooled together to create an aggregate device survival curve for the standard set (Figure 2, Left).

For the 7-day EIS, data were taken from the registered clinical pivotal investigation, “Evaluation of Extended Wear Infusion Set (EWIS) in Patients with Type 1 Diabetes,” (https://clinicaltrials.gov/, NCT04113694) to demonstrate device survival results (Figure 2, Left). In this trial, individuals with type 1 diabetes aged 18–80 years used the EWIS with the MiniMed 670G insulin pump system. The study design

| Set lifespan (days) | Set changes per year | Annual insulin waste estimates, assuming insulin units wasted per set change | Annual costs of insulin wastage ($) |
|-------------------|----------------------|--------------------------------------------------------------------------------|-----------------------------------|
|                   |                      | 60 U/set | 80 U/set | 100 U/set | Low (60 U/set) | High (100 U/set) |
| 2                 | 182                  | 10920U  | 14560U  | 18200U    | $3695         | $6160             |
| 3                 | 121                  | 7260U   | 9680U   | 12100U    | $2457*        | $4095*            |
| 7                 | 52                   | 3120U   | 4160U   | 5200U     | $1056*        | $1760*            |

*Potential cost-savings (3-day vs. 7-day): $1401 $2335

Figure 2. Left: Survival data from standard infusion set studies and the EWIS clinical trial were used as to estimate device lifetime in the MCMC models. Right: Histogram of the total daily dosage of insulin, derived from the EWIS clinical trial, was used as a basis for determining insulin consumption rates.
details from all clinical trials used in this analysis are summarized in Table 2.

In addition to survival data, insulin consumption rates were also tracked and reported (Figure 2, Right). The distribution follows a 3-parameter log-logistic distribution, with the median user consuming 46.1 U/day. On the lower end, 25% of users required a TDD of 35 U or less; on the high end, 25% of users required more than 62 U/day. These values served as a basis for the insulin consumption rates when calculating insulin wastage, accounting for approximately half of all adult end users.

**Survival model structure**

Device reliability was assessed using a script written in Python 3. An overview of the EIS model is shown in Figure 3. At each iteration, a new device was assigned a lifetime probability based on a random draw generated from the trial-based survival curves (Figure 2, Left), corresponding to device failure at specific time intervals (every 24 h for the EIS, see Figure 3, or every 10 h for the standard set, see Supplemental Information Figure S1), as well as for the maximum lifetime for the intended use (168 h for the EIS; 72 h for the standard 2- to 3-day set). For example, the random draw of the first EIS iteration assigned the device a 3.05% probability of device failure at 24 h, 1.95% probability of failure at 48 h, 3.00% probability of failure at 72 h, etc. Device wear times were capped at 3 days for the standard infusion set and 7 days for the EIS to simulate on-label usage: in this case, the removal was considered “scheduled.”

In the event of device failure, the failure mode was also recorded, where the frequency of each cause for device removal was categorized into the following: Scheduled Removal, Unscheduled Removal, or an Adverse Event. Scheduled removal occurred the most frequently and was assigned as the cause for device removal if and only if the device lifetime equaled the value for on-label use. The rates of Unscheduled Removal or Adverse Events were calculated based on the relative probability of device failure and were assumed to be time-independent for simplicity. After device failure, the lifetime was recorded and the model continued with a new device until the total lifetime reached over 100,000,000 h.

**Results**

**Essential insulin waste calculations**

As seen in Figure 2, for each infusion set use/change, a minimum amount of insulin wastage was required for essential fluid path preparation and function. The amount calculated here was based on CAD design calculations and experimentally validated: a minimum volume of 21.3 U was required for the pump to reliably deliver insulin (Medtronic pumps have a minimum alarm level of 10 U and a physical dead volume of 11.3 U). In addition, 20 U of insulin would be lost in a typical reservoir fill. In total, each reservoir fill was estimated to produce 41.3 U of essential insulin waste.

For the standard infusion set, 17.4 U and 23.3 U were used for filling and priming the set with 23” and 43” tubing, respectively. For the EIS, due to additional components and design complexity, 19.2 U and 25.1 U were required for filling.

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**Table 2.** Clinical data sources used to determine device failure probabilities over time.

| Study, Year | Infusion set model(s) | Sample size and number of wears | Maximum wear duration | Total weeks of wear |
|-------------|------------------------|---------------------------------|-----------------------|---------------------|
| Patel et al., 2014 | Quick-Set | $n = 20$, two wears | 1 week | 39 weeks |
| Sure-T | $n = 20$, two wears | 1 week | 38 weeks |
| Karlin et al., 2016 | Silhouette | $n = 20$, two wears | 1 week | 40 weeks |
| Comfort | $n = 20$, two wears | 1 week | 40 weeks |
| NCT04113694, 2020 | Extended wear infusion set (EWIS) | $n = 248$, 12 wears | 1 week and 6 h | 2976 weeks |
A Total Daily Dose (TDD) of insulin of 35 U/day represents the lowest quartile of users; 46 U/day is the median; 62 U/day represents the highest quartile (see Figure 2, Right).

**Table 3.** Insulin wastage when using a standard 3-day infusion set compared to EIS due to infusion set and reservoir changes with 23° and 43° tubing.

| Infusion set | User TDD | Tubing length | Infusion set changes per year | Essential insulin wasted per infusion set change | Reservoir changes per year | Essential insulin wasted per reservoir change | Total annual units of essential insulin |
|--------------|----------|---------------|------------------------------|-----------------------------------------------|---------------------------|---------------------------------------------|--------------------------------------|
| Standard set (3-Day) | 35 U/day | 23° | 132.8 | 17.4 U | 132.8 | 4.13 U | 7790 U |
| 46 U/day | 23° | 132.8 | 17.4 U | 132.8 | 4.13 U | 7790 U |
| 62 U/day | 23° | 132.8 | 17.4 U | 132.8 | 4.13 U | 7790 U |
| 35 U/day | 43° | 132.8 | 23.3 U | 132.8 | 4.13 U | 8576 U |
| 46 U/day | 43° | 132.8 | 23.3 U | 132.8 | 4.13 U | 8576 U |
| 62 U/day | 43° | 132.8 | 23.3 U | 132.8 | 4.13 U | 8576 U |
| EIS (7-Day) | 35 U/day | 23° | 57.8 | 19.2 U | 57.8 | 4.13 U | 3496 U |
| 46 U/day | 23° | 57.8 | 19.2 U | 57.8 | 4.13 U | 4124 U |
| 62 U/day | 23° | 57.8 | 19.2 U | 57.8 | 4.13 U | 5883 U |
| 35 U/day | 43° | 57.8 | 25.1 U | 57.8 | 4.13 U | 3838 U |
| 46 U/day | 43° | 57.8 | 25.1 U | 57.8 | 4.13 U | 4466 U |
| 62 U/day | 43° | 57.8 | 25.1 U | 57.8 | 4.13 U | 6225 U |

A Total Daily Dose (TDD) of insulin of 35 U/day represents the lowest quartile of users; 46 U/day is the median; 62 U/day represents the highest quartile (see Figure 2, Right).

and priming the infusion set with 23° and 43° tubing, respectively. These calculated values represented the absolute minimum amount, that is, essential insulin waste; in practice, more insulin would likely be discarded with each reservoir change due to safety concerns and user preference.

Having derived the amount of essential insulin lost for each infusion set and reservoir change, estimates on the infusion set change frequency were determined from the statistical model. Tracking the number of infusion set changes over 100,000,000 subject-hours, the standard 3-day set average lifetime was found to be 65.95 h, and the EIS average lifetime was 151.6 h. Based on these averages, a typical user would need 132.8 standard 3-day sets per year or 57.8 EIS per year, resulting in approximately 75 fewer infusion set changes per year. These figures were contingent on current device design/labeling, where reservoir changes are synchronized with the 3-day infusion set changes. For the 7-day EIS, reservoir changes may be performed independent of infusion set changes.

Based on the evaluation parameters provided above, a summary of the calculations for insulin wastage is shown in Table 3. The price of rapid-acting insulins was found in the IBM Micromedex Red Book, with average wholesale prices being $329.64 for 1000 U of Humalog and $347.23 for Novolog®. The mean of these two prices, $338.44, was used in the cost estimations, shown in Table 5. The typical 46 U/day users would spend approximately $5753.48 for 17 vials per year (i.e. 16,801 U per year), and these estimates are comparable with other figures published in literature. Of note, the cost of wasted insulin during an infusion set change ranged from $5.81 to $7.88 for a standard set and $6.49 to $8.50 for an EIS, and the cost of a reservoir change was $13.98. Users requiring 35 U/Day or less would benefit the most from the EIS, saving up to $1603 per year from minimizing essential insulin waste alone, as can be derived from the data shown in Table 3.

**Improved device lifetime**

Results from the 2-to 3-day studies were first compared to the 7-day set lifetimes to quantify the improvement when using the EIS. The improvement in EIS survivability was significantly higher compared to the standard set after 59 h as shown in Figure 2, Left (p < .0153). Only 37.8% of the standard infusion sets lasted 7 days, while 74.9% of EIS remained functional through seven days. Device survival and failure rates are summarized in Table 4.

**Estimated residual insulin waste**

While essential insulin wastage was minimized primarily through the reliability of the EIS, the insulin remaining in the reservoir during unintended removals could also be significant. Typical use patterns involve discarding a reservoir with residual insulin during unintended removals could be significant. Typical use patterns involve discarding a reservoir with residual insulin when the infusion set fails towards the end of the expected lifetime. For instance, if a standard set fails while only a day’s insulin remains in the reservoir, the one-day supply would be considered residual waste. By setting thresholds of a day’s worth of insulin for the standard set and the EIS, waste associated with reservoir residuals could be approximated using the results from Figure 2 and Table 3.

For the standard set, 18.7% of devices failed early per labeled standards; annually, this corresponds to 24.8 devices. Assuming a uniform probability of failure over the first 72 h, there is a 33.3% chance that the device will have less than one day’s worth of insulin, resulting in residual reservoir waste. Depending on the TDD, the annual reservoir waste would amount to 289 U, 380 U, and 512 U for people with diabetes using 35 U/day, 46 U/day, and 62 U/day, respectively.

**Table 4.** Events causing device removal, from clinical data and the Markov model, capped at 3 days for the standard set and 7 days for the EIS (i.e. on-label use).

| Removal event | Events per 100,000,000 subject-hours (modeled results) |
|---------------|------------------------------------------------------|
| Scheduled removal | 1,245,671 (82.2%) | 493,764 (74.9%) | $2,523 |
| Unscheduled removal | 0 (0.0%) | 40,957 (6.2%) | N/A |
| Adverse event | 1,516,310 (17.8%) | 124,881 (18.9%) | $12.14 |

The majority of devices were removed as scheduled, but there was an approximately 2.5-fold decrease in the number of EIS required to reach 100,000,000 subject-hours. Device failures were reduced 12-fold.
For the EIS, 14.6 (25.2%) devices failed early. Considering insulin waste when the device contains less than one day’s worth of insulin (i.e. 14.3% chance for 35 U/day users and 20.0% chance for 46 U/day users; a 28.6% chance for those using 62 U/day due to the extra reservoir fill per week), there would be 72.8 U, 134 U, and 258 U lost for a TDD of 35 U/day, 46 U/day, and 62 U/day, respectively. Thus, 35 U/day users can expect to save an additional $73/year from residual insulin savings, for a total of $1677 net savings overall (essential plus residual insulin). These results are added to the findings from Table 3 and summarized in Table 5 and Figure 4.

**Table 5.** Amount and costs of wasted insulin (per infusion set and reservoir change, plus residual reservoir waste) for the various use-cases and the potential insulin and cost-savings with EIS.

| User TDD | Tubing length | 3-day set | 7-day EIS |
|----------|---------------|-----------|-----------|
| 35 U     | 23”           | 8079 U ($2,734) | 3569 U ($1,208) | 4510 U ($1,526) |
| 35 U     | 43”           | 8865 U ($3,000)  | 3911 U ($1,324) | 4954 U ($1,677) |
| 46 U     | 23”           | 8170 U ($2,765)  | 4258 U ($1,441) | 3912 U ($1,324) |
| 46 U     | 43”           | 8956 U ($3,031)  | 4600 U ($1,557) | 4356 U ($1,474) |
| 62 U     | 23”           | 8302 U ($2,810)  | 6142 U ($2,079) | 2161 U ($731) |
| 62 U     | 43”           | 9088 U ($3,076)  | 6484 U ($2,194) | 2604 U ($881) |

Cost per 1000 U vial of insulin was estimated to be $338.44 [43].

**Discussion**

The main objective of this study was to quantify the potential insulin cost savings due to decreased insulin waste when using the EIS. To elucidate the inefficiencies associated with insulin wastage in the standard 2- to 3-day infusion sets compared to the EIS, a computational model was constructed based on typical end-user behavior. The data generated by our model based on clinical trial outcomes show that the EIS can provide substantial yearly savings due to reduced insulin wastage with fewer set changes compared to the standard 2- to 3-day infusion set. In particular, users with a TDD of 35 U can expect to save $1677 annually from minimizing insulin waste alone. These values specifically apply for users who use one reservoir and infusion set per week. Those requiring more insulin will benefit as well, with $1,474 annual cost savings for a TDD of 47 U and $881 for a TDD of 62 U, where increased insulin usage necessitates additional reservoir changes.

Another significant result from the model showed a 12-fold decrease in adverse events. While the type of adverse events was not the main focus of this study, the importance of decreasing the frequency of adverse events, especially regarding unexplained hyperglycemia and its sequela, diabetic ketoacidosis (DKA), cannot be understated as these may be costly and have the potential of being life-threatening. A failure related to DKA occurs when an individual has a triad of hyperglycemia, ketosis, and acidemia[47]. Notably, no instances of DKA were reported from the EIS clinical trial; therefore, the modeled results reported in this study are...
likely over-reporting the adverse events related to DKA. A study of DKA events in the US estimated that the costs of events requiring hospitalization were approximately $29,139 (inflation-adjusted to 2020 dollars)\textsuperscript{48}. Therefore, any cost-savings associated with fewer DKA events among EIS users may increase the annual estimated savings in health care costs estimated here.

A limitation of this study is that, while the existing data were useful for predicting device lifetimes, additional long-term studies must be performed to accurately quantify the improvements from having a more reliable and consistent infusion set, for example, health-related quality of life. Analyses involved data from studies in which participants would regularly visit the clinic and may have exhibited a form of Hawthorne Effect, that is, they may have changed their behavior and become more careful or cautious simply because they knew they were being observed\textsuperscript{49}. However, by modeling variability in insulin dosage and device options, our findings represent a range of plausible potential avoidance of insulin wastage and associated cost-savings. Future work may consider extending this model to include device-effectiveness and quality of life inputs that would allow estimation of the incremental benefit or cost-effectiveness of EIS compared to the standard set.

Another limitation of this study stemmed from the inherent variability in the cost and performance of insulin, and its effect on the end-user. In this study, we used the Red Book price of insulin\textsuperscript{43}; however, it is well known that manufacturer rebates offset the list price of insulin\textsuperscript{50}. While it is difficult to quantitatively determine the actual net savings and benefits to the end-user due to the complex nature of pharmaceutical rebates and the insulin supply chain, the savings due to the rebates primarily benefit the payers as the savings are not typically passed onto end users\textsuperscript{51}. In situations where end-users pay a fraction of the list price (e.g., cost-sharing, coinsurance, deductibles, underinsured) the end-user will directly benefit from reducing costs due to decreasing insulin wastage.

As a third limitation in this analysis, the modeled use of insulin infusion sets followed product labeling and instructions for use. Real-world use of insulin infusion sets that extends beyond the device labeling (e.g., wearing a 3-day set for 5 days) was not reflected in this simulation. Therefore, the estimates presented in this study could be considered as rough estimates on the potential savings.

A fourth limitation pertains to the number of use-cases analyzed. In practice, people with diabetes may not follow strict insulin dosing, depending on different lifestyles and day-to-day dietary variations, which may impact the number of infusion set changes and the results shown here. For simplicity, only three TDDs (35 U/day, 46 U/day, and 62 U/day) were considered, chosen based on the median and the upper and lower quartiles to represent the wide range of user needs. Still, these clinical trials only enrolled adults; when considering pediatric people with diabetes who typically require lower amounts of insulin, the TDD statistics will likely shift even lower, where more users can benefit from the cost-savings from minimizing essential insulin waste through the EIS (see Supplemental Information, Figure S2 for a discussion on low TDD use cases).

The use of CSII systems has resulted in decreased mortality rates and improved quality of life, especially when used in conjunction with rapid-acting insulins. Additionally, users who switch over from multiple daily injections (MDI) to CSII often experience a 20–26% decrease in insulin use\textsuperscript{52–54}. However, the cost of diabetes care has also risen dramatically within the last few decades, even to the point of posing as an inaccessible barrier to people with diabetes\textsuperscript{55,56}. In response to these rising costs, efficiency innovations such as the EIS play an important role in decreasing costs so that more users may benefit from the improved devices. In particular, the EIS solved the serious problem of short-lived infusion sets lasting only two or three days. While continuous glucose monitoring systems have expanded to 7-day and even 14-day wear, infusion sets could not last beyond 3 days until the EIS was developed. The discrepancy in device lifetimes posed a significant challenge to end-users as the device wear cycles would often become desynchronized. However, with the EIS, synchronized device replacement becomes a new possibility, decreasing the burden.

Moreover, the EIS increases insulin usage efficiency to improve outcomes while being affordable and cost-saving by reducing insulin costs for payers and users. Importantly, additional impacts on the quality-adjusted life years (QALYs) would be expected from a more reliable infusion set, but these impacts require additional segmented data for further quantitative analysis. For example, to gauge device performance, the Markov Chain Monte Carlo model parameters and probability distribution can be updated to reflect the sample population (e.g., incorporating age and BMI) as well as the degree of each failure mode. Closer monitoring of insulin reservoir fill patterns and residual waste connected to the infusion set can also provide more accurate estimates of essential insulin wastage.

**Conclusion**

Solely based on the lower insulin-related costs resulting from using the EIS, both payers and people with diabetes are likely to benefit from adopting and using this device, with potential savings of $1324 to $1677 per year for typical users from decreased essential and residual insulin wastage. This potential cost-savings due to EIS increases further when considering cost-savings due to reduction in adverse effects associated with device failures and minimizing the environmental impact from decreased plastic wastage due to a reduction in the number of sets used per year.

**Notes**

i. Humalog, Eli Lilly and Company, Indianapolis, IN, USA.
ii. Novolog, Novo Nordisk Inc., Plainsboro, NJ, USA.
iii. Sure-T, Unomedical, Osted, Denmark.
iv. Quick-Set, Unomedical, Osted, Denmark.
v. Silhouette, Unomedical, Osted, Denmark.
vi. Comfort, Unomedical, Osted, Denmark.


Transparency

Declaration of funding

This study was funded by Medtronic.

Declaration of financial/other relationships

SC, TK, KS, KW, and GZ are employees of Medtronic.

JME peer reviewers on this manuscript have received an honorarium from JME for their review work, but have no other relevant financial relationships to disclose.

The Medtronic Extended-Wear Infusion Set (branded as Medtronic Extended) is a CE-marked device in EU, and an investigational device in the US; it is currently not approved for use in the US.

Author contributions

SC and GZ aggregated the experimental data. TK validated the data and designed the model. TK, GZ, KS, KW, and SC analyzed and interpreted the results. TK and GZ drafted the manuscript. All authors contributed to the critical revision and final review of the manuscript.

Acknowledgements

The authors thank Vivian Chen for providing the EWIS clinical trial data, and Marie Tieck and Tom Miller for providing experimental data and performing the initial computations.

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References

[1] Lin X, Xu Y, Pan X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep. 2020;10(1):14790.
[2] Lawrence JM, Imperatore G, Dabelea D, et al. Trends in incidence of type 1 diabetes among non-Hispanic White youth in the U.S., 2002–2009. Diabetes. 2014;63(11):3938–3945.
[3] Patterson CC, Harjutsalo V, Rosenbauer J, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. Diabetologia. 2019;62(3):408–417.
[4] Sussman M, Benner J, Haller MJ, et al. Estimated lifetime economic burden of type 1 diabetes. Diabetes Technol Ther. 2020;22(2):121–130.
[5] Hua X, Carvalho N, Tew M, et al. Expenditures and prices of anti-hyperglycemic medications in the United States: 2002-2013. JAMA. 2016;315(13):1400–1402.
[6] Biniek JF, Johnson W. Spending on individuals with type 1 diabetes and the role of rapidly increasing insulin prices. Health Care Cost Institute; 2019.
[7] Chattaraj S, Fieneup M, Zhang G, et al. 1167-P: CSII and insulin: does extending the wear duration of infusion sets save expensive insulin? Diabetes. 2020;69. doi:10.2337/db20-1167-P
[8] Inteso C, Isaacs D. The rising cost of insulin: practical tools and resources. ADCES Pract. 2021;9(1):40–47.
[9] Rajkumar SV. The high cost of insulin in the United States: an urgent call to action. Mayo Clin Proc. 2020;95(1):22–28.
[10] Herkert D, Vijayakumar P, Luo J, et al. Cost-related insulin under-use among patients with diabetes. JAMA Intern Med. 2019;179(1):112–114.
[11] Bailey TS, Walsh J, Stone JY. Emerging technologies for diabetes care. Diabetes Technol Ther. 2018;20(2):78–84.
[12] Jendle J, Pohllmann J, de Portu S, et al. Cost-effectiveness analysis of the MiniMed 670G hybrid closed-loop system versus continuous subcutaneous insulin infusion for treatment of type 1 diabetes. Diabetes Technol Ther. 2019;21(3):110–118.
[13] Patterson CC, Karuranga S, Salpea P, et al. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107842.
[14] Puckrein GA, Nunlee-Bland Z, Garg S, et al. Impact of CMS competitive bidding program on Medicare beneficiary safety and access to diabetes testing supplies: a retrospective, longitudinal analysis. Dia Care. 2016;39(4):563–571.
[15] Association AD. Economic costs of diabetes in the U.S. in 2017. Diabetes Care. 2018;41:917–928.
[16] Lee CHY, Goode B, Nortoft E, et al. The cost of diabetes and obesity in Australia. J Med Econ. 2018;21(10):1001–1005.
[17] Cummins E, Royle P, Snaithe A, et al. Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. Health Technol Assess. 2010;14(11):iii–ix, x.
[18] Roze S, Smith-Palmer J, Valentine WJ, et al. Long-term health economic benefits of sensor-augmented pump therapy vs continuous subcutaneous insulin infusion alone in type 1 diabetes: a UK perspective. J Med Econ. 2016;19(3):236–242.
[19] Vettoretti M, Facchinetti A. Combining continuous glucose monitoring and insulin pumps to automatically tune the basal insulin infusion in diabetes therapy: a review. Biomed Eng Online. 2019;18(1):37.
[20] Colquitt J, Green C, Sidhu M, et al. Clinical and cost effectiveness of continuous subcutaneous insulin infusion for diabetes. Health Technol Assess. 2004;8(43). DOI:10.3310/hta8430.
[21] Bruttomesso D, Costa S, Bartussio A. Continuous subcutaneous insulin infusion (CSII) 30 years later: still the best option for insulin therapy. Diabetes Metab Res Rev. 2009;25(2):99–111.
[22] Pickup JC. Is insulin pump therapy effective in type 1 diabetes? Diabet Med. 2019;36(3):269–278.
[23] Jendle JH, Rawshani A, Svensson A-M, et al. Indications for insulin pump therapy in type 1 diabetes and associations with glycaemic control. J Diabetes Sci Technol. 2016;10(5):1027–1033.
[24] Scuffham P, Carr L. The cost-effectiveness of continuous subcutaneous insulin infusion compared with multiple daily injections for the management of diabetes. Diabet Med. 2003;20(7):586–593.
[25] Roze S, Valentine WJ, Zakrzewska KE, et al. Health-economic comparison of continuous subcutaneous insulin infusion with multiple daily injections for treatment of type 1 diabetes in the UK. Diabet Med. 2005;22(9):1239–1245.
[26] Roze S, Smith-Palmer J, Valentine W, et al. Cost-effectiveness of continuous subcutaneous insulin infusion versus multiple daily injections of insulin in type 1 diabetes: a systematic review. Diabet Med. 2015;32(11):1415–1424.
[27] Doubova SV, Roze S, Ferreira-Hermosillo A, et al. Cost-effectiveness of the use of the continuous subcutaneous insulin infusion pump versus daily multiple injections in type 1 diabetes adult patients at the Mexican Institute of Social Security. Cost Eff Resour Alloc. 2019;17(1):19.
[28] Heinemann L, Krikelis L. Insulin infusion set: the Achilles heel of continuous subcutaneous insulin infusion. J Diabetes Sci Technol. 2012;6(4):954–964.
[29] Johansson U-B, Adamson U, Lins P-E, et al. Patient management of long-term continuous subcutaneous insulin infusion. J Adv Nurs. 2005;51(2):112–118.
[30] Evert AB, Bode BW, Buckingham BA, et al. Improving patient experience with insulin infusion sets: practical guidelines and future directions. Diabetes Educ. 2016;42(4):470–484.
Cescon M, DeSalvo DJ, Ly TT, et al. Early detection of infusion set failure during insulin pump therapy in type 1 diabetes. J Diabetes Sci Technol. 2016;10(6):1268–1276.

Patel PJ, Benasi K, Ferrari G, et al. Randomized trial of infusion set function: steel versus teflon. Diabetes Technol Ther. 2014;16(1):15–19.

Chantelau E, Spraul M, Mählihauer I, et al. Long-term safety, efficacy and side-effects of continuous subcutaneous insulin infusion treatment for Type 1 (insulin-dependent) diabetes mellitus: a one centre experience. Diabetologia. 1989;32(7):421–426.

Zhang E, Cao Z. Tissue response to subcutaneous infusion catheter. J Diabetes Sci Technol. 2020;14(2):226–232.

Teutsch SM, Herman WH, Dwyer DM, et al. Mortality among diabetic patients using continuous subcutaneous insulin-infusion pumps. N Engl J Med. 1984;310(6):361–368.

Messer LH, Berget C, Beatson C, et al. Preserving skin integrity with chronic device use in diabetes. Diabetes Technol Ther. 2018;20(52):54–64.

Waldenmaier D, Zsomborak E, Buhr A, et al. A prospective study of insulin infusion set use for up to 7 days: early replacement reasons and impact on glycemic control. Diabetes Technol Ther. 2020;22(10):734–741.

Ilany J, Cohen O, Konvalina N, et al. 994-P: clinical study of a new extended wear infusion set. Diabetes. 2020;69(1):994.

Simic A, Schendorff PK, Stumpe T, et al. Survival assessment of the extended-wear insulin infusion set featuring lantern technology in adults with type 1 diabetes mellitus by glucose clamp technique. Diabetes Obes Metab. 2021;23(6):1402–1408.

Zhang JY, Shang T, Chattaraj S, et al. Advances in insulin pump infusion sets symposium report. J Diabetes Sci Technol. 2021;15(3):705–709.

Mathieu C, Gillard P, Benhalima K. Insulin analogues in type 1 diabetes mellitus: getting better all the time. Nat Rev Endocrinol. 2017;13(7):385–399.

Bode B, Garg S, Norwood P, et al. Compatibility and safety of ultra rapid lispro with continuous subcutaneous insulin infusion in patients with type 1 diabetes: PRONTO-pump study. Diabetes Technol Ther. 2021;23(1):41–50.

Humalog N. DRUGDEX(R), IBM Micromedex(R) [Internet]. Greenwood Village (CO): Trueven Health Analytics. 2021 [cited 2021 Mar 3]. Available from: https://micromedexsolutions.com

Karlin AW, Ly TT, Pyle L, et al. Duration of infusion set survival in lipohypertrophy versus nonlipohypertrophied tissue in patients with type 1 diabetes. Diabetes Technol Ther. 2016;18(7):429–435.

Deeb A, Abdelrahman L, Tomy M, et al. Impact of insulin injection and infusion routines on lipohypertrophy and glycemic control in children and adults with diabetes. Diabetes Ther. 2019;10(1):259–267.

Crossen S, Xing G, Hoch JS. Changing costs of type 1 diabetes care among US children and adolescents. Pediatr Diabetes. 2020;21(4):644–648.

Umpierrez GE, Kitabchi AE. Diabetic ketoacidosis: risk factors and management strategies. Treat Endocrinol. 2003;2(2):95–108.

McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. J Clin Epidemiol. 2014;67(3):267–277.

Kakani P, Chernew M, Chandra A. Rebates in the pharmaceutical industry: evidence from medicines sold in retail pharmacies in the U.S. [Internet]. Cambridge (MA): National Bureau of Economic Research; 2020 [cited 2021 Jun 14]. Available from: https://www.nber.org/papers/w26846

Cefalu WT, Dawes DE, Gavlak G, et al. Insulin access and affordability working group: conclusions and recommendations. Diabetes care. 2018;41(6):1299–1311.

Wan W, Skandari MR, Minc A, et al. Cost-effectiveness of initiating an insulin pump in T1D adults using continuous glucose monitoring compared with multiple daily insulin injections: the DIAMOND Randomized Trial. Med Decis Making. 2018;38(8):942–953.

Hoogma RPLM, Hammond PJ, Gomis R, et al. Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial. Diabet Med. 2006;23(2):141–147.

Wahleqvist P, Warner J, Morlock R. Cost-effectiveness of simple insulin infusion devices compared to multiple daily injections in uncontrolled type 2 diabetics in the United States based on a simulation model. J Health Econ Outcomes Res. 2018;6(1):84–95.

Whaley CM, Bollyky JB, Lu W, et al. Reduced medical spending associated with increased use of a remote diabetes management program and lower mean blood glucose values. J Med Econ. 2019;22(9):869–877.

Beran D, Lazo-Porras M, Mba CM, et al. A global perspective on the issue of access to insulin. Diabetologia. 2021;64(5):954–962.