
# A Cost-Utility and Budget Impact Analysis of long-acting insulin analogues (detemir, glargine and degludec) for the treatment of adults with type 1 diabetes in South Africa.

**MPH specialising in Health Economics**

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**VRRMAR001**

Dissertation submitted to the University of Cape Town for the degree of Master of Public Health, specialising in Health Economics in part fulfilment of the MPH degree.

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## Dedication

To my parents, Stephen and Sabine, for their unwavering support.

**Declaration**

I, *Mark Trevor Verryn*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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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 and has received much research and development over the years. In South Africa, intermediate-acting Neutral Protamine Hagedorn (NPH) insulin has been the mainstay basal insulin recommended in the public sector. Newer (ultra) long-acting insulin analogues, however, have subsequently been approved for use. Cost-utility and budget impact analyses of the newer long-acting insulin analogues detemir, glargine and degludec have yet to be performed in the South African public health sector context.

**Methods:** A systematic search for clinical evidence was performed to inform the economic evaluation. A cost-utility analysis was carried out utilising Markov modelling. Seven comparators were modelled representing the various insulin types and treatment regimens. For each comparator, three Markov states were created, one in which no complications occurred and another two states representing nocturnal and daytime hypoglycaemic events respectively. Three scenarios were modelled in order to capture the variable rates of complications reported in the clinical evidence. Quality-Adjusted Life Years per patient year was the health outcome utilised. Costs were included as South African Rands and then converted to United States dollars. A cost-effectiveness threshold range appropriate for the South African context was used to assess value for money. Thereafter, a budget impact analysis was conducted.

**Results:** Three systematic reviews were identified in the systematic search for inclusion in this study. Subsequently, three scenarios were modelled in order to capture the clinical significance identified in the three systematic reviews. All three models favoured NPH insulin over the alternatives, as NPH insulin dominated most other insulins, barring insulin detemir, insulin glargine-U300 and insulin degludec. Insulin detemir was the most cost-effective option of the alternatives to NPH insulin (ICER of 10,783.75 USD/QALY). However, insulin detemir was still not cost-effective in relation to South Africa's cost-effectiveness threshold (CET 1,175 - 8,909 USD/QALY). The NPH insulin twice daily regimen was also found to dominate the NPH once daily regimen.

**Conclusions:** 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. Further research and consideration could be made for the use of NPH insulin twice daily, as opposed to once daily.

# Acknowledgements

**Associate Professor Susan Cleary**: Primary supervision for this dissertation, particularly relating to economic evaluation performed.

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Table of Contents

# Part A: Protocol

# 1. Background

## 1.1 Epidemiology

In response to the overwhelming premature mortality attributed to Non-Communicable Disease (NCD) worldwide, the United Nations outlined Sustainable Development Goal (SDG) target 3.4, which aims to reduce by one third the premature mortality attributable to NCDs by 2030, compared to 2015 estimates (1). Diabetes is considered one of the four priority NCDs that ought to be targeted by world leaders (2).

Diabetes mellitus is an NCD characterised by poor blood glucose, or glyaemic, control. There are many forms of diabetes mellitus, the most prevalent being type 1 (T1DM) and type 2 (T2DM) diabetes mellitus. T1DM is characterised by the absence or deficiency of insulin, a hormone produced by the pancreas that allows glucose to enter cells to be used for metabolism. In contrast, T2DM is not characterised by insulin deficiency but rather by insulin resistance and does not fall in the scope of this review. In 2019, the burden of T1DM in South Africa is estimated to be around 130 000 for the adult population above 20 years of age, which equates to a rate of about 3.7 per 1000 adult individuals (3).

Diabetes accounted for 2.8% of all disability-adjusted life years (DALYs) globally in 2019, making it the 8$^{th}$ leading cause, which represents a climb from being the 20$^{th}$ leading cause in 1990 (1.1% of global DALYs) (4). The increasing trend of DALYs attributed to diabetes can also be appreciated in sub-Saharan Africa (SSA), where diabetes was responsible for 623 DALYs per 100 000 population in 2017, representing an 8.4% increase from 1990 (5). In South Africa specifically, an estimated 12.8% of adults live with diabetes, with premature adult deaths attributed to diabetes having increased by 38% between 1999 and 2006 (6, 7). In response to these trends, the *Lancet Diabetes and Endocrinology* Commission on Diabetes in SSA suggests that diabetes in SSA requires effective use of limited resources to screen and manage the disease (8).

## 1.2 Complications

Complications of poorly controlled blood glucose levels in T1DM can have severe impacts on health, both in the acute and chronic setting. Acute complications primarily consist of diabetic ketoacidosis (DKA), a condition arising from the need to utilise lipolysis, or fat breakdown, as a means of energy production, in the presence of hyperglycaemia, i.e. high blood glucose,

resulting in a life-threatening acidotic state. Lifelong poor glycaemic control can lead to a host of chronic complications that lead to an increased all-cause mortality and reduction in quality of life. These are generally categorised by microvascular and macrovascular complications. Microvascular complications include diabetic retinopathy, nephropathy and neuropathy. In other words, diabetes is known to cause blindness, kidney failure as well as decreased functioning of nerves. Macrovascular complications result in increased risk of cerebrovascular events, myocardial infarction and peripheral vascular disease. In addition to these, diabetic patients are known to have worse clinical outcomes when admitted for medical and surgical treatment of many conditions unrelated to diabetes.

## 1.3 Physiology of glycaemic control

Insulin is an anabolic hormone that, under normal physiology, is produced by the beta-islet cells of the pancreas and acts on the tyrosine kinase receptor pathway in order to allow the uptake of glucose. Through uptake, glycaemic levels are decreased, maintaining homeostasis through a tightly regulated range of blood glucose. In healthy individuals, there is a constant basal secretion of insulin with spikes in insulin secretion occurring in response to raised glucose levels, usually occurring after meals (see Figure 1).

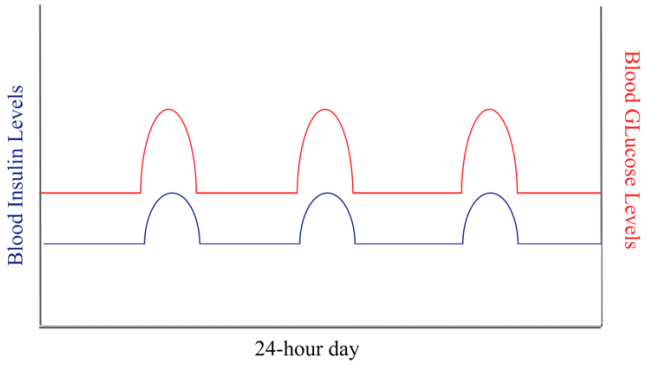



**Figure 1.** Conceptual depiction of the relationship between insulin and glucose levels.

## 1.4 Management

T1DM is a congenital condition of insulin deficiency, postulated to be secondary to autoimmune pancreatic beta-islet cell destruction of unknown cause, without an existing preventative strategy, requiring early detection and management. Management of T1DM consists of daily exogenous insulin administration in order to allow glucose, a major source of energy for cellular function, to be taken up from blood into cells. There are many forms of

exogenous insulin, which can be categorised by their pharmacokinetics. In particular, the time to onset of action, peak of action and total duration of action are of importance (see Table 1). The variation in the properties of insulin are born out of the necessity to imitate physiologic control of blood glucose levels. This includes the need to replicate basal insulin levels alongside spikes in insulin corresponding to meals, as outlined previously. However, considerations must be made of the adverse drug reactions of insulin. Of particular concern is that of iatrogenic hypoglycaemia, in which an inappropriately high dose of insulin causes a dangerous drop in glucose levels, leading to associated complications including the risk of death. Furthermore, severe nocturnal hypoglycaemia can also occur with insulin use, where potentially dangerous drops in blood glucose occur at night, causing significant distress. Since T1DM patients require lifelong insulin given mostly via an injection, minor side-effects of exogenous insulin administration, such as injection discomfort and fat build up, or lipohypertrophy, at injection sites, should also be considered. Therefore, an ideal insulin treatment regime consist of the minimum number of daily insulin subcutaneous injections required to achieve a basal level of insulin, with appropriate increases in insulin concentration occurring soon after meals, in order to maintain glycaemic control, all the while avoiding adverse drug events such as low blood glucose (hypoglycaemic) episodes. To monitor glycaemic control, frequent blood-glucose tests (either laboratory or finger-prick) can be employed to evaluate short-term control, or the percentage glycosylated haemoglobin A1, known as HbA1c, can be evaluated to monitor long-term control, specifically for an indication of glucose control over the preceding 3 months.

**Table 1**. Insulin types and pharmacokinetics (9-11).

| **Insulin Type** | **Name** | **Onset of action (hours)** | **Peak of action (hours)** | **Duration of action (hours)** |
|---|---|---|---|---|
| Short-acting | Regular | 0.5 | 2-5 | 5-8 |
| Intermediate-acting | NPH | 1-3 | 6-12 | 16-24 |
| Biphasic (mixture) | Regular+NPH | 0.5 | 2-12 | 16-24 |
| Long-acting | Detemir | 3-4 | 6-8 | <24 |
| Long-acting | Glargine | - | No pronounced peak | >24 |
| Long-acting | Degludec | - | 9 | 72-96 |

### 1.5 T1DM Treatment Guidelines in South Africa

The Standard Treatment Guidelines and Essential Medicines List (EML) for South Africa (2020) details the following goals for the management of T1DM: maintenance of glycaemic control within acceptable limits, prevention of chronic complications and prevention of acute complications. It also outlines the insulin preparations under recommendation, namely regular short-acting insulin, intermediate-acting NPH insulin and a combination of both as recommendations for the treatment of T1DM (9). The pharmacokinetics, or how these drugs are metabolised by the body, are outlined in Table 1. The recommendation stands that all T1DM be managed on a basal bolus regimen, consisting of pre-meal short-acting insulin (actrapid and the likes) and bedtime intermediate-acting insulin (NPH). The total recommended daily dose of insulin is 0.6 units/kg body weight. Of this total daily insulin dose, 40-50% is made up by the intermediate-acting bedtime basal dose, whereas the remainder is divided by the pre-meal short-acting insulin doses.

Although this treatment regimen has proven useful and effective, it is not without adverse effects. The effectiveness of using different types of insulin to manage T1DM can be assessed by evaluating the management outcomes outlined above, namely, glycaemic control and prevention of complications (acute and chronic).

The intermediate-acting insulin that is currently recommended (NPH insulin) was first developed in 1946 and has since been widely used. More recently, however, new long-acting insulin analogues have been approved by the South African Health Products Regulatory Authority (SAHPRA), with detemir being approved in 2005, glargine being approved in 2000 and degludec being approved in 2015. Therefore, in the interest of South African T1DM patients, these medications ought to be reviewed for inclusion in the EML. Without an evidence-based economic review, however, sound equitable judgment cannot be passed.

## 2. Aims and Objectives

*Aim*

The aim of this research is to assess the cost-utility and budget impact of long-acting insulin analogues (detemir, glargine and degludec) compared to the current standard of care of

intermediate-acting insulin Neutral Protamine Hagedorn (NPH Insulin) for Type 1 Diabetics in South Africa.

*Objectives*

The objectives are to compile an economic evaluation, consisting of:

- clinical and economic evidence appraisal,
- cost-utility analysis and budget impact analysis

# 3. Technology Details

## 3.1 Anatomical Therapeutic Classification

Glargine ATC code: A10AE04

Detemir ATC code: A10AE05

Degludec ATC code: A10AE06

## 3.2 Formulation/s available in South Africa

Glargine

The active substance is insulin glargine. Each millilitre contains 3.64mg insulin glargine, equating to 100 U human insulin. Metacresol (2.7 mg/ml) preservative is present. Further ingredients include: glycerol, hydrochloric acid, sodium hydroxide, water and zinc oxide. The 10ml vial contains polysorbate 20 as an additional stabiliser (12).

Detemir

Detemir is a clear, colourless, aqueous, neutral sterile solution. Each millilitre of detemir contains 100 U (14.2 mg/mL) insulin detemir. In addition, it contains 65.4 mcg zinc, 2.06 mg metacresol, 30.0 mg mannitol, 1.80 mg phenol, 0.89 mg disodium phosphate dihydrate, 1.17 mg sodium chloride and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. Detemir has a pH of approximately 7.4 (10).

Degludec

Each mL contains 100 units (600 nmol) of insulin degludec and glycerol (19.6 mg), metacresol (1.72 mg), phenol (1.50 mg), zinc (32.7 mcg), and Water for Injection, USP.

# 4. Conceptual Framework

Disparities in health care, be it access, quality or financial risk protection, have resulted in the development of the concept of Universal Health Coverage (UHC), which aims to address these disparities by "ensuring that all people can use the promotive, preventative, curative, rehabilitative and palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship" (13).

Achieving UHC is multi-faceted and complex. A proposed intermediate objective to achieving UHC is efficiency of health systems. A target of efficiency in healthy systems are the technologies they employ, including pharmaceuticals. Therefore, one tool that has been promoted by the World Health Organization (WHO) to move further towards UHC is Health Technology Assessment (HTA) (14, 15). HTA is "a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle" and its purpose "is to inform decision-making in order to promote an equitable, efficient, and high-quality health system" (16)1. HTA allows for a formalised evaluation process to be brought into the decision-making space when it comes to health technologies. This is of particular importance in South Africa, as the proposed National Health Insurance (NHI) aims to cover total health care costs for the whole population for a selected number of health services in order to step closer to attaining UHC. Deciding which health care services or health technologies to include in the NHI ought to be determined on economic evaluation to ensure efficiency and equity.

There are many forms of economic evaluation, that can aid in decision making. In this study, a cost-utility analysis (CUA) will be performed. A (CUA) employs multi-dimensional outcomes, such as Quality-Adjusted Life Years (QALYs) or Disability-Adjusted Life Years (DALYs). In other words, a CUA is an economic evaluation in which two interventions' costs and health gains are compared. Through this, the cost per unit health gained by the intervention under review, compared to the *status quo* or a comparator intervention, can be established. Therefore, a CUA aids in representing economic considerations in decision-making surrounding the implementation of a new health technology.

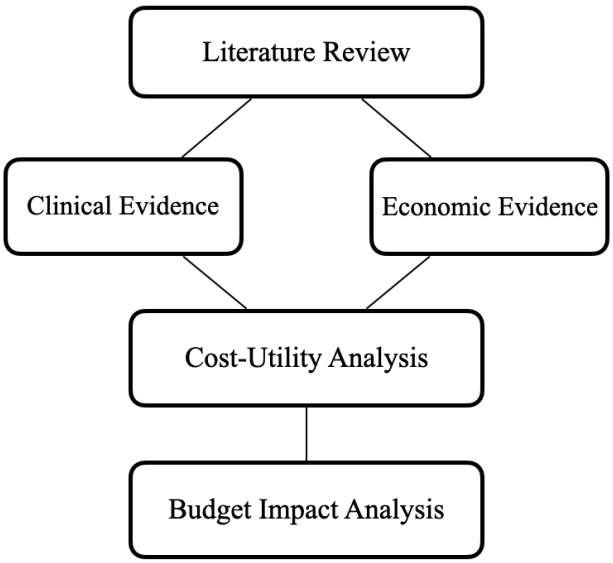
Each country has a limited health care budget to expend, as is well understood in the study of scarcity. With budgetary constraints in mind, health authorities are charged with the

responsibility to utilize funds most effectively. The established incremental cost-effectiveness ratio (ICER) in the analysis of health technologies under review, however, must be able to inform a decision based on relative criteria. One such proposed criteria is the cost-effectiveness threshold (CET). The CET is considered the measure of the marginal productivity of the health care system in question. The CET provides a value to what one would consider a cut-off for the inclusion or exclusion of a health technology in a health care system.

Determining the cost-effectiveness of an intervention under consideration, however, is not sufficient to determine how readily it may be implemented in a resource-constrained environment, such as South Africa's public health care sector. In addition to cost-effectiveness, budget impact can be evaluated. This can be done through the use of a Budget Impact Analysis (BIA). Through a BIA, the expected change in health care expenditure through the implementation of a new intervention can be evaluated. This study aims to incorporate a BIA in order to aid in informing the relevant decision-making authorities.

## 5. Proposed study design

The following proposed study design is structured according to the Health Technology Assessment Guidelines by Wilkinson and Wilkinson, focusing only on the economic evaluation component of the guide (17).



## 5.1 Review and appraise clinical evidence

In order to recommend a health technology, clinical evidence needs to be appraised and reviewed. From a brief literature search, it is evident that there are ample strong studies available to draw from, including a Cochrane review published in 2021 on the insulin regimens and their comparators under consideration for T1DM (18).

## 5.2 Economic Evidence

*Pharmaceutical costs* (17)

Pharmaceutical costs of both the interventions and comparators should be investigated. These costs include the unit pricing and additional economic costs of implementation of the proposed insulins. This data can be obtained from the Master Health Product List if possible, otherwise the Single Exit Price (SEP) used in the private health care sector may be used. In addition, inpatient and outpatient unit costs can be drawn from the District Health Barometer (DHB), in which the cost per visit and cost per inpatient day can be obtained. If neither of these sources of costing data are available, a pricing analysis may need to be done. Medication costs should include the cost of a dose, as stipulated by the South African Health Products Regulatory Authority (SAHPRA), with costs of wastage accounted for. If drug doses are not uniform (e.g. based off the user's weight) then an appropriate average should be sought from literature. These costs should be presented as the average cost per patient per day as well as the cost to treat for a year, as T1DM is a chronic health condition.

*Costs of T1DM Management*

Unit costs must be translated into utilisation costs. This includes costs surrounding inpatient care, calculated as inpatient days per year multiplied by cost per inpatient day, as well as outpatient costs, calculated in a similar fashion. Estimates for inpatient and outpatient days per year for T1DM will be drawn from literature.

*Summary of HTA agency decisions*

A review and summation of relevant HTA agency decisions will be conducted to establish current practice in other institutions.

## 5.3 Rapid systematic search

### 5.3.1 Search approach

This review follows an approach set out in HTA Methods Guide (17).

Databases to be searched include

- Systematic reviews and primary studies: 1) Pubmed, 2) Epistemonikos
- Economic evaluations and HTAs: EconLit and HTA producing/publishing organisations
- Clinical Practice Guidelines: Clinical guideline producing/publishing organisations

Search restrictions:

- Only English language studies included.
- Only studies, guidelines, HTAs or economic evaluations published after 2000 will be included – this is the earliest year in which one of the long-acting insulin analogues under review was approved for use by US Food and Drug Administration.

### 5.3.2 Selecting studies for inclusion

Database searching, including title and abstract screening as well as full text screening, will be performed in duplicate.

Similarly, grey literature searching, including HTA agency decisions and clinical guidelines, will be performed in duplicate.

Clinical data:

Study selection will be focussed on identification of systematic reviews, with primary studies only included if no up to date or relevant systematic review is identified.

Economic data and clinical guidelines:

Only guidelines, economic evaluations and/or HTAs directly relevant to the review question will be selected.

### 5.3.3 Data extraction

Data will be extracted by single reviewer and checked by second reviewer. Key characteristics of included studies will be extracted, with a summary of the findings.

### 5.3.4 Appraisal of study quality

- Systematic reviews will be appraised using AMSTAR
- Economic evaluations will be appraised using the Economic Evaluation Critical Appraisal Checklist presented in Appendix 1 of the HTA Methods Guide
- Guidelines will be appraised with AGREE II
- HTAs from reputable HTA agencies will not be appraised for quality (as suggested in HTA Methods Guide)

### 5.3.5 Data synthesis/Analysis

- Evidence from systematic reviews will be synthesised narratively.
- Relevant information from published clinical practice guidelines and HTAs will be summarised narratively.
- Evidence from economic evaluations will be used to inform the cost-utility analysis and budget impact analysis.

### 5.3.6 Study PICO (18)

| Criteria | Details |
|---|---|
| **Population** | Adults aged 18 year or older with diabetes mellitus type 1 (requiring insulin) accessing care through the public health care sector of South Africa. |
| **Intervention** | Long-acting insulin analogues:<br>- glargine<br>- detemir<br>- degludec<br>Replacement therapy: The proposed intervention/s will be used instead of the current intermediate-acting NPH insulin used to achieve basal levels of insulin (not an add-on therapy)**.** |
| **Comparison** | Intermediate-acting Neutral Protamine Hagedorn (NPH) insulin |
| **Outcomes (18)** | Primary<br>- All-cause mortality<br>- Health-related quality of life<br>- Severe hypoglycaemia<br><br>Secondary*<br>- Diabetic ketoacidosis (DKA)<br>- HbA1c<br>- Severe nocturnal hypoglycaemia<br>- Non-fatal myocardial infarction/stroke<br>- Serious adverse events<br>- End-stage renal disease<br>- Blindness<br>- Serious adverse events<br>- Non-serious adverse events<br>- Nocturnal hypoglycaemia<br>- Mild/moderate hypoglycaemia<br>- Socioeconomic effects |

| | |
|---|---|
| | - Combined HbA1c levels and severe hypoglycaemia<br><br>Timeline of outcome<br>Short-term: 24-52 weeks<br>- All-cause mortality<br>- Health-related quality of life<br>- Severe hypoglycaemia<br>- Non-fatal myocardial infarction/stroke<br>- Severe nocturnal hypoglycaemia<br>- Serious adverse events<br>- HbA1c<br><br>Medium-term: 1-2 years<br>Long-term: more than 2 years |
| **Likely study designs or data sources to be included** | Systematic reviews of trials<br>Primary studies (if needed)<br>Clinical practice guidelines (CPGs) and health technology assessments (HTAs)<br>Economic evaluations |

# 6. Establish cost implications on health care sector

## 6.1 Cost-utility analysis

To conduct a CUA, careful consideration has to be made surrounding the disease process, the associated costs and the robustness of the results. Since meticulous data collection of recruited patients randomised to different treatment arms is not always feasible, modelling is rather employed. Modelling allows researchers to infer results based on mathematical structures of real-world economic and health scenarios. One such model particular utilised in CUAs is Markov Modelling, which will be employed in this research.

### 6.2 Markov Modelling

Markov Modelling allows for consideration of different disease states that an individual may enter during their illness, in this case T1DM. Treeage Pro is used in order to perform the Markov Model analysis. Each model includes the likelihood of transitioning from one disease state to another, through the incorporation of transition probabilities. Transition probabilities are inferred from existing research. In this research, the systematic reviews identified by the clinical effectiveness review are used to inform the model. In addition, each disease state has two features ascribed.

The first is the costs associated with each state. Unit costs that will inform utilisation costs in each Markov cycle include prices of medication, diagnostics, outpatient visits and inpatient days. These costs must be accounted for and can be evaluated using different perspectives, such as the provider, societal or patient perspectives. In this analysis, the provider perspective

is assumed, as this research aims to investigate the cost from the perspective of the South African Department of Health.

The second feature of each Markov state is the relative health outcome. In each health state, the patient can be expected to have a unique experience of their illness. In this analysis, QALYs will be the outcome measured. QALYs represent the health-related quality of life (HRQoL) multiplied by life years. These outcomes are applied in each Markov state in order to measure the associated outcome.

Once the features mentioned above have been described for each Markov state, a time horizon for the model and Markov cycle lengths need to be specified. Once the model is fully specified, it is run in order to estimate lifetime costs and lifetime outcomes in each comparator. Thereafter, the Incremental Cost-Effectiveness Ratio (ICER) is estimated. The ICER describes the cost per health gain through the implementation of the health technology under review, compared to its comparator. This value attributed to the ICER, however, must be interpreted for a decision to be made on the inclusion or exclusion of the health technology under review.

### 6.3 Cost-Effectiveness Threshold

The CET used is often contentious, with many reported methodologies for its estimation having been described. Given that CET is the marginal productivity of the health care system in question, each country should ideally identify and utilise its own CET.

### 6.4 Sensitivity Analysis

Since model inputs are inferred from existing research that may be subject to variation due to sampling and other sources of errors, considerable effort has to be made that the results of the model are robust. Sensitivity analysis is the variation in model inputs in order to analyse the impacts on the derived ICER. It allows for the identification of model inputs that drive the ICER most as well as investigating if any changes in model inputs result in rendering the intervention under consideration cost-effective or not. Two forms of sensitivity analysis exist, namely simple sensitivity analysis and probabilistic sensitivity analysis. In this study, simple sensitivity analysis is performed.

### 6.5 Budget Impact Analysis

The BIA essentially compares the current treatment situation for the disease or technology under review and the proposed treatment situation and what impact the change may have on the health care budget. The key factors involved in this analysis are: the incidence and prevalence of the disease under review, the proportion of those with the disease who are actually diagnosed, the proportion of those diagnosed who receive the treatment being evaluated, the proportion of individuals treated in the public health sector, the unit costs of the treatment and the costs incurred elsewhere (e.g. health systems costs or adverse event costs) (19).

This study assumes the public sector payer perspective and includes pharmaceutical and the larger public health system budget constraints. The eligible population data will be derived from Statistics South Africa. Rapid and slow adoption scenarios will be calculated for a 5-year time horizon.

## 7. Expected results and implications of the research

This research aims to estimate the cost-effectiveness and budget impact of the implementation of long acting insulin analogues (detemir, glargine or degludec), when compared to the *status quo* (NPH insulin).

The implications of this study's results are that it will potentially inform state authorities responsible for drug inclusion/exclusion in the essential medicines list.

## 8. Possible difficulties and solutions

Potential difficulties arise in defining Markov states in such a way that as many as possible disease states for T1DM are represented, without overburdening the analysis with too much complexity.

Furthermore, finding data surrounding the model, including data around HRQoL, disease states, transition probabilities, utilisation rates and unit costs, may prove challenging.

The utilisation of existing peer-reviewed data will aid in identifying disease states, HRQoL, transition probabilities and costs. In particular, use of similar research performed elsewhere,

preferably at HTA agencies, will aid in decision-making and data-collection with regards to the Markov Model. Where literature and experience elsewhere cannot provide values, either brief primary data collection or the researchers' best estimates will be used.

## 9. Ethical considerations

Since this study aims to utilize secondary data from peer-reviewed journals, governmental and para-statal organizations (health technology agencies and health product regulatory organizations), there are no ethical concerns of note. No participants are required to participate in this study and thus there is no risk of exploitation of vulnerable populations or threat to individuals' autonomy. This study does not draw from any sources of data that may link to identifiable individuals and therefore poses no risks in data protection. The knowledge that will be gained through this study will outweigh the non-existing risks. Justice will be advocated for as the study will be able to, in part, inform equity in resource distribution within the public health care system of South Africa.

## 10. Timeline

Protocol Submission: November 2021

Literature Review: March 2022

Cost-utility analysis and Budget Impact analysis: June 2022

Final mini-dissertation submission: September 2022

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# Part B: Literature review

# 1. Background

Type 1 diabetes mellitus (T1DM) is a disease hallmarked by insulin deficiency, resulting in uncontrolled high levels of blood glucose, that leads to life-threatening metabolic states. To treat the condition, exogenous insulin has been prescribed. In order to fully replicate normal insulin physiology, insulins of varying pharmacodynamic and pharmacokinetic properties have been developed.

In treating T1DM adequately, acute life-threatening complications, such as diabetic ketoacidosis, as well as chronic complications, such as myocardial infarction and cerebrovascular accidents, can be averted. Insulin, however, may also cause acute adverse events, namely hypoglycaemia, in which insulin levels are in excess relative to blood glucose levels, dropping blood glucose levels dangerously.

The Standard Treatment Guidelines and Essential Medicines List (EML) for South Africa (2020) details the following goals for the management of T1DM: maintenance of glycaemic control within acceptable limits, prevention of chronic complications and prevention of acute complications. It also outlines the insulin preparations under recommendation, namely regular short-acting insulin, intermediate-acting NPH insulin and a combination of both as recommendations for the treatment of T1DM (9).

The recommendation stands that T1DM be managed on a basal bolus regimen, consisting of pre-meal short-acting insulin and bedtime intermediate-acting insulin (NPH). The intermediate-acting insulin, in South Africa's case being NPH insulin, is delivered once, as in the basal-bolus regiment, or twice daily, as in the biphasic treatment regimen.

The intermediate-acting insulin that is currently recommended (NPH insulin) was first developed in 1946 and has since been widely used. More recently, however, new long-acting insulin analogues have been approved by the South African Health Products Regulatory Authority (SAHPRA), with detemir being approved in 2005, glargine being approved in 2000 and degludec being approved in 2015 (20).

The newer long-acting insulin analogues may prove to be superior in long-term glycaemic control and thus in preventing chronic complications. Furthermore, they may have a better

safety profile and therefore may avert short-term complications such as hypoglycaemia. These long-acting insulins, however, come at an increased cost compared to NPH insulin.

An economic evaluation, particularly a cost-utility analysis and budget impact analysis, of long-acting insulin analogues compared to NPH insulin has not yet been performed in the South African setting. However, to conduct a thorough economic evaluation, sound clinical and economic evidence is required.

# 2. Objectives

The objectives of this literature review, therefore, are:

1) To review literature on the methodology to be utilized, both historical literature as well as current guidelines. Methodology to be reviewed include Markov Modelling as part of cost-utility analysis (CUA) and Budget Impact Analysis (BIA).
2) To perform a systematic search on literature pertaining to clinical evidence of the long-acting insulins under review (insulins glargine, degludec and detemir) as well as the comparator, the intermediate acting insulin currently utilized, namely Neutral Protamine Hagedorn (NPH) insulin, for use in Type 1 Diabetes.
3) Identify relevant literature surrounding parameters of a Budget Impact Analysis, including epidemiology of the disease, treatment course and patient preferences.
4) To perform a review of economic evidence, including a summary of Health Technology Assessment Agencies' decisions, recommendations by international organizations and a collation of economic evidence found in peer-reviewed literature.

# 3. Review of Methodology

## 3.1 Overview of Economic Evaluation

### 3.1.1 Cost-Comparison Analysis

There are many forms of economic evaluation that can aid in decision making. One such method is a cost-comparison analysis, in which costs between two interventions are compared. This is a particularly useful method of evaluating two interventions through a financial lens. It does not, however, include differences in health outcomes between the interventions in question.

### 3.1.2 Cost-Effectiveness Analysis

A cost-effectiveness analysis (CEA) is similar to a cost-comparison analysis except that it includes single measure health outcomes, such as life years gained or reduction in pain, for example. This allows researchers to compare the cost between two interventions and their relative health outcome. However, given the complexity of health as an outcome, the use of a single measure health outcome to capture the complete health benefit of an intervention is often not extensive enough.

### 3.1.3 Cost-utility analysis

Cost-utility analysis (CUA) goes further by incorporating multi-dimensional health outcomes, such as Quality-Adjusted Life Years (QALYs) or Disability-Adjusted Life Years (DALYs). Multidimensional health outcomes are composite variables consisting of years of life gained or lost, as well as the quality of life lived. Therefore, CUA is a closer approximation to capturing the totality of health outcomes of a given intervention. In other words, a CUA is an economic evaluation in which two interventions' costs and multi-dimensional health gains are compared. Through this, the cost per unit health gained by the intervention under review, compared to the *status quo* or a comparator intervention, can be established. A CUA thus aids in representing economic considerations in decision-making surrounding the implementation of a new health technology.

### 3.1.4 Budget Impact Analysis

Determining the cost-effectiveness of an intervention under consideration, however, is not sufficient to determine how readily it may be implemented in a resource-constrained environment, such as South Africa's public health care sector. In addition to cost for utility, budget impact must be evaluated. This can be done through the use of a Budget Impact Analysis (BIA). Through a BIA, the expected change in health care expenditure through the implementation of a new intervention can be evaluated.

The BIA essentially compares the current treatment for the disease or technology under review and the proposed treatment and what impact the change may have on the health care budget. The key factors involved in this analysis are: the incidence and prevalence of the disease under review, the proportion of those with the disease who are actually diagnosed, the proportion of those diagnosed who receive the treatment being evaluated, and the unit costs of the treatment

(19). In addition to this, rapid and slow adoption scenarios of the technology should be calculated over the long term (5 years) in order to capture a range of realistic estimates of what impact the adoption of a new technology may have.

This study will assume the public sector payer perspective and include pharmaceutical and the larger public health system budget constraints. The eligible population data will be derived from Statistics South Africa. Rapid and slow adoption scenarios will be calculated for a 5-year time horizon.

## 3.2 Methodology of economic evaluation

### 3.2.1 Decision analytic modelling

To conduct a CUA, careful consideration has to be made surrounding the disease process, the associated costs and the robustness of the results. Since meticulous data collection of recruited patients randomised to different treatment arms is not always feasible, modelling is rather employed. Modelling allows researchers to infer results based on mathematical structures of real-world economic and health scenarios. One such model particular utilised in CUAs is Markov modelling, which will be employed in this research.

Markov modelling is used in order to represent processes that are random and evolve over time. This type of modelling allows for costs and health outcomes to be considered simultaneously and for this reason it is particularly applicable in the field of Pharmacoeconomics, specifically in economic evaluation (21). In the context of chronic disease, a field in which Markov modelling proves particularly useful, it allows for consideration of different disease states that an individual may enter during their illness. Markov modelling has been widely employed in the evaluation of prevention, treatment and monitoring of diabetes mellitus and its associated outcomes (22-24). Software has been created in order to assist researcher with performing Markov modelling. One such program is TreeAge Pro, which will be utilized in this study (25).

To elaborate on how Markov modelling is performed, one can expand on the functions that the costs and health outcomes comprise of. Markov models are built on the disease states in which individuals suffering from a condition may be. The disease states included should capture all possible states in which an individual may find themselves in, to a varying degree of detail. However, the greater the detail or resolution of various disease states included, the greater the

complexity. Naturally, individuals can enter or exit disease states throughout their chronic illness, barring a few exceptions such as death. Through literature review, one can identify what the probability of transitioning from one disease state to the next might be. This is termed the transition probability and is included in the Markov model.

Once the disease states and the transition probabilities have been established, data can be ascribed to each state. The first is the cost associated with each state. Unit costs, in conjunction with utilisation rates, will inform the costs of each Markov cycle. Unit costs include costs of medication, diagnostics and services rendered. The number of outpatient visits, inpatient days and dosages of medication on the other hand, are examples of utilisation rates. These costs must be accounted for and can be evaluated using different perspectives, such as the provider, societal or patient perspectives. This research will focus on the provider perspective, which in this case is the South African Department of Health.

The second feature of each Markov state is the relative health outcome. In each health state, the patient can be expected to have a unique experience of their illness. In this analysis, Quality Adjusted Life Years (QALYs) will be the outcome measured. QALYs represent the health-related quality of life (HRQoL) multiplied by life years in each disease state.

Once the features mentioned above have been described for each Markov state, a time horizon for the model and cycle lengths need to be specified. Based on the literature, a lifetime horizon will be applied with annual cycle lengths, which will influence the number of times the model will run. The number of cycles and the time horizon along with the transition probabilities influence the proportion of simulated individuals found in each disease state. Once the proportions in each disease state are estimated, lifetime costs and lifetime outcomes can be applied and evaluated for each treatment group.

### 3.2.2 Sensitivity analysis

Since model inputs are inferred from existing research that may be subject to variation due to sampling and other sources of error, considerable effort has to be made to ensure the results of the model are robust. Sensitivity analysis is the variation in model inputs in order to analyse the impacts on the results and decision model. It allows for the identification of model inputs

that drive the results the most as well as investigating if any changes in model inputs result in rendering the intervention under consideration cost-effective or not.

## 3.3 Interpreting economic evaluation results

### 3.3.1 Incremental Cost-Effectiveness Ratio and Cost-Effectiveness Threshold

In order to compare the cost-effectiveness of different health technologies, an Incremental Cost-Effectiveness Ratio (ICER) can be calculated. The ICER describes the cost per health gain through the implementation of one health technology over another. The established ICER in the analysis of health technologies under review, however, must be interpreted in conjunction with a decision-making criterion. One such proposed criterion is the cost-effectiveness threshold (CET). The CET is considered the measure of the marginal productivity of the health care system in question. The CET provides a value to what one would consider a cut-off for the inclusion or exclusion of a health technology in a health care system.

The CET used is often contentious, with many reported methodologies for its estimation having been described. Given that the CET is the marginal productivity of the health care system in question, each country should ideally identify and utilise its own CET. Using the country-level cost-effectiveness thresholds (CETs) by Woods et al (2016), the CET for South Africa can be expected to lie between 1,175 and 8,909 USD/QALY (midpoint 5,042 USD/QALY) for the year 2013 (26).

=-0With this threshold in mind, the results of this research can inform a practical decision by the South African health authorities.

### 3.3.2 Budget Impact Analysis

The BIA generated in this study does not represent the full economic nor social impact of the technologies in question. Rather, the BIA estimates the net financial costs of adopting these technologies, focussing primarily on the pharmaceutical acquisition costs. Therefore, the BIA can be used to inform budget planning and affordability of the new technologies under review.

# 4. Review of Clinical Evidence

## 4.1 Systematic Search

A systematic search was conducted in order to identify relevant studies to inform the clinical effectiveness review. Search terms included the interventions (long-acting insulin analogues

detemir, glargine and degludec), the relevant patient population (adult type 1 diabetics) and the comparator (NPH insulin). Studies included involved adult patients with T1DM and at least one of the interventions under review. Studies were excluded if they involved biosimilar insulins, continuous subcutaneous infusion administration of insulin, focussed on excluded patient populations (for example pregnant women) or if they were not a systematic review or meta-analysis. No exclusion criteria were set for study setting or date. The exact search terms used can be found in the Appendix B. Databases included in the search were Epistimikos, PubMed and Cochrane Database of Systematic Reviews.

A total of 208 records were identified. After duplicate removal, abstract and title screening as well as full text review, three were identified for inclusion in this review. The studies drawn on for this clinical effectiveness were thus a Cochrane Review by Hemmingsen et al. (2020), a review by the National Institute of Health and Care Excellence (NICE) (2021) and a review by Martin et al. (2021) (18, 27, 28). These final three reviews were chosen as they included most of the relevant primary studies (see study composition analysis in Appendix C).

### 4.2 Study comparison

The three studies included for review differ slightly in their methodology. This is important to consider when interpreting their results.

Firstly, the Cochrane review included studies on non-adults, but stratified for this in the sub-analysis. It also used a study length cut-off of 24 weeks. The insulins reviewed fell under broad categories by insulin type and were not stratified into first- or second-generation insulins, or by dosing frequency (i.e. once or twice daily).

The review by Martin et al., only included studies on adults. The authors primarily used studies that were at least 24 weeks long in duration, but as part of their sensitivity analysis, extended their inclusion criteria to studies with a duration of 12 weeks. The main methodological difference, however, is that the reviewers compared first-generation insulin (NPH, detemir and glargine-U100) to second generation insulins (degludec and glargine-U300).

Finally, the NICE review only included studies on adults. This review also placed no study length cut-off, a significant difference to the other two reviews. This review also stratified

insulins the most out of all reviews, grouping insulins by type, generation and dosing frequency.

### 4.3 Clinical Effectiveness

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.

The long-acting insulins (detemir, glargine and degludec) were shown to be noninferior with regards to the primary outcomes of long-term blood glucose control, through the HbA1c test value, and mortality risk. Health-related quality of life was either shown to lack sufficient data for comment in the studies or it was not reported on.

The only area of clinical significance was identified in the rates of low blood glucose, or hypoglycaemia. Of particular clinical significance is severe hypoglycaemia. The study of severe hypoglycaemia, however, is limited due to its highly variable definition. In comparison to moderate hypoglycaemia, severe hypoglycaemia encompasses the need for third party assistance, ranging from by-stander assistance to medical professional help, as well as serologically confirmed hypoglycaemia. Severe hypoglycaemia can also further be classified into daytime or nocturnal hypoglycaemia. The importance of this distinction lies in the differing associated HRQoL, with severe nocturnal hypoglycaemia expected to incur greater disutility than daytime severe hypoglycaemia. Furthermore, since the definition of severe hypoglycaemia includes the possibility of hospital visits and/or admission, it is of particular significance when conducting an economic evaluation.

The three reviews present conflicting evidence when it comes to severe hypoglycaemia. The various review findings are summarised in Table 1. From the network meta-analysis (NMA), the NICE review found insulin detemir to be superior to NPH insulin in reducing severe hypoglycaemia. In contrast, in the adult sub-analysis, the Cochrane review did not find insulin detemir to be superior to NPH insulin with regards to severe hypoglycaemia (RR 0.71, CI 0.49, 1.03). The review by Martin et al. showed a significant reduction in severe hypoglycaemic events when using glargine-U300 or degludec compared to NPH insulin with risk ratios of 1.98 (CI 1.08, 3.68) and 1.88 (CI 1.30, 2.71) respectively.

**Table 1.** Review findings of severe hypoglycaemia.

| **Cochrane Review** | | |
|---|---|---|
| **Intervention** | **Comparator** | **Risk ratio (M-H, Random, 95% CI)** |
| Detemir | NPH | 0.71 [0.49, 1.03] |
| Glargine | NPH | 0.78 [0.58, 1.05] |
| Detemir | Glargine | 0.59 [0.13, 2.63] (combined) |
| Degludec | Detemir | 1.01 [0.57, 1.78] |
| Degludec | Glargine | 1.22 [0.82, 1.82] |
| **Martin et al.** | | |
| **Intervention** | **Comparator** | **Risk ratio (95% CI)** |
| NPH | Degludec-U100 | 2.03 (0.98, 4.07) |
| Glargine-U100 | Degludec-U100 | 1.25 (0.73, 2.14) |
| Detemir | Degludec-U100 | 1.51 (0.82, 2.78) |
| NPH | Glargine-U300 | 0.90 (0.31, 2.49) |
| Glargine-U100 | Glargine-U300 | 0.56 (0.24, 1.23) |
| Detemir | Glargine-U300 | 0.67 (0.24, 1.80) |
| **NICE** | | |
| **Intervention** | **Comparator** | **Risk ratio (M-H, Random, 95% CI)** |
| Detemir once/twice daily | NPH once/twice daily | 0.31 (0.25, 0.38) |

'Combined' indicates when the authors of the Cochrane review combined both child and adult data in cases in which insufficient data on adults existed.

The reviews all found statistically significant differences in rates of nocturnal hypoglycaemia. In the NICE review, insulin degludec appeared to have the safest profile surrounding nocturnal hypoglycaemia. Insulin glargine-U100 was also found to be safer with regards to severe nocturnal hypoglycaemia, however not as safe as insulin degludec. Of the twice daily regimens, insulin detemir proved to reduce rates of severe nocturnal hypoglycaemia compared to NPH twice daily. In the adult sub-analysis of the Cochrane review, significant reduction in rates of severe nocturnal hypoglycaemia were identified in the insulin detemir group compared to NPH insulin (RR 0.57, 0.35, 0.93). There was insufficient data to report on precise risk ratios in severe nocturnal hypoglycaemia analysis of the review by Martin et al.

**Table 2.** Review findings of severe nocturnal hypoglycaemia.

| **Cochrane Review** | | |
|---|---|---|
| **Intervention** | **Comparator** | **Risk ratio (M-H, Random, 95% CI)** |
| Detemir | NPH | 0.57 [0.35, 0.93] |
| Glargine | NPH | 0.87 [0.60, 1.27] |
| Detemir | Glargine | 0.11 [0.01, 2.02] (published) |
| Degludec | Detemir | 1.21 [0.43, 3.38] |
| Degludec | Glargine | 1.39 [0.59, 3.27] (combined) |
| **Martin et al.** | | |
| **Intervention** | **Comparator** | **Risk ratio (95% CI)** |
| NPH | Degludec-U100 | 3.16 (0.58, 14.9) |
| Glargine-U100 | Degludec-U100 | 2.04 (0.49, 8.59) |
| Detemir | Degludec-U100 | 2.07 (0.61, 6.79) |
| NPH | Glargine-U300 | 0.76 (0.06, 6.93) |
| Glargine-U100 | Glargine-U300 | 0.49 (0.10, 2.21) |
| Detemir | Glargine-U300 | 0.50 (0.06, 3.78) |
| **NICE review** | | |
| **Intervention** | **Comparator** | **Risk ratio (95% CI)** |
| Degludec-U100 | Glargine-U100 | 0.65 (0.47, 0.89) |
| Degludec-U100 | Detemir once daily | 0.49 (0.30, 0.74) |
| Degludec-U100 | NPH once daily | 0.43 (0.24, 0.73) |
| Glargine-U100 | NPH once daily | 0.77 (0.67, 0.88) |
| NPH twice daily | Detemir twice daily | 1.39 (1.04, 1.89) |
| Detemir twice daily | Glargine-U100 | 0.75 (0.61, 0.92) |

'Combined' indicates when the authors of the Cochrane review combined both child and adult data in cases in which insufficient data on adults existed.

There were no additional significant findings or sufficient data to comment between the insulins under review pertaining to secondary outcomes such as rates of diabetic ketoacidosis, weight change, blindness, serious adverse events, end-stage renal disease, non-serious adverse events and non-fatal myocardial infarction or stroke.

## 4.3 Summary

From the systematic search and reviews identified, it is apparent that much evidence of varying quality exists. Of the three reviews included, it is evident that many methods of reviewing insulins exist. Reviews grouped insulins by type, separated insulins based on dosing frequency or compared first- and second-generation insulins.

The evidence suggests that there is little significant difference between the insulins under review. The only clinically relevant difference was found in the rates of severe hypoglycaemia.

This outcome has added complexity in the laxity of its definition as well as the subdivision into daytime and nocturnal severe hypoglycaemia. Nevertheless, it is an important and relevant difference in the economic evaluation of these insulins.

# 5. Budget Impact Analysis Parameter Review

## 5.1 Introduction

In order to conduct a BIA on this topic various demographic, epidemiological and treatment guideline data are required. Demographic estimates are needed relating to population size, population growth and the proportion of the population who access public health facilities. Demographic data are obtained from Statistics South Africa Mid-Year Population estimates for 2020 with an annual growth rate of 1.4% assumed. Regarding epidemiological data, the proportion of said population who have T1DM needs to be estimated, as well as the proportion of which who are actually diagnosed and those you are ultimately placed on treatment (i.e. insulin). Finally, treatment guidelines inform what quantity of the drug in question the public sector buyer might purchase. With the quantity established, costs can be applied in order to calculate the potential budget impact.

## 5.2 Incidence and prevalence of 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 rate of about 3.7 per 1000 individuals (3).

## 5.3 The proportion of those with the disease who are actually diagnosed and treated

It can be assumed that all patients with T1DM are diagnosed and given treatment, as T1DM is a fatal condition when left untreated. Patients with T1DM usually present to the emergency department in a state of diabetic ketoacidosis (DKA), a medical emergency and life-threatening event.

## 5.4 Treatment recommendations and actual treatment regimen received

The total recommended daily dose of insulin ranges between is 0.5-1 unit/kg body weight. Of this total daily insulin dose, 33-50% is consists of the intermediate-acting bedtime basal dose,

whereas the remainder is divided into three pre-meal short-acting insulin doses. Whether these guidelines are adhered to in practice, however, has been a cause for investigation.

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 (29). 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 (30). 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 (31).

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 (31). 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 biphasic insulin, which is a mixture of intermediate- and short-acting insulin. For this treatment regimen, however, daily glucose monitoring is recommended.

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, however, this is beyond the scope of this review.

## 5.5 Budget Impact Analysis Summary

Regarding BIA parameters, the prevalence of T1DM can be assumed to equate that of the proportion of the population actually diagnosed with T1DM and receiving treatment. The treatment regimen received, however, may have significant variation. The proportion of the T1DM population actually receiving the recommended treatment regimen, compared to the

alternative regimen, should be noted. However, these two regimens do not impact the total units of insulin utilized by patients and thus the regimen used by patients does not have particular bearing on the BIA in this review.

# 6. Review of Economic evidence

The following rapid review of economic evidence, including health technology agency (HTA) decisions and the respective tables are adapted from the Health technology Assessment Methods guide by Wilkinson and Wilkinson for the South African context (17). This review accordingly utilizes the following process: 1) identification of economic evaluations, 2) critical appraisal of the evaluations, 3) assessment both in applicability of the context and methodology of the evidence and 4) summary of the evidence collected.

## 6.1 Identification of economic evidence

Economic evidence was searched for using databases of independent journal articles and HTA agency reviews. The list of databases used included the International Network of Agencies for Health Technology Assessment (INAHTA), Centre for the Evaluation of Value and Risk in Health at Tufts Medical Centre, National Health Service Economic Evaluation Database (NHS EED) and EconLit (32-34). Search terms used aimed to include any economic evaluations on any of the insulins under review (insulins degludec, glargine, detemir and NPH insulin). No restriction was placed on country in which study was performed. Studies were excluded if they focussed on non-adult populations or pregnant women or if they were reviewed newer insulin administration technologies (such as insulin infusion pumps).

## 7.2 Critical Appraisal

As per the HTA Methods Guide by Wilkinson and Wilkinson, critical appraisal is not necessarily required for economic evidence reviewed and approved by reputable HTA agencies. Limitations and conflicts of interest of original studies included in this review are mentioned below.

## 7.3 Applicability of Context and Methodology

Applicability of context and methodology for each economic evidence review was assessed using the proposed scoring system by the HTA methods guide. The context and methodology

applicability scores of the economic evidence reviewed, both by HTA decisions and individual studies, are shown in Appendix E.

## 7.4 Economic Evidence

Through literature review, it is evident that there is great interest in determining the cost-effectiveness and affordability of newer long-acting insulin analogues for use in T1DM. Studies and reviews are spread fairly consistently from the early 2000s leading up to 2021. Studies included reviewed insulin glargine, detemir and degludec, with insulins glargine and detemir being most frequently evaluated. In most cases long-acting insulins are compared to NPH insulin and in a few studies long-acting insulins are compared to one another. No study conducted for or on the African continent was identified and, therefore, the context applicability of the studies included is low.

The recommendations reached in the studies and reviews were interpreted bearing in mind the perspective or context of the study, the certainty attained, the model used to determine rates of clinical outcomes, the sources that inform the model parameters, the CET used and the sources of funding for the studies/reviews. These factors are important to consider for numerous reasons (17). Firstly, the applicability of the context to South Africa provides insight as to whether or not the decision is made in a similar resource constrained environment. One such variable describing the context of the health system is the CET used. Secondly, the certainty attained allows an estimate of the robustness of the results to be made. Furthermore, the methodology used, particularly the model used, if any, as well as the parameters used, informs whether or not results are somewhat comparable between studies. Finally, the sources of funding of the study and/or the model used greatly impacts the way results ought to be interpreted, as undue influence and selective parameter setting may have biased the results.

### 7.4.1 Germany

There exist differing opinions on the cost-effectiveness of insulin glargine compared to NPH insulin. On the one hand, a study by Pfohl et al. found that insulin glargine was dominant over NPH insulin (35). The authors created a CRC DES model to evaluate the cost-effectiveness of insulin glargine when compared to NPH insulin for the German Statutory Health Insurance. The model simulated a cohort of 10 000 patients over a 40 year period. Transition functions were incorporated to include two acute and five chronic complications. Acute complications

included DKA and three grades of hypoglycaemia (severe, nocturnal hypoglycaemia and symptomatic). DKA rates and fatality were taken from the CORE model (36). A starting HbA1c of 8.8% was used with an increased absolute reduction of 0.3% when insulin glargine was used in place of NPH insulin. Rates of hypoglycaemia for NPH insulin were derived from literature and were estimated to be 0.392, 5.994 and 22.11 events per patient per year for severe, nocturnal and symptomatic hypoglycaemic events respectively (37, 38). In correspondance, rates of hypoglycaemia were estimated to decrease by 24.1% for both severe and nocturnal hypoglycaemia and by 23.2% for symptomatic hypoglycaemia when NPH insulin was substituted by insulin glargine (37, 38). The chronic complications predicted were end-stage renal disease, retinopathy, amputation (neuropathy), first myocardial infarction and first stroke. Costs included were insulin administration packs, self-monitored blood glucose (SMBG) and in- and outpatient visit costs. A 3% discount rate was utilized. The authors concluded that glargine was cost effective or even cost saving over NPH insulin, depending on the scenario (including when no difference in clinical effectiveness was assumed) (35). Unlike most other studies included here, the results were primarily driven by cheaper acquisition costs of insulin glargine.

A systematic review by Hagenmeyer et al., also taking the perspective of the German Statutory Health Insurance, included 6 studies in which found variable ICERs when comparing insulin glargine to NPH insulin (39). One study found glargine to be dominant, whereas the other five derived ICERs ranging from 3 859 euros to 57 002 euros. However, their cost-minimisation analysis found NPH insulin to be cheaper. The authors concluded that insulin glargine most likely provided good value for money for the German Health Sector.

### 7.4.2 Canada

The findings above are not concordant with the findings of a study by Cameron and Bennett (2009) in which, similar to Pfohl et al., the CORE diabetes model was used to estimate complication rates (40). The study took the perspective of the Canadian public health provider. Costs of inpatient and outpatient visits, emergency visits and long-term home care were included. Severe hypoglycaemia was calculated to infer a disutility of 0.549 for 24 hours and mild hypoglycaemic episode was calculated to confer a disutility of 0.167 for 15 minutes. However, rates of hypoglycaemia did not differ significantly between insulin glarigne and NPH insulin. A vast array of other complications were included. Insulin glargine improved QALYs

but at an increased cost, compared to NPH insulin. The ICER calculated amounted to 87 932 Canadian Dollars, which, when compared to the CET used of 50 000 Canadian dollars per QALY, deemed glargine not cost-effective, with a probability of cost-effectiveness of 42.5%. However, when fear for hypoglycaemic episodes, which has been studied elsewhere, was incorporated into the QALY estimates, the ICERs for glargine fell to 17 225 canadian dollars per QALY (41, 42). In contrast, when no difference in HbA1c control was assumed between insulin glargine and NPH, the ICER increased dramatically.

These findings, however, contradict an earlier Canadian study conducted in 2007 by Grima et al. in which the authors modelled the cost-effectiveness of insulin glargine versus NPH insulin and concluded that insulin glargine was cost-effective for T1DM in the Canadian health care sector (43).

In the same study by Cameron and Bennett, insulin detemir was compared to NPH insulin in the context of the Canadian public health care provider (40). Similar to insulin glargine, insulin detemir improved QALYs at an increased cost. In contrast to insulin glargine, insulin detemir was assumed to confer a significant protective relative risk of 0.84 (0.74-0.97 95% CI) and 0.74 (0.58-0.96 95% CI) for mild and severe hypoglycaemic events when compared to NPH insulin. The ICER calculated amounted to 387 729 Canadian Dollars per QALY. With a CET of 50 000 Canadian Dollars per QALY, insulin detemir had a 29.2% probability of being cost-effective. Again, when fear of hypoglycaemic episodes was incorporated in the model, the ICER dropped to 25 666 Canadian Dollars per QALY. When no difference in HbA1c control was assumed, the ICER increased dramatically.

A further study conducted in Canada in the same year by Tunis et al, which was funded by a pharmaceutical company, with different model parameters found that detemir was cost-effective with an ICER of 24 389 Canadian Dollars per QALY (44). Parameters included HbA1c reduction for detemir of -0.94%±1.07 and -0.82%±1.01 for NPH and rates of major hypoglycaemic events of 0.2 for detemir and 0.8 for NPH insulin. In this study, differences in costs between the insulin detemir and NPH insulin were primarily driven by differences in hypoglycaemic episodes and associated costs.

Guillermin et al. also took on the Canadian health care provider perspective and sought to compare insulin glargine once daily to insulin detemir twice daily (45). In their cost-

minimisation analysis based on the CORE Diabetes Model, in which no difference in glycaemic control or adverse outcomes were assumed, the authors found that insulin galrgine conferred greater cost savings compared to insulin detemir, with a resultant lifetime saving cost of 4 659 Canadian dollars. The drivers of this result included a 22% lower dose of insulin galrgine required to achieve similar HbA1c control to insulin detemir, as well as lower unit costs of inuslin glargine.

As mentioned above, a model parameter that has great influence on the cost-effectiveness is HbA1c control. A more recent meta-analysis by Tricco et al. (2014) explored the effectiveness and cost-effectiveness of insulins glargine and detemir compared to NPH insulin (46). The analysis found that there was a small reduction in HbA1c with detemir and glargine use compared to NPH use, however, this was deemed a clinically insignificant reduction in HbA1c (less than 0.5% reduction). Insulin glargine appeared to have slightly better safety profile with regards to weight gain and hypoglycaemic episodes compared to NPH insulin, with insulin detemir having a better safety profile than insulin glargine. This meta-analysis of evidence surrounding cost-effectiveness of insulin glargine and detemir compared to NPH insulin found that results were inconsistent across studies (46).

Similar to the above study, an earlier meta-analysis performed in 2007 on behalf of Canadian Agency for Drugs and Technologies in Health sought to review the cost-effectiveness of insulin glargine and insulin detemir compared to NPH insulin (47). Again, clinically insignificant reduction in HbA1c was found between insulins detemir and glargine compared to NPH insulin, however, the greatest reduction in HbA1c was seen in insulin glargine use. Insulin detemir was identified to have five RCTs report a significant reduction in severe and nocturnal hypoglycaemic episodes, with relative risk compared to NPH reported at 0.7 (0.52-0.95 95% CI) and 0.84 (0.73-0.95 95% CI) respectively. Insulin glargine, on the other hand, had statistically insignificant reduction in episodes of hypoglycaemia. The analysis identified that the type of bolus insulin used (aspart vs human insulin) influenced rates of hypoglycaemia greatly. Overall, the study found inconsistent data and therefore the authors could not make a recommendation.

### 7.4.3 Denmark, Sweden, Finalnd, Netherlands and USA

The following three studies report unique findings out of keeping with many other reports. Importantly to note, these studies have serious limitations due to potential conflicts of interest.

A study by Valentine et al. (2012) performed a cost-utility analysis between NPH and detemir in the context of Denmark, Sweden, Finland and the Netherlands (48). A simple decision tree with 1 year time horizon and a public health provider perspective was utilized. The primary focus was on hypoglycaemic events. The cost of insulin and single self-monitoring glucose strips were included. ICERs calculated for each country ranged between 12 000 to 16 000 Euros per QALY, deeming it cost-effective according to the authors. The probability of detemir being cost-effective in this context was 86%. The CET used was based on the outdated recommendation recommendation by the World Health Organization, in which a country's per-capita GDP determines the CET.

Similarly, Valentine and Palmer et al. (2006) studied the cost-efectiveness of insulin detemir versus NPH insulin for the the primary care setting in the USA, taking the Medicare perspective (49). The CORE model used to predict long-term outcomes and costs. The model indicated a reduction in HbA1c and hypoglycaemic episodes for detemir. Detemir was shown to increase QALYs at a higher costs. A low ICER of 14 974 US Dollars per QALY was calculated with a 100% probability of being cost-effective when compared to the CET used of 50 000 US Dollars. Sensitivity analysis showed that pharmacy acquisition costs were most influential. In a sub-analysis of detemir versus glargine, the authors determined that insulin detemir dominated.

Palmer and Valentine et al. conducted yet another study in which they utlized a simulation model to compare patients treated with detemir and aspart to those treated with NPH insulin and human insulin (i.e. a long acting plus a rapid acting insulin) (50). The NHS perspective was used with 3.5% discount rate. Treatment with analogue insulin (i.e. detemir) showed decreased long-term complications and improved QALYs at an increased cost. The ICER calculated was robust and showed cost-effectiveness for the UK.

### 7.4.4 Wales

In addition, there may be noteworthy differences within the subtype of long-acting insulins. For example, in 2015 the All Wales Therapeutics and Toxicology Centre (AWMSG) reviewed the cost-effectiveness of two formulations of insulin glargine, namely the lantus and abasalgar formulations, which are biosimilar (51). Abasalgar had been determined as non-inferior or equivalent to lantus in the ELEMENT-1 trial with regards to HbA1c control as the primary endpoint and other secondary endpoints, including change in HbA1c, blood glucose levels, basal insulin levels, weight and safety (52). A cost minimisation analysis was conducted due to the biosimilarity between abasalgar and lantus. An average cost saving per T1DM patient per annum when using abasalgar compared to lantus amounted to approximately 38 British pounds. The BIA determined that 3 071 British pounds would be saved annually by substituting lantus with abasalgar for use in T1DM.

Insulin degludec produced the fewest search results for reviews and/or studies. A review of insulin degludec by the AWMSG had previously been rejected, after which a resubmission had been made and accepted, with changes in prices and additional information. Clinical efficacy for T1DM was reviewed in large RCTs comparing insulin degludec to insulin glargine and insulin detemir respectively. Noninferiority was concluded between insulin degludec and detemir or glargine when assessing the primary endpoint of HbA1c. After pooling of the studies to reach adequate statistical power, the studies showed no significant superiority or inferiority with regards to secondary endpoints, including treatment-emergent confirmed hypoglycaemic episodes and severe nocturnal hypoglycaemia. The safety profile of the three insulins considered were similar, including parameters of treatment-emergent adverse events and mild to moderate adverse events (including nasopharyngitis, upper respiratory tract infections etc.).

The authors went on to perform a cost-utility analysis. The price of treating a patient for one year with insulin degludec was found to be cheaper than insulin glargine. The authors referred to the UK Hypoglycaemia Study in order to estimate baseline rates of hypoglycaemia (53). This group found that T1DM patients above the age of 15 years had a mean of 3.2 (1.6-4.9 95% CI) and 29 (16.4-41.8 95% CI) severe and mild self-reported hypoglycaemic episodes per year respectively. The proportion of individuals who had at least one severe or mild hypoglycaemic episode within a year was 0.46 (0.34-0.59 95% CI) and 0.85 (0.73-0.92 95% CI) respectively. When interstitial glucose was monitored and a threshold of 2.2mmol/dL ($LIG_{2.2}$) was used for hypoglycaemia, a mean of 2.06 to 2.96 $LIG_{2.2}$ hypoglycaemic events

occurred per person per week, with the proportion of individuals having at least one $LIG_{2.2}$ hypoglycaemic event being between 0.55 and 0.61. With these rates of severe and mild hypoglycaemic episodes, the authors then drew from two studies in order to assign costs for such episodes (54, 55). QALYs were determined by applying a disutility to hypoglycaemic events. The results indicated that degludec dominated insulin glargine for patients with T1DM, by being both cheaper and more effective. A probabilistic sensitivity analysis was performed and 40% of the simulation indicated a loss in QALYs and a 100% of simulations showed cost savings (56).

### 7.4.5 United Kingdom

In concordance, a study by Evans et al. found insulin degludec to not be inferior to glargine in effectiveness of glycaemic control (57). To assess cost-effectiveness, a short-term model was employed as there were no significant differences reported in long-term effectiveness between the two insulins. In this model, a focus on hypoglycaemic episodes, number of self-monitored blood glucose (SMBG) and dosing differences were primarily evaluated. Rates of hypoglycaemic events for insulin glargine were derived from clinical trial data. The baseline rates of daytime and nocturnal non-severe hypoglycaemia were 46.66 and 7.19 episodes per patient per year respectively. The rate of severe hypoglycaemic events was estimated to be 0.27 episodes per patient per year. Hypoglycaemic event rates for insulin degludec were derived from the aforementioned baseline event rate of insulin glargine and a reported event ratio between insulin glargine and degludec, by Vera et al (58). Through this calculation, daytime and nocturnal non-severe hypoglycaemic event rates of 46.66 and 5.97 per person year were calculated respectively. There was no difference in severe hypoglycaemic event rates (at 0.27 events per person per year).

A one-year time horizon was utilised, and the perspective of the UK National Health Service was taken. The two costs included were treatment costs as well as cost per hypoglycaemic episode. The costs per hypoglycaemic episode were estimate for both severe and non-severe events. Disutility per hypoglycaemic event was drawn from a large multinational time trade-off study (59). This study reported a disutility of 0.0565 for a severe event, as well as disutilities of 0.0041 and 0.0067 for non-severe daytime and nocturnal severe events respectively. Degludec had similar rates of severe and daytime non-severe events as glargine, with the only difference occurring between non-severe night-time events, with degludec providing fewer

events. The resultant utility gain from degludec was determined to be 0.0082. The ICER calculated from the sensitivity analysis ranged from 5 983 to 31 489 British pounds per QALY (with varying hypoglycaemic event rates). Using equal mean insulin doses impacted the ICER significantly, bordering the CET. Varying disutility from non-severe hypoglycaemic events also impact the ICER greatly. The study concluded that overall, degludec was cost-effective for adult T1DM patients in the UK, with an average ICER of 16 985 British pounds per QALY.

The most recent and robust evidence, however, arises from the NICE economic review for the management of adults with T1DM, conducted in 2021 (27). This review screened 211 studies and included 51 studies in the analysis, making it the largest review. The authors employed a Markov model, with parameters drawn from the IQVIA CORE model (a validated diabetic model) much like other studies already mentioned (35, 40, 49). Palmer et al. (2004) go into much detail about the CORE diabetes model (36).

In this extensive review, HbA1c control was deemed comparable across the long-acting insulin analogues and therefore was not influential in the cost-effectiveness analysis. Rates of hypoglycaemia and treatment acquisition costs, on the other hand, were considered differential. Data on rates of hypoglycaemia were inconsistent and thus the reviewers generated three scenarios to capture the range of possible differences in rates of hypoglycaemia based on the calculation method used. In scenario one, the risk ratios identified in the systematic review of clinical evidence network meta-analysis (NMA) were applied to rates of severe hypoglycaemia for the detemir twice daily group, whose rate was determined using a random effects meta-analysis from the systematic review of clinical evidence (27). In scenario two, the authors used the random effects meta-analysis from the systematic review of clinical evidence for all treatment groups, therefore not applying relative risks as in scenario one. In scenario three, no difference in the rates of severe hypoglycaemia was assumed.

In scenario one, in which uncertainty was greatest, amongst the twice-daily regimens, insulin detemir and NPH insulin ranked first and second with regard to cost-effectiveness respectively. In the once-daily regimen analysis, insulin glargine was most cost-effective with insulin degludec the second most cost-effective. In scenario two, in which more certainty prevailed, insulin detemir ranked first again amongst the twice-daily regimens, whereas insulin glargine ranked second with insulin degludec considered most cost-effective in the once-daily regimen analysis. The reviewers deemed that scenario three be weighted very low in the analysis, due

to the authors certainty that hypoglycaemic events are to be considered clinically significant. The authors, therefore, conclude that a twice daily detemir regimen for adults with T1DM is primarily recommended. However, a once daily insulin regimen of insulin degludec or glargine can be used if twice daily detemir is not tolerated well.

**Table 3.** Summary of HTA agencies reviews.

| | Country + HTA agency | Year | Indication | Intervention | Comparator | Modelling approach | Results | Major areas of uncertainty | Ethical, social, legal issues | Recommendation | Context applicability score /6 | Methods applicability score /6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AWMSG: Insulin glargine (abasalgar) compared to lantus (56) | Wales: AWMSG | 2015 | DM >2 y/o | Insulin glargine (abasalgar) | Insulin glargine (lantus) | Cost Minimisation Analysis | Equivocal to lantus with cheaper costs | Likely underestimation of cost of lantus | None | Recommended DM >2 y/o | 2 | 3 |
| AWMSG: Insulin degludec (Tresiba) compared to glargine (lantus) (61) | Wales: AWMSG | 2016 | DM >1y/o | Insulin degludec (tresiba) | Insulin glargine (lantus) | cost-utility analysis | Insulin degludec is superior and less costly (compared to glargine) in T1DM | No major areas, only some limitations | None | Recommended for restricted use in adult population where basal insulin required. Not recommended for children. | 3 | 5 |
| Canadian Agency for Drugs and Technologies in Health (52) | Canadian Agency for Drugs and Technologies in Health | 2007 | T1DM | Insulin glargine and Detemir | NPH Insulin | Meta-analysis | Inconclusive results when considering conflicts of interest in published articles. | Significance of clinical efficacy and safety profile. | Studies in support of long-acting analogues were funded by pharmaceutical companies with vested interests. | Inconclusive results. No recommendation can be made. | 3 | 4 |
| NIHR: Health Technology Assessment Programme (66) | UK: NIHR HTA programme | 2007 | T1DM and T2DM | Insulin glargine | NPH | Systematic review and Aventis model | No difference in glycaemic control. Glargine appears to reduce number of hypoglycaemic episodes. | Reviewed by INAHTA and found to use poor modelling technique | None | Further research required before recommendation can be made | No access, not for inclusion | No access, not for inclusion |
| NICE: Evidence review for T1DM (30) | UK: NICE | 2021 | T1DM | Degludec, glargine, detemir | NPH | Review of economic and clinical evidence. Model: IQVIA CORE Diabetes model (lifetime Markov simulation model). | No difference in HbA1c control amongst long-acting analogues. Highly variable evidence on hypoglycaemic episodes, various models created and all predicted at variable degree the following: Detemir twice daily most cost-effective of all. Glargine once daily most cost-effective once daily option. | Rates of hypoglycaemic episodes. | None | Detemir twice daily most cost-effective, followed by glargine once daily. | 6 | 5 |

**Table .** Summary of economic evaluations.

| Author | Year | Context (country and health system) | Indication | Intervention | Comparator | Economic evaluation type | Modelling approach | Results | Major areas of uncertainty | Context applicability score /6 | Methods applicability score /6 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Evans et al. (62) | 2015 | UK, NHS | T1DM adults | Degludec | Glargine | CEA | Short-term model | Degludec is cost-effective | Sensitivity analysis results | 3 | 5 |
| Valentine et al. (53) | 2012 | Nordic countries | T1DM | Detemir | NPH | Simple decision tree | one-year time horizon | Detemir is cost-effective | Appears to be robust | 3 | 4 |
| Pfohl et al. (41) | 2012 | Germany, statutory health insurance | T1DM | Glargine | NPH | CEA and CUA | CRC DES | Glargine dominated NPH | Not all health outcomes (heart disease) and costs (pens, SMBG) included | 3 | 5 |
| Cameron et al. (46) | 2009 | Canadian Health system | T1DM and T2DM | Detemir and glargine | NPH | CEA | Center for Outcomes Research (CORE) Diabetes Model (42) | Likely not to be cost-effective except potentially for those suffering from hypoglycaemia. Further research required. | Uncertain results. Based on model that may not reflect true population. Hypoglycaemia scores may bias analogues. | 3 | 6 |
| Grima et al. (49) | 2007 | Canadian Health system | T1DM and T2DM | Glargine | NPH | CEA | Long-term state transition model | Glargine is cost-effective for T1DM | Validity of estimates for costs and outcomes. | 3 | 6 |

## 7.5 Recommendations

In this review of economic evidence, most studies and economic evaluations lacked high levels of certainty when determining the cost-effectiveness of newer long-acting insulin analogues. Studies were ultimately often contradictory of one another, especially when reporting on differences in HbA1c control and differences in rates of hypoglycaemic events. In light of the most robust evidence from the clinical effectiveness review, recommendations should only be drawn from those studies or reports in which no difference in HbA1c was assumed and in which no other significant differences between insulins, barring severe hypoglycaemia, were included in the respective models. In those studies, in which high levels of certainty pertaining to cost savings were established, significant investment by pharmaceutical companies was evident. The undue influence from pharmaceutical companies may have impacted model parameters and/or the models themselves.

The analysis on behalf of the German Statutory Health Insurance in totality showed that insulin glargine was most likely cost-effective, with five out of the seven studies reviewed in that context indicating cost-effectiveness or even dominance (35).

The two Canadian meta-anlyses on the cost-effectiveness of insulin glargine and detemir versus NPH insulin determined that, in light of the sparse and inconsistent safety and effectiveness data available, the cost-effectiveness analyses were deemed largely inconclusive in order to make a recommendation for the Canadian public health authorities (46, 47). The evidence reviewing insulin degludec, however, seemed to favour it over insulin glargine (56, 57). Similarly, the results from the AWMSG indicated that degludec dominated insulin glargine for patients with T1DM, by being both cheaper and more effective.

The most comprehensive evidence arose from the NICE review of 2021, in which the authors assumed no differences in HbA1c control (and therefore many long-term complications of diabetes) with some differences in rates of hypoglycaemic episodes, to a variable degree. The reviewers concluded that for a twice daily regimen, insulin detemir ranked first, with NPH ranked second. With regards to once daily regimens, insulins glargine and degludec ranked first and second respectively. Twice daily insulin detemir was favoured across variable

scenarios of rates of hypoglycaemia. However, insulin glargine was considered second-most cost-effective in scenarios in which hypoglycaemic episodes was considered less heavily.

## 7. Conclusion and Gaps

The understanding of the pathogenesis of T1DM is ever-growing. Up to date, however, no known cure or effective prevention exists. The isolation of insulin and its subsequent use to treat T1DM has turned the disease from a death sentence to a manageable chronic condition. The treatment of the disease has been well studied and effective regimens have been established. With further developments in biotechnology, newer insulin agents have been created, namely the (ultra-) long-acting insulin analogues.

These new drugs garnered a lot of interest initially from smaller research groups, mostly funded by parties with vested interests. Only in the last couple of years have larger governmental and non-governmental groups reviewed the existing evidence surrounding these newer drugs. Their research has highlighted and provided the highest quality evidence to date regarding the clinical effectiveness of the drugs in review. Most of the important questions surrounding clinical effectiveness have been answered sufficiently by these newer reviews.

A gap in clinical effectiveness knowledge, however, is that pertaining to the only major difference identified between the insulins under review, namely severe hypoglycaemia. In particular, the definition used to categorise or classify hypoglycaemia are highly variable. Further research into the classifications and definitions used in the study of hypoglycaemia and long-acting insulins is required, although some research has already been initiated (60).

Regarding economic evidence, many organisations have made decisions regarding the cost-effectiveness on the insulins in question. These conclusions, however, are often highly variable and contradictory. This can be explained in part by the variable clinical effectiveness evidence available at the time, that influenced the economic models used and their relevant inputs. This literature review has sought to identify only the highest available clinical evidence for the use in economic models around this topic.

Finally, there is a sparsity of evidence surrounding T1DM in the South African population. This includes accurate data on the prevalence of T1DM, rates of diagnosis, treatment regimen

used as well as rates of adverse events and subsequent health system utilisation, especially with regards to hypoglycaemia. To date, no economic evaluation has been conducted on the potential use of long-acting insulins for the treatment of adults with T1DM in the South African public health sector.

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# Part C: Journal Manuscript

Journal of interest: BMC Health Economics

Author instructions can be found in Appendix F

# MPH-HE Mini-Dissertation

Journal Manuscript

# A Cost-Utility and Budget Impact 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 and has received much research and development over the years. In South Africa, intermediate-acting Neutral Protamine Hagedorn (NPH) insulin has been the mainstay basal insulin recommended in the public sector. Newer (ultra) long-acting insulin analogues, however, have subsequently been approved for use. Cost-utility and budget impact analyses of the newer long-acting insulin analogues detemir, glargine and degludec have yet to be performed in the South African public health sector context.

**Methods:**

A systematic search for clinical evidence was performed to inform the economic evaluation. A cost-utility analysis was carried out utilising Markov modelling. Seven comparators were modelled representing the various insulin types and treatment regimens. For each comparator, three Markov states were created, one in which no complications occurred and another two states representing nocturnal and daytime hypoglycaemic events respectively. Three scenarios were modelled in order to capture the variable rates of complications reported in the clinical evidence. Quality-Adjusted Life Years per patient year was the health outcome utilised. Costs were included as South African Rands and then converted to United States dollars. A cost-effectiveness threshold range appropriate for the South African context was used to assess value for money. Thereafter, a budget impact analysis was conducted.

**Results:**

Three systematic reviews were identified in the systematic search for inclusion in this study. Subsequently, three scenarios were modelled in order to capture the clinical significance identified in the three systematic reviews. All three models favoured NPH insulin over the

alternatives, as NPH insulin dominated most other insulins, barring insulin detemir, insulin glargine-U300 and insulin degludec. Insulin detemir was the most cost-effective option of the alternatives to NPH insulin (ICER of 10,783.75 USD/QALY). However, insulin detemir was still not cost-effective in relation to South Africa's cost-effectiveness threshold (CET 1,175 - 8,909 USD/QALY). The NPH insulin twice daily regimen was also found to dominate the NPH once daily regimen.

**Conclusions:**

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. Further research and consideration could be made for the use of NPH insulin twice daily, as opposed to once daily.

**Keywords**: Diabetes, type 1 diabetes, adult, cost-effectiveness, South Africa, Budget-Impact, Insulin, cost-utility

**Total Word Count**: 5,885

# 1. Background

The United Nations Sustainable Development Goal (SDG) target 3.4 aims to reduce premature mortality attributable to 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 trend globally 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 (4) (5). In South Africa specifically, it is estimated that premature adult deaths attributed to diabetes has increased by 38% between 1999 and 2006 (6, 7).

One of the major subtypes of diabetes is Type 1 Diabetes Mellitus (T1DM). T1DM disease is hallmarked by high levels of blood glucose secondary to insulin deficiency that, when left untreated, is fatal. 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. The aetiology of decreased or ceased production insulin by beta-islet cells of the pancreas is poorly understood, with no widely accepted cures for the condition evident. 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 (3).

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. In South Africa, Neutral Protamine Hagedorn (NPH) insulin, an intermediate-acting insulin, has been used to replicate basal levels of inter-prandial insulin in conjunction with rapid-acting insulins,

which replicate spikes in insulin in relation to meals, in order to achieve physiologically comparable insulin levels in adult T1DM patients.

With insulin use, acute and chronic complications of T1DM, including diabetic ketoacidosis and micro- and macrovascular complications respectively, can be averted. Exogenous insulin, however, has noticeable adverse drug events. Insulin in excess relative to blood glucose levels can cause 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 (<2mmol/L) to hypoglycaemia requiring third-party assistance (ranging from non-medically trained individuals to hospital admission) and has subsequently received further research interest (60).

In response to acute and chronic complications as well as potential adverse drug events, research and development has led to the creation of newer insulins of varying pharmacokinetic and pharmacodynamic properties. Recently, new (ultra-) long-acting insulin analogues have been approved by the South African Health Products Regulatory Authority (SAHPRA), with insulin glargine being approved in 2000, insulin detemir being approved in 2005 and insulin degludec being approved in 2015 (20).

The newer (ultra-) long-acting insulin analogues have received much clinical attention and subsequent research into their clinical efficacy. Furthermore, they have also received much attention from health technology assessment agencies in order to determine the cost-utility of the drugs for respective health systems (47, 51, 56, 61, 62). Many individual studies also exist,

most of which report highly variable conclusions on cost-effectiveness, primarily driven by highly variable clinical effectiveness data available at the time (35, 40, 43, 48-50, 57, 63). This variability may in part be due to consequences of funding received from pharmaceutical groups with vested interest amongst the primary clinical effectiveness studies. However, with recent extensive, more impartial and high-quality systematic reviews available, better judgement can be passed surrounding the cost-effectiveness of newer long-acting insulin analogues.

Finally, an economic evaluation of these newer (ultra-) long-acting insulin analogues has yet to be performed for the South African adult T1DM population. The aims of this study, therefore, are to review relevant clinical evidence and economic data in order to inform a cost-utility analysis and budget impact analysis of newer long-acting insulins (detemir, glargine and degludec) in comparison to the *status quo* in South Africa, namely, intermediate-acting NPH insulin.

# 2. Methodology

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

## 2.1 Clinical effectiveness review

A systematic search was conducted in order to identify relevant studies to inform the clinical effectiveness review. Search terms included the interventions (long-acting insulin analogues detemir, glargine and degludec), the relevant patient population (adult type 1 diabetics) and the comparator (NPH insulin). Studies included involved adult patients with T1DM and at least one of the interventions under review. Studies were excluded if they involved biosimilars, continuous subcutaneous infusion, focussed on excluded patient populations (for example

pregnant women) or if they were not a systematic review or meta-analysis. No exclusion criteria were set for study setting or date. The exact search terms used can be found in Appendix B. Databases included in the search were Epistimikos, PubMed and Cochrane Database of Systematic Reviews.

## 2.2 Economic Evaluation

### 2.2.1 Cost-utility analysis

The clinical effectiveness review informed a cost-utility analysis (CUA) that primarily drew its structure from a recent health technology assessment guideline specifically for the South African public health sector by Wilkinson and Wilkinson (17). The CUA was performed using a Markov model using TreeAge Pro software (2021) (25). The provider perspective was taken, and health outcomes were measured in Quality-Adjusted Life Years (QALYs). A single year time frame was used with one cycle as the only appreciable differences across insulin types were rates of acute complications (i.e. severe hypoglycaemia). Since the model had a single cycle length and one-year time horizon, no discount rate was applied. The price year assumed was March 2020 to February 2021 and the average South African Rand (ZAR) to United States Dollar (USD) exchange rate for this year was 16.5045 ZAR/USD.

Three Markov model scenarios were created in order to represent the clinical effectiveness findings from the three systematic reviews identified. The findings included in the model were primarily the differences in severe hypoglycaemia identified by the systematic reviews. For each Markov model, various comparators were created in order to represent the different insulin types and their potential variation in dosing and formulation included in the studies. Only insulins and their formulation that showed significant differences in the studies from which clinical evidence is drawn are included as Markov states. For each modelling scenario,

three Markov states were created: T1DM with no complications, T1DM with severe daytime hypoglycaemic events and T1DM with severe nocturnal hypoglycaemic events.

| Three Markov Models | Comparators | Markov states of each model |
|---|---|---|
| *NICE* model | NPH once daily (status quo) | 1) Healthy<br>2) Severe daytime hypoglycaemia<br>3) Severe nocturnal hypoglycaemia |
| | NPH twice daily | |
| | Detemir once daily | |
| | Detemir twice daily | |
| | Glargine U300 once daily | |
| | Glargine U100 once daily | |
| | Degludec once daily | |
| *Cochrane* model | NPH once daily (status quo) | |
| | NPH twice daily | |
| | Detemir once daily | |
| | Detemir twice daily | |
| *Martin et al.* model | NPH once daily (status quo) | |
| | Glargine U300 once daily | |
| | Degludec once daily | |

**Figure 1.** Markov model scenarios, their respective insulin comparators and Markov states.

Transition probabilities of severe daytime and nocturnal hypoglycaemia were drawn from rates of severe hypoglycaemia in an economic model on T1DM in adults performed by the National Institute for Health and Care Excellence (NICE) and will be elaborated on later (62).

The included multi-dimensional outcome was Health-related Quality of Life (HRQoL). The yearly HRQoL for the T1DM with no complication state (0.839) was drawn from Peasgood et al (2016) and the HRQoL for severe daytime (0.777) and severe nocturnal (0.773) hypoglycaemic events were derived from a study by Evans et al (2013) (64, 65). These HRQoL values represent the quality of life per hypoglycaemic event per year and were selected as they were identified to be the most robust of the little data available surrounding this topic.

### 2.2.2 Utilisation rates

T1DM patients are placed on both rapid- and intermediate/long-acting insulin. The total amount of daily insulin prescribed, i.e. rapid- and intermediate/long-acting, is generally derived from the patient's weight. To determine how much intermediate/long-acting insulin to prescribe, drug labelling information recommend a percentage of the total daily insulin, discussed previously, that the intermediate/long-acting insulin should constitute. Utilisation rates of insulin per patient per year, therefore, were calculated using the recommended total units of insulin per kilogram per day as well as the proportion of total daily insulin that consists of basal intermediate- to long-acting insulin, according to the South African Primary Health Care Level Standard Treatment Guidelines and Essential Medicines List as well as the recommendations made in the U.S. Food and Drug Administration drug labelling information (9, 66-69). A mean weight of 81.2kg (SD 17.8) was used and is derived from a study conducted in the United Kingdom that included adult T1DM patients with a slight predilection for males (59% of participants were male) (70).

Utilisation rates of health services were derived from a study by Hammer et al (2009), in which utilisation rates of health services for severe hypoglycaemic events experienced by T1DM patients are investigated in Spain, Germany and the United Kingdom (UK) (55). Data pertaining to the UK cohort were primarily used as these results were the most conservative with regards to length of inpatient stay and best reflected the likely average length of stay in South Africa. In the sensitivity analysis, the lower value for average length of stay was one inpatient day.

Rates of severe hypoglycaemia experienced by different insulin types and regimens were drawn from the NICE economic model report of long-acting insulin analogues, as this was the

only review that reported rates per person-year for all insulins under review (62). Here the authors utilised data collated in the NICE clinical effectiveness review of long-acting insulin in adults for T1DM and created three scenarios for the rates of severe hypoglycaemia. These scenarios represented differing methods of calculating severe hypoglycaemic rates (27). In scenario one, the risk ratios identified in the systematic review of clinical evidence network meta-analysis (NMA) were applied to rates of severe hypoglycaemia for the detemir twice daily group, whose rate was determined using a random effects meta-analysis from the systematic review of clinical evidence. In scenario two, the authors used the random effects meta-analysis from the systematic review of clinical evidence for all treatment groups, therefore not applying relative risks as in scenario one. In scenario three, no difference in the rates of severe hypoglycaemia was assumed. Using these three scenarios, lower, base case and upper values were identified and used accordingly for the economic evaluation in the current study.

In order to estimate the rates of severe hypoglycaemia occurring during the day and at night, proportions of each reported in the same NICE economic model report were used. The authors drew from the same clinical effectiveness review mentioned prior, where the NMA was used to estimate relative effects of nocturnal hypoglycaemia (27). These relative effects were applied to the proportion of severe hypoglycaemia that occurred at night in the detemir twice daily group in order to estimate the proportions for all other insulin groups. These estimates constituted the rates of severe hypoglycaemia for the NICE Markov model.

With the base case rates of severe hypoglycaemia identified in the NICE model, risk ratios between rates of severe hypoglycaemia reported in the other two systematic reviews were

applied in order to estimate rates of severe hypoglycaemia for the remaining two Markov models (see Table 3).

**Table 1.** Utilisation rates of inpatient hospitalisation, insulin utilisation and rates of severe hypoglycaemia.

| **Inpatient Hospitalisation** | | | |
|---|---|---|---|
| | **Base** | **Range** | **Source** |
| Proportion of severe hypoglycaemia requiring inpatient hospital admission | 32.89% | 25.25% to 36.26% | Hammer (55) |
| Length of stay (days) | 2 | 1 to 6 | Hammer (55) |
| **Insulin utilisation** | | | |
| | **Base** | **Range** | **Source** |
| Mean weight (kg) | 81.2 | ± 17.8 | Heller (70) |
| Total units of insulin per kg per day (U/kg/day) | 0.60 | 0.5-1 | EML and FDA (9, 66-69) |
| Proportion of total insulin that is NPH insulin | 0.45 | 0.4-0.5 | EML |
| Proportion of total insulin that is insulin Detemir | 0.33 | - | FDA (67) |
| Proportion of total insulin that is insulin Glargine-U100 | 0.33 | - | FDA (66) |
| Proportion of total insulin that is insulin Glargine-U300 | 0.33 | 0.33-0.5 | FDA (68) |
| Proportion of total insulin that is insulin Degludec | 0.33 | 0.33-0.5 | FDA (69) |

### 2.2.3 Utilisation costs

Unit costs of treatment with insulin were derived from the South African Master Health Product List (MHPL) of October 2020 and South African Single Exit Prices from the Medicines Price Registry (MPR) of December 2020. The cheapest formulation per unit of insulin was included. Since the cost per unit of insulin was cheapest in the 10ml (100U/ml) injection formulation, this was preferentially chosen as the cost input. Where cost information for this formulation was not available, the second cheapest formulation was used, namely the cost per 5 packs of 3ml (100U/ml) cartridge of insulin. The cost of insulin needles was also included. The insulin costs per patient per year were 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, cost per needle and the number of days in a year.

Costs of health services, particularly inpatient stays from hypoglycaemic events, were derived from the district health barometer (2019/2020) (71). The patient day equivalent (PDE), specifically, was utilised and is a weighted measure combining inpatient days, day patient headcounts, outpatient department and emergency casualty headcounts to derive resource requirements for one inpatient day. The costs derived from health services are therefore comprised of the rate of severe hypoglycaemia, the proportion of which require inpatient hospital admission, the average length of stay and the cost per patient day equivalent.

**Table 2.** Cost data.

| **Inpatient Hospitalisation costs** | | | |
|---|---|---|---|
| | **Cost (USD)** | | **Source** |
| Cost per patient day | 192.61 | | DHB 2019/20 |
| **Insulin costs** | | | |
| | **Cost (USD)** | **Insulin cost per patient per day (USD)** | **Source** |
| NPH: Protaphane injection 10ml (100U/ml) | 2.25 | 0.0494 | MHPL Oct 2020 |
| Detemir: Levemir cartridge 5 x 3ml (100U/ml) | 28.48 | 0.3052 | MPR Dec 2020 |
| Glargine-U100: Lantus injection 10ml (100U/ml) | 29.69 | 0.4774 | MHPL Oct 2020 |
| Glargine-U300: Teajou pen 3 x 1.5ml (300U/ml) | 32.63 | 0.3886 | MPR Dec 2020 |
| Degludec: Tresiba cartridge 5 x 3ml (100U/ml) | 59.39 | 0.6365 | MPR Dec 2020 |
| **Needle cost** | | | |
| | **Cost (USD)** | **Cost per needle (USD/needle)** | **Source** |
| Insulin needle 31G 5mm (100 needles per pack) | 4.47 | 0.0447 | MHPL Oct 2020 |

From the Markov models created, incremental cost-effectiveness ratios (ICERs) were calculated for each comparison pair by dividing the difference health utility of the insulin pair by the difference in their costs.

### 2.2.4 Sensitivity Analysis

A one-way simple sensitivity analysis was performed using upper and lower limits of model inputs where available. If no ranges were available, the input was varied by 10% in both directions.

### 2.2.5 Budget Impact Analysis

A budget Impact Analysis (BIA) was also performed, drawing its structure from the aforementioned health technology assessment guide. The South African public sector payer perspective was assumed. All T1DM patients in South Africa are assumed to be diagnosed and placed on treatment, as the condition presents itself with acute complications and is fatal without treatment. A proportion representative of the South African population consuming public health care (84%) was then applied to the prevalence in order to identify the prevalence of T1DM in the public health sector (72). A standard population growth of 1.4% was assumed, according to the mid-year population estimates by statistics South Africa. The costs of treatment and costs on the health system were derived from the CUA and applied. In addition, rapid and slow adoption scenarios were created. In the rapid adoption scenario, a 60% first year market share was assumed for the NPH insulin, the remainder of which was attributed to the comparator. A 40% decrease in market share was applied to NPH insulin yearly, with the change being directed towards the comparator. Similarly, in the slow adoption scenario, NPH insulin received a 90% first year market share and a 20% decrease was applied yearly. BIAs were performed for the top two insulin alternatives identified in the CUA.

# 3. Results

## 3.1 Clinical effectiveness review

### 3.1.1 Systematic search

From the search, a total of 208 records were identified for further screening. One additional review was identified after checking reference lists of relevant articles. After duplicate removal and title, abstract and full text review for exclusion, 39 studies were identified for full text review. Of these, eight were included for further study composition comparison (Appendix C), from which three studies were selected for the clinical effectiveness review. Therefore, the

three studies included were a Cochrane Review by Hemmingsen et al., a review by the National Institute for Care Excellence (NICE) and a review by Martin et al. (18, 27, 28). These were appraised in duplicate using the A Measurement Tool to Assess Systematic Review (AMSTAR) tool and were found to be of good quality. The main methodological differences to note between the reviews are summarised in Appendix D.

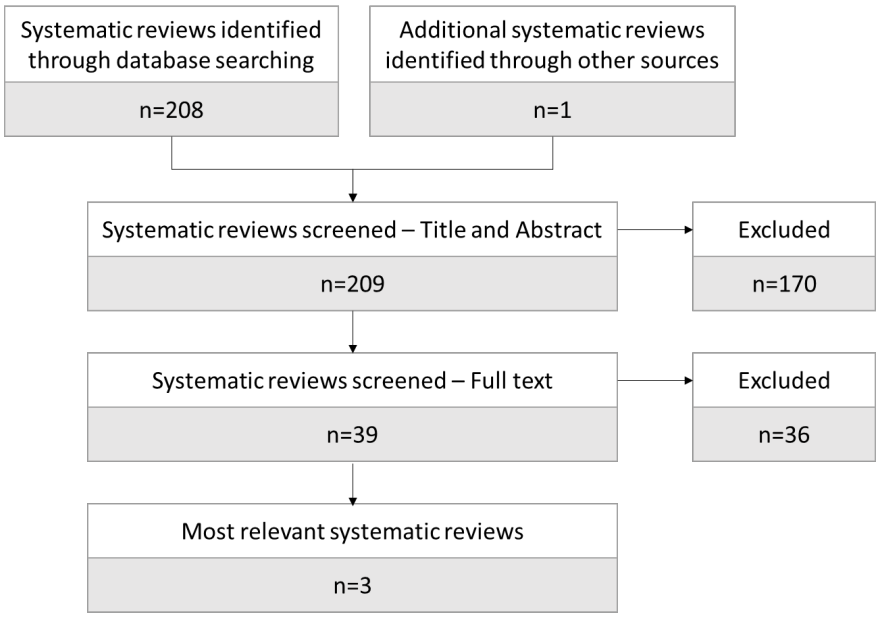



**Figure 2.** Search strategy and study selection.

### 3.1.2 Clinical effectiveness

#### HbA1c, all-cause mortality and HRQoL

The clinical effectiveness reviews by Cochrane, Martin et al and NICE found all insulins under review to be non-inferior with regard to HbA1c control. The Cochrane review was the only review to include all-cause mortality as an outcome and found no difference between insulins. The reviews by Cochrane and NICE lacked data in order to comment of differences in HRQoL and the review by Martin et al. did not include HRQoL as an outcome.

**Severe Hypoglycaemia**

The NICE review identified a significant reduction in severe hypoglycaemia in the pairwise NMA in the detemir twice daily vs NPH once/twice daily and detemir once/twice daily vs NPH once/twice daily analyses. This reduction in severe hypoglycaemia, however, is accompanied by wide confidence intervals, suggesting uncertainty. The detemir once/twice daily versus NPH once/twice daily analysis was based off a single study by Bartley (2008) and found the rate ratio of severe hypoglycaemia to be 0.31 (CI 0.25, 0.38) (73). In the NPH once/twice daily versus detemir twice daily analysis the risk rate was 3.28 (CI 1, 10.77).

The Cochrane Review found a statistically significant reduction in severe hypoglycaemia in the detemir group versus the NPH group in the combined analysis (including paediatric studies), with rates of 8.5% vs 11.5% respectively (RR 0.69, CI 0.52, 0.92). In the adult subgroup analysis, rates of severe hypoglycaemia showed insignificant results and thus no difference could be concluded (RR 0.71, CI 0.49, 1.03). In the severe nocturnal hypoglycaemia adult subgroup analysis, however, statistically lower rates were shown in the detemir group versus the NPH insulin group (RR 0.57, CI 0.35, 0.93). The Cochrane review found no further significant differences between all insulins.

The review by Martin et al. showed no significant differences in severe daytime hypoglycaemia and HbA1c control between first-generation insulins (NPH insulin, insulins detemir and glargine-U100) and second-generation insulins (insulins degludec and glargine-U300). The review found that a significantly greater proportion of NPH insulin users had severe nocturnal hypoglycaemia compared to the insulins degludec (HR 2.84, CI 1.88, 4.38) and the glargine-U300 (HR 2.78, CI 1.69, 4.68).

**Table 3.** Model inputs for severe hypoglycaemia.

| NICE model rates of severe hypoglycaemia (per 100 person years) (62) | | | | |
|---|---|---|---|---|
| **Insulin** | **Lower** | **Base** | **Upper** | **Proportion nocturnal hypoglycaemia** |
| NPH once daily | 30.17 | 50.65 | 68.61 | 0.2215 |
| NPH twice daily | 30.17 | 34.29 | 42.50 | 0.1839 |
| Detemir once daily | 30.17 | 40.81 | 57.21 | 0.2000 |
| Detemir twice daily | 30.17 | 30.17 | 36.53 | 0.1396 |
| Glargine-U100 | 30.17 | 49.67 | 65.70 | 0.1569 |
| Glargine-U300 | 30.17 | 50.26 | 91.82 | 0.1417 |
| Degludec | 30.17 | 45.68 | 57.17 | 0.1081 |
| **Cochrane model rates of nocturnal severe hypoglycaemia (per 100 person years) (18)** | | | | |
| **Insulin** | **Lower** | **Base** | **Upper** | **Risk ratio applied to NICE NPH nocturnal hypoglycaemia rates** |
| NPH once daily | 6.68 | 11.22 | 15.20 | - |
| NPH twice daily | 5.55 | 6.31 | 42.50 | - |
| Detemir once daily | 3.93 | 6.39 | 10.43 | RR 0.57, CI 0.35, 0.93 |
| Detemir twice daily | 2.21 | 3.59 | 5.87 | RR 0.57, CI 0.35, 0.93 |
| **Martin et al. model rates of severe nocturnal hypoglycaemia (per 100 person years) (28)** | | | | |
| **Insulin** | **Lower** | **Base** | **Upper** | **Hazard Ratio applied to NICE NPH once daily nocturnal hypoglycaemia rates** |
| NPH once daily | 6.68 | 11.22 | 15.20 | - |
| Glargine-U300 | 2.36 | 4.04 | 6.62 | HR 0.36, CI 0.21, 0.59 |
| Degludec | 2.58 | 3.93 | 5.95 | HR 0.35, CI 0.23, 0.53 |

## 3.2 Economic Evaluation

### 3.2.1 Cost-utility analysis

Three Markov models were created in order to model the variable findings of the clinical effectiveness reviews by NICE, Cochrane and Martin et al. The pertinent main finding modelled was that of severe hypoglycaemia, both nocturnal and daytime. In particular, the effects of severe hypoglycaemia in relation to quality of life and inpatient hospitalisation were captured. The cost of each group essentially comprised of costs of the medicines cost as well as the cost incurred from hospitalisations.

To interpret the results of the cost-utility analysis, the marginal productivity of the South African public health system was estimated. Using the country-level cost-effectiveness thresholds (CETs) by Woods et al (2016), the CET for South Africa can be expected to lie between 1,175 and 8,909 USD/QALY (midpoint 5,042 USD/QALY) for the year 2013 (26).

In the first model, emulating the findings in the NICE economic review, differences in rates of severe hypoglycaemia were assumed between all insulin types and regimens, as outlined in Table 1. In the analysis of all regimens, comparator insulins were not better buys compared to NPH insulin, with NPH insulin dominating all other insulin formulations and regimens except for detemir twice daily. The incremental costs of twice daily detemir were modest with minor incremental benefits resulting in a large ICER of 22,530.33 USD/QALY compared to NPH twice daily insulin. In the sub-analysis in which only once-daily regimens were included, NPH insulin once daily similarly dominated all groups other than the detemir group. Here the ICER for utilising detemir once daily over NPH insulin once daily was lower at 10,783.75 USD/QALY. In addition, NPH twice daily was shown to dominate NPH once daily as a treatment strategy.

**Table 4a.** Incremental cost-effectiveness ratio from the model incorporating findings by the NICE review including twice daily insulin regimens.

| Dominance | Strategy | Cost (USD) | Incr Cost (USD) | Effect (QALY) | Incremental Effect (QALY) | ICER (USD/QALY) |
|---|---|---|---|---|---|---|
| undominated | NPH twice daily | 91.32 | | 0.8175 | | |
| abs. dominated | NPH once daily | 97.13 | 5.81 | 0.8071 | -0.0103 | -562.07 |
| undominated | Detemir twice daily | 150.76 | 59.44 | 0.8201 | 0.0026 | 22,530.33 |
| abs. dominated | Detemir once daily | 164.24 | 13.48 | 0.8134 | -0.0068 | -1,995.76 |
| abs. dominated | Glargine U300 | 206.97 | 56.21 | 0.8075 | -0.0126 | -4,466.70 |
| abs. dominated | Glargine U100 | 253.87 | 103.11 | 0.8079 | -0.0122 | -8,428.59 |
| abs. dominated | Degludec | 307.48 | 156.72 | 0.8105 | -0.0096 | -16,248.37 |

**Table 4b.** Incremental cost-effectiveness ratio from the model incorporating findings by the NICE review: once daily regimen analysis.

| Dominance | Strategy | Cost (USD) | Incr Cost (USD) | Effect (QALY) | Incremental Effect (QALY) | ICER (USD/QALY) |
|---|---|---|---|---|---|---|
| undominated | NPH once daily | 97.13 | | 0.8071 | | |
| undominated | Detemir once daily | 164.24 | 67.11 | 0.8134 | 0.0062 | 10,783.75 |
| abs. dominated | Glargine U300 | 206.97 | 42.73 | 0.8075 | -0.0058 | -7,329.65 |
| abs. dominated | Glargine U100 | 253.87 | 89.63 | 0.8079 | -0.0055 | -16,360.12 |
| abs. dominated | Degludec | 307.48 | 143.24 | 0.8104 | -0.0029 | -49,555.97 |

In the second model, the pertinent result of the Cochrane review, namely the significant difference noted in the adult sub-analysis of the rates of severe nocturnal hypoglycaemia in the detemir group compared to NPH insulin group, was applied whilst no difference in severe hypoglycaemia was assumed between all other insulin groups. In the twice daily analysis, comparators were not cost-effective compared to NPH insulin, with the ICER for detemir twice daily being 34,210.18 USD/QALY. Similarly, in the once daily analysis, insulin detemir imposed an ICER of 23,073.04 USD/QALY when compared to NPH insulin.

**Table 5a.** Incremental cost-effectiveness ratio from the model incorporating findings of the Cochrane review: twice daily regimen analysis.

| Dominance | Strategy | Cost (USD) | Incr Cost (USD) | Effect (QALY) | Incr Eff (QALY) | ICER (USD/QALY) |
|---|---|---|---|---|---|---|
| undominated | NPH twice daily | 86.44 | | 0.8199 | | |
| undominated | Detemir twice daily | 147.67 | 61.22 | 0.8217 | 0.0018 | 34,210.18 |

**Table 5b.** Incremental cost-effectiveness ratio from the model incorporating findings of the Cochrane review: once daily regimen analysis.

| Dominance | Strategy | Cost (USD) | Incr Cost (USD) | Effect (QALY) | Incr Eff (QALY) | ICER (USD/QALY) |
|---|---|---|---|---|---|---|
| undominated | NPH once daily | 77.75 | | 0.8166 | | |
| undominated | Detemir once daily | 151.22 | 73.46 | 0.8198 | 0.0032 | 23,073.04 |

In the third model, NPH insulin once daily was compared to glargine-U300 and degludec. Hazard ratios of severe nocturnal hypoglycaemia identified by Martin et al. were applied on the base case rate of severe nocturnal hypoglycaemia for NPH insulin identified by the NICE economic model. Comparators were demonstrated to not be cost-effective, with insulin glargine-U300 conferring an ICER of 21,347.00 USD/QALY and insulin degludec resulting in an ICER of 1,887,783.81 USD/QALY, compared to NPH insulin.

**Table 6.** Incremental cost-effectiveness ratio from the model incorporating findings by Martin et al.

| Dominance | Strategy | Cost (USD) | Incr Cost (USD) | Effect (QALY) | Incr Eff (QALY) | ICER (USD/QALY) |
|---|---|---|---|---|---|---|
| undominated | NPH once daily | 77.75 | | 0.8166 | | |
| undominated | Glargine U300 | 178.96 | 101.21 | 0.8214 | 0.0047 | 21,347.00 |
| undominated | Degludec | 285.19 | 106.23 | 0.8214 | 0.0001 | 1,887,783.81 |

### 3.2.2 Sensitivity Analysis

One-way sensitivity analyses were performed on all variables included in each of the three modelling scenarios. The five variables with the greatest impact are depicted in the relevant tornado diagrams for each model. Across the sensitivity analyses, the rates of severe hypoglycaemia, quality of life associated with severe hypoglycaemia and average length of inpatient hospital stay were the greatest drivers of the analysis, as expected. Insulin detemir once daily in the model utilising the NICE economic evaluation rates of severe hypoglycaemia showed that length of inpatient stay, quality of life for severe daytime and nocturnal hypoglycaemia as well as total units of insulin recommended per day had the potential impact of bringing insulin detemir once daily into South Africa's potential CET range of 1,175 to 8,909 USD/QALY (Figure 3b). When taking the midpoint of this wide CET range (5,042 USD/QALY), then only the increase in length of inpatient stay from two days to eight days

rendered insulin detemir cost-effective. The upper rate of severe hypoglycaemia for NPH insulin twice daily also drove detemir twice daily into the cost-effective range (Figure 3a).

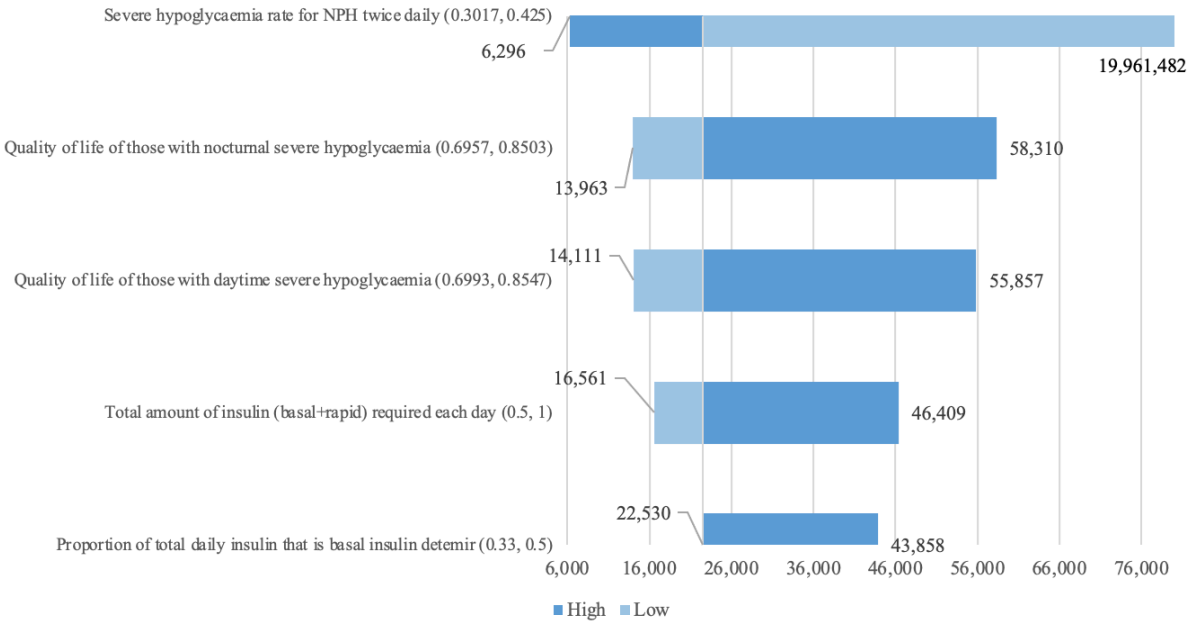



**Figure 3a.** Tornado diagram between NPH twice daily and Detemir twice daily from the model incorporating findings by the NICE review.

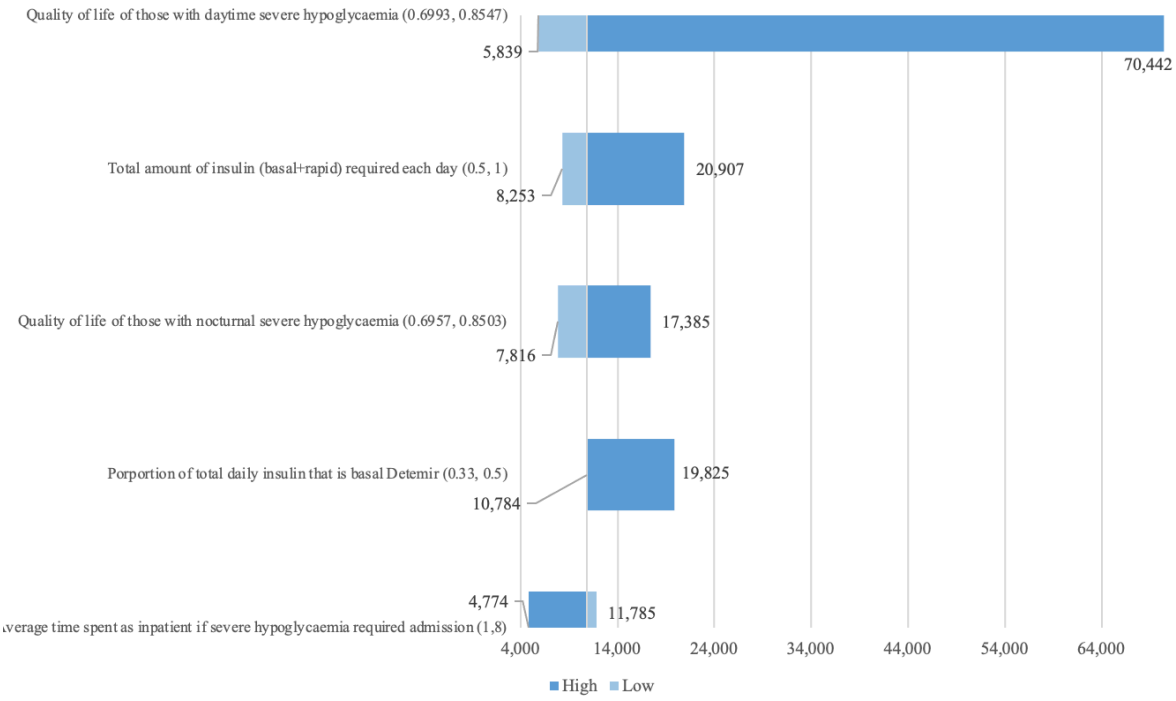



**Figure 3b.** Tornado diagram between NPH once daily and Detemir once daily from the model incorporating findings by the NICE review.

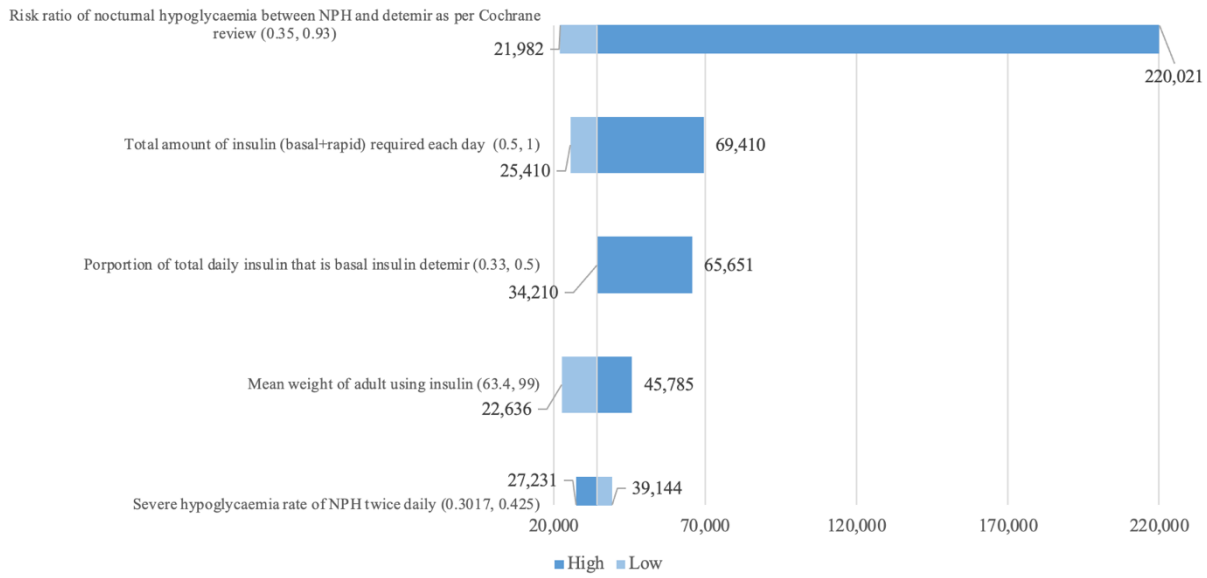



**Figure 4a.** Tornado diagram between NPH twice daily and detemir twice daily from the model incorporating findings by the Cochrane review.

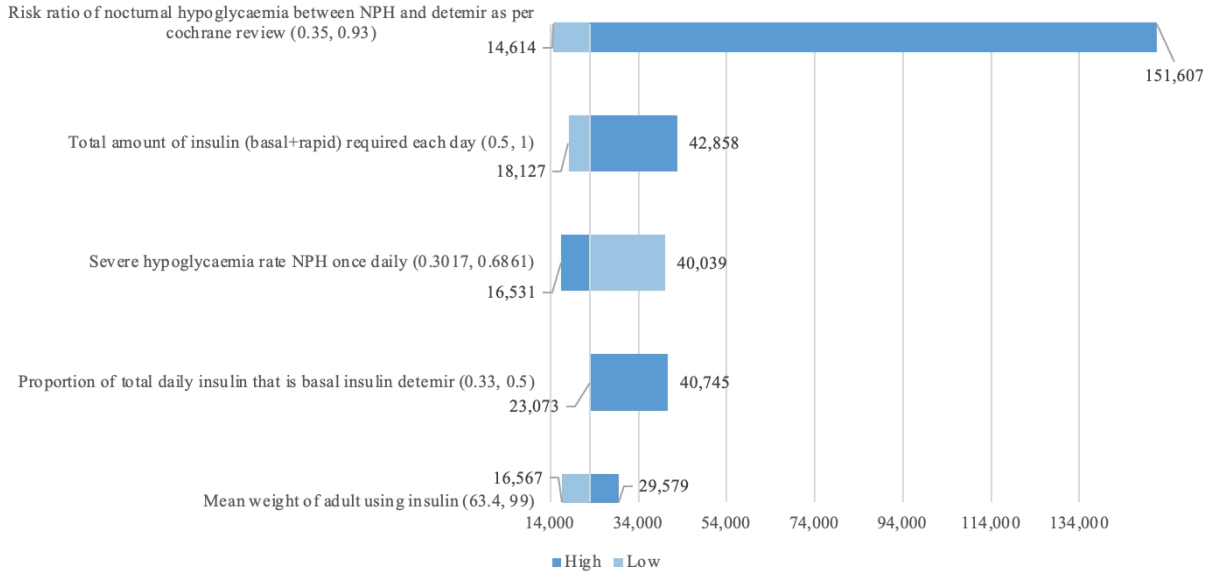



**Figure 4b.** Tornado diagram between NPH once daily and detemir once daily from the model incorporating findings by the Cochrane review.

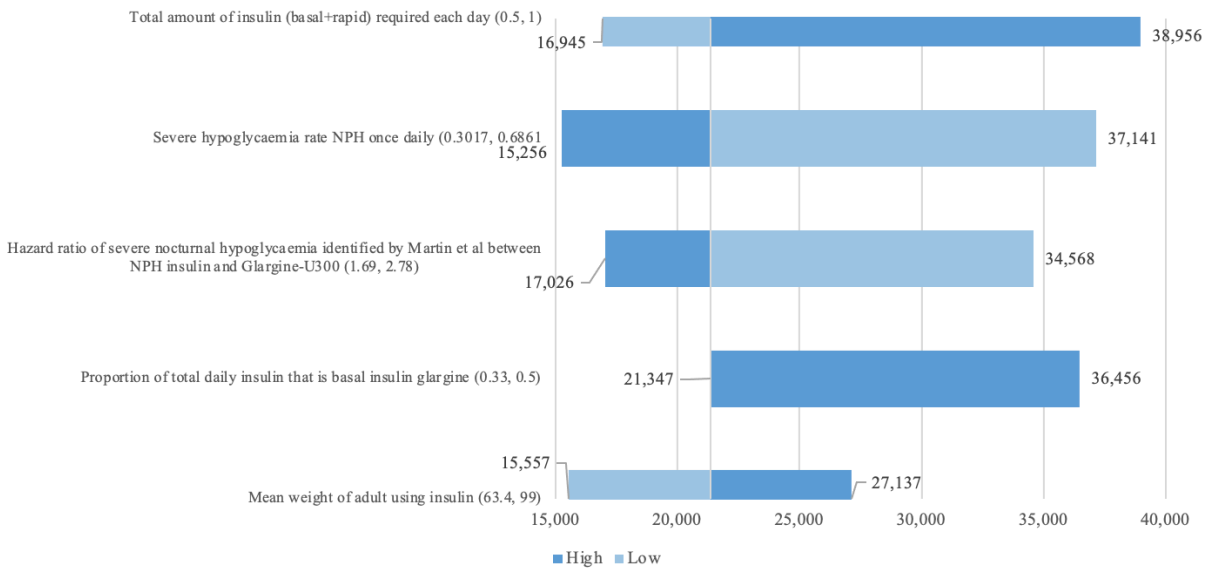
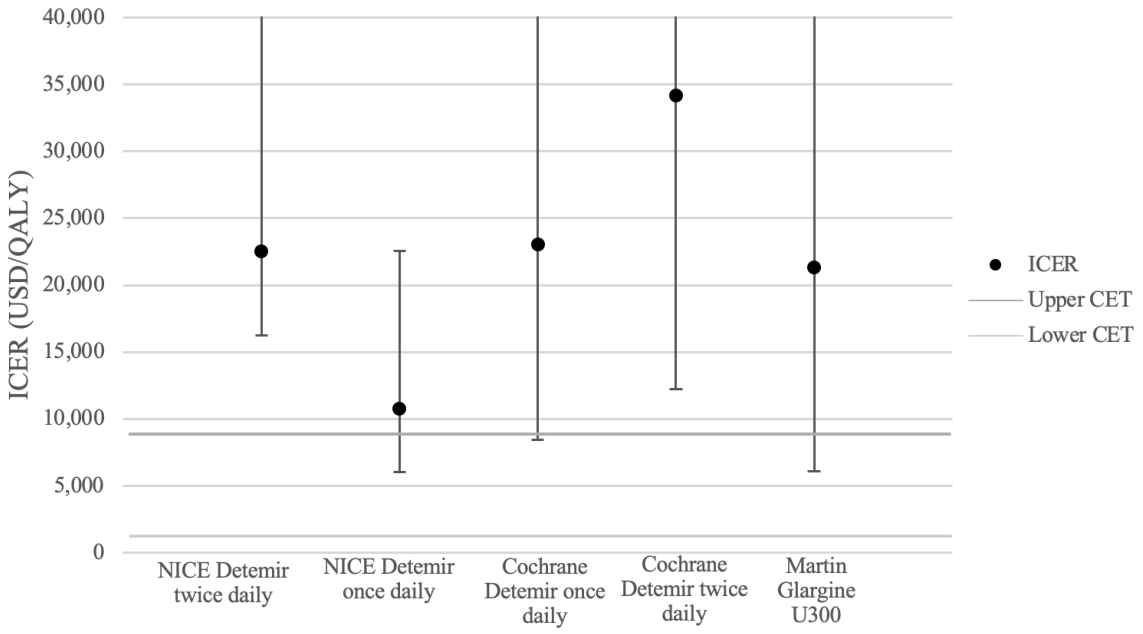



**Figure 5.** Tornado diagram between NPH once daily and glargine-U300 once daily from the model incorporating findings by the Martin et al.




Ranges indicate the single most impactful variation in model input identified in the sensitivity analyses for each Markov model.

**Figure 6.** Depiction of relevant ICERs of long-acting insulins compared to their NPH insulin counterpart in the respective Markov models.

### 3.2.3 Budget Impact Analysis

Given that detemir once daily was the most cost-effective insulin of the comparators to NPH insulin, as identified in the NICE Markov models, a BIA was performed comparing insulin detemir to the *status quo* (Appendix E). These results are presented in Table 7. It is evident from this analysis that implementation of insulin detemir would incur great costs to the health budget.

**Table 7.** BIA of implementing detemir once daily over five-year period.

| Strategy | Scenario | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|---|
| NPH once daily | Status quo | $11,147,349.25 | $11,303,412.14 | $11,461,659.91 | $11,622,123.15 | $11,784,832.88 |
| Detemir once daily | Rapid | $14,227,968.07 | $16,301,408.10 | $17,669,920.59 | $18,611,053.61 | $19,293,688.37 |
| | Slow | $11,917,503.96 | $13,490,035.38 | $14,819,188.65 | $15,951,662.79 | $16,925,350.53 |
| **Net total costs** | **Rapid** | **$3,080,618.81** | **$4,997,995.96** | **$6,208,260.68** | **$6,988,930.46** | **$7,508,855.49** |
| | **Slow** | **$770,154.70** | **$2,186,623.23** | **$3,357,528.74** | **$4,329,539.64** | **$5,140,517.66** |

# 4. Discussion

From the systematic search and review of clinical evidence of long-acting insulins, it is apparent that conflicting data exist. In the past, this uncertainty had led to some health technology assessment initiatives preferring not to make a recommendation based on available evidence (46, 47). The need for greater certainty around clinical evidence, however, has been met by the more recent reviews included in this analysis.

The clinical effectiveness reviews identified indicate that there is little difference between the insulins under review. Notably, the evidence suggests no difference in major outcomes of long-term complications of diabetic control. The main difference noted in the reviews, however, is that of severe hypoglycaemia, where the reviews differ in the reported statistical significance between total, daytime and nocturnal severe hypoglycaemia.

In the cost-utility analysis, the short-term complications of severe hypoglycaemia are modelled. In the three models incorporating varying rates of severe hypoglycaemia from the clinical effectiveness reviews, NPH insulin was cheaper and inferred greater health benefit than most insulins and, where it did not, the use of the alternative generated high ICERs that were not cost-effective from the South African public health care provider perspective. Sensitivity analyses also suggest the results demonstrated are largely robust, as variation in model inputs did not provide sufficient evidence for potential changes in cost-effectiveness rankings of most insulins in relation to the South African CET. The only variation in model input that suggested potential cost-effectiveness over the *status quo* was noted in the model incorporating findings of the NICE economic evaluation, particularly in the once daily regimen analysis. The increase of the average length of inpatient hospital stay following hypoglycaemia from two days to eight days suggested that insulin could potentially be cost-effective compared to the midpoint of South Africa's estimated CET. An average inpatient length of stay of eight days for iatrogenic severe hypoglycaemia, however, is highly unlikely in the South African setting. A ten percent reduction in quality of life for severe daytime and nocturnal hypoglycaemia, as well as seventeen percent reduction total units of insulin recommended per day, had the potential impact of bringing insulin detemir once daily into South Africa's potential CET range, however, the likelihood of this being the reality is uncertain.

The recommendations from this analysis thus favour NPH insulin over the newer long-acting insulin analogues included in this review. This recommendation is in line with a recent clinical practice guideline by the World Health Organization, that draws its evidence from a review by Tricco et al. (46, 74).

Disparities in recommendations by other economic evaluations, however, do exist and depend on study setting and clinical effectiveness assumptions. For example, the recommendation of this study differs with the NICE NG17 clinical practice guidelines that draw their evidence from both the NICE clinical effectiveness review as well as the NICE economic evaluation of which some data was used to inform this analysis (75). In this guideline, the authors recommend detemir twice daily as the primary recommendation. The results of this study also differ to other economic evaluations, with one evaluation finding insulin glargine to be the most cost-effective option (35). Again, uncertainty around these findings come to light as evidence exists favouring insulin degludec over insulin glargine, which was not replicated here, likely due to the country sepcific CETs used and costing data (56, 57).

It is evident from this study that NPH insulin twice daily confers significant benefit over NPH insulin once daily, which may warrant further investigation and discussion. A twice daily intermediate-acting basal insulin regimen is distinct from the "biphasic" insulin regimen many patients already use. Despite the recommendation by the South African EML that the basal bolus regimen, i.e. once daily intermediate-acting insulin at night with daily short-acting insulins administered with meals, 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 (31). The biphasic regimen consists of twice daily "pre-mixed" or biphasic insulin, which consists of a mixture of intermediate- and short-acting insulin. For this treatment regimen, however, daily glucose monitoring is recommended.

Therefore, further research is required to investigate the potential superiority of twice daily NPH insulin compared to once daily NPH insulin, whilst appreciating the practicality of a twice

daily basal insulin regimen for adult South Africans with T1DM. From the BIA, it is apparent that the potential alternative (insulin detemir) to the *status quo* would incur great financial costs to the already resource-constrained health care system.

It is clear that there are disparities in the evidence between the clinical effectiveness of the different insulins under review. This was also evident in the minor disparities in the findings of the three reviews identified. Therefore, clinical effectiveness and the related model inputs are a potential limitation of this study, despite accounting for this in the sensitivity analysis. Furthermore, price data for three of the insulins under review were derived from the single exit price, which is a closer representation of private health sector drug prices than public sector prices and thus are likely to overestimate costs.

## 5. Conclusion

This study has highlighted the need for sound clinical effectiveness evidence in economic models. Through an extensive systematic search, a broad range of high-quality evidence was used to inform an economic model to reach the decision of recommending intermediate-acting NPH insulin, the *status quo,* over long-acting insulins (detemir, degludec and glargine) as the basal insulin in the management of adult T1DM patients in South Africa receiving care in the public health sector.

## 6. Conflicts of Interest

The authors declare no conflicts of interest. No funding was received for the preparation of this work.

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# Part D: Appendices

# Appendix A: Ethics Approval

**UNIVERSITY OF CAPE TOWN**
**Faculty of Health Sciences**
**Human Research Ethics Committee**

**Room G50- Old Main Building**
**Groote Schuur Hospital**
**Observatory 7925**
**Telephone** [021] 406 6492
**Email:** hrec-enquiries@uct.ac.za
**Website**: www.health.uct.ac.za/fhs/research/humanethics/forms

21 October 2021

**HREC REF: 670/2021**

**Prof S Cleary**
Division of Health Economics Division
Public Health & Family Medicine
Email: susan.cleary@uct.ac.za
Student: vrrmar001@myuct.ac.za

Dear Prof Cleary

**PROJECT TITLE: COST-EFFECTIVENESS AND BUDGET IMPACT ANALYSIS OF LONG-ACTING INSULIN ANALOGUES (DETEMIR AND GLARGINE) IN SOUTH AFRICA-MASTERS CANDIDATE-MR MARK VERRYN**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020; 06 July 2020 & 01 July 2021.**

**Approval is granted for one year until the 30 October 2022.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

***The HREC acknowledge that the student: Mr Mark Verryn will also be involved in this study.***

**Please quote the HREC REF 670/2021 in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

**PROFESSOR M BLOCKMAN**
**CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE**

HREC/REF 670/2021sa

# Appendix B: Clinical evidence search strategy

| Concept | Search terms |
|---|---|
| Diabetes | (diabetes) OR (diabet*) OR (DM) |
| Type 1 | (type 1) OR (type1) OR (type one) OR (t1) OR (t-1) |
| Long-acting | long acting OR (long*act*) OR (longact*) OR (ultra*long*) OR (ultralong*) OR (ultralent*) |
| Insulin | (insulin) |
| Brand names for long-acting insulins currently available | (detemir) OR (levemir)<br>(degludec) OR (tresiba) OR (xultophy)<br>(Glargine) OR (Lantus) OR (Solostar) OR (Suliqua) OR (Soliqua) |

**PUBMED SEARCH**

| Search number | Query | Filters | Results | Time |
|---|---|---|---|---|
| 13 | ((((("diabetes"[All Fields]) OR (diabet*)) OR (DM)) AND (((((("type 1"[All Fields]) OR ("type1"[All Fields])) OR ("type one"[All Fields])) OR ("t1"[All Fields])) OR (t-1))) AND (((((long acting [All Fields] OR (long*act*) OR (longact*) OR (ultra*long*) OR (ultralong*) OR (ultralent*)) AND ("insulin"[All Fields])) OR ((detemir) OR (levemir))) OR ((degludec) OR (tresiba) OR (xultophy))) OR ((Glargine) OR (Lantus) OR (Solostar) OR (Suliqua) OR (Soliqua))) | Meta-Analysis, Systematic Review | **66** | 12:57:04 |
| 12 | ((((("diabetes"[All Fields]) OR (diabet*)) OR (DM)) AND (((((("type 1"[All Fields]) OR ("type1"[All Fields])) OR ("type one"[All Fields])) OR ("t1"[All Fields])) OR (t-1))) AND (((((long acting [All Fields] OR (long*act*) OR (longact*) OR (ultra*long*) OR (ultralong*) OR (ultralent*)) AND ("insulin"[All Fields])) OR ((detemir) OR (levemir))) OR ((degludec) OR (tresiba) OR (xultophy))) OR ((Glargine) OR (Lantus) OR (Solostar) OR (Suliqua) OR (Soliqua))) | Systematic Review | 39 | 12:57:01 |

| | | | | |
|---|---|---|---|---|
| 11 | ((((("diabetes"[All Fields]) OR (diabet*)) OR (DM)) AND (((((("type 1"[All Fields]) OR ("type1"[All Fields])) OR ("type one"[All Fields])) OR ("t1"[All Fields])) OR (t-1))) AND (((((long acting [All Fields] OR (long*act*) OR (longact*) OR (ultra*long*) OR (ultralong*) OR (ultralent*)) AND ("insulin"[All Fields])) OR ((detemir) OR (levemir))) OR ((degludec) OR (tresiba) OR (xultophy))) OR ((Glargine) OR (Lantus) OR (Solostar) OR (Suliqua) OR (Soliqua))) | | 1,810 | 12:56:50 |
| 10 | ((((long acting [All Fields] OR (long*act*) OR (longact*) OR (ultra*long*) OR (ultralong*) OR (ultralent*)) AND ("insulin"[All Fields])) OR ((detemir) OR (levemir))) OR ((degludec) OR (tresiba) OR (xultophy))) OR ((Glargine) OR (Lantus) OR (Solostar) OR (Suliqua) OR (Soliqua)) | | 7,083 | 12:17:35 |
| 9 | (long acting [All Fields] OR (long*act*) OR (longact*) OR (ultra*long*) OR (ultralong*) OR (ultralent*)) AND ("insulin"[All Fields]) | | 5,276 | 12:17:15 |
| 8 | "insulin"[All Fields] | | 440,563 | 12:16:53 |
| 7 | (Glargine) OR (Lantus) OR (Solostar) OR (Suliqua) OR (Soliqua) | | 3,358 | 11:55:19 |
| 6 | (degludec) OR (tresiba) OR (xultophy) | | 777 | 11:55:10 |
| 5 | (detemir) OR (levemir) | | 1,093 | 11:54:56 |
| 4 | long acting [All Fields] OR (long*act*) OR (longact*) OR (ultra*long*) OR (ultralong*) OR (ultralent*) | | 33,308 | 11:54:37 |
| 3 | ((("diabetes"[All Fields]) OR (diabet*)) OR (DM)) AND (((((("type 1"[All Fields]) OR ("type1"[All Fields])) OR ("type one"[All Fields])) OR ("t1"[All Fields])) OR (t-1)) | | 111,385 | 11:51:28 |
| 2 | ((((("type 1"[All Fields]) OR ("type1"[All Fields])) OR ("type one"[All Fields])) OR ("t1"[All Fields])) OR (t-1) | | 403,517 | 11:23:28 |
| 1 | (("diabetes"[All Fields]) OR (diabet*)) OR (DM) | | 914,224 | 11:20:28 |

## COCHRANE DATABASE OF SYSTEMATIC REVIEWS

Issue 3 of 12, March 2022 – searched on 8 March 2022

### Search terms

"long acting insulin" in Title Abstract Keyword OR (detemir) OR (levemir) in Title Abstract Keyword OR (degludec) OR (tresiba) OR (xultophy) in Title Abstract Keyword OR (Glargine) OR (Lantus) OR (Solostar) OR (Suliqua) OR (Soliqua) in Title Abstract Keyword - (Word variations have been searched)

**Result: 8**

**EPISTIMIKOS** – searched on 8 March 2022

(title:((title:(long acting OR (long*act*) OR (longact*) OR (ultra*long*) OR (ultralong*) OR (ultralent*)) OR abstract:(long acting OR (long*act*) OR (longact*) OR (ultra*long*) OR (ultralong*) OR (ultralent*))) AND (title:(insulin*) OR abstract:(insulin*))) OR abstract:((title:(long acting OR (long*act*) OR (longact*) OR (ultra*long*) OR (ultralong*) OR (ultralent*)) OR abstract:(long acting OR (long*act*) OR (longact*) OR (ultra*long*) OR (ultralong*) OR (ultralent*))) AND (title:(insulin*) OR abstract:(insulin*)))) OR (title:((detemir) OR (levemir)) OR abstract:((detemir) OR (levemir))) OR (title:((degludec) OR (tresiba) OR (xultophy)) OR abstract:((degludec) OR (tresiba) OR (xultophy))) OR (title:((Glargine) OR (Lantus) OR (Solostar) OR (Suliqua) OR (Soliqua)) OR abstract:((Glargine) OR (Lantus) OR (Solostar) OR (Suliqua) OR (Soliqua))) AND (title:((((("diabetes"[All Fields]) OR (diabet*)) OR (DM)) AND (((((type 1) OR (type1)) OR (type one)) OR (t1)) OR (t-1))) OR abstract:((((("diabetes"[All Fields]) OR (diabet*)) OR (DM)) AND (((((type 1) OR (type1)) OR (type one)) OR (t1)) OR (t-1))))

**Result: 134 records**

# Appendix C: Clinical evidence study composition comparison

| | Dżygało 2015 | Woo 2017 | Laranjeira 2018 | Dawood 2018 | Zhang 2018 | Hemmingsen 2021 (cochrane) | NICE (2021) - short + long term | Martin 2021 | Tricco 2021 |
|---|---|---|---|---|---|---|---|---|---|
| Francis 1986 | | | | | | | | | |
| Tunbridge 1989 | | | | | | | | | Tunbridge 1989 |
| Garg 1995 | | | | | | | | | |
| Zinman 1999 | | Zinman 2011, Zinman 2013 | | | | | | | |
| Anderson 1997 | | | | | | | | | |
| Ciofetta 1999 | | | | | | | | | |
| Home 2000 | | | | | | | | | |
| Pieber 2000 | | | | Pieber 2000 | | *4 week follow-up* | Pieber 2000 | | Pieber 2000 |
| Raskin 2000A | | | Raskin 2000A | Raskin 2000 | | *12 week follow-up* | Raskin 2000 | Raskin 2000 | Raskin 2000 |
| Raskin 2000B | | | | | | | | | |
| Ratner 2000 | | | Ratner 2000 | Ratner 2000 | | Ratner 2000 | Ratner 2000 | Ratner 2000 | Ratner 2000 |
| Rosenstock 2000 | | | | Rosenstock 2000 | | *4 week follow-up* | Rosenstock 2000 | | Rosenstock 2000 |
| Bode 2001 | | | | | | | | | |
| Hermanson 2001 | | | Hermanson 2001 | | | *6 week follow-up* | Hermanson 2001 | | |
| Tamas 2001 | | | | | | | | | |
| Witthaus 2001 | | | | | | *Part of Home 2005* | Witthaus 2001 | | Witthaus 2001 |
| Bode 2002 | | | | | | | | | |
| Schober 2002 (paeds) | | | Schober 2002 (paeds) | | | Schober 2002 (paeds) | | | |
| Devries 2003 | | | | | | | | | |
| Murphy 2003 (paed) | | | Murphy 2003 (paed) | | | | | | |
| Rossetti 2003 | | | Rossetti 2003 | Rossetti 2003 | | *12 week follow-up* | Rossetti 2003 | Rossetti 2003 | Rossetti 2003 |
| Vague 2003 | | | Vague 2003 | Vague 2003 | | Vague 2003 | Vague 2003 | Vague 2003 | Vague 2003 |
| Hermanson 2004 | | | Hermanson 2004 | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Hershon 2004 (subgroup Ratner 2000) | | | | | | | | | |
| Home 2004 | | | Home 2004 | Home 2004 | | *16 week follow-up* | Home 2004 | Home 2004 | Home 2004 |
| Porcellati 2004 | | | Porcellati 2004 | Porcellati 2004 | | Porcellati 2004 | Porcellati 2004 | Porcellati 2004 | Porcellati 2004 |
| Russell-Jones 2004 | | | Russell-Jones 2004 | Russell-Jones 2004 | | Russell-Jones 2004 | Russell-Jones 2004 | Russell-Jones 2004 | Russell-Jones 2004 |
| Standl 2004 | | | Standl 2004 | Standl 2004 | | Standl 2004 | Standl 2004 | Standl 2004 | Standl 2004 |
| NCT00595374 (unpublished) - completed 2004 (paeds) | | | | | | NCT00595374 (unpublished) - completed 2005 (paeds) | | | |
| NCT00605137 (unpublished) - completed 2005 (paeds) | | | | | | NCT00605137 (unpublished) - completed 2004 (paeds) | | | |
| De Leeuw 2005 | | | | De Leeuw 2005 | | *Part of Vague 2003* | De Leeuw 2005 | De Leeuw 2005 | De Leeuw 2005 |
| Fulcher 2005 | | | Fulcher 2005 | Fulcher 2005 | | Fulcher 2005 | Fulcher 2005 | Fulcher 2005 | Fulcher 2005 |
| Home 2005 | | | Home 2005 | Home 2005 | | Home 2005 | Home 2005 | Home 2005 | Home 2005 |
| NN304-1476 2005 | | | NN304-1476 2005 | | | | | | |
| Pieber 2005 | | | Pieber 2005 | Pieber 2005 | | *16 week follow-up* | Pieber 2005 | | Pieber 2005 |
| Ashwell 2006 | | | Ashwell 2006 | | | *4 week follow-up* | Ashwell 2006 | | |
| Home 2006 | | | | | | | | | |
| Kolendorf 2006 | | | Kolendorf 2006 | Kolendorf 2006 | | *16 week follow-up`* | Kolendorf 2006 | | |
| Chatterjee 2007 | | | Chatterjee 2007 | Chatterjee 2007 | | *16 week follow-up* | Chatterjee 2007 | Chatterjee 2007 | Chatterjee 2007 |
| Kobayashi 2007 | | | | | | Kobayashi 2007 | Japanese study | | Kobayashi 2007 |
| Mianovska 2007 | | | Mianovska 2007 | | | | | | |
| Pieber 2007 | | | | | | Pieber 2007 | Pieber 2007 | Pieber 2007 | Pieber 2007 |
| Robertson 2007 (paeds) | | | Robertson 2007 (paeds) | | | Robertson 2007 (paeds) | | | |
| Bartley 2008 | | | Bartley 2008 | Bartley 2008 | | Bartley 2008 | Bartley 2008 | Bartley 2008 | Bartley 2008 |
| Chase 2008 (adolescents) | | | Chase 2008 (adolescents) | | | Chase 2008 (adolescents) | | | |
| Bolli 2009 | | Bolli 2015 | Bolli 2009 | Bolli 2009 | | Bolli 2009 | Bolli 2009 | Bolli 2009 | Bolli 2009 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Hassan 2008 | | | Hassan 2008 | | | | | | |
| Heller 2009 | | | | Heller 2009 | | Heller 2009 | Heller 2009 | Heller 2009 | Heller 2009 |
| Le Floch 2009 | | | | | | *16 week follow-up* | Le Floch 2009 | | Le Floch 2009 |
| Renard 2011 | | | | Renard 2011 | | 16 week follow-up | Renard 2011 | Renard 2011 | Renard 2011 |
| Birkeland 2011, Home 2012 | Birkeland 2011 | Birkeland 2011 | | Birkeland 2011 | Birkeland 2011, Home 2012 | 16 week follow-up | Birkeland 2011, Home 2012 | Birkeland 2011 | |
| Zachariah 2011 | | | | Zachariah 2011 | | *16 week follow-up* | Zachariah 2011 | Zachariah 2011 | Zachariah 2011 |
| Heller 2012, Bode 2013 | | Heller 2012, Bode 2013 | | | | BEGIN Basal-Bolus Type 1 | Heller 2012, Bode 2013 | Bode 2013 | |
| Heise 2012 | | | | | Heise 2012 | 12 day follow-up | Heise 2012 | | Heise 2012 |
| Danne 2013 (PRESCHOOL) | | | Danne 2013 (PRESCHOOL) | | | Danne 2013 (PRESCHOOL) | | | |
| Iwamoto 2013 | | | | Iwamoto 2013 | | *6 week follow-up* | Iwamoto 2013 | | |
| Mathieu 2013 | Mathieu 2013 | Mathieu 2013 | | Mathieu 2013 | BEGIN Flex T1 | BEGIN Flex T1 | Mathieu 2013 | Mathieu 2013 | Mathieu 2013 |
| Thalange 2013 (paeds) | | | Thalange 2013 (paeds) | | | Thalange 2013 (paeds) | | | |
| Van Golen 2013 | | | | Van Golen 2013 | | *12 week follow-up* | Van Golen 2013 | Van Golen 2013 | |
| Davies 2014 | | | | | | Davies 2014 | Davies 2014 | Davies 2014 | |
| Pedersen-Bjergaard 2014 | | | Pedersen-Bjergaard 2014 | | | | | | |
| Home 2015, Home 2018 | | Home 2015 | | | | ? | Home 2015, Home 2018 | Home 2018 | |
| Jannouchi 2015 | | | | | | *8.4 week follow-up* | Jannouchi 2015 | | |
| Thalange 2015 (paeds) - BEGIN YOUNG | | | | | | Thalange 2015 (paeds) - BEGIN YOUNG | | | |
| Liu 2016 (paeds) | | | | | | Liu 2016 (paeds) | | | |
| Matsuhisa 2016 A | | Matsuhisa 2014 | | | | ? | Matsuhisa 2016 A | Matsuhisa 2016 | |
| Matsuhisa 2016 B | | | | | | ? | Matsuhisa 2016 B | | |
| Bergenstal 2017 | | | | | | *16 week follow-up* | Bergenstal 2017 | Bergenstal 2017 | |
| Heise 2017 | | | | | | *12 day follow-up* | Heise 2017 | | Heise 2017 |
| Iga 2017 | | | | | | *12 week follow-up* | Iga 2017 | | Iga 2017 |
| Lane 2017 | | | | | | Part of SWITCH 1 | Lane 2017 | Lane 2017 | Lane 2017 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Onda 2017 | | | | | | *4 week follow-up* | Onda 2017 | | |
| Urakami 2017 (paeds) | | | | | | Urakami 2017 (paeds) | | | |
| Pettus 2019 | | | | | | *16 week follow-up* | Pettus 2019 | Pettus 2019 | |
| Heller 2012 | Heller 2012 | | | Heller 2012 | | | | | |
| Hirsch 2012 | Hirsch 2012 | | | | | | | Hirsch 2012 | |
| Birkeland 2011 | Birkeland 2011 | | | | | | | Birkeland 2011 | Birkeland 2011 |
| BEGIN Basal bolus Type 2 | | BEGIN Basal bolus Type 2 (garber 2012, hollander 2015) | | | BEGIN Basal bolus Type 2 | | | | |
| BEGIN EASY AM | | BEGIN EASY AM (Zinman 2013) | | | BEGIN EASY AM | | | | |
| BEGIN EASY PM | | BEGIN EASY PM (Zinman 2013) | | | BEGIN EASY PM | | | | |
| BEGIN Flex | | BEGIN Flex (Meneghini 2013) | | | BEGIN Flex | | | | |
| BEGIN Low Volume | | BEGIN Low Volume (Gough 2013) | | | BEGIN Low Volume | | | | |
| BEGIN Once Asia | | | | | BEGIN Once Asia | | | | |
| Onishi 2013 | | | | | Onishi 2013 | | | | |
| Kumar 2016 | | | | | Kumar 2016 | | | | |
| Pan 2016 | | | | | Pan 2016 | | | | |
| SWITCH 2 2017 | | | | | SWITCH 2 2017 | | | | |
| SWITCH 1 2017 | | | | | SWITCH 1 2017 | | | | |
| DEVOTE 2017 | | | | | DEVOTE 2017 | | | | |
| Ashwell 2006 | | | | | | | | | Ashwell 2006 |
| Bailey 2018 | | | | | | | | | Bailey 2018 |
| Birtwell 1984 | | | | | | | | | Birtwell 1984 |
| Blevins 2015 | | | | | | | | | Blevins 2015 |
| Blevins 2018 | | | | | | | | | Blevins 2018 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Bode 2013 | | | | | | | | | Bode 2013 |
| Crutchlow 2018 | | | | | | | | | Crutchlow 2018 |
| Danne 2003 | | | | | | | | | Danne 2003 |
| Davies 2016 | | | | | | | | Davies 2016 | Davies 2016 |
| Derosa 2015 | | | | | | | | | Derosa 2015 |
| Eichner 1988 | | | | | | | | | Eichner 1988 |
| Hamann 2003 | | | | | | | | | Hamann 2003 |
| Heise 2004 | | | | | | | | | Heise 2004 |
| Heise 2015 | | | | | | | | | Heise 2015 |
| Heise 2016 | | | | | | | | | Heise 2016 |
| Hermansen 2001 | | | | Hermansen 2001 | | | | | Hermansen 2001 |
| Ikushima 2016 | | | | | | | | | Ikushima 2016 |
| Koehler 2014 | | | | | | | | | Koehler 2014 |
| Kølendorf 2006 | | | | | | | | Kølendorf 2006 | Kølendorf 2006 |
| Korsatko 2013 | | | | | | | | | Korsatko 2013 |
| Linnebjerg 2017 | | | | | | | | | Linnebjerg 2017 |
| Mathiesen 2012 | | | | | | | | | Mathiesen 2012 |
| Oswald 1987 | | | | | | | | | Oswald 1987 |
| Pedersen 1987 | | | | | | | | | Pedersen 1987 |
| Pešić 2007 | | | | | | | | | Pešić 2007 |
| Philippo 2007 | | | | | | | | | Philippo 2007 |
| Portolés 2010 | | | | | | | | | Portolés 2010 |
| Radman 2007 | | | | | | | | | Radman 2007 |
| Richard 1984 | | | | | | | | | Richard 1984 |
| Stades 2002 | | | | | | | | | Stades 2002 |
| van Golen 2014 | | | | | | | | | van Golen 2014 |
| Vaughan 2017 | | | | | | | | | Vaughan 2017 |
| Verma 2011 | | | | | | | | | Verma 2011 |
| Fulcher 2006 | | | | Fulcher 2006 | | | | | |
| Hermansen 2004 | | | | Hermansen 2004 | | | | Hermansen 2004 | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Le Floch 2005 | | | | Le Floch 2005 | | | | | |
| Renard 2011 A | | | | Renard 2011 A | | | | | |
| Hirsch 2017 | | | | | | | | Hirsch 2017 | |
| Rodbard 2013 | | Rodbard 2013 | | | | | | | |
| Philis-Tsimikas 2013 | | Philis-Tsimikas 2013 | | | | | | | |
| Riddle 2014 | | Riddle 2014 | | | | | | | |
| Riddle 2015 | | Riddle 2015 | | | | | | | |
| Yki-Jarvinen 2014 | | Yki-Jarvinen 2014 | | | | | | | |
| Yki-Jarvinen 2015 | | Yki-Jarvinen 2015 | | | | | | | |
| Terauchi 2014 | | Terauchi 2014 | | | | | | | |
| Terauchi 2015 | | Terauchi 2015 | | | | | | | |

# Appendix D: AMSTAR appraisals of systematic reviews

AMSTAR review of Cochrane systematic review by Hemmingsen et al.

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

**1. Did the research questions and inclusion criteria for the review include the components of PICO?**

| For Yes: | Optional (recommended) | |
|---|---|---|
| ● Population<br>● Intervention<br>● Comparator group<br>● Outcome | ● Timeframe for follow-up | ● Yes<br>□ No |

**2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**

| For Partial Yes:<br>The authors state that they had a written protocol or guide that included ALL the following: | For Yes:<br>As for partial yes, plus the protocol should be registered and should also have specified: | |
|---|---|---|
| □ review question(s)<br>□ a search strategy<br>□ inclusion/exclusion criteria<br>□ a risk of bias assessment | ● a meta-analysis/synthesis plan, if appropriate, *and*<br>● a plan for investigating causes of heterogeneity<br>● justification for any deviations from the protocol | ● Yes<br>□ Partial Yes<br>□ No |

**3. Did the review authors explain their selection of the study designs for inclusion in the review?**

| For Yes, the review should satisfy ONE of the following: | |
|---|---|
| □ *Explanation for* including only RCTs<br>□ OR *Explanation for* including only NRSI<br>□ OR *Explanation for* including both RCTs and NRSI | □ Yes<br>● No |

**4. Did the review authors use a comprehensive literature search strategy?**

| For Partial Yes (all the following): | For Yes, should also have (all the following): | |
|---|---|---|
| □ searched at least 2 databases (relevant to research question)<br>□ provided key word and/or search strategy<br>□ justified publication restrictions (e.g. language) | ● searched the reference lists / bibliographies of included studies<br>● searched trial/study registries<br>● included/consulted content experts in the field<br>● where relevant, searched for grey literature<br>● conducted search within 24 months of completion of the review | ● Yes<br>□ Partial Yes<br>□ No |

**5. Did the review authors perform study selection in duplicate?**

| For Yes, either ONE of the following: | |
|---|---|
| ● at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include<br>□ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. | ● Yes<br>□ No |

AMSTAR review of NICE systematic review.

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

**1. Did the research questions and inclusion criteria for the review include the components of PICO?**

| For Yes: | Optional (recommended) | |
|---|---|---|
| ● Population | ☐ Timeframe for follow-up | ● Yes |
| ● Intervention | | ☐ No |
| ● Comparator group | | |
| ● Outcome | | |

**2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**

| For Partial Yes: | For Yes: | |
|---|---|---|
| The authors state that they had a written protocol or guide that included ALL the following: | As for partial yes, plus the protocol should be registered and should also have specified: | ● Yes |
| ☐ review question(s) | ● a meta-analysis/synthesis plan, if appropriate, *and* | ☐ Partial Yes |
| ☐ a search strategy | ● a plan for investigating causes of heterogeneity | ☐ No |
| ☐ inclusion/exclusion criteria | ☐ justification for any deviations from the protocol | |
| ☐ a risk of bias assessment | | |

**3. Did the review authors explain their selection of the study designs for inclusion in the review?**

| For Yes, the review should satisfy ONE of the following: | |
|---|---|
| ☐ *Explanation for* including only RCTs | ☐ Yes |
| ☐ OR *Explanation for* including only NRSI | ● No |
| ☐ OR *Explanation for* including both RCTs and NRSI | |

**4. Did the review authors use a comprehensive literature search strategy?**

| For Partial Yes (all the following): | For Yes, should also have (all the following): | |
|---|---|---|
| ● searched at least 2 databases (relevant to research question) | ☐ searched the reference lists / bibliographies of included studies | ☐ Yes |
| ● provided key word and/or search strategy | ☐ searched trial/study registries | ● Partial Yes |
| ● justified publication restrictions (e.g. language) | ☐ included/consulted content experts in the field | ☐ No |
| | ☐ where relevant, searched for grey literature | |
| | ☐ conducted search within 24 months of completion of the review | |

**5. Did the review authors perform study selection in duplicate?**

| For Yes, either ONE of the following: | |
|---|---|
| ● at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include | ● Yes |
| ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. | ☐ No |

AMSTAR review of systematic review by Martin et al.

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

**1. Did the research questions and inclusion criteria for the review include the components of PICO?**

| For Yes: | Optional (recommended) | |
|---|---|---|
| ● Population | ☐ Timeframe for follow-up | ● Yes |
| ● Intervention | | ☐ No |
| ● Comparator group | | |
| ● Outcome | | |

**2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**

| For Partial Yes: | For Yes: | |
|---|---|---|
| The authors state that they had a written protocol or guide that included ALL the following: | As for partial yes, plus the protocol should be registered and should also have specified: | ☐ Yes |
| ● review question(s) | ☐ a meta-analysis/synthesis plan, if appropriate, *and* | ● Partial Yes |
| ● a search strategy | ☐ a plan for investigating causes of heterogeneity | ☐ No |
| ● inclusion/exclusion criteria | ☐ justification for any deviations from the protocol | |
| ● a risk of bias assessment | | |

**3. Did the review authors explain their selection of the study designs for inclusion in the review?**

| For Yes, the review should satisfy ONE of the following: | |
|---|---|
| ● *Explanation for* including only RCTs | ● Yes |
| ☐ OR *Explanation for* including only NRSI | ☐ No |
| ☐ OR *Explanation for* including both RCTs and NRSI | |

**4. Did the review authors use a comprehensive literature search strategy?**

| For Partial Yes (all the following): | For Yes, should also have (all the following): | |
|---|---|---|
| ● searched at least 2 databases (relevant to research question) | ☐ searched the reference lists / bibliographies of included studies | ● Yes |
| ● provided key word and/or search strategy | ☐ searched trial/study registries | ☐ Partial Yes |
| ● justified publication restrictions (e.g. language) | ☐ included/consulted content experts in the field | ☐ No |
| | ☐ where relevant, searched for grey literature | |
| | ☐ conducted search within 24 months of completion of the review | |

**5. Did the review authors perform study selection in duplicate?**

| For Yes, either ONE of the following: | |
|---|---|
| ● at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include | ● Yes |
| ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. | ☐ No |

# Appendix E: Context applicability scoring of economic evidence and HTA agency review

**Table** . Context applicability scoring of economic evidence and HTA agency decisions.

| | **AWMSG: Insulin glargine (abasalgar) compared to lantus** (51) | **AWMSG: Insulin degludec (Tresiba) compared to glargine (lantus)** (56) | **Canadian Agency for Drugs and Technologies in Health** (47) | **NIHR: Health Technology Assessment Programme** (61) | **NICE: Evidence review for T1DM** (27) | **Evans et al. degludec vs glargine** (57) | **Valentine et al. detemir vs NPH** (48) | **Pfohl et al. Glargine vs NPH** (35) | **Cameron et al. Glargine vs NPH and detemir vs NPH** (40) | **Grima et al. Glargine vs NPH** (43) |
|---|---|---|---|---|---|---|---|---|---|---|
| Is the population similar to South African patients? | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Is the technology administered in a similar way as in the South African public sector? | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Is the comparator similar to the comparator defined in the Technical Review? | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Is the clinical management of patients indicated for the technology being assessed similar to the South African public sector? | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Is the health system context similar to the South African public sector? | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Are there significant differences in costs and costs structures compared to the South African public sector? | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| *Total score (/6)* | *2* | 3 | 3 | 3 | 6 | 3 | 3 | 3 | 3 | 3 |

Scoring higher equates with higher applicability, where a score of 1 is given if in agreement and 0 given if not in agreement or unsure.

**Table** . Methodology applicability scoring of economic evidence and HTA agency decisions.

| | AWMSG: Insulin glargine (abasalgar) compared to lantus (51) | AWMSG: Insulin degludec (Tresiba) compared to glargine (lantus) (56) | Canadian Agency for Drugs and Technologies in Health (47) | NIHR: Health Technology Assessment Programme (61) | NICE: Evidence review for T1DM (27) | Evans et al. degludec vs glargine (57) | Valentine et al. detemir vs NPH (48) | Pfohl et al. Glargine vs NPH (35) | Cameron et al. Glargine vs NPH and detemir vs NPH (40) | Grima et al. Glargine vs NPH (43) |
|---|---|---|---|---|---|---|---|---|---|---|
| Is the type of economic evaluation a cost-utility analysis? | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
| Are health effects reported direct health effects experienced by patients and health effects on informal caregivers? | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Is the value of health effects expressed in terms of Quality Adjusted Life years? | 0 | 1 | 1 | ? | 1 | 1 | 1 | 1 | 1 | 1 |
| Is the analysis over a time horizon that captures all relevant differences in costs and effects between the intervention and comparator? | 1 | 1 | 1 | ? | 1 | 1 | 0 (1 year) | 1 | 1 | 1 |
| Are costs reported from the perspective of a 3rd-party payer (e.g. public sector)? | 1 | 1 | 1 | ? | 1 | 1 | 1 | 1 | 1 | 1 |
| Are costs and effects discounted at an annual rate of 5%? | 0 | 0 | 0 | ? | 0 (3.5%) | 0 | 0 | 0 (3% used) | 1 | 1 |
| *Total score (/6)* | 3 | 5 | 4 | No access | 5 | 5 | 4 | 5 | 6 | 6 |

## Appendix F: BMC Health Economics Submission guidelines

https://bmcresnotes.biomedcentral.com/submission-guidelines/preparing-your-manuscript

## Appendix G: Budget Impact Analysis

The BIA is shown below in South African Rand (ZAR). An average exchange rate of 16.5045431 ZAR/USD for the price year of March 2020 to February 2021 was applied for Table 5.

| South African population | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | |
|---|---|---|---|---|---|---|
| Whole population (number) | 59,622,350 | 60,457,063 | 61,303,462 | 62,161,710 | 63,031,974 | 1.40% |

| Adoption Scenarios | | | | |
|---|---|---|---|---|
| | Intervention NPH | | Comparator Detemir | |
| | % market share in year 1 | % increase in market share each year | % market share in year 1 | % contribution to increase/decrease in market share each year |
| STATUS QUO market share | 100.00% | | 0.00% | |
| RAPID ADOPTION: Change in market share | 60.00% | -40.00% | 40.00% | 100.00% |
| SLOW ADOPTION: Change in market share | 90.00% | -20.00% | 10.00% | 100.00% |

| Market Share | | | | | | |
|---|---|---|---|---|---|---|
| Scenario | Treatment | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
| **Status Quo:**<br>**Market share of existing treatment(s) only** | Intervention NPH | 100.00% | 100.00% | 100.00% | 100.00% | 100.00% |
| | Comparator Detemir | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Total** | | **100.00%** | **100.00%** | **100.00%** | **100.00%** | **100.00%** |
| **Rapid Adoption Scenario** | Intervention NPH | 60.00% | 36.00% | 21.60% | 12.96% | 7.78% |
| | Comparator Detemir | 40.00% | 64.00% | 78.40% | 87.04% | 92.22% |
| **Total** | | **100.00%** | **100.00%** | **100.00%** | **100.00%** | **100.00%** |
| **Slow Adoption Scenario** | Intervention NPH | 90.00% | 72.00% | 57.60% | 46.08% | 36.86% |
| | Comparator Detemir | 10.00% | 28.00% | 42.40% | 53.92% | 63.14% |
| **Total** | | **100.00%** | **100.00%** | **100.00%** | **100.00%** | **100.00%** |

**Pharmaceutical costs**

**PHARMACEUTICAL ACQUISITION COSTS**

| | **Intervention NPH** | | **Comparator Detemir** | |
|---|---|---|---|---|
| | **Description** | **Source** | **Description** | **Source** |
| **Total cost of medicine per year (per person)** | R543.96 | NICE Markov model pharmaceutical costs of Detemir once a day | R1,857.31 | NICE Markov model pharmaceutical costs of Detemir once a day |

**ESTIMATED PHARMACEUTICAL ACQUISITION COSTS PER PATIENT PER ANNUM**

| | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
|---|---|---|---|---|---|
| **Intervention NPH** | R543.96 | R543.96 | R543.96 | R543.96 | R543.96 |

| | | | | | |
|---|---|---|---|---|---|
| **Comparator Detemir** | R1,857.31 | R1,857.31 | R1,857.31 | R1,857.31 | R1,857.31 |

*Assumed no change in costs

**TOTAL PHARMACEUTICAL ACQUISITION COSTS PER ANNUM~**

| | **Treatment** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
|---|---|---|---|---|---|---|
| **Status Quo** | Intervention NPH | R58,937,049.23 | R59,762,167.92 | R60,598,838.27 | R61,447,222.01 | R62,307,483.11 |
| | Comparator Detemir | R0.00 | R0.00 | R0.00 | R0.00 | R0.00 |
| | **Total** | **R58,937,049.23** | **R59,762,167.92** | **R60,598,838.27** | **R61,447,222.01** | **R62,307,483.11** |
| **Rapid Adoption Scenario** | Intervention NPH | R35,362,229.54 | R21,514,380.45 | R13,089,349.07 | R7,963,559.97 | R4,845,029.89 |
| | Comparator Detemir | R80,494,426.73 | R130,594,157.92 | R162,217,533.26 | R182,615,891.48 | R196,201,171.05 |
| | **Total** | **R115,856,656.26** | **R152,108,538.37** | **R175,306,882.33** | **R190,579,451.46** | **R201,046,200.93** |
| **Slow Adoption Scenario** | Intervention NPH | R53,043,344.31 | R43,028,760.90 | R34,904,930.84 | R28,314,879.90 | R22,969,030.58 |
| | Comparator Detemir | R20,123,606.68 | R57,134,944.09 | R87,729,890.44 | R113,127,859.25 | R134,318,150.76 |
| | **Total** | **R73,166,950.99** | **R100,163,704.99** | **R122,634,821.28** | **R141,442,739.15** | **R157,287,181.33** |

*~Combines number of eligible patients treated each year according to market share projections with estimated pharmaceutical acquisition costs per patient per annum*

**AVERAGE PHARMACEUTICAL ACQUISITION COSTS PER PATIENT PER ANNUM (AVERAGE ACROSS ALL THERAPIES)**

| | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
|---|---|---|---|---|---|
| Status Quo | 543.96 | 543.96 | 543.96 | 543.96 | 543.96 |
| Rapid Adoption Scenario | 1069.3 | 1384.504 | 1573.6264 | 1687.09984 | 1755.183904 |
| Slow Adoption Scenario | 675.295 | 911.698 | 1100.8204 | 1252.11832 | 1373.156656 |

**ESTIMATION OF THE NET IMPACT ON THE PHARMACEUTICAL BUDGET**

**COST PER PATIENT**

| **Gross medicine acquisition costs [per patient]** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
|---|---|---|---|---|---|
| > In a market without new medicine [status quo] | R543.96 | R543.96 | R543.96 | R543.96 | R543.96 |
| > In a market with rapid adoption of the new medicine | R1,069.30 | R1,384.50 | R1,573.63 | R1,687.10 | R1,755.18 |
| > In a market with slow adoption of the new medicine | R675.30 | R911.70 | R1,100.82 | R1,252.12 | R1,373.16 |
| **Net medicine acquisition costs [per patient]** | | | | | |
| > In a market with rapid adoption of the new medicine | R525.34 | R840.54 | R1,029.67 | R1,143.14 | R1,211.22 |
| > In a market with slow adoption of the new medicine | R131.34 | R367.74 | R556.86 | R708.16 | R829.20 |

**TOTAL PHARMACEUTICAL COSTS**

| **Gross medicine acquisition costs** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
|---|---|---|---|---|---|
| > In a market without new medicine [status quo] | R58,937,049.23 | R59,762,167.92 | R60,598,838.27 | R61,447,222.01 | R62,307,483.11 |
| > In a market with rapid adoption of the new medicine | R115,856,656.26 | R152,108,538.37 | R175,306,882.33 | R190,579,451.46 | R201,046,200.93 |
| > In a market with slow adoption of the new medicine | R73,166,950.99 | R100,163,704.99 | R122,634,821.28 | R141,442,739.15 | R157,287,181.33 |
| **Net medicine acquisition costs** | | | | | |
| > In a market with rapid adoption of the new medicine | R56,919,607.03 | R92,346,370.45 | R114,708,044.06 | R129,132,229.45 | R138,738,717.82 |
| > In a market with slow adoption of the new medicine | R14,229,901.76 | R40,401,537.07 | R62,035,983.01 | R79,995,517.14 | R94,979,698.22 |

**Health care resource use costs**

**HEALTHCARE RESOURCE USE COSTS FOR INTERVENTION AND COMPARATOR TECHNOLOGIES PER PATIENT**

| | **Intervention NPH** | | **Comparator Detemir** | |
|---|---|---|---|---|
| | **Description** | **Source and justification** | **Description** | **Source and justification** |

| **Resource 1: inpatient stay from Severe hypoglycaemia** | | | | |
|---|---|---|---|---|
| **Per year (ZAR)** | 1059.17 | NICE Markov model healthcare costs of NPH once a day | 853.4 | NICE Markov model healthcare costs of detemir once a day |

**HEALTHCARE RESOURCE USE COSTS ASSOCIATED WITH TREATMENT OPTIONS PER ANNUM PER PATIENT**

| Resource | Technology | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|---|
| **Resource 1: inpatient stay from Severe hypoglycaemia** | Intervention NPH | R1,059.17 | R1,059.17 | R1,059.17 | R1,059.17 | R1,059.17 |
| | Comparator Detemir | R853.40 | R853.40 | R853.40 | R853.40 | R853.40 |

**TOTAL HEALTHCARE RESOURCE USE COSTS PER ANNUM**

| Implementation scenario | Treatment | Resource | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|---|---|
| **Status Quo** | **Resource 1: inpatient stay from Severe hypoglycaemia** | Intervention NPH | R114,759,089.70 | R116,365,716.96 | R117,994,836.99 | R119,646,764.71 | R121,321,819.42 |
| | | Comparator Detemir | R0.00 | R0.00 | R0.00 | R0.00 | R0.00 |
| | | Total | **R114,759,089.70** | **R116,365,716.96** | **R117,994,836.99** | **R119,646,764.71** | **R121,321,819.42** |
| | **TOTAL [Healthcare resources costs for Status Quo scenario]** | | **R114,759,089.70** | **R116,365,716.96** | **R117,994,836.99** | **R119,646,764.71** | **R121,321,819.42** |
| | | Intervention NPH | R68,855,453.82 | R41,891,658.10 | R25,486,884.79 | R15,506,220.71 | R9,433,984.68 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Rapid Adoption Scenario** | **Resource 1: inpatient stay from Severe hypoglycaemia** | Comparator Detemir | R36,985,717.93 | R60,005,628.77 | R74,535,991.78 | R83,908,664.57 | R90,150,852.24 |
| | | Total | **R105,841,171.75** | **R101,897,286.87** | **R100,022,876.57** | **R99,414,885.28** | **R99,584,836.92** |
| | **TOTAL [Healthcare resources costs for Rapid Adoption scenario]** | | **R105,841,171.75** | **R101,897,286.87** | **R100,022,876.57** | **R99,414,885.28** | **R99,584,836.92** |
| **Slow Adoption Scenario** | **Resource 1: inpatient stay from Severe hypoglycaemia** | Intervention NPH | R103,283,180.73 | R83,783,316.21 | R67,965,026.11 | R55,133,229.18 | R44,724,075.51 |
| | | Comparator Detemir | R9,246,429.48 | R26,252,462.59 | R40,310,281.27 | R51,980,183.75 | R61,716,735.42 |
| | | Total | **R112,529,610.21** | **R110,035,778.79** | **R108,275,307.37** | **R107,113,412.93** | **R106,440,810.93** |
| | **TOTAL [Healthcare resources costs for Slow Adoption scenario]** | | **R112,529,610.21** | **R110,035,778.79** | **R108,275,307.37** | **R107,113,412.93** | **R106,440,810.93** |

**Combines number of eligible patients treated each year according to market share projections with estimated health care resource use costs per patient per annum*

**AVERAGE HEALTHCARE RESOURCE USE COSTS PER PATIENT PER ANNUM (AVERAGE ACROSS ALL THERAPIES)**

| **Implementation scenario** | **Resource** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
|---|---|---|---|---|---|---|
| Status Quo | Resource 1: inpatient stay from Severe hypoglycaemia | R1,059.17 | R1,059.17 | R1,059.17 | R1,059.17 | R1,059.17 |
| | **Average healthcare resources costs for Status Quo scenario** | **R1,059.17** | **R1,059.17** | **R1,059.17** | **R1,059.17** | **R1,059.17** |
| Rapid Adoption Scenario | Resource 1: inpatient stay from Severe hypoglycaemia | R976.86 | R927.48 | R897.85 | R880.07 | R869.40 |
| | **Average healthcare resources costs for Rapid Adoption scenario** | **R976.86** | **R927.48** | **R897.85** | **R880.07** | **R869.40** |
| Slow Adoption Scenario | Resource 1: inpatient stay from Severe hypoglycaemia | R1,038.59 | R1,001.55 | R971.92 | R948.22 | R929.26 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **Average healthcare resources costs for Slow Adoption scenario** | **R1,038.59** | **R1,001.55** | **R971.92** | **R948.22** | **R929.26** |

**ESTIMATION OF THE NET IMPACT OF HEALTHCARE RESOURCES ON THE HEALTHCARE BUDGET**

**COST PER PATIENT**

| **Gross health care resource use costs per patient** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
|---|---|---|---|---|---|
| > In a market without new medicine [status quo] | R1,059.17 | R1,059.17 | R1,059.17 | R1,059.17 | R1,059.17 |
| > In a market with rapid adoption of the new medicine | R976.86 | R927.48 | R897.85 | R880.07 | R869.40 |
| > In a market with slow adoption of the new medicine | R1,038.59 | R1,001.55 | R971.92 | R948.22 | R929.26 |
| **Net health care resource use costs per patient** | | | | | |
| > In a market with rapid adoption of the new medicine | -R82.31 | -R131.69 | -R161.32 | -R179.10 | -R189.77 |
| > In a market with slow adoption of the new medicine | -R20.58 | -R57.62 | -R87.25 | -R110.95 | -R129.91 |

**TOTAL HEALTH CARE RESOURCE USE COSTS**

| **Gross health care resource use costs** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
|---|---|---|---|---|---|
| > In a market without new medicine [status quo] | R114,759,089.70 | R116,365,716.96 | R117,994,836.99 | R119,646,764.71 | R121,321,819.42 |
| > In a market with rapid adoption of the new medicine | R105,841,171.75 | R101,897,286.87 | R100,022,876.57 | R99,414,885.28 | R99,584,836.92 |
| > In a market with slow adoption of the new medicine | R112,529,610.21 | R110,035,778.79 | R108,275,307.37 | R107,113,412.93 | R106,440,810.93 |
| **Net health care resource costs** | | | | | |
| > In a market with rapid adoption of the new medicine | -R8,917,917.95 | -R14,468,430.08 | -R17,971,960.43 | -R20,231,879.43 | -R21,736,982.50 |
| > In a market with slow adoption of the new medicine | -R2,229,479.49 | -R6,329,938.16 | -R9,719,529.62 | -R12,533,351.78 | -R14,881,008.49 |

**Net Budget Impact**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Patient population that will receive the new technology** | **108,348** | **109,865** | **111,403** | **112,963** | **114,544** |
| **Status quo implementation scenario** | | | | | |
| Pharmaceutical costs | R58,937,049.23 | R59,762,167.92 | R60,598,838.27 | R61,447,222.01 | R62,307,483.11 |
| Healthcare resource use costs | R114,759,089.70 | R116,365,716.96 | R117,994,836.99 | R119,646,764.71 | R121,321,819.42 |
| *Total cost of current treatment pathway* | **R173,696,138.93** | **R176,127,884.87** | **R178,593,675.26** | **R181,093,986.72** | **R183,629,302.53** |
| **Rapid adoption of new technology implementation scenario** | | | | | |
| Pharmaceutical costs | R115,856,656.26 | R152,108,538.37 | R175,306,882.33 | R190,579,451.46 | R201,046,200.93 |
| Healthcare resource use costs | R105,841,171.75 | R101,897,286.87 | R100,022,876.57 | R99,414,885.28 | R99,584,836.92 |
| *Total cost of future treatment pathway (rapid adoption)* | **R221,697,828.01** | **R254,005,825.25** | **R275,329,758.89** | **R289,994,336.73** | **R300,631,037.85** |
| **Slow adoption of new technology implementation scenario** | | | | | |
| Pharmaceutical costs | R73,166,950.99 | R100,163,704.99 | R122,634,821.28 | R141,442,739.15 | R157,287,181.33 |
| Healthcare resource use costs | R112,529,610.21 | R110,035,778.79 | R108,275,307.37 | R107,113,412.93 | R106,440,810.93 |
| *Total cost of future treatment pathway (slow adoption)* | **R185,696,561.20** | **R210,199,483.79** | **R230,910,128.66** | **R248,556,152.08** | **R263,727,992.26** |
| **NET BUDGET IMPACT** *(future - current treatment pathway costs)* | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Net pharmaceutical costs** | | | | | |
| > In a market with rapid adoption of the new medicine | R56,919,607.03 | R92,346,370.45 | R114,708,044.06 | R129,132,229.45 | R138,738,717.82 |
| > In a market with slow adoption of the new medicine | R14,229,901.76 | R40,401,537.07 | R62,035,983.01 | R79,995,517.14 | R94,979,698.22 |
| **Net healthcare resource use costs** | | | | | |
| > In a market with rapid adoption of the new medicine | -R8,917,917.95 | -R14,468,430.08 | -R17,971,960.43 | -R20,231,879.43 | -R21,736,982.50 |
| > In a market with slow adoption of the new medicine | -R2,229,479.49 | -R6,329,938.16 | -R9,719,529.62 | -R12,533,351.78 | -R14,881,008.49 |
| **Net total costs** | | | | | |
| > In a market with rapid adoption of the new medicine | R48,001,689.08 | R77,877,940.37 | R96,736,083.63 | R108,900,350.02 | R117,001,735.32 |
| > In a market with slow adoption of the new medicine | R12,000,422.27 | R34,071,598.91 | R52,316,453.39 | R67,462,165.36 | R80,098,689.73 |

# Part E: Policy Brief

# Type 1 Diabetes in adults seeking care in the South African Public Sector: Is there a need to change the basal insulin?

## Introduction

Type 1 diabetes mellitus (T1DM) is a disease in which the body does not produce a type of hormone called insulin. Insulin is what allows cells of the body to take up glucose, a compound that provides the cell with energy, from the bloodstream. Without insulin, cells cannot use glucose available in blood and therefore struggle to perform their functions which ultimately leads to death. There are about 130,000 adults in South Africa who have T1DM.

To treat T1DM, insulin that has been extracted or synthesised is given to patients. However, since there is a constant level of insulin, called the basal level, as well as spikes in insulin levels that correspond with meals (sources of glucose), different types of insulin exist. These different types of insulin are broken down by the body at different rates. Therefore, insulins that are broken down slower, called intermediate- or long-acting insulins, and insulins that are broken down faster by the body, called rapid acting insulins, are used as a combination in the treatment of T1DM. In South Africa, an intermediate-acting insulin, Neutral Protamine Hagedorn (NPH) insulin, is used alongside rapid-acting insulins to treat T1DM.

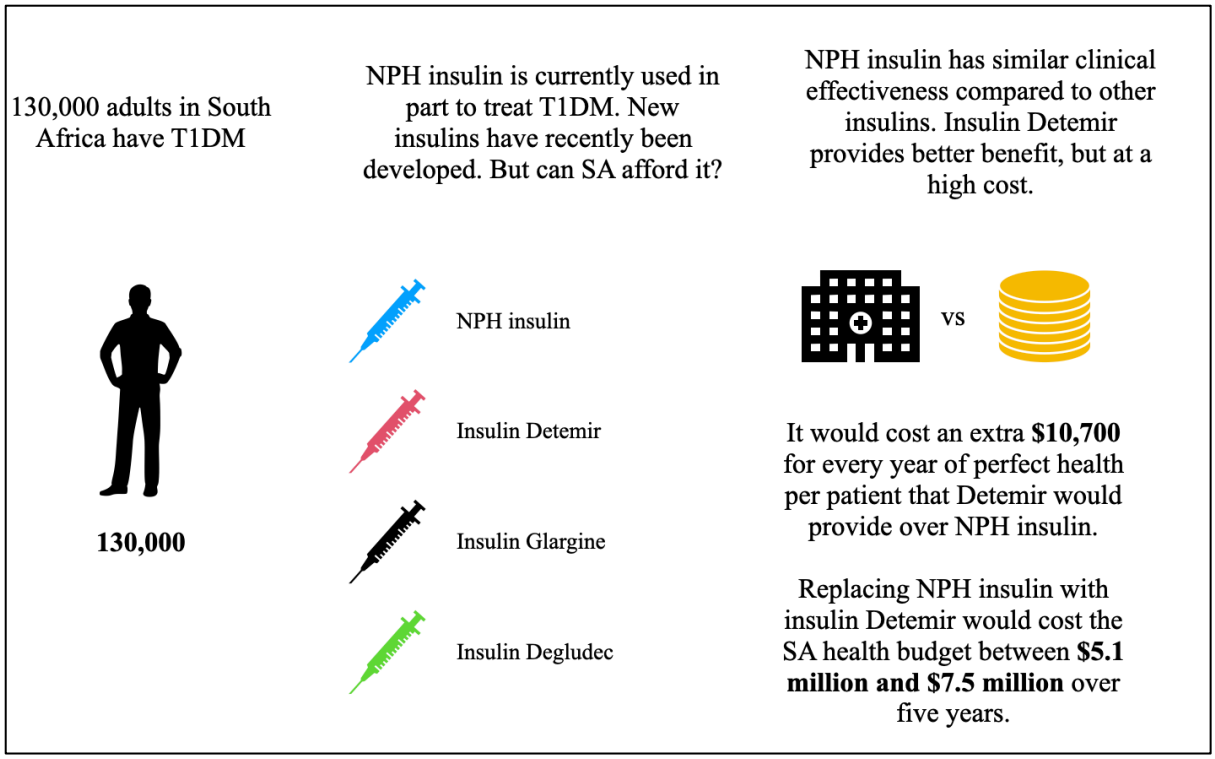
With insulin, T1DM patients can live long lives. A health challenge, however, is that patients need to use insulin well enough to control their blood glucose levels. If blood glucose levels are too high for too long, complications such as heart attacks or strokes can occur. Conversely, if too much insulin is taken, blood glucose levels may be dropped dangerously low, which can cause death.

A lot of research and development has taken place in order to create safer and improved insulins. More recently, newer long-acting insulins, namely insulins detemir, glargine and degludec, have been developed, although these are more expensive than NPH insulin. It is poorly understood if the benefits of the newer long-acting insulins compared to the intermediate-acting NPH insulin outweigh the added costs.

To answer this, an extensive review of the clinical profiles and potential benefits of the insulins under question was performed. With this evidence surrounding potential benefits of the drugs

can be established. Furthermore, an economic evaluation of the costs of the drugs as well as the cost implications on the health system were evaluated. Using clinical and economic evidence, a model was created to estimate what the total costs and benefits of each drug compared with one another could be. With this information, a recommendation is made surrounding the cost-effectiveness of the drugs under review and which drug, ultimately, is the best option for South Africa's resource-limited public health system.

## Policy Bulletin




## Methods

### Clinical Effectiveness

In order to evaluate the clinical effectiveness of the insulins under review, an extensive search of available evidence was done. Here multiple databases and sources of information were used. A refined search strategy was used in order to limit the data to only the highest available evidence. The evidence was then synthesised narratively in order to understand the most likely true differences in clinical effectiveness between the different insulins.

### Economic Evidence

Cost information was primarily drawn from the Master Health Product List (MHPL) of October 2020. This is a list of agreed upon prices of medicines purchasable by the national department of health. In instances where such cost data was not available, the single exit price (SEP) was derived from the Medicines Price registry of December 2020. The SEP represents the prices of medicines in the private health sector. These unit costs were then applied to the standard treatment regimen for an average adult with T1DM to calculate the treatment costs for one patient per year.

Cost data was also required for potential hospital admission related to any adverse event of T1DM, particularly that of low blood glucose. Using the District Health Barometer (DHB) of 2019/2020, the average cost of staying in the hospital for one day was calculated. Using available literature, the average length of stay for an adverse event was derived. With the average length of stay and cost per day of inpatient care, health system utilisation costs were calculated.

### Economic Evaluation

By synthesising the clinical profiles as well as the costs of each drug, an economic evaluation was conducted. Here, a Markov model was employed. Markov modelling creates a hypothetical scenarios of different disease states, the likelihood of being in each state, the quality of life associated with each disease state and the costs associated with each. The model was informed by clinical and economic evidence identified. The output of the model is essentially a cost-benefit ratio. It represents how much money has to be paid in order to derive a health benefit, in this case a year of perfect health for one patient.

Furthermore, a budget impact analysis was performed. Here the potential total costs of a health system for providing a new drug are calculated and does not include health benefits in the calculation.

## Results

### Clinical Effectiveness

From the extensive search, 208 high-quality studies were identified, of which three were considered the most extensive summary of all clinical evidence. The three studies identified,

however, vary in their methodology, particularly how they represented the different insulin types. These studies concluded that the newer long-acting insulins were not superior to intermediate acting NPH insulin in control long-term blood sugar levels and with that all the potential long-term complications, such as heart attacks and strokes. The only appreciable difference noted by these three studies was in the rates of severe hypoglycaemia (low blood glucose), which is a short-term potentially life-threatening problem that insulin can cause. The three studies, however, reported varying rates of severe low blood glucose.

**Table 1.** Cost data.

| **Inpatient Hospitalisation costs** | | | |
|---|---|---|---|
| | **Cost (USD)** | | **Source** |
| Cost per patient day | 192.61 | | DHB 2019/20 |
| **Insulin costs** | | | |
| | **Cost (USD)** | **Insulin cost per patient per day (USD)** | **Source** |
| NPH: Protaphane injection 10ml (100U/ml) | 2.25 | 0.0494 | MHPL Oct 2020 |
| Detemir: Levemir cartridge 5 x 3ml (100U/ml) | 28.48 | 0.3052 | MPR Dec 2020 |
| Glargine-U100: Lantus injection 10ml (100U/ml) | 29.69 | 0.4774 | MHPL Oct 2020 |
| Glargine-U300: Teajou pen 3 x 1.5ml (300U/ml) | 32.63 | 0.3886 | MPR Dec 2020 |
| Degludec: Tresiba cartridge 5 x 3ml (100U/ml) | 59.39 | 0.6365 | MPR Dec 2020 |
| **Needle cost** | | | |
| | **Cost (USD)** | **Cost per needle (USD/needle)** | **Source** |
| Insulin needle 31G 5mm (100 needles per pack) | 4.47 | 0.0447 | MHPL Oct 2020 |

## Economic Evidence

### Cost-Utility Analysis

From available cost information, the cost to treat a patient with each type of insulin was calculated. The cost of using NPH insulin was by in large the cheapest option out of all other insulins, costing about USD 32 per patient per year. Other insulins were more expensive, with insulin detemir, insulin glargine and insulin degludec costing about USD 112, USD 160 and USD 250 per patient per year respectively.

Using international literature, it was also identified that roughly 33% of severe low blood glucose resulted in hospital admission and that the average length of stay was about two days. The cost per patient day incurred by the state was also identified to be 193 per patient per day in the hospital.

The rates of severe low blood sugar were primarily drawn from the clinical evidence identified in the NICE review and included a range of potential rates depending on how the authors of the review calculated it. These are summarised in Table 1 below.

**Table 2.** Utilisation rates of inpatient hospitalisation, insulin utilisation and rates of severe hypoglycaemia.

| **Inpatient Hospitalisation** | | | |
|---|---|---|---|
| | **Base** | **Range** | **Source** |
| Proportion of severe hypoglycaemia requiring inpatient hospital admission | 32.89% | 25.25% to 36.26% | Hammer (55) |
| Length of stay (days) | 2 | 1 to 6 | Hammer (55) |
| **Insulin utilisation** | | | |
| | **Base** | **Range** | **Source** |
| Mean weight (kg) | 81.2 | ± 17.8 | Heller (70) |
| Total units of insulin per kg per day (U/kg/day) | 0.6 | 0.5-1 | EML and FDA (9, 66-69) |
| Proportion of total insulin that is NPH insulin | 0.45 | 0.4-0.5 | EML |
| Proportion of total insulin that is insulin Detemir | 0.33 | - | FDA (67) |
| Proportion of total insulin that is insulin Glargine-U100 | 0.33 | - | FDA (66) |
| Proportion of total insulin that is insulin Glargine-U300 | 0.33 | 0.33-0.5 | FDA (68) |
| Proportion of total insulin that is insulin Degludec | 0.33 | 0.33-0.5 | FDA (69) |
| **Rates of severe hypoglycaemia (per 100 person years)** (62) | | | |
| **Insulin** | **Lower** | **Base** | **Upper** |
| NPH once daily | 30.17 | 50.65 | 68.61 |
| NPH twice daily | 30.17 | 34.29 | 42.5 |
| Detemir once daily | 30.17 | 40.81 | 57.21 |
| Detemir twice daily | 30.17 | 30.17 | 36.53 |
| Glargine-U100 | 30.17 | 49.67 | 65.7 |
| Glargine-U300 | 30.17 | 50.26 | 91.82 |
| Degludec | 30.17 | 45.68 | 57.17 |

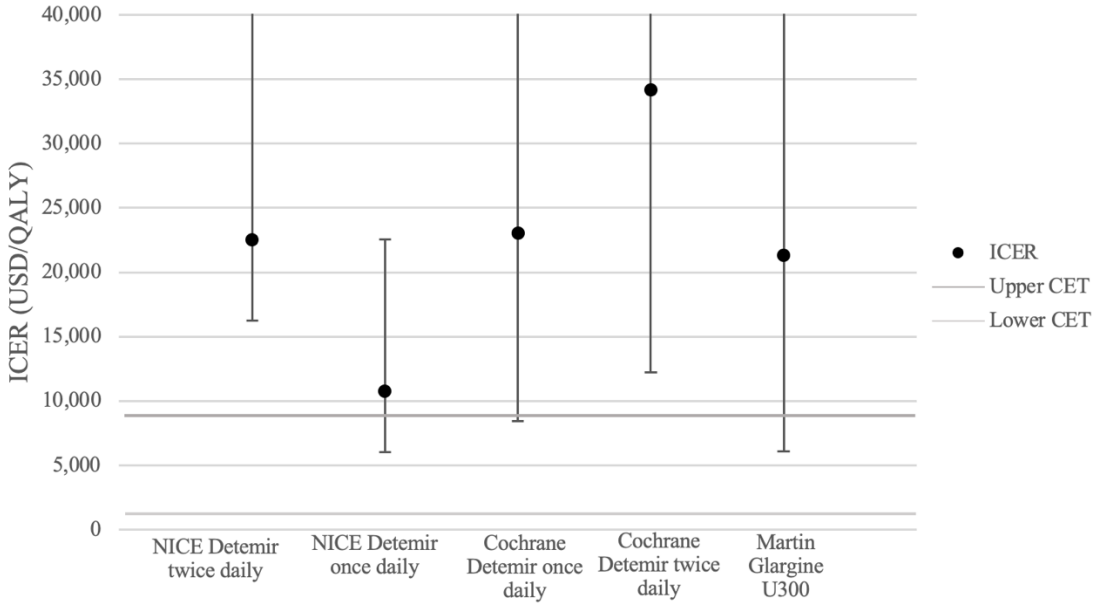
The quality of life (HRQoL) associated with T1DM with no complications, T1DM with yearly severe daytime low blood glucose and T1DM with yearly severe night-time low blood glucose were identified in literature to be 0.839, 0.777 and 0.773 respectively. As is evident, having severe low blood glucose affects a patient's quality of life, particularly if there are night time events.

Using these costs, rates and quality of life, the model was generated. The results showed NPH insulin provided better health outcomes over insulins glargine and degludec as well as being cheaper. Insulin detemir provided health benefit, however, at too great a cost, at USD 10,783.75 per patient per year of perfect health. The marginal productivity of the South African public health has been estimated to be 1,175 and 8,909 USD (midpoint 5,042 USD) per year of perfect

health. In other words, other interventions that we already use generate health at a lower cost, which means that replacing NPH insulin with detemir would not be cost-effective.

In order to ensure that the results were robust, variation in the model inputs, such as cost, rates of low blood glucose and quality of life were applied. In some instances, variations in these inputs were reported in literature, particularly surrounding rates of low blood sugar. In those instances, in which no ranges were evident, the inputs were varied at 10%.

From this sensitivity analysis, it was evident that the model results were mostly robust, as variation in the inputs did not alter the results enough to change the cost-effectiveness significantly (see Figure 1). The inputs that had the greatest impact on the results were the average length of inpatient hospital stay, the quality of life associated with severe low blood sugar at night/day as well as the total amount of insulin needed each day. In one model's sensitivity analysis, shown in Figure 2, detemir once daily compared to NPH insulin once daily was shown to potentially be cost-effective under the aforementioned model input changes, although the likelihood of these changes in inputs to represent the reality is difficult to establish.




Ranges indicate the single most impactful variation in model input identified in the sensitivity analyses for each Markov model.

**Figure 1.** Depiction of relevant ICERs of long-acting insulins compared to their NPH insulin counterpart in the respective Markov models.

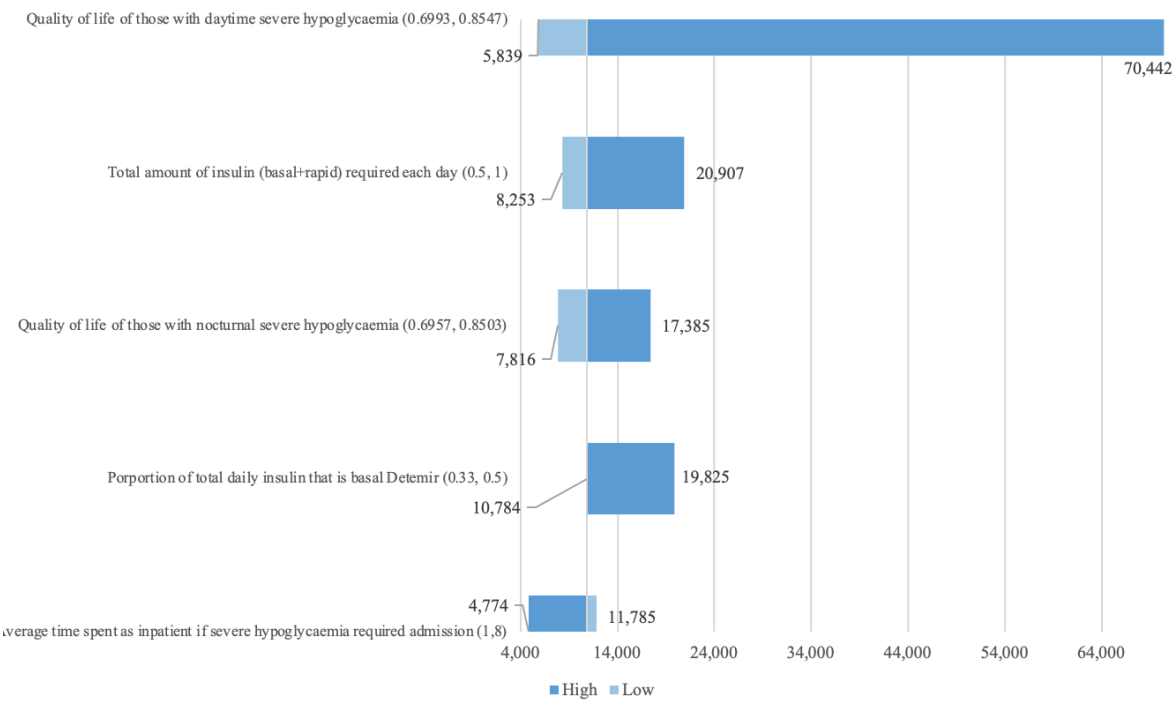



**Figure 2.** Sensitivity analysis of the NPH and detemir once daily Markov model drawing model inputs from the NICE review.

**Budget Impact Analysis**

In the budget impact analysis, the costs on the budget over five years of the current treatment strategy is compared to the potential impact of an alternative treatment. To fully capture the potential scenarios of budget impact, slow and rapid adoption scenarios of the alternative treatment are calculated. Here the rate change from the *status quo* treatment to the alternative are manipulated. The budget impact is calculated over a five-year period.

In the cost-utility analysis, insulin detemir was the only other potential alternative to NPH insulin. As is evident in Table, transitioning from NPH insulin to insulin detemir would result in an estimated $5,140,517.66 to $7,508,855.49 additional costs to the health system over a five-year period compared to the current treatment trajectory.

**Table 3.** BIA of implementing detemir once daily over five-year period.

| Strategy | Scenario | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|---|
| **NPH once daily** | Status quo | $11,147,349.25 | $11,303,412.14 | $11,461,659.91 | $11,622,123.15 | $11,784,832.88 |
| **Detemir once daily** | Rapid | $14,227,968.07 | $16,301,408.10 | $17,669,920.59 | $18,611,053.61 | $19,293,688.37 |
| | Slow | $11,917,503.96 | $13,490,035.38 | $14,819,188.65 | $15,951,662.79 | $16,925,350.53 |
| **Net total costs** | **Rapid** | **$3,080,618.81** | **$4,997,995.96** | **$6,208,260.68** | **$6,988,930.46** | **$7,508,855.49** |
| | **Slow** | **$770,154.70** | **$2,186,623.23** | **$3,357,528.74** | **$4,329,539.64** | **$5,140,517.66** |

## Discussion

This study has highlighted the need for robust clinical evidence for the use of economic evaluations. Many other economic evaluations have been performed elsewhere in which clinical differences are assumed that are not replicated in the high-quality evidence identified in the systematic search conducted in this analysis. These studies tend to favour the newer long-acting insulins (detemir, glargine or degludec) (35, 40, 44, 49).

There are, however, some economic evaluations that have incorporated the findings of the clinical evidence identified in this study (46, 56, 57). These studies have found less favourable evidence for long-acting insulins. However, it is difficult to draw on economic evaluations performed elsewhere, as costs and marginal productivity of health systems vary drastically across countries.

Having utilised robust clinical evidence, this study has provided the first economic evaluation of long-acting insulins for the treatment of adults with T1DM in South Africa. The results thereof indicate little clinically significant difference between the insulins under review, with most long-acting insulins incurring too great a cost for the marginal benefit. Insulin detemir was identified to be the only potential alternative to NPH insulin, with the sensitivity analysis suggesting that it may be possible that insulin detemir could be cost-effective. However, when using the base case, the costs that would be incurred for the benefits gained from insulin detemir are too great for the South African public health sector. In the budget impact analysis, the costs of adapting insulin detemir were demonstrated to be large.

The recommendation thus is that the South African public health sector should only provide NPH insulin in the treatment of adults with T1DM, as this is the most cost-effective option.

This is in line with the recommendation by the World Health Organization, that primarily drew its evidence form a study by Tricco et al. (46, 74).

## Conclusion

This study has identified high-quality evidence surrounding the clinical effectiveness of the insulins under review. By incorporating this evidence into an economic evaluation, the recommendation for the *status quo*, NPH insulin, to be utilised as the basal insulin in the management of adults with T1DM in South Africa is made.

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