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Cost Effectiveness and Resource Allocation

RESEARCH

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A cost-utility analysis of long-acting insulin analogues (detemir, glargine and degludec) for the treatment of adult type 1 diabetes in South Africa

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Abstract

Background Type 1 Diabetes Mellitus (T1DM) is a life-threatening condition that is managed with administered insulin. Intermediate- to long-acting insulin represents the basal insulin constituent of the total insulin used in treating T1DM. In South Africa, intermediate-acting Neutral Protamine Hagedorn (NPH) insulin has been the mainstay basal insulin recommended in the public sector, despite the availability of newer (ultra) long-acting insulin analogues. A cost-utility analysis of the newer long-acting insulin analogues insulins degludec, glargine U100, glargine U300 and detemir in comparison to current practice (NPH insulin) has yet to be performed in the South African public health sector context.

Methods A cost-utility analysis was carried out utilising Markov modelling. Long-acting insulins degludec, glargine and detemir were compared to NPH insulin in the model. For each comparator, two Markov states were created, one in which no complications occurred and another representing severe nocturnal hypoglycaemic events. Quality-Adjusted Life Years (QALYs) gained per patient year was the health outcome assessed over a one-year time horizon.

Results NPH insulin was the least costly and least effective; while Determir and Glargine U100 were extended and absolutely dominated respectively. The ICER for Glargine U300 in comparison to NPH was USD 40,104.91 per QALY gained, while Degludec was USD 64,831.20 per QALY gained in comparison to Glargine U300.

Conclusions The ICERs of long acting insulins were considerably higher than South Africa's indicative cost-effectiveness threshold. The *status quo* of NPH insulin in the management of T1DM in adults remains the most cost-effective option for the South African public health sector.

Keywords Diabetes, Type 1 diabetes, Adult, Cost-effectiveness, South Africa, Insulin, Cost-utility, Long-acting insulin

Background

The United Nations Sustainable Development Goal (SDG) target 3.4 aims to reduce premature mortality attributable to non-communicable diseases (NCDs) by one third by 2030, compared to 2015 estimates [1]. One of the four priority NCDs to be targeted by world leaders is diabetes mellitus [2].

There is an appreciable growing global trend in Disability Adjusted Life Years (DALYs) attributed to diabetes, which is also realised in sub-Saharan Africa, where diabetes was responsible for 623 DALYs per 100,000 population in 2017, representing an 8.4% increase from 1990 [3, 4]. In South Africa specifically, it is estimated that premature adult deaths attributed to diabetes have increased

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by 38% between 1999 and 2006 [5, 6]. One of the major subtypes of diabetes is Type 1 Diabetes Mellitus (T1DM). The estimated burden of T1DM in South Africa as of 2019 is approximately 130,000 for the adult population above 20 years of age, which equates to a prevalence of about 3.7 per 1000 individuals [7].

The disease (T1DM) is hallmarked by high levels of blood glucose secondary to insulin deficiency that is fatal when left untreated. Insulin promotes the uptake of glucose from the vascular space into the intracellular space, where glucose is utilized to fuel the functions of the cell. Under normal physiology, a basal level of insulin circulates in the bloodstream with additional spikes of insulin corresponding to meals. The treatment of T1DM, therefore, aims to imitate physiological levels and responses of insulin in inter-prandial and prandial states. With insulin use, acute and chronic complications of T1DM, including diabetic ketoacidosis and micro- and macrovascular complications, can be averted. Exogenous insulin, however, can result in severe adverse drug events like hypoglycaemia, a medical emergency and potentially life-threatening condition characterised by low blood glucose and associated symptoms. Severe hypoglycaemia in particular is an important adverse drug event. Its significance, however, is complicated by disparities in the definition used in studies of the condition. Definitions range from serologically confirmed hypoglycaemia (<2 mmol/L) to hypoglycaemia requiring third-party assistance (ranging from non-medically trained individuals to hospital admission) and has subsequently received further research interest [8].

In South Africa's public health care system, Neutral Protamine Hagedorn (NPH) insulin, an intermediate-acting insulin, has been used to replicate basal levels of inter-prandial insulin, and is used in conjunction with rapid-acting insulins in order to achieve physiologically comparable insulin levels in adult T1DM patients. In addition to NPH and rapid-acting insulins, (ultra-) long-acting insulin analogues are also registered for use in South Africa [9], but these drugs are not included in South Africa's Essential Medicines List nor recommended for use in South Africa's public health care system [10].

The cost-effectiveness of the newer (ultra-) long-acting insulin analogues has been assessed by many health technology assessment agencies outside of South Africa [11–15] and in individual economic studies [16–23], but no evaluation has been done for the South African adult T1DM population. With this study, we explored the cost-effectiveness of newer long-acting insulins (detemir, glargine and degludec) compared to intermediate-acting NPH insulin in adults with type 1 diabetes mellitus in South Africa.

Methodology

Study design

We conducted a modelled cost-utility analysis (CUA) of long-acting insulins degludec, glargine U100, glargine U300 and detemir in comparison to the status quo of NPH insulin. Our overall study design was based on the South African guidelines for Health Technology Assessment, which are used to guide the selection of medicines for the public health sector [24]. The scope of costs included the full costs associated with the change in insulin from a public sector provider's perspective, expressed in 2020/21 prices and converted to United States Dollar (USD) using the average South African Rand (ZAR) to USD exchange rate over the same period (16.50 ZAR/USD) [25]. Outcomes were expressed as Quality Adjusted Life Years (QALYs). Analysis was undertaken in Microsoft Excel and TreeAge Pro (2021) [26].

Incremental cost-effectiveness ratios (ICERs) were calculated by ordering each insulin option from least to most costly. After excluding any options with extended or absolute dominance, ICERs were calculated as the difference in costs divided by the difference in outcomes (QALYs) between adjacent options. The resulting ICERs were then compared to the marginal productivity of health spending in the South African public sector which estimates that approximately USD 3012 of marginal spending will avert one DALY [27]. Given the lack of an agreed cost effectiveness threshold (CET) for South Africa, this threshold was used as an indicative CET to interpret QALY based ICERs.

Clinical evidence

A comprehensive literature search for clinical literature was performed to inform clinical parameters and model structure (Appendix 1). Our search identified 209 systematic reviews of which three were selected for further review. Of these three, the National Institute for Health and Care Excellence (NICE) review (2021) [28] was selected to form the basis of the evidence on clinical effectiveness for this current paper, given that it most closely matched our decision problem, it included relevant primary studies, and was judged to be of high quality (see Appendix 2). In evaluating the evidence it was judged that the only significant clinical difference between insulins was rates of severe nocturnal hypoglycaemia, as shown by the summary of primary and secondary endpoints between the three systematic reviews evaluated (Appendix 3).

Modelling approach

Using a Markov modelling approach, and based on the clinical findings of the (NICE) review (2021) [28], we developed models for each alternative insulin with two

Table 1 Model inputs: rates of severe nocturnal hypoglycaemia per 100 person years [15]

Insulin	Base	Range	Proportion nocturnal hypoglycaemia
NPH once daily	50.65	30.17–68.61	0.2215
Detemir once daily	40.81	30.17–57.21	0.2000
Glargine-U100	49.67	30.17–65.70	0.1569
Glargine-U300	50.26	30.17–91.82	0.1417
Degludec	45.68	30.17–57.17	0.1081

Markov states: T1DM with no complications and T1DM with severe nocturnal hypoglycaemic events. As mentioned, given the absence of significant differences, we did not model death, adopted a time horizon of one year and therefore did not discount results. Because insulin dosage is weight dependent, we modelled an adult T1DM population with a mean weight of 81.2 kg (SD 17.8) [29].

Our modelling approach therefore required data on rates of severe nocturnal hypoglycaemia, insulin utilisation by weight and associated costs, inpatient admission and costs, and health related quality of life; appropriate to each comparator and Markov state. These data are summarized in Tables 1 and 2. Rates of severe hypoglycaemia for different insulin types and regimens were drawn from the NICE economic model [15], which accompanied the previously mentioned review [28]. These data allowed for the generation of base case, lower and upper values, as well as for an estimation of the proportion of severe hypoglycaemia occurring at night [28].

In terms of insulin utilisation, the total recommended daily dose ranges between 0.5 and 1 unit/kg body weight, of which 33–50% consists of the intermediate-acting bedtime basal dose and the remainder is divided into three pre-meal short-acting insulin doses. Although patient and clinician practice may differ, we followed relevant South African Standard Treatment Guidelines complemented where necessary by the recommendations from the U.S. Food and Drug Administration [10, 30–33]. The analysis only includes once daily regimens as this is recommended in the South African public health sector. Unit costs of insulin were derived from the South African Master Health Product List (MHPL) of October 2020 which lists public sector prices [34]. Because not all insulins are available in the public sector, we also used prices from the Medicines Price Registry (MPR) of December 2020 which provides private sector prices. The cheapest formulation per unit of insulin (10 ml (100 U/ml) injection formulation was selected as the cost input [35]. Where the injection formulation was not available or does not exist, the next cheapest formulation was used, namely the cost per 5 pack of 3 ml (100 U/ml) cartridges

Table 2 Model inputs: insulin utilisation, inpatient admission, unit costs and health related quality of life

Parameters	Base value	Range for PSA	Source
Insulin utilisation			
Mean weight (kg)	81.2	± 17.8	Heller [29]
Total units of insulin per kg per day (U/kg/day)	0.60	0.5–1.0	EML and FDA [10, 30–33]
Proportion of total that is NPH insulin	0.45	0.40–0.50	EML
Proportion of total that is insulin Detemir	0.33	-	FDA [31]
Proportion of total that is insulin Glargine-U100	0.33	-	FDA [30]
Proportion of total that is insulin Glargine-U300	0.33	0.33–0.50	FDA [32]
Proportion of total that is insulin Degludec	0.33	0.33–0.50	FDA [33]
Inpatient utilisation			
Proportion of severe hypoglycaemia requiring inpatient admission	0.33	0.25–0.36	Hammer [36]
Length of stay (days)	2.0	1.0–6.0	Hammer [36]
Insulin cost per patient day (USD)			
NPH: Protaphane injection 10 ml (100 U/ml)	0.05		Calculated using MHPL Oct 2020 [34]
Detemir: Levemir cartridge 5 × 3 ml (100 U/ml)	0.31		Calculated using MPR Dec 2020 [35]
Glargine-U100: Lantus injection 10 ml (100 U/ml)	0.48		Calculated using MHPL Oct 2020 [34]
Glargine-U300: Teajou pen 3 × 1.5 ml (300 U/ml)	0.39		Calculated using MPR Dec 2020 [35]
Degludec: Tresiba cartridge 5 × 3 ml (100 U/ml)	0.64		Calculated using MPR Dec 2020 [35]
Cost per inpatient day (US$)	192.61		DHB 2019/20 [37]
Health related quality of life values			
T1DM no complications	0.84	0.76–0.92	Evans [36]
T1DM nocturnal hypoglycaemia	0.77	0.70–0.85	Evans [36]

Table 3 Cost-utility results (USD, 2020–2021 prices)

Strategy	Cost (USD)	QALYs	ICER (USD per QALY gained)
NPH once daily	32.27	0.8321	
Detemir once daily	121.84	0.8343	Ext. dominated
Glargine U300	150.74	0.8351	40,104.91
Glargine U100	184.40	0.8344	Abs. dominated
Degludec	238.78	0.8365	64,831.20

of insulin. The insulin cost per patient per year was thus calculated as a function of weight, total daily dose of insulin, proportion of total daily dose of insulin that is basal insulin, cost per unit of insulin and the number of days in a year.

Given that the scope of costs for this study includes any potential changes in provider costs owing to a change in insulin, we included admissions for severe nocturnal hypoglycaemic events based on a study of T1DM patients in Spain, Germany and the United Kingdom (UK) [36]. We assumed utilisation rates from the UK cohort as these were lowest. The cost per inpatient day was taken from the District Health Barometer (2019/2020) which summarizes these costs across all public sector hospitals in South Africa [37] (see Table 2).

Finally, the Health-Related Quality of Life (HRQoL) of T1DM patients with no complications (0.844) or with severe nocturnal hypoglycaemic events (0.77) was derived from a study by Evans et al. (2013). When expressed as disutilities, these values were similar to that found in other available literature [38–40].

Sensitivity analysis

Probabilistic sensitivity analyses with 10,000 iterations were performed using the ranges on certain model inputs as shown in Tables 2 and 3. In addition, deterministic sensitivity analysis included a threshold analysis on insulin prices (solving for cost neutrality) as well as a 40% price reduction on private sector medicine prices to approximate public sector prices, as recommended by HTA guidance for South Africa [24].

Results

Cost-utility analysis

Base case

Base case economic evaluation results are presented in Table 3. NPH insulin was the least costly and least

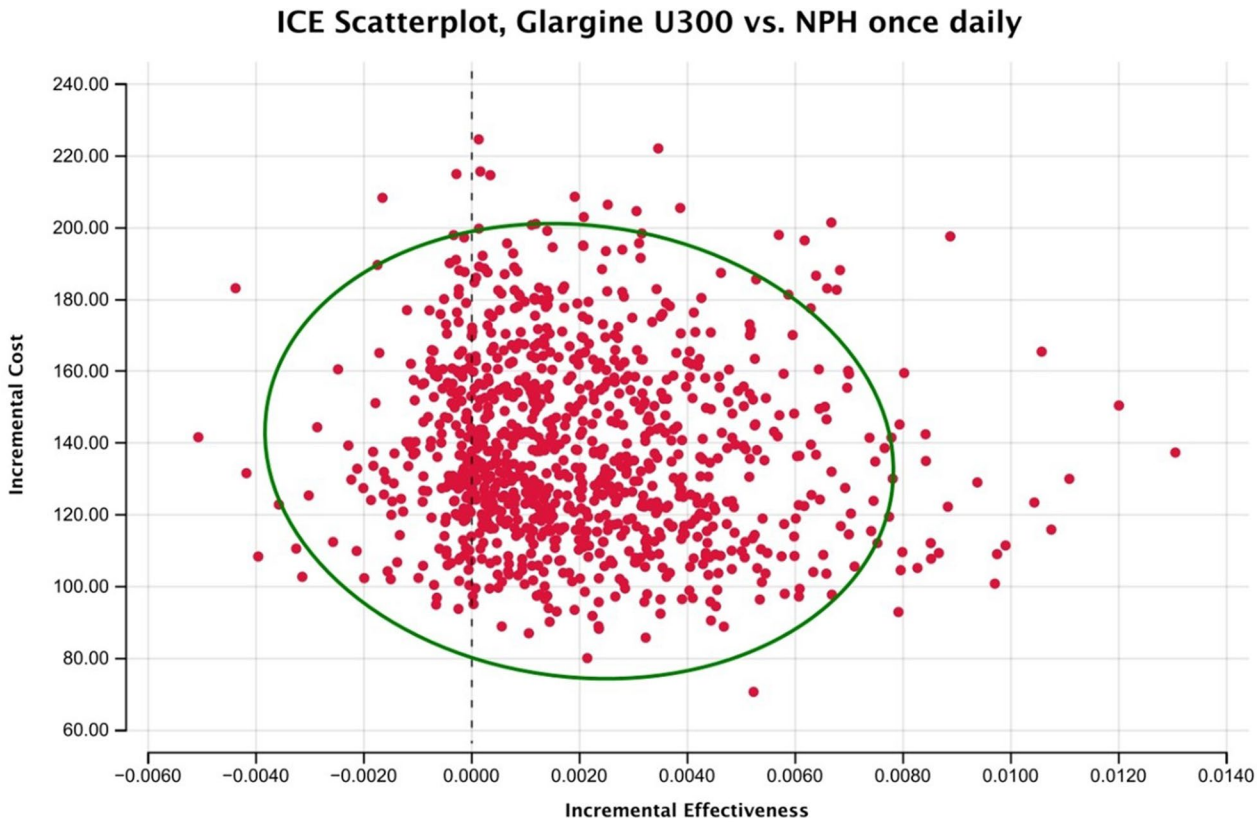

Fig. 1 Probabilistic sensitivity analysis results Glargine U300 vs NPH (USD, 2021 prices)

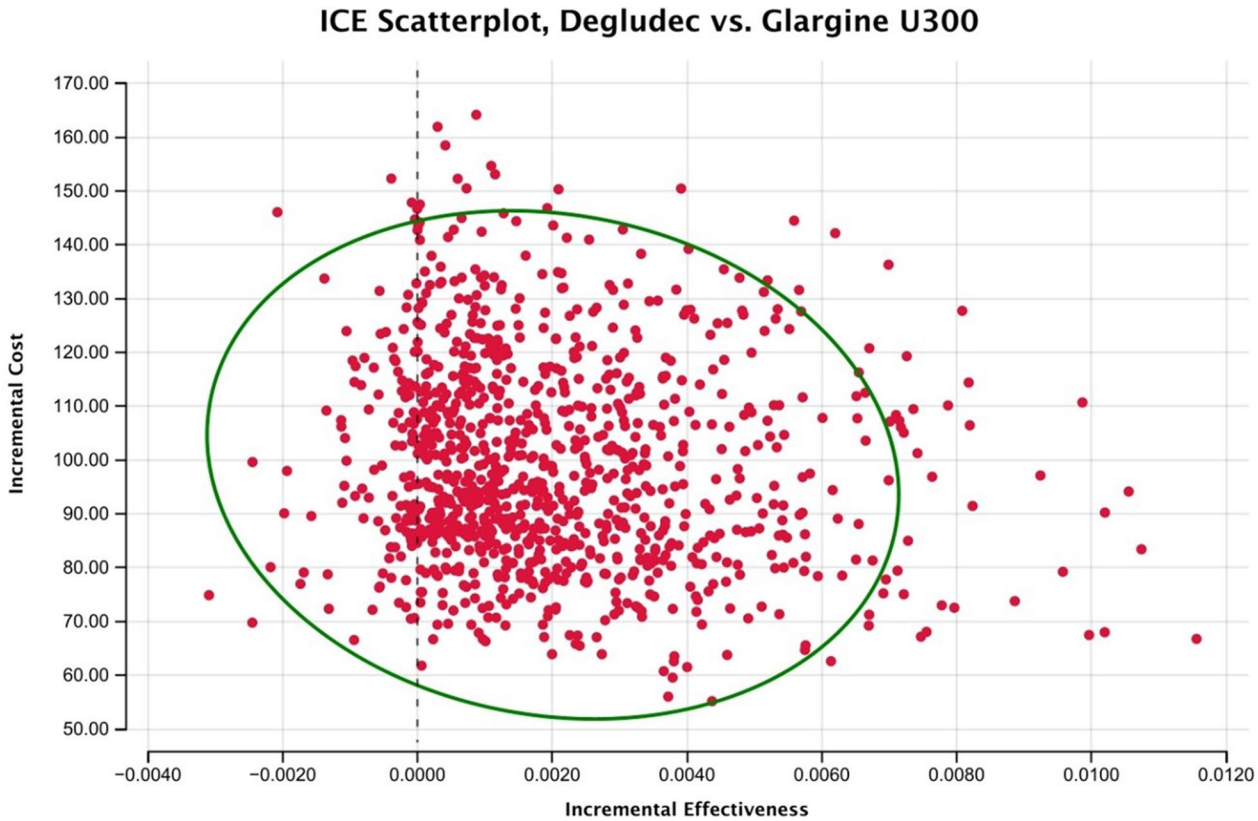

Fig. 2 Probabilistic sensitivity analysis results Degludec vs Glargine U300 (USD, 2021 prices)

Table 4 Cost-effectiveness analysis results with 40% reduction in single exit price applied (USD, 2020–2021 prices)

Strategy	Cost (USD)	QALY	ICER (USD/QALY gained)
NPH once daily	32.27	0.8321	
Detemir once daily	77.28	0.8343	Ext. dominated
Glargine U300	94.00	0.8351	20,898.47
Glargine U100	114.71	0.8344	Abs. dominated
Degludec	145.84	0.8365	38,172.30

effective; while Determir and Glargine U100 were extended and absolutely dominated respectively. The ICER for Glargine U300 in comparison to NPH was USD 40,104.91 per QALY gained, while Degludec was USD 64,831.20 per QALY gained in comparison to Glargine U300. These ICERs are higher than a South African indicative CET of USD 3012.00 per DALY averted.

Sensitivity analysis

Results of the probabilistic sensitivity analyses are presented as scatter plots in Figs. 1 and 2. These are provided for Glargine U300 in comparison to NPH and for Degludec in comparison to Glargine U300 given that these are the only undominated alternatives. As shown, all model runs indicate positive incremental costs; however, there are many model runs indicating negative incremental effects, indicating the uncertainty regarding whether the long acting insulins are more effective than NPH. In terms of deterministic sensitivity analysis, the results of the 40% price reduction on private sector prices is shown in Table 4. Insulin glargine U300 remained the most cost-effective alternative to NPH with an ICER of USD 20,898.47 per QALY gained. Insulin degludec followed, with an ICER of USD 238,172.30 per QALY gained. Insulin detemir was extended dominated whilst Glargine U100 remained absolutely dominated, as expected, as its price was not affected by the price reduction since it was drawn from the Master Health Product List.

The price threshold analysis (see Fig. 3) shows that significant price reductions for the long acting insulins would be needed to achieve cost neutrality to NPH.

A cost-breakdown analysis shows that the pharmaceutical costs of NPH insulin once-daily are about USD 18 per patient per year, compared to insulin degludec, which costs about USD 232 (see Fig. 4). The costs incurred by

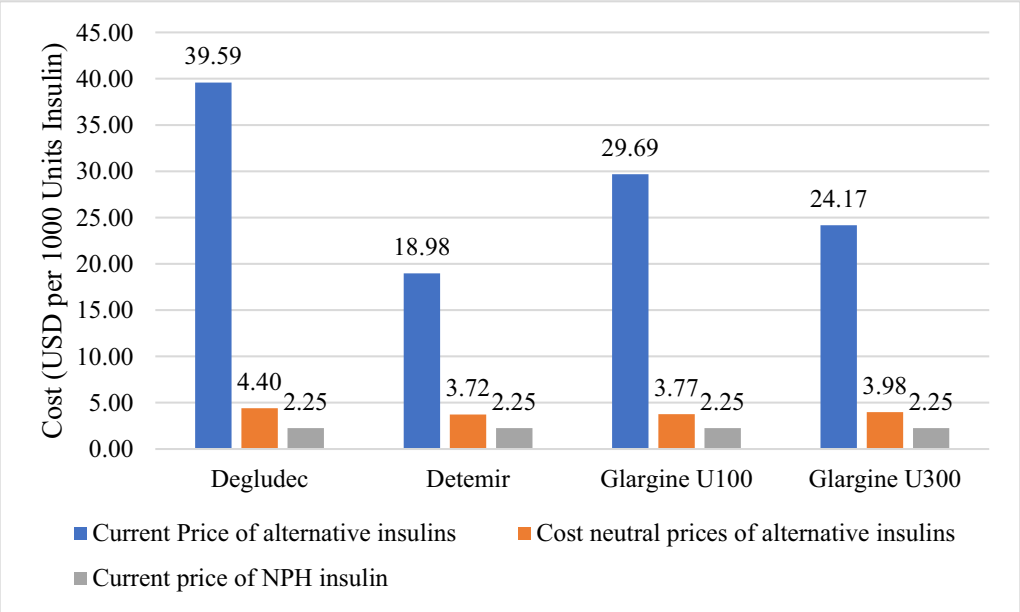

Fig. 3 Price threshold analysis at which insulin acquisition price results in cost neutrality

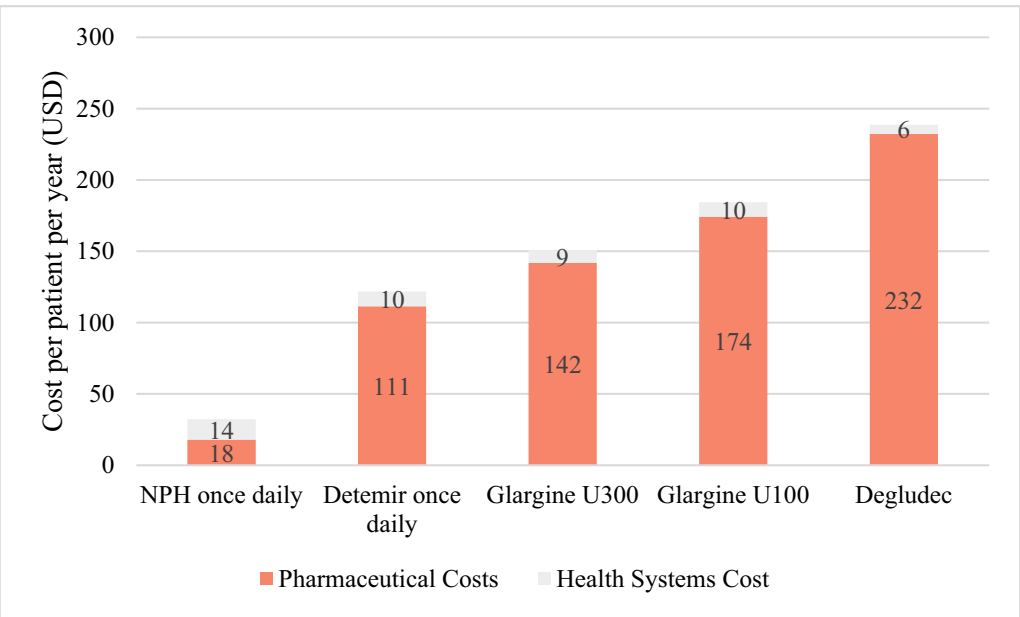

Fig. 4 Cost breakdown of each insulin per patient per year (USD, 2020–2021 prices)

the health system (i.e. inpatient care to manage adverse events) are about USD 14 for NPH insulin, which is higher than for insulin degludec, at about USD 6 per patient per year (Fig. 4). This is due to the relatively lower risk of severe hypoglycaemia assumed for insulin degludec in the model, which results in an estimated 0.05 fewer severe hypoglycaemic episodes per patient per year.

Discussion

This study aimed to inform the use of intermediate- and long-acting acting insulins in the management of adults with T1DM in South Africa by means of cost-utility analysis modelling.

After review of the available evidence, it was concluded that the insulins under review have few clinically significant differences. The evidence included, derived from systematic review of best available evidence, suggests no significant difference in key outcomes, including all-cause mortality and HbA1c control. Differences in reductions in harm, particularly hypoglycaemia, however, were noted in the NICE NMA [28].

The findings from this study indicate that the long-acting insulin analogues detemir, glargine U100, glargine U300 and degludec are not cost-effective compared to NPH insulin, with insulin detemir being extended dominated and insulin glargine U100 being absolutely dominated. Insulin glargine U300, followed by insulin degludec, proved to be the next cost-effective options in both the main and sensitivity analyses. The cost breakdown suggests that the primary driver of costs for the insulins under review are pharmaceutical costs, as opposed to hospitalisation costs. The point of cost-neutrality sits well below the current pricing of the long-acting insulin analogues.

Therefore, the recommendations from this analysis favour NPH insulin over the newer long-acting insulin analogues. This recommendation is in line with a recent clinical practice guideline recommendation made by the World Health Organization, that draws its evidence from a review by Tricco et al. [41, 42].

Disparities in recommendations from other economic evaluations, however, do exist and depend on study setting, insulin pricing, clinical effectiveness assumptions and the cost-effectiveness threshold used. For example, the recommendation of this study differs with the NICE NG17 clinical practice guideline recommendations for the United Kingdom that was based on evidence generated using many of the clinical efficacy and economic parameters utilised in this analysis [15]. A German economic evaluation found insulin glargine to be the most cost-effective option [21]. In addition, some studies comparing insulins degludec to glargine favoured insulin degludec, which was also not replicated in this review [11, 16].

In this economic evaluation, limitations arise from the input variables identified, some of which were drawn from small studies conducted in a setting not necessarily similar to South Africa. This includes the estimates of hospitalization following severe nocturnal hypoglycaemic events, which are likely overestimates of hospitalization rates in South Africa. The exclusion of

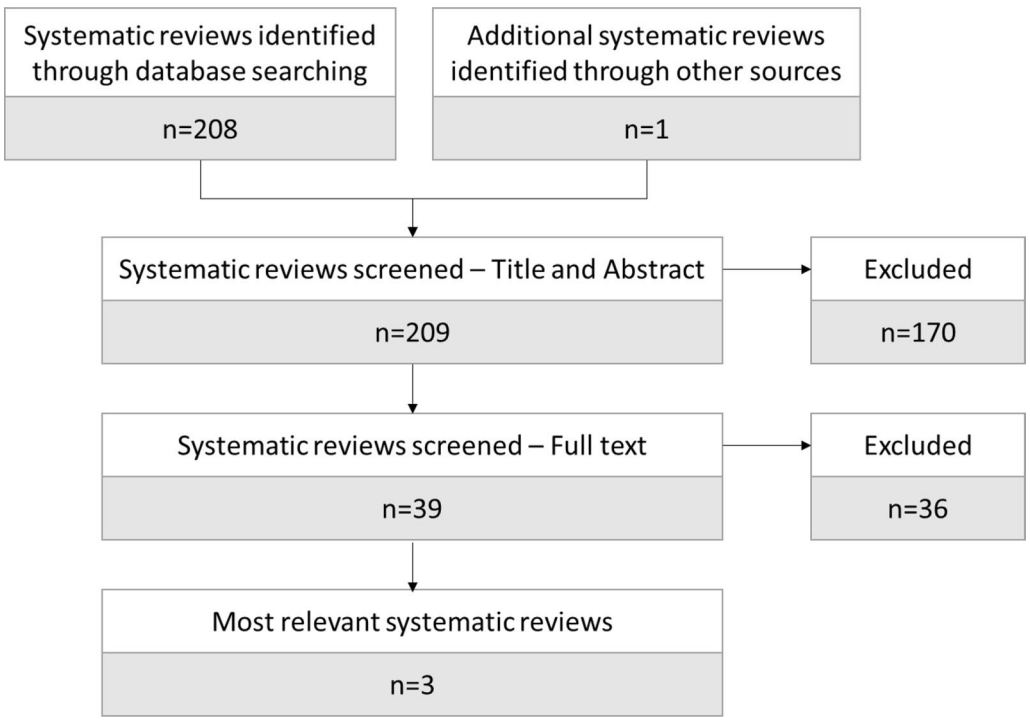

Fig. 5 PRISMA flow diagram

Table 5 Overview of systematic reviews

	Cochrane	NICE	Martin
Number of RCTs included	n = 26	n = 51	n = 31
Methods	Random effects model meta-analysis	Network Meta-analysis	Network Metanalysis
Search date	24 August 2020	Unclear. Most recent study from 2018	January 2021. Most recent study from 2018
Review question/scope	To compare the effects of long-term treatment with (ultra-)long-acting insulin analogues to NPH insulin (neutral protamine Hagedorn) or another (ultra-)long-acting insulin analogue in people with type 1 diabetes mellitus	Detemir versus degludec versus glargine versus NPH	First generation insulin analogues (detemir, NPH and glargine-U100) vs second generation insulin analogues (degludec-U100, glargine-U300)
Comparisons considered	Detemir vs NPH Glargine vs NPH Detemir vs Glargine Degludec vs Detemir Degludec vs Glargine	Detemir vs NPH: Detemir once daily vs NPH once daily Detemir once/twice daily vs NPH once/twice daily Detemir twice daily vs NPH twice daily Detemir vs Glargine-U100: Detemir twice daily vs Glargine once daily Detemir once/twice daily vs Glargine once daily Degludec-U100 once daily vs Glargine-U100 once daily: Degludec-U200 once daily vs Glargine-U300 once daily Degludec vs Glargine (concentration not defined) Degludec once daily vs Glargine twice daily Degludec once daily vs Glargine once daily Glargine-U100 vs NPH: Glargine-U100 once daily vs NPH four times daily Glargine-U100 once daily vs NPH once/twice daily Glargine-U100 once daily vs NPH twice daily Glargine-U100 once daily vs NPH twice or more daily Degludec-U100 once daily vs Detemir once daily Glargine-U300 once daily vs Glargine-U100 once daily Glargine-U100 once daily vs Glargine-U100 twice daily Detemir once daily vs Detemir twice daily:	:
Inclusion criteria	Included studies on children and subsequently also performed subgroup analyses on studies that included adults Only included studies > 24 weeks in length Included unpublished data (subgroup analysis also performed)	Excluded studies in which participants were younger than 18 Included studies of any duration	Only included adults Excluded studies if < 12 weeks duration. Main analysis reported > 24 weeks (main analysis), > 12 weeks reported as sensitivity analysis Had to report on at least one of the following: HbA1c, weight change, severe hypoglycaemia (event requiring assistance), nocturnal severe hypoglycaemia severe hypoglycaemia occurring at night defined at 23:00–06:00), confirmed hypoglycaemia (< 3 mmol/L), nocturnal confirmed hypoglycaemia Excluded participants with recurrent severe hypoglycaemia • Excluded if pregnant, child or breastfeeding

Table 5 (continued)

	Cochrane	NICE	Martin
Primary trial outcomes	All-cause mortality Health-related quality of life Severe hypoglycaemia Non-fatal myocardial infarction/stroke Severe nocturnal hypoglycaemia Serious adverse events HbA1c	HbA1c Nocturnal hypoglycaemia Severe hypoglycaemia DKA Time in target glucose range Time spent in hypoglycaemic range Quality of life including patient satisfaction Adverse events o Cancer o Injection site issues o Weight gain/loss o Hospital admissions o Frequency of hospitalization related to diabetes o Ambulance call-outs o Mental health outcomes (daily burden, fear of hypoglycaemia, treatment burden, diabetes burnout)	Efficacy: HbA1c Safety: Confirmed hypoglycaemia Confirmed nocturnal hypoglycaemia Severe hypoglycaemia Nocturnal severe hypoglycaemia Change in body weight

Table 6 Change in HbA1c as reported in the Cochrane evidence review

Intervention	Comparator	Mean difference (IV, random, 95% CI)
Detemir	NPH	−0.03 [−0.14, 0.07]
Glargine	NPH	−0.01 [−0.16, 0.13]
Detemir	Glargine	−0.01 [−0.13, 0.12] (combined)
Degludec	Detemir	0.00 [−0.18, 0.18]
Degludec	Glargine	0.11 [0.00, 0.21]

Reported values are for adult subgroup analysis. Where this subgroup analysis was not available, the analysis group is indicated in parentheses.

Table 7 Change in HbA1c as reported in the evidence review by Martin et al.

Intervention	Comparator	Mean difference (IV, random, 95% CI)
NPH	Degludec-U100	−0.08 (−0.05, 0.22)
Glargine-U100	Degludec-U100	0.00 (−0.11, 0.10)
Detemir	Degludec-U100	−0.01 (−0.14, 0.12)
NPH	Glargine-U300	−0.02 (−0.19, 0.24)
Glargine-U100	Glargine-U300	−0.06 (−0.25, 0.13)
Detemir	Glargine-U300	−0.07 (−0.29, 0.16)

long term sequalae of diabetes such as HbA1c and all-cause mortality, on the grounds of available evidence selected, is a major limitation as slight differences in these outcomes may drastically impact cost-effectiveness. Furthermore, given the lack of an agreed-upon CET for South Africa, the ICERs are interpreted in relation to an indicative CET. However, given the large difference in ICERs in comparison to CET, the overall interpretation of cost-effectiveness findings is unlikely to change.

Africa and South Africa's diabetic population have demonstrated varying utilisation rates of insulin, making it difficult for the model to accurately reflect diabetic care. Regarding dosing and frequency, large multicentre study based on a German/Austrian database concluded that, on average, NPH insulin was used 1.9 times a day for T1DM patients. The study further identified that the mean adjusted daily NPH dose was 0.36 IU/kg, lower than the recommended dosing of 0.5–1 IU/kg outlined by the standard treatment guidelines [10, 43]. However, a smaller study, by Mbanya et al., conducted across the African continent, which included 49 patients with T1DM in South Africa, found that on average, across all countries, total daily dose of basal and postprandial insulin amounted to 0.78 IU/kg [44]. In a South African study by Sehloho and van Zyl, the authors found that the mean basal and postprandial insulin dose was 59.8 (standard deviation of 36.7) IU/day [45].

Furthermore, patient practices may vary in the insulin regimen used. Despite the recommendation by the South African EML that the basal bolus regimen be employed in the management of T1DM, a small South African study by Sehloho and van Zyl found that a mere 15.2% of participants used the basal bolus regimen whereas the remainder used the alternative, namely the biphasic regimen [45]. This result was not replicated in the study by Mbanya et al., where the authors found that roughly 33% of T1DM included in the study utilized the biphasic insulin regimen. The alternative treatment regimen, the biphasic regimen, consists of twice daily "pre-mixed" or

Table 8 Change in HbA1c as reported in the NICE evidence review

	Detemir twice daily	NPH twice daily	Detemir once daily	NPH once daily	Detemir once/twice daily	NPH once/twice daily	Glargine U100 once daily	Degludec U100 once daily	NPH twice or more daily	Glargine U300 once daily	Glargine twice daily
Detemir twice daily		−0.09 (−0.018, 0.01)	−0.10 (−0.24, 0.04)								
NPH twice daily	0.09 (−0.01, 0.2)						0.19 (−0.17, 0.55)				
Detemir once daily	0.08 −0.10, 0.27)	0.01 (−0.22, 0.19)		−0.12 (−0.25, 0.02)				0.00 (−0.18, 0.18)			
NPH once daily	0.20 (−0.06, 0.45)	0.10 (−0.17, 0.37)	0.11 (−0.06, 0.29)								
Detemir once/twice daily	0.00 (−0.31, 0.30)	−0.10 (−0.41, 0.21)	−0.09 (−0.37, 0.20)	−0.20 (−0.53, 0.13)		0.30 (−0.35, 0.95)	0.00 (−0.14, 0.14)				
NPH once/twice daily	−0.01 (−0.29, 0.25)	−0.11 (−0.39, 0.15)	−0.10 (−0.35, 0.15)	−0.21 (−0.52, 0.09)	−0.01 (−0.20, 0.17)		0.01 (−0.10, 0.13)				
Glargine U100 once daily	−0.02 (−0.28, 0.23)	0.12 (−0.38, 0.13)	−0.10 (−0.34, 0.12)	0.22 (0.51, 0.07)	−0.02 (−0.19, 0.15)	−0.01 (−0.10, 0.09)		−0.07 (−0.17, 0.03)	0.00 (−0.23, 0.23)	−0.02 (−0.11, 0.06)	0.00 (−0.53, 0.53)
Deglu-dec U100 once daily	0.06 (−0.19, 0.30)	0.04 (−0.29, 0.21)	−0.01 (−0.23, 0.18)	−0.14 (−0.41, 0.13)	0.06 (−0.15, 0.27)	0.07 (−0.08, 0.23)	0.08 (−0.05, 0.21)				
NPH twice or more daily	−0.02 (−0.40, 0.34)	−0.12 (−0.49, 0.25	−0.11 (−0.46, 0.25)	−0.22 (−0.62, 0.17)	−0.02 (−0.34, 0.30)	−0.01 (−0.30, 0.28)	0.00 (−0.28, 0.27)	0.08 (−0.39, 0.22)			
Glargine U300 once daily	−0.01 (−0.29, 0.26)	−0.10 (−0.39, 0.17)	−0.09 (−0.35, 0.16)	−0.21 (−0.52, 0.10)	0.00 (−0.21, 0.20)	0.01 (−0.14, 0.15)	0.01 (−0.10, 0.13)	−0.07 (−0.24, 0.10)	0.02 (−0.28, 0.31)		
Glargine twice daily	−0.02 (−0.63, 0.57)	0.12 (−0.72, 0.48)	−0.10 (−0.70, 0.48)	−0.22 (−0.84, 0.39)	−0.02 (−0.59, 0.55)	−0.01 (−0.56, 0.54)	0.00 (−0.54, 0.54)	−0.08 (−0.64, 0.48)	0.00 (−0.28, 0.31)	−0.01 (−0.57, 0.54)	

Table 9 Cochrane review all-cause mortality results

Intervention	Comparator	Risk ratio (M-H, fixed, 95% CI)
Detemir	NPH	4.97 [0.79, 31.38]
Glargine	NPH	0.14 [0.00, 6.98]
Detemir	Glargine	No deaths
Degludec	Detemir	No deaths
Degludec	Glargine	1.34 [0.15, 11.93] (combined)

Reported values are for adult subgroup analysis. Where this subgroup analysis was not available, the analysis group is indicated in parentheses.

biphasic insulin, which is a mixture of intermediate- and short-acting insulin.

Although the literature suggests that the recommended treatment regimen, dosing and frequency is most often not utilized by patients, similar total amounts of basal insulin are likely to be utilised across both the recommended and alternative treatment regimens. There may be significant differences between the two regimens with regards to clinical outcomes, which should be a topic for further research. Furthermore, research investigating long-term outcomes of diabetic control between different long-acting insulins in a local context is needed to fully inform clinical practice.

Conclusion

This review has highlighted the need for robust clinical effectiveness evidence in economic models. This review recommends intermediate-acting NPH insulin, the *status quo,* over long-acting insulins as the basal insulin in the management of adult T1DM patients in South Africa receiving care in the public health sector.

Appendix 1: Literature search

Description of systematic reviews selected for inclusion

From the database search conducted on 8 March 2022, 208 systematic reviews were identified for screening. One additional systematic review was identified through checking reference lists of eligible reviews and clinical guidelines. After duplicate removal, and title and abstract review, 39 systematic reviews were selected for full text review. Of these, 8 eligible systematic reviews were identified for further study composition comparison, from which three systematic reviews were selected for inclusion in this report.

The three studies were selected as they most closely aligned with the review question, included relevant primary studies, were published recently (in past two years), and were conducted using transparent methods. The three studies included were a Cochrane review by Hemmingsen et al., a review conducted by NICE to inform a clinical guideline recommendation, and a review conducted by Martinson et al. [5–7]. The quality of these three systematic reviews were appraised (in duplicate) using the AMSTAR tool and were found to be of good quality (Fig. 5).

Appendix 2: Study composition analysis

Description of systematic reviews

We identified three up to date systematic reviews and meta-analyses of good quality that compared the efficacy and safety of insulin glargine, insulin detemir, insulin degludec, and NPH. An overview of the three systematic reviews is presented in Table 5, and the characteristics of all studies included in each reported in Table 6.

Appendix 3: Literature review findings and interpretation

All three reviews identified little difference between the clinical effectiveness of long-acting insulin analogues detemir, glargine and degludec compared to one another and compared to NPH insulin.

These insulins were shown to be noninferior with regards to primary outcomes HbA1c and mortality risk.

HbA1c

All three reviews found no significant differences in HbA1c control between long-acting insulin analogues and NPH insulin (Tables 7, 8).

Mortality

The Cochrane review was the only review to report on differences in mortality. No significant differences were found (Table 9).

Quality of life

Health-related quality of life was shown to lack sufficient data or not reported on.

Abbreviations

T1DM	Type 1 Diabetes Mellitus
NPH	Neutral Protamine Hagedorn
QALY	Quality-Adjusted Life Year
ICER	Incremental Cost-Effectiveness Ratio
SDG	Sustainable Development Goal
NCD	Non-Communicable Disease
DALY	Disability-Adjusted Life Year
NICE	National Institute for Health and Care Excellence
HRQoL	Health-Related Quality of Life
CUA	Cost-Utility Analysis
USD	United States Dollar
ZAR	South African Rand
CET	Cost-Effectiveness Threshold
NMA	Network Meta-Analysis
UK	United Kingdom
MHPL	Master Health Product List
MPR	Medicines Price Registry

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Author contributions
M.V. performed the search for literature from which model inputs were derived. M.V. and S.C. built the Markov Model accordingly. M.V. was primarily responsible for the writing of the manuscript. S.C. provided extensive input and assisted with editing the final manuscript. All authors read and approved the manuscript.

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Availability of Data and Materials
The Markov Model TreeAge Pro Microsoft Excel file has been attached with this submission.

Declarations

Ethics approval and consent to participate
Secondary data was used throughout the study and ethics approval was granted by the University of Cape Town Human Research Ethics Committee (HREC REF: 670/2021).

Competing Interests
The authors declare no competing interests.

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References

1. United Nations. NCD Countdown 2030: worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4. Lancet. 2018;392(10152):1072–88.
2. World Health Organization. Global report on diabetes. Geneva: World Health Organization; 2016.
3. Global Burden of Disease Study. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204–22.
4. Gouda HN, Charlson F, Sorsdahl K, Ahmadzada S, Ferrari AJ, Erskine H, et al. Burden of non-communicable diseases in sub-Saharan Africa, 1990 & 2013: results from the Global Burden of Disease Study. Lancet Glob Health. 2019;7(10):e1375–87.
5. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. Lancet. 2009;374(9693):934–47.
6. International Diabetes Federation. Brussels. 2020. Available from: https://www.idf.org/our-network/regions-members/africa/members/25-south-africa.
7. Global Health Data Exchange. Prevalence of Type 1 Diabetes in South Africa 2019 Available from: http://ghdx.healthdata.org/gbd-results-tool.
8. Ipsen E, Hemmingsen B, Petersen L, Metzendorf M-I, Richter B. Definitions and reporting of hypoglycaemia in trials of long-acting insulin analogues in people with type 1 diabetes mellitus. Cochrane Database Syst Rev. 2020;2020(12): CD013824.
9. South African Health Products Regulatory Authority. Registered Health Products.
10. South African National Department of Health. Standard Treatment Guidelines and Essential Medicines List for South Africa. Hospital Level, Adults. PHC Chapter 9: Endocrine Conditions. 7 ed. South Africa: National Department of Health 2020.
11. All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Insulin degludec (Tresiba®) 100 units/ml and 200 units/ml solution for injection in prefilled pen (FlexTouch®) or 100 units/ml solution for injection in cartridge (Penfill®). Reference number: 3158. 2016.
12. All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Insulin glargine (Abasaglar®) 100 units/ml solution for injection. Reference number: 2307. 2015.
13. Tran K, Banerjee S, Li H, Cimon K, Daneman D, Simpson S, et al. Long-acting insulin analogues for diabetes mellitus: Meta-analysis of clinical outcomes and assessment of cost-effectiveness. York (UK): Centre for Reviews and Dissemination; 2007.
14. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine [Internet]. NIHR Health Technology Assessment programme. 2007.
15. National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management. Insulin therapy. Economic model report. United Kingdom; 2021.
16. Evans M, Wolden M, Gundgaard J, Chubb B, Christensen T. Cost-effectiveness of insulin degludec compared with insulin glargine in a basal-bolus regimen in patients with type 1 diabetes mellitus in the UK. J Med Econ. 2015;18(1):56–68.
17. Valentine WJ, Jendle J, Saraheimo M, Thorsteinsson B, Pollock RF, Lammert M. Evaluating the cost-effectiveness of reduced mild hypoglycaemia in subjects with Type 1 diabetes treated with insulin detemir or NPH insulin in Denmark, Sweden, Finland and the Netherlands. Diabet Med. 2012;29(3):303–12.
18. Valentine WJ, Palmer AJ, Erny-Albrecht KM, Ray JA, Cobden D, Foos V, et al. Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine, and NPH. Adv Ther. 2006;23(2):191–207.
19. Palmer AJ, Valentine WJ, Ray JA, Foos V, Lurati F, Smith I, et al. An economic assessment of analogue basal–bolus insulin versus human basal–bolus insulin in subjects with type 1 diabetes in the UK. Curr Med Res Opin. 2007;23(4):895–901.
20. Valentine WJ, Van Brunt K, Boye KS, Pollock RF. Treating type 1 diabetes mellitus with a rapid-acting analog insulin regimen vs. regular human insulin in Germany: a long-term cost-effectiveness evaluation. Appl Health Econ Health Policy. 2018;16(3):357–66.
21. Pfohl M, Schädlich PK, Dippel FW, Koltermann KC. Health economic evaluation of insulin glargine vs NPH insulin in intensified conventional therapy for type 1 diabetes in Germany. J Med Econ. 2012;15(Suppl 2):14–27.
22. Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. Can Med Assoc J. 2009;180(4):400.
23. Grima DT, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. Pharmacoeconomics. 2007;25(3):253–66.
24. Wilkinson T, Wilkinson M. Health Technology Assessment Methods Guide. To inform the selection of medicines to the South African National Essential Medicines List. South Africa. https://www.health.gov.za/wp-content/uploads/2024/04/HTA-Methods-Guide_FINAL_Sep-2023.pdf.2021.
25. X-Rates. Historical monthly average exchange rates. Available from: https://www.x-rates.com.
26. TreeAge Software. TreeAge Pro, R1. Williamstown, MA; Available at http://www.treeage.com. 2021.
27. Edoka IP, Stacey NK. Estimating a cost-effectiveness threshold for health care decision-making in South Africa. Health Policy Plan. 2020;35(5):546–55.
28. National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management: evidence reviews for long-acting insulins for optimal diabetic control. In: Service NH, editor. United Kingdom; 2021.
29. Heller S, White D, Lee E, Lawton J, Pollard D, Waugh N, et al. A cluster randomised trial, cost-effectiveness analysis and psychosocial evaluation of insulin pump therapy compared with multiple injections during flexible intensive insulin therapy for type 1 diabetes: the REPOSE Trial. Health Technol Assess. 2017;21(20):1–278.
30. U.S. Food and Drug Administration. Drug labelling information: LANTUS® (insulin glargine injection) for subcutaneous injection Initial U.S. Approval: 2000. 2018.

31. U.S. Food and Drug Administration. Drug labelling information: LEVEMIR® (insulin detemir injection), for subcutaneous use Initial U.S. Approval: 2005. 2019.
32. U.S. Food and Drug Administration. Drug labelling information: TOUJEO (insulin glargine injection) U-300, for subcutaneous use Initial U.S. Approval: 2015. 2015.
33. U.S. Food and Drug Administration. Drug labelling information: TRESIBA® (insulin degludec injection), for subcutaneous use Initial U.S. Approval: 2015. 2015.
34. National Department of Health. Master Health Product List of South Africa. South Africa. 2020.
35. National Department of Health. Medicines Price Registry. South Africa.2019.
36. Hammer M, Lammert M, Mejías SM, Kern W, Frier BM. Costs of managing severe hypoglycaemia in three European countries. J Med Econ. 2009;12(4):281–90.
37. Naomi Massyn CD, Noluthando Ndlovu, Thesandree Padayachee. District Health Barometer. Health Systems Trust. 2019/20.
38. Evans M, Khunti K, Mamdani M, Galbo-Jørgensen CB, Gundgaard J, Bøgelund M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. Health Qual Life Outcomes. 2013;11:90.
39. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The impact of diabetes-related complications on preference-based measures of health-related quality of life in adults with type I diabetes. Med Decis Making. 2016;36(8):1020–33.
40. Zhou T, Guan H, Wang L, Zhang Y, Rui M, Ma A. Health-related quality of life in patients with different diseases measured with the EQ-5D-5L: A systematic review. Front Public Health. 2021;9: 675523.
41. Tricco AC, Ashoor HM, Antony J, Beyene J, Veroniki AA, Isaranuwatchai W, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: Systematic review and network meta-analysis. BMJ. 2014;349: g5459.
42. World Health Organization (WHO). Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non- pregnant adults with diabetes mellitus. Geneva: WHO; 2018.
43. Laubner K, Molz K, Kerner W, Karges W, Lang W, Dapp A, et al. Daily insulin doses and injection frequencies of neutral protamine hagedorn (NPH) insulin, insulin detemir and insulin glargine in type 1 and type 2 diabetes: a multicenter analysis of 51 964 patients from the German/Austrian DPV-wiss database. Diabetes Metab Res Rev. 2014;30(5):395–404.
44. Mbanya JC, Naidoo P, Kolawole BA, Tsymbal E, McMaster A, Karamchand S, et al. Management of adult patients with type 1 diabetes mellitus in Africa: A post-hoc cohort analysis of 12 African countries participating in the International Diabetes Management Practices Study (Wave 7). Medicine (Baltimore). 2020;99(25): e20553.
45. Sehloho TSA, Van Zyl DG. Effects of exogenous human insulin dose adjustment on body mass index in adult patients with type 1 diabetes mellitus at Kalafong Hospital, Pretoria, South Africa, 2009–2014. S Afr Med J. 2017;107(6):528–34.

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