



Health-Economic Modelling of Improved Behavior in Insulin Injection Technique in Belgium

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Abstract

Background Adequate insulin injection technique (IIT) is crucial to optimize the efficacy of diabetes therapy. Widespread non-practice of injection-site rotation and frequent reuse of insulin pen needles (PN) promote high rates of lipohypertrophy (LH) among people living with diabetes (PwD). LH is associated with increased insulin requirement and suboptimal insulin absorption leading to worsened glycemic control and increased risk for hypoglycemia. Avoiding out-of-the-pocket patient costs of PN could reduce PN reuse, thereby limiting its contribution to LH occurrence.

Objectives A model was developed to compute the impact of a behavior shift in reuse on clinical and economic outcomes for type 1 and insulin-treated type 2 diabetes populations in Belgium.

Methods Patient populations were characterized by treatment-specific characteristics and grouped by their frequency of PN replacement. The intervention was modelled to cause a change in reuse frequency, with the effects propagating downstream of the model. Model and input parameters were based on literature research and expert opinions from a Delphi panel, since available data was found to be limited, incomplete or inconsistent and assumptions were needed.

Results Using the current situation as comparator, this analysis showed a reduction of healthcare expenditures following an improvement in IIT. Considering a 5-year time horizon, this study yields potential savings of 52.6 million euros (28.1–77.9 million euros) when 55% of PwD improve PN reuse behavior.

Conclusion Our model shows that even in an era of technological advances and established diabetes care, lack of adherence to correct IIT has an important impact on economic and health outcomes of PwD in Belgium.

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Key Points for Decision Makers

Providing insulin pen needles without patient out-of-pocket costs may contribute to the improvement of health outcomes and reduction of diabetes-related complications.

Reducing pen needle reuse by 55% could result in healthcare savings of 52.6 million euros over 5 years in Belgium.

Correct adherence to insulin injection technique recommendations remains important despite technological advances in diabetes care.

1 Introduction

Diabetes mellitus (DM) is a major chronic disease with a prevalence that has been steadily increasing over the past few decades, mostly driven by type 2 diabetes mellitus (T2DM), with almost 1 out of 10 people worldwide living with diabetes today [1]. While interventions through a combination of diet, physical activity and non-insulin anti-diabetic treatments can effectively control blood glucose for most people living with diabetes (PwD), a significant proportion of PwD are dependent on insulin treatment for their management of diabetes. While all people living with type 1 DM (T1DM) require insulin treatment for their survival, it is estimated that 10% of people living with T2DM require insulin treatment [2].

The correct insulin injection technique (IIT) is pivotal to optimize the efficacy of insulin therapy [3], as it has been demonstrated that improvements in injection practices can have positive effects on glycemic control [4–7]. It is strongly recommended to systematically rotate subcutaneous injection sites and change the insulin pen needles (PN) with each new injection while avoiding injection into lipohypertrophic areas. However, widespread lack of site rotation and frequent reuse of insulin PN promote high rates of lipohypertrophy (LH) among PwD [8, 9]. The presence of LH, poorly reversible even after moving further injections away from the affected area and/or using adequate IIT within LH sites, has been associated with suboptimal insulin absorption, leading to an increase in the total daily dose (TDD) of insulin injected and to an increased risk for long-term complications and hypoglycemic events [4–6, 9–11].

In addition to a health impact at the individual level, the consequences of worsened glycemic control represent a significant economic burden to the healthcare system. In total, health costs related to diabetes amounted in 2018 to 5.82 billion euros at the expense of the Belgian social security, of which 94% was used for the treatment of diabetes-related complications [12, 13]. In addition to intensified education on injection technique, it has been shown that lower out-of-pocket expenditure for PN can reduce the rate of needle reuse, which will have positive effects on the management of diabetes patients and lower the corresponding economic burden [14]. In countries where PwD pay out of pocket for their PN, reuse was found to be high with reuse rates up to 97.3% [4, 7, 14]. Similarly, a high prevalence of 95% PN reuse has been reported in Belgium in the absence of reimbursement [4, 15, 16]. By contrast, 89.7% of the Lipohypertrophy Monitoring (LIMO) study patients in Belgium, who were educated on correct IIT, confirmed that they would reduce the reuse of PN if they were to be reimbursed [4].

The objective of this study was to estimate health care expenditures resulting from impaired adherence to insulin

injection recommendations for people with T1DM and T2DM, adopting a cost perspective of the National Health Insurance in Belgium.

2 Materials and Methods

2.1 Economic Evaluation Approach

This objective was investigated by an economic modelling approach that evaluated the impact of improved reuse behavior on outcomes related to insulin consumption, hypoglycemic events and diabetes-related complications. The comparison of a situation of insulin injection without PN provisioning with the situation where PwD are provided with PNs and targeted educational support enabled us to calculate savings in health care expenditures. The initiation of model development and population was guided by a narrative literature search to identify the clinical benefits of PN reuse rate reduction. Belgium represents a rare exception in Europe as one of the few countries where insulin PN are not reimbursed. Due to the lack of data on this aspect, input from Belgian clinical experts was deemed essential to further guide this economic evaluation.

A validation process was established, consisting of three sequential stages. Belgian experts in diabetes clinical management and health economics were consulted individually to provide relevant inputs and insights. After completing the initial version of the model, a technical briefing document and a structured questionnaire were sent to all experts. This material outlined the current efforts and asked the experts whether they agreed with the model's inputs and assumptions. If any expert disagreed with a specific assumption or parameter value, they were given the opportunity to suggest an alternative. In the next stage, an in-person consensus meeting with six clinical experts was held to discuss the survey results and gather additional recommendations. A final report was then prepared, summarizing the consensus on the model's configuration and parameters, which was reviewed and approved by all experts. In cases where the clinical experts did not agree with certain parameter estimates from the initial model configuration, a midpoint value was calculated and used as the input for the base-case configuration. The following sections provide more details on the study's evaluation, including the sources, selection process and population of model parameters and assumptions (Tables 1, 2).

2.2 Model Structure

The analytical modelling framework was developed in the programming language R and captures dependencies between PN reuse and LH status as well as between LH

Table 1 Model input parameters and source

Category	Parameter	Value	Source
Patient populations	Patient groups	T1 diabetes convention (T1)	[17]
		T2 diabetes convention (T2conv)	
		T2 Diabetes Care Pathway (T2care)	
	Group patient size (<i>N</i>)	33035 (T1)	[17]
		74752 (T2conv)	[17]
		62609 (T2care)	Farmanet
Reuse prevalence	Number of daily injections (<i>N</i>)	4 (T1)	[17]
		3.5 (T2conv)	[17]
		1.2 (T2care)	Expert input
Lipohypertrophy	Before (%)	90	[4]
	After (%)	35 (20–50)	[4]—Expert panel
	Reuse categories (<i>N</i>)	1; 2; 3–5; 6–10; > 10	[18]
Insulin TDD	Prevalence in SU patients (%)	37 (27–47)	Expert panel—[4]
	Category risk ratios when reusing (RR)	1; 1.1; 1.25; 1.5; 1.75	[18]
Hypoglycemic events	Increase in IU when LH+	10	Table S3 (ESM)
HbA1c	CGM uptake (%)	81.4 (T1)	[29]
		50 (T1conv)	Assumption
		0 (T2care)	[40]
	Risk for event when LH+	2.96 (2.05–3.87)	Expert panel—[9]
	Pre-CGM severe hypo events T1/T2 (e/p/y)	0.90/0.41	[24]
	Pre-CGM hospitalized hypo events T1/T2 (e/p/y)	0.065/0.028	[26]
Prevalence of long-term complications	Post-CGM severe hypo events T1/T2 (e/p/y)	0.61/0.27	[24]
	Post-CGM hospitalized hypo events T1/T2 (e/p/y)	0.034/0.017	[26]
	Reduction (%) when LH– status	0.3	[4] (observed in subset of patients)
Lower risk of complications per 1% decrease in HbA1c	Cardiovascular T1/T2 (%)	16/50	[29]
	Vascular eye T1/T2 (%)	35/38	[29]
	Kidney T1/T2 (%)	13/49	[29]
	Foot T1/T2 (%)	19/32	[29]
	Cardiovascular (%)	14	[31]
	Vascular eye (%)	19	[31]
	Kidney (%)	18	[31]
	Foot (%)	43	[31]

CGM continuous glucose monitoring, e/p/y events/patient/year, ESM electronic supplementary material, IU insulin units, LH lipohypertrophy, RR relative risk, SU single use, T1 type 1, T2 type 2, TDD total daily dose

Table 2 Cost input parameters and source

Category	Sub-category	Value	References
Insulin	Unit price	€0.0256	Table S3 (ESM)
Hypoglycemic events	Severe T1/T2	€552/€1036	[34]
	Hospitalized T1/T2	€4733/€9607	[20]; [35]
Long-term complications	Cardiovascular complications	€6861.80	Table S9 (ESM)
	Vascular eye complications	€2994.51	Table S9 (ESM)
	Kidney	€5168.67	Table S9 (ESM)
	Foot	€5267.29	Table S9 (ESM)

ESM electronic supplementary material, T1 type 1 diabetes, T2 type 2 diabetes

status and health care expenditures. The structure of the implemented model is depicted in Fig. 1 and illustrates the flow of patients. [A] The model starts with a set of structural parameters and defined subpopulations. [B] The starting patient population is then divided into different groups based on usage frequency of a single insulin PN. [C] Patients within each group are assigned an LH positive (LH+) or LH negative (LH-) status, with the prevalence of LH+ and LH- in each group proportional to the increased risk of LH associated with increased PN reuse. A negative LH status refers to regression (a reduction in prevalence or size) of existing LH nodules, mitigation of incident LH development, as well as the practice of not systematically injecting into LH nodules. A positive status refers to the persistence of inadequate IIT, existing nodules or the development of new LH nodules. [D] Patients' LH status is linked to a value for insulin TDD, the number of hypoglycemic episodes per year and the risk of long-term complications (as a function of HbA1c). The time horizon of the analysis was set at 1 and 5 years, reflecting time windows used in Belgium for economic modelling of budgetary impact in the context of reimbursement submissions.

2.3 Model Input Parameters

2.3.1 Patient Population

The target population includes all PwD with T1DM and T2DM in Belgium that require insulin injections using PN. We defined three subpopulations depending on diabetes type and the care system in Belgium in which people were enrolled. In Belgium, education and self-monitoring materials are provided through the Diabetes Convention or the Diabetes Care Pathway. The diabetes convention is aimed at people with type 1 (subpopulation 1) or type 2 (subpopulation 2) diabetes treated with complex insulin therapy (three or more daily injections). The care pathway is for people with type 2 diabetes who are treated with one or two daily injections (subpopulation 3). Population numbers were obtained from the IKED study (Audit 11), a quality

assurance database of Diabetes Convention patients [17] and from Farmanet, a public database of pharmacies (RIZIV). Subpopulation 1 included 33,035 PwD in Diabetes Convention, subpopulation 2 included 74,752 PwD in Diabetes Convention and subpopulation 3 included 62,609 PwD in Diabetes Care Pathway (Table 1). The average number of injections for each patient population was calculated as per the LIMO [4] and IKED studies [17] for the Diabetes Convention, and suggested by clinical experts for the Diabetes Care Pathway.

2.3.2 Frequency of PN Reuse

An estimate of reuse prevalence in the Belgian target population was informed by the Worldwide Injection Technique Questionnaire (ITQ) and LIMO studies [4, 16] (Table S1, see electronic supplementary material [ESM]). We further grouped the reusing population into four categories according to frequency of PN replacement. The proportion of PwD across single use or the different reuse categories was based on the LIMO study [4].

2.3.3 Risk for Lipohypertrophy

Impaired adherence to injection guidelines has been associated with an increased risk for LH+ status. The increasing risks for LH+ for each of the different reuse categories and an overall risk ratio for reuse, compared with single use, were obtained from Blanco et al. [18] (Table 3). These risk ratios were used to quantify the prevalence of LH among the different reuse categories, using the prevalence of LH+ in single use PwD.

While the current LH+ prevalence in single-use PwD is unknown for Belgium, an LH+ prevalence of 63% was reported among a patient population frequently re-using PNs [4]. From a back-calculation based on the overall risk ratio of 1.34 (Table 3), an estimate of 47% can be obtained for the prevalence of LH+ in single-use PwD in Belgium. Clinical experts did not agree with this estimate and selected a prevalence estimate of 27% as the lowest value from a range of

Fig. 1 Model structure and the different building blocks. Letters denote the different building blocks as discussed in the Methods section. Flow of PwD across the model is shown from sections A to C, and the outcomes considered as output in section D. *LH* lipohypertrophy, *TDD* total daily dose

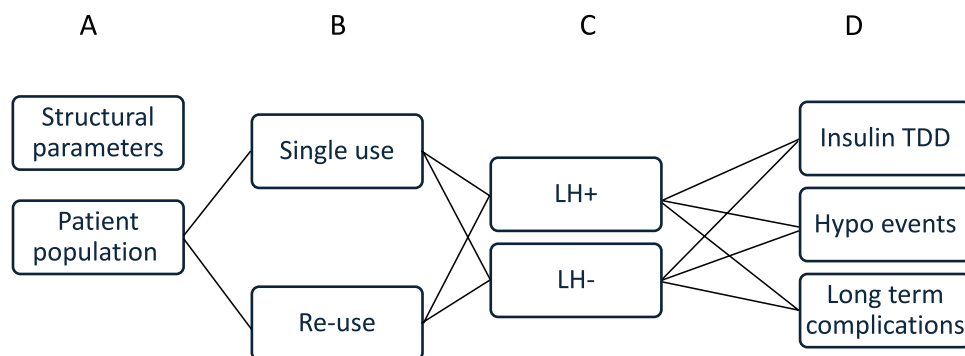


Table 3 Risk ratio and LH prevalence

Injections/PN needle	Risk ratio	LH prevalence (%)
1 (SU)	1.00	37.0
2	1.10	40.7
3–5	1.25	46.3
6–10	1.50	55.5
> 10	1.75	64.8

LH lipohypertrophy, PN pen needle, SU single use

options. As a result, a midpoint value of 37% for the prevalence of LH+ in the single-use population was included in the base-case analysis (Table 1).

2.3.4 Insulin

Research shows that LH often leads to an increase in insulin TDD, although the magnitude of the observed increase varied across studies, up to 35% (Table S3, see ESM) [4, 11, 15, 18–20]. Guided by clinical expert opinion, a TDD difference of 10 IU per LH status was chosen to reflect the consensus among clinical experts and the distribution of values collected. The cost of one unit of insulin was obtained from a weighted average of the cost of insulins provided in Belgium in 2022 (Table S3, see ESM).

2.3.5 Hypoglycemic Events

This study only took ‘severe’ and hypoglycemic events ‘requiring hospitalization’ into consideration. Severe hypoglycemic events were defined as events leading to unconsciousness, requiring assistance of a third person, often associated with blood glucose levels below a predefined threshold [21, 22]. Because of a lack of standardized definitions, this threshold value can vary across studies [23]. Estimates on the number of events per year were collected to calculate the burden of hypoglycemic events depending on the LH status of PwD.

The number of severe events per year per person for T1DM was obtained from the Belgian FUTURE study [24], which reported estimates before and after the use of continuous glucose monitoring (CGM) (Table S4, see ESM). The rate of severe events for PwD with T2DM was calculated using the T1DM/T2DM ratio from Tzogiou et al. [25]. The number of events requiring hospitalization for PwD with T1DM and T2DM was extracted from the RELIEF study [26], which reported event rates before and after use of CGM.

For each DM type, we calculated the number of hypoglycemic events per patient per year by using the before-CGM and after-CGM rates balanced for the proportion of patients

on CGM in each group (CGM-uptake weighted averages) [17]. The obtained numbers of hypoglycemic events were further rescaled towards LH+ and LH– status to reflect an increased risk of experiencing a hypoglycemic event if LH+ [9] (Table S5, see ESM).

Costs associated with severe hypoglycemic events for PwD with T1DM and T2DM were derived from de Groot et al. [27], who assessed per-patient costs of hypoglycemia in 2016 among PwD with T1DM and T2DM in The Netherlands. Costs associated with an event requiring hospitalization for PwD with T1DM were reported in the RESCUE study [28] for 2018, while the respective cost for PwD with T2DM was estimated using the T1DM/T2DM cost ratio of severe events.

2.3.6 Long-Term Complications

The prevalence of the different types of chronic clinical complications among Belgian Diabetes Convention PwD with T1DM and T2DM was obtained from Lavens [29] (Table 1, Table S6 in the ESM). The UK Prospective Diabetes Study (UKPDS) has shown that improved glycemic control over 10 years can reduce vascular complications of PwD with T2DM, quantifying the relative risk reduction for long-term complications with each 1.0% decrease in HbA1c [30, 31]. Converted to 1-year and 5-year probabilities, these HbA1c-driven risk reductions were applied for both T1DM and T2DM populations in the model. For the difference in HbA1c between LH status, we used the value of improvement reported for a subset of patients with non-optimal metabolic control in the LIMO study [4] (Table S7, see ESM). For each category of long-term complications, a weighted mean cost per patient was calculated from the related APR-DGR for 2021 [32].

2.3.7 Impact of the Intervention

The effect of free PN provisioning complemented with targeted educational support on single PN use was modelled to cause a shift in reuse distribution (Table S2, see ESM). A reduction in reuse prevalence from 90% to almost 20% was reported following the intervention in the LIMO study [4], while clinical experts indicated that a reduction to 50% was more appropriate according to their expertise. Following the mid-point strategy, a reduction in reuse prevalence from 90% to 35% was implemented, implying a shift towards single use behavior for 55% of PwD (Table 4). Furthermore, the remaining PwD reusing PN largely shifted towards lower reuse frequency (Fig. 2).

Importantly, due to the model structure, a change towards a LH– status was only predicted for a subset of persons who improved IIT, with the size of this subset being dependent on the difference in LH+ prevalence between single using

Table 4 Patient population and LH prevalence before and after the intervention after 5 years

Injections/ PN needle	Before intervention		After intervention	
	Patients (N)	LH+ patients	Patients (N)	LH+ patients
1 (SU)	17,040	6305	110,757	40,980
2	7668	3121	26,837	10,923
3–5	90,480	41,847	30,416	14,067
6–10	29,138	16,171	0	0
>10	26,071	16,881	2386	1545
Total	170,396	84,325	170,396	67,515

LH lipohypertrophy, PN pen needle, SU single use

and reusing populations. Moreover, the impact on model outcomes was introduced in a gradual and delayed manner. The time window and magnitude of LH status improvement was calculated from literature and modelled to affect, every 6 months, 65% of the respective PwD subset (Table S8, see ESM). This estimate corresponds to the proportion of patients in the ISTERP-2 control group who experienced full or partial remission of LH after 6 months, with this group being considered representative of the current situation in Belgium [5]. The model was run in absence and in presence of the intervention, with a time horizon of 5 years to calculate the difference in economic burden for the PwD

population in this study. No discounting was applied for cost or effects.

2.4 Scenario and Sensitivity Analyses

A deterministic sensitivity analysis of the base-case configuration by varying parameter values by 20% was performed to assess the robustness of the model and factors impacting the model's outcomes. The model's base-case configuration was established using parameter values that reflected a consensus between estimates from the literature search and the opinions of clinical experts on the Delphi panel and parameters for which a midpoint value was selected in absence of consensus. To explore the impact of the source for these latter parameters, two scenario analyses were conducted, one using only input values from the literature and the other using the input values as provided by the clinical experts. A third and fourth scenario analysis was conducted to evaluate to what extent the magnitude of CGM uptake had an effect on the model outcomes. While the base-case analysis reflected the current clinical practice in Belgium, with varying levels of CGM use across the patient populations, the scenario analyses considered scenarios where CGM was not yet part of diabetes management or where it was well established with all PwD using CGM.

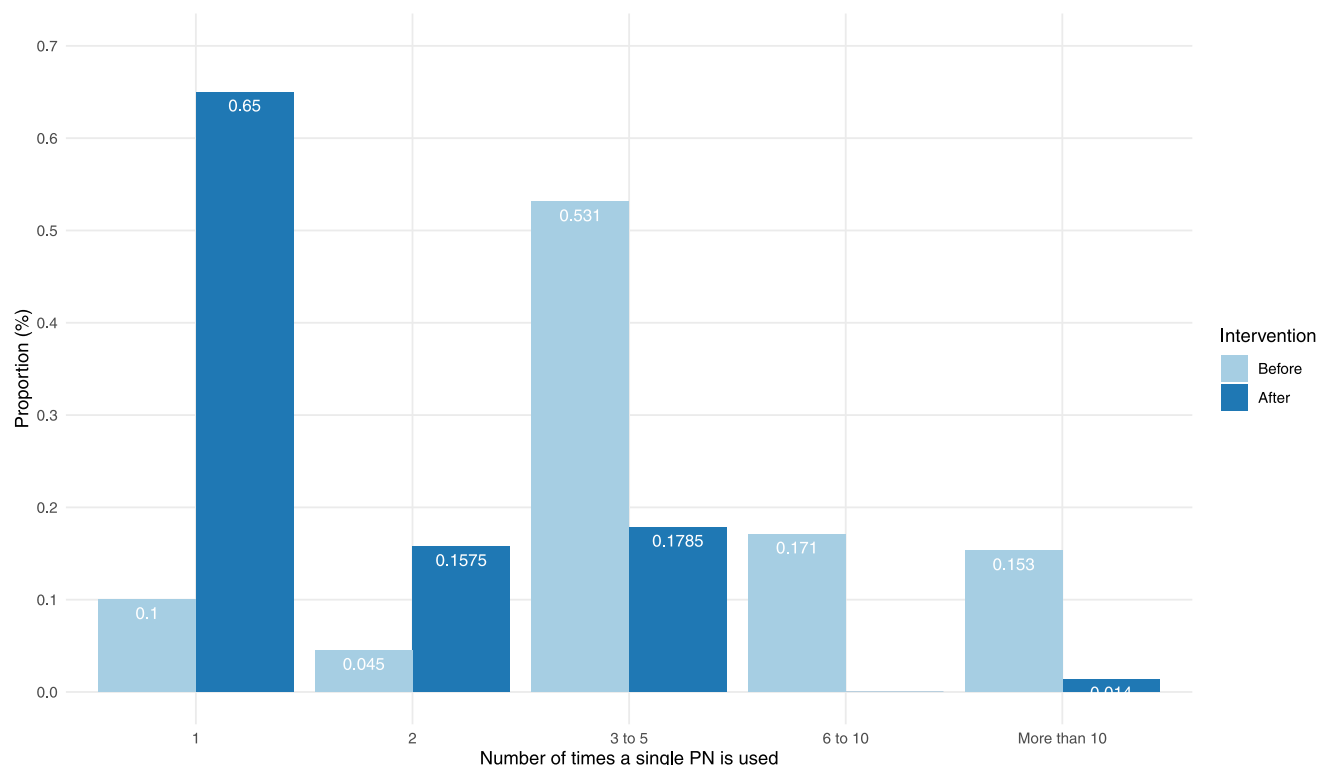


Fig. 2 Population distribution across reuse categories. For each category denoting the number of times a single PN is used, the proportion (%) of the population is shown before and after the intervention

3 Results

3.1 Model Outcomes

In the base-case setting, the behavior shift in reuse resulted in a decrease of LH+ prevalence from 49.4 to 39.6% LH+ in the entire PwD population. A total of 255.1 million fewer insulin units were consumed over a 5-year period, resulting in a cost reduction of 6.53 million euros. This represents a 1.8% decrease in current insulin expenses for the target population. Table S4 displays the annual per-patient number of hypoglycemic events, categorized by LH status, both with and without mitigation by glucose monitoring devices (see ESM). By applying hypoglycemic event rates adjusted for CGM usage, a calculated reduction of 30,668 severe events and 1966 hospitalization-requiring events was observed, resulting in savings of 27.35 million euros and 15.18 million euros, respectively. This corresponds to a reduction of 7.2% compared with pre-intervention costs. The decrease in HbA1c levels led to 129, 151, 161 and 276 fewer patients experiencing long-term complications related to cardiovascular issues, microvascular problems, kidney conditions and foot complications, respectively. This resulted in savings of 3.63 million euros over a 5-year period. Figure 3 presents a summary of the various savings achieved over a 5-year period, amounting to a total of 52.7 million euros.

3.2 Scenario and Sensitivity Analysis

Additional scenarios are also provided in Figure 3. The main drivers identified were the reduction of severe hypoglycemic events, followed by reduction in events requiring hospitalization and insulin units sparing. Assuming no CGM use, savings increased to 59.9 million euros. Conversely, full adoption of CGM in all patient populations yielded a total saving of 41.9 million euros. The deterministic sensitivity analysis of the base-case scenario, shown in Fig. 4, identified the parameters that most affected savings when varied by 20% in opposite directions. The risk of LH+ associated with insulin PN reuse was found to have the greatest impact on overall savings, followed by the prevalence of LH+ among single-use PwD and the risk of a hypoglycemic event in the presence of LH+. In contrast, variations in TDD and the risk of long-term complications were found to have the lowest impact.

4 Discussion

This study evaluated the economic savings that could be achieved with improved adherence to IIT guidelines by insulin-treated PwD, with a particular focus on reuse of PN with every injection. Despite international guidelines advocating for site rotation and single PN use, failure to adhere can precipitate incident LH, otherwise preventable and associated with detrimental effects on individual health outcomes and consequently on healthcare economic outcomes. Avoiding pain, convenience and lack of education are the main drivers for incorrect injection technique, with out-of-pocket expenses for PN being an additional driver for reuse [16, 33]. While the frequency of PN reuse is low (~37%) in European countries where PNs are made freely available for PwD (embecta market research 2022, see ESM), PNs are currently not reimbursed in Belgium and PN reuse is common among PwD (95%) [4, 16]. The LIMO study reported a 70% reduction in reuse when PN were provided, in addition to intensified online educational support over 6 months of study duration [4]. Referencing the current scenario in Belgium, our modelling analysis demonstrated that decreasing needle reuse by 55% could significantly reduce healthcare costs. The most notable impact of this reduction was observed in the lowered rates of hypoglycemic events, alongside more modest savings in the overall use of insulin units and in the prevention of long-term complications.

Model structure and parameters were informed from available literature, insights from clinical and health economic experts or both, thereby balancing between model complexity and data validity. Clinical input differed markedly from the initial literature-based scenario for a selection of input parameters. The experts attributed these discrepancies to the lack of robust supporting research, which is illustrated by the absence of similar modelling attempts for Europe. Consequently, the midpoint value was taken for these parameters and scenario analyses with expert and literature values were performed, aligned with the methodology described by Weinstein et al. [34].

Even if this study modelled a significant improvement in reuse behavior, only < 10% of all PwD experienced a change in LH status. The extent to which PwD improve in their LH status is driven by LH+ presence in the single-use patient population and the increased risks associated with reusing. The LIMO study reported an LH+ prevalence of 63% in Belgium, among a population characterized by high rates of PN reuse [4]. This prevalence translated back into an LH+ prevalence of almost 50% for single use when we applied the LH+ risk ratios used in this study. As the true extent of LH+ in the single-use patient population in Belgium is unknown, we were also

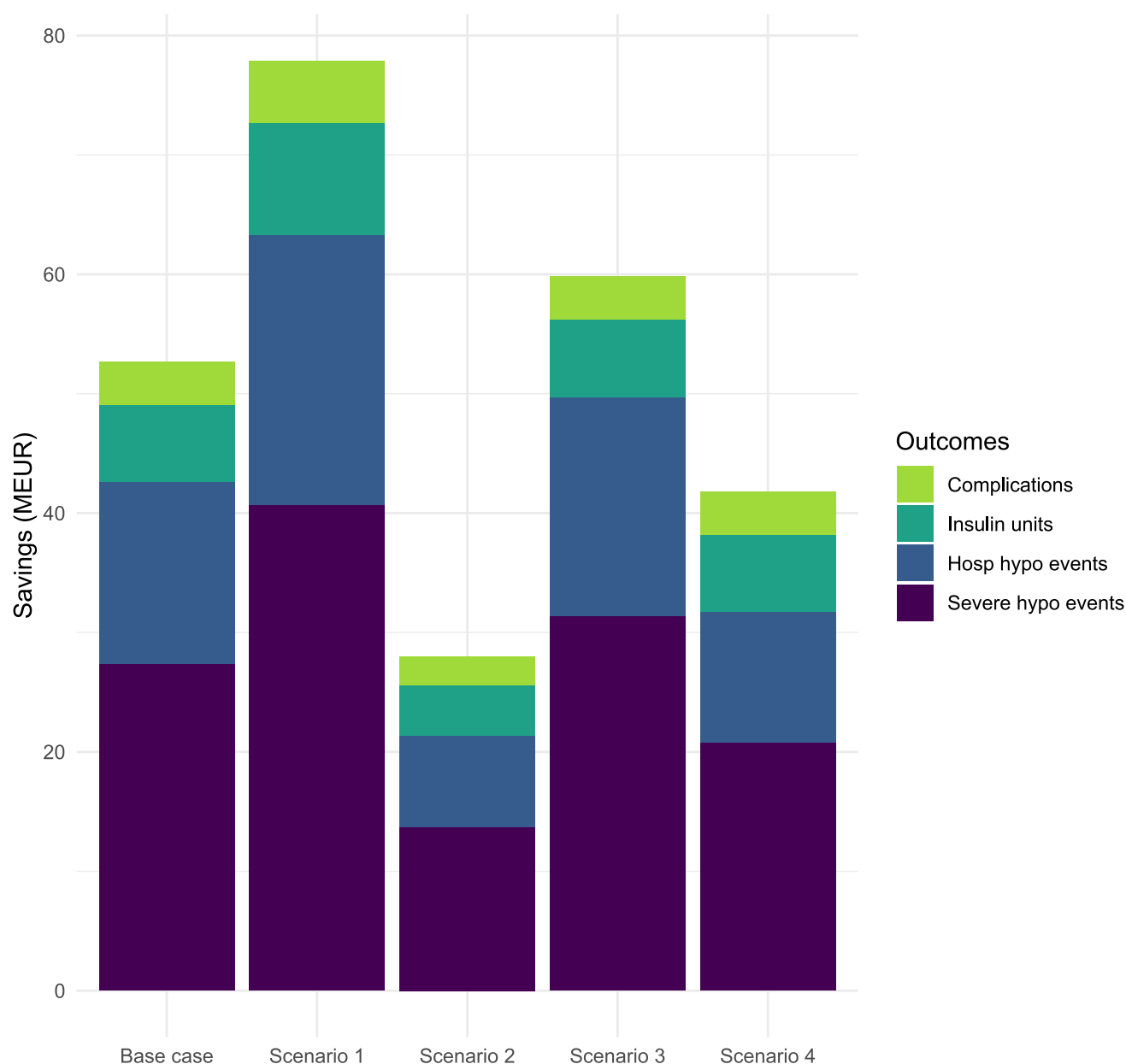


Fig. 3 Scenario analysis of the overall monetary savings. Savings in million euros (MEUR) for each scenario are broken down into the different outcomes evaluated in the model. The base case represents the model-expected configuration of parameters (use of mid-point values). Scenarios 1 and 2 are variations to the base-case configuration when input for three specific parameters is respectively informed

by literature findings (scenario 1) or by expert opinion (scenario 2). Scenarios 3 and 4 are variations of the midpoint configuration with, respectively, the use of only pre-CGM (scenario 4) or only post-CGM (scenario 5) rates for hypoglycemic events for all PwD populations. *CGM* continuous glucose monitoring, *PwD* people with diabetes

guided by clinical experts during a Delphi panel. A prevalence estimate of 27% was selected as the lowest value from a range of options, resulting in a midpoint value of 37% in the base-case analysis.

The LIMO study did not evaluate the intervention impact on LH+ prevalence, as the observation period was considered too short [4]. Clinical experts indicated that LH status change in practice is not frequently observed

and is strongly dependent on the extent and duration of LH+ presence. In contrast, regression of LH nodules has been reported in a large set of LH+ PwD over a reasonably limited time window [5, 35–37]. For the subset of PwD improving in LH status, we implemented a delayed and gradual intervention impact on model outcomes, which resulted over a time horizon of 5 years in 75% savings

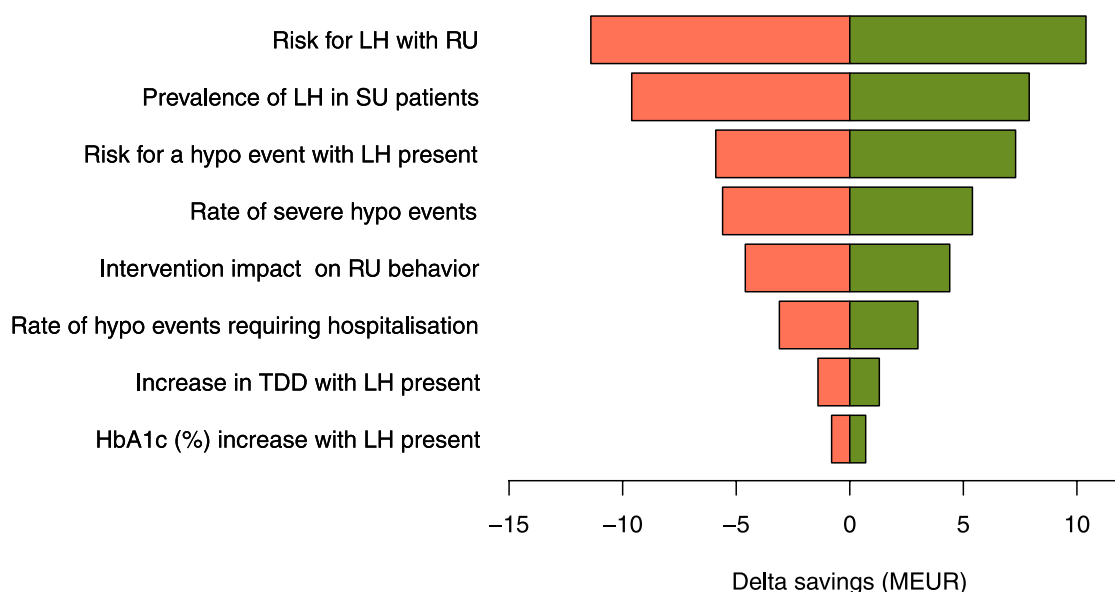


Fig. 4 Sensitivity analysis to identify impact of variation in input parameters. The graph illustrates the effect on total savings in million euros (MEUR) when the base-case value of a specific parameter is adjusted, displaying a 20% decrease (shown in red) and a 20% increase (shown in green). *hypo* hypoglycemic event, *LH* lipohypertrophy, *RU* reuse, *SU* single use, *TDD* total daily dose of insulin

compared with a situation where effects would take place simultaneously with the intervention.

Hypoglycemic events represented the largest contribution to cost savings, in line with the knowledge that hypoglycemia remains a significant barrier for optimal management of diabetes [38]. Model inputs for hypoglycemic event rates were derived from recent studies that accounted for the impact of CGM technology on reducing the frequency of hypoglycemic events, thus reflecting the current standard in DM treatment in Belgium. Given the rising adoption of CGM in Belgium, albeit with varying degrees of uptake among PwD populations, we applied a weighted average of rates before and after CGM implementation, tailored to the Belgian situation. Additionally, in a scenario analysis, we examined model outcomes using estimates from before CGM's introduction, to accommodate for variations in health care systems geographically, as well as scenarios assuming complete CGM adoption within the target population.

The economic impact of interventions targeting improved adherence to the correct IIT of PwD has been reported by other studies, although addressing a different question or conducted in a different setting. One study evaluated the economic impact of changing needle length for insulin pens as part of the correct IIT [39]. When complemented with targeted education, the adoption of shorter PNs resulted in significant improvement in blood glucose control and decrease in insulin consumption. A resulting reduction in expenses for the Italian healthcare system was demonstrated by a budget impact analysis. The ISTERP-3 study demonstrated economic benefits of

structured therapeutic education sessions on correct IIT in Italy, with a focus on the mitigation of hypoglycemic events [19]. This study patient population displayed non-optimal injection habits before the intervention, with high rates of missing rotation (90%), injecting into LH nodules (98%) and reuse of PN (95%). Apart from the extent of reuse, the LIMO study found significant lower percentages of non-optimal injection habits in Belgium, which illustrates the high quality of educational support on IIT in Belgium [4].

This study constitutes the first in-depth analysis on the impact of improved IIT to date in Belgium, with a focus on PN reuse, using a validated health-economic methodology, and recent and local estimates for cost and incidence parameters. However, the study outcomes are subject to limitations with respect to the inclusion of several assumptions in both model structure and parameters. The time horizon modelled was limited to 5 years, despite diabetes being a chronic illness. Costs were used as reported in the original source without adjustment, given uncertainty in data collection. This conservative approach likely resulted in a slight underestimation of actual savings. While any intervention of diabetes management is expected to incur long-lasting effects on health outcomes, our study design did not allow us to grasp the full consequences of the modelled intervention. A narrative and broad literature search was conducted to inform model development, and although this type of analysis has many strengths, a less rigorous search strategy is also prone to introduce bias and to yield different interpretations and insights.

Furthermore, data needed to support the modeling framework were often limited or only partially available in literature. For example, model parameters were not adjusted by the type of insulin used, although potentially impacting the prevalence for LH, as the required additional granularity in the consulted sources was not available. A similar observation was made for some other model parameters with respect to populating in a more detailed differentiation, and the lack of sufficient distinctiveness along the entire model was the primary motivation to not perform subgroup analyses. As the Belgian FUTURE study only reported a rate of severe hypoglycemic events for T1DM, we derived a corresponding rate for T2DM by applying a ratio obtained from Tzogiou et al. [25]. This Swiss study reported a comparable T1DM event rate as in FUTURE with the addition of an event rate for T2DM. A cost ratio derived from the severe event costs was also applied to the reported cost for T1DM in Belgium to estimate the cost of T2DM hypoglycemic events requiring hospitalization. The costs associated with severe events were sourced from an analysis from the Netherlands due to lack of Belgian data. Hyperglycemic events were not considered in this analysis, given that we did not consider them as major drivers for PwD being diagnosed and receiving insulin treatment. Next, as data for T1DM was not readily available, UKPDS-based risk reductions for long-term complications due to HbA1c improvement were also used for T1DM. However, risk reductions are likely to differ as HbA1c values are influenced by different factors in the two DM populations. Moreover, average HbA1c levels in the Belgian population have shown consistent improvement over the past decade, and the relevance of the UKPDS landmark study should be critically viewed within the context of an evolving landscape of changing guidelines and advancements in diabetes treatment.

The estimated cost savings are subject to uncertainty due to the wide range of model input values found in literature, the marked discrepancies between literature findings and clinical expert opinion and by heterogeneity in definitions used. Sensitivity analysis showed that variation of LH+ prevalence, both for single use and reuse, had a substantial influence on the overall estimated savings. Although LH+ prevalence of 70% and more has been reported in insulin-injecting PwD [10, 15, 18, 20], estimates are highly variable due to heterogeneity in methodology and characteristics of the study populations. The development of LH+ is not only caused by improper IIT but also reflects the direct anabolic effect of insulin injection at the same site over an extended period [36]. Similarly, non-severe events were not considered in this analysis given the lack of consensus definitions or differences in the definition of hypoglycemia across clinical and observational studies. Also, the lack of consensus on a glycemia threshold for severe hypoglycemic events represents a limitation when combining source data

in the model. Another limitation of this study arises from the rapidly evolving landscape of DM treatment, characterized by the ongoing introduction of new treatments and technological advancements. For example, increasing availability of CGM for people with T1DM or T2DM, and new drug classes of glucagon-like-peptide-1 receptor agonists (GLP-1RA) and sodium-glucose cotransporter-2 (SGLT2) inhibitors available for people with T2DM, have been associated with improved glycemic control and reduced risk of diabetes-related complications. This dynamic environment poses a risk that the model's assumptions and input values may quickly become outdated. We maximally attempted to mitigate this risk by using recent data when possible and applying hypoglycemia rates weighted by CGM uptake in the different populations. While the uptake of CGM was set at 81.4% for PwD with T1DM [17], values of 50% and 0% were assumed for PwD with T2DM from the Diabetes Convention and Diabetes Care Pathway. While the uptake of CGM is currently estimated at 25.3% for Diabetes Convention PwD with T2DM, corresponding to the 18,900 persons eligible since July 1, 2023 [40], the uptake is expected to increase to 75%, similar to T1DM; hence the midpoint of 50% for the horizon modelled. Finally, the impact of reduced PN reuse can be difficult to distinguish from other improvements in injection practices, while interdependence is likely to be present in clinical outcomes collected from literature parameters, thereby challenging the interpretation of published findings.

5 Conclusion

This analysis assessed the cost savings that could result from improved PN use by means of an analytical framework tailored towards insulin-treated PwD in Belgium. Our evaluation shows that, even with the advent of CGM tools, the correct use of IIT could bring about potential savings of almost 53 million euros in health care expenditure. Further prospective research is needed to confirm the findings and diminish the uncertainties identified in this analysis.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s41669-024-00547-x>.

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Declarations

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Potential Competing Interests K.T., S.V. and F.V. are employees of AxTalis, a consultancy company for medical affairs and market access, which was paid a fixed fee by embecta International. K.Z. and T.N. are employees of embecta International, a manufacturer of pen needles and main sponsor of this study. The other authors have received honoraria for their expert advice on the topic or their participation in the Delphi panel, but declare they have no competing interests. They also received grants and honoraria from various pharmaceutical companies, all unrelated to this study.

Availability of Data and Material All data generated or analyzed during this study are included in this published article and its supplementary information files.

Ethics Approval This study involved participation of clinical experts to a Delphi panel, which did not involve the collection of personal health data or the participation of patients. Ethical approval was not required, as the Delphi method solicits expert opinion and does not involve human participants as defined by typical clinical trials.

Consent for Publication This article does not contain identifiable photos or patient data.

Consent to Participate All clinical experts involved in the Delphi panel provided their informed consent to participate in the research. No patients participated in this study and no patient data were collected.

Code Availability R code supporting this study is available upon reasonable request to the corresponding author.

Author Contributions K.T., S.V. and F.V. designed the modelling framework, collected the data and performed the analysis. The first draft of the manuscript was written by K.T. and F.V. and all authors critically reviewed previous versions of the manuscript. All authors read and approved the final manuscript.

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