COST-EFFECTIVENESS OF ANALOGUE AND HUMAN INSULIN: A SYSTEMATIC REVIEW

April 2018

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Cost-effectiveness of Analogue and Human Insulin: A Systematic Review

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**Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDP pc</td>
<td>Gross domestic product per capita</td>
</tr>
<tr>
<td>LMICs</td>
<td>Low-and middle-income countries</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>CEA</td>
<td>Cost-effectiveness analysis</td>
</tr>
<tr>
<td>QALYs</td>
<td>Quality-adjusted life years</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost effectiveness ratio</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycated haemoglobin</td>
</tr>
<tr>
<td>NPH</td>
<td>Neutral protamine hagedorn</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>EED</td>
<td>Economic Evaluation Database</td>
</tr>
<tr>
<td>CRD</td>
<td>Centre for Reviews and Dissemination</td>
</tr>
<tr>
<td>CORE</td>
<td>Center for Outcomes Research Diabetes</td>
</tr>
<tr>
<td>CEVR</td>
<td>Center of Evaluation of Value and Risk in Health</td>
</tr>
<tr>
<td>INN</td>
<td>International Nonproprietary Name</td>
</tr>
</tbody>
</table>
Executive Summary

Objective
To conduct a systematic literature review of published cost-effectiveness studies comparing analogue versus human insulin for the treatment of diabetes mellitus.

Methodology
A systematic literature review of published cost-effectiveness studies comparing analogue versus human insulin in type 1 and type 2 diabetes was conducted using the Tufts cost-effectiveness analysis (CEA) registry and National Health Service (NHS) Economic Evaluation Database (EED).

Results
Twenty-four out of 30 (80 percent) cost-effectiveness studies in this review were conducted in North America or Europe. Only three studies described results in settings outside of high-income countries. The pharmaceutical industry or insulin manufacturers sponsored 28 of the 30 studies (93 percent).

All studies used computer simulation models to calculate incremental cost-effectiveness ratios. The Center for Outcomes Research Diabetes (CORE) diabetes model was used in 17 (57 percent) studies. Treatment effect assumptions varied widely between studies. The quality of evidence supporting most treatment effect assumptions was low to moderate.

Costs of analogue insulins ranged from ‘no difference relative to human insulins’ to a maximum of 1140 percent higher priced. Twenty-seven (90 percent) CEA studies found that analogue insulins were cost-effective when compared to human insulin. However, this finding should be treated with caution because the two independent CEA studies not funded by insulin manufacturers found that analogues were generally not cost-effective. Furthermore, industry sponsored studies selected clinical treatment effects most likely to show an advantage towards analogue insulins.

The determination of cost-effectiveness for an insulin product is related to the country setting (high-income versus lower-income), the source of funding of the study, and the comparative price of the analogue insulin product.

Recommendations
1) **Type 2 diabetes:** Low- or middle-income countries (LMICs) may wish to procure long-acting analogues when their prices are comparable or slightly higher priced than human insulins (i.e., neutral protamine hagedorn [NPH] and 70/30). Long-acting analogues may not be cost-effective in lower income settings.

2) **Type 1 diabetes:** Policy-makers in LMICs should choose rapid-acting analogues only when the price difference between the analogue and human insulin is negligible or small. Based on cost-effectiveness, policy-makers may wish to avoid long-acting analogues because one independently funded study found that detemir and glargine were not cost-effective compared against human insulin, even in a high-income setting (Canada).
1. Introduction

Insulin is a life-saving medicine for the millions of people worldwide who live with type 1 and type 2 diabetes. Despite the fact that it has been almost 100 years since this medicine was first used clinically, access to insulin products is still far from universal (1).

In wealthy countries, the use of newer, more expensive analogue insulin products have surpassed older human insulin products produced using recombinant DNA technology (2,3). In many countries, analogue insulin products are five to 10 times higher price than comparable human insulins. While both types of insulin are safer and more effective than the products originally developed by the co-inventors of insulin, it is debatable whether analogue insulins are, in fact, superior to human insulin for the majority of people who need insulin (4). Evidence of clinical comparative superiority is easier to demonstrate in the setting of type 1 diabetes, where patients are more prone to developing low blood sugar, or hypoglycaemia (5). Untreated severe hypoglycaemia may result in coma or, in rare cases, death. In those with type 2 diabetes, the evidence for clinical benefit is more equivocal and many diabetologists and clinical experts suggest that the marginal value for these products may not reflect their differential price (6).

For the 20th version of the World Health Organization’s (WHO) Model list of Essential Medicines, an application was submitted to list new long-acting analogue insulin, based on new evidence suggesting that these medicines were both superior and cost-effective for the treatment of type 1 diabetes. In essence, the authors were arguing that long-acting analogue insulin met the criteria for an essential medicine: namely one that satisfies the priority health needs of the population. Furthermore, the authors argued that prices for analogue insulins would soon fall, as follow-on biosimilar insulin products enter the market in response to increased global demand. However, the WHO expert committee concluded that the benefits of analogue insulin in terms of reduced glycated haemoglobin (HbA1c) and reduced hypoglycaemia were only modest and did not justify the current large differences in price.

This decision is significant because this implies that the most authoritative WHO normative review panel did not believe that insulin analogues are sufficiently superior to human insulins to warrant their classification as a priority need. Additionally, their decision suggests that analogue insulins are likely priced much higher in today’s international markets than their overall clinical value.

Is there any clinical benefit that would justify a higher price for analogue insulin? And if so, at what price would a decision-maker trying to procure insulin for a large national health programme in a LMIC be indifferent to choosing between analogue versus human insulin? This summary report attempts to address these problems through an empirical approach.
2. Methods

This report sought to determine the relative value of analogue insulin versus human insulin through a systematic review of published CEA studies comparing these two types of insulin.

2.1. Data Sources

The Tufts CEA registry is an online searchable database of over 5,500 published cost-utility analyses (7). The registry is maintained and updated by the Center of Evaluation of Value and Risk in Health (CEVR), based at Tufts Medical Center, in Boston, United States (US). Three times a year, the CEA registry team searches Medline using the terms, “QALYs,” “Quality,” or “Cost-utility analysis.” Published articles in English that contain an original cost-utility estimate measuring health benefits as quality-adjusted life years (QALYs) are included in the registry. Reviews, methodologic pieces, and editorials are excluded from the registry.

The NHS EED project is a publicly searchable database of structured abstracts of published economic evaluations of health technologies (8). The purpose of the database is to help identify and disseminate findings to researchers and decision makers in the NHS.

2.2 Search Algorithm

A search was conducted in the Tufts CEA registry using the word, “insulin” on 21 March, 2017. Of the original 106 resulting abstracts, 81 were excluded based on title only because these studies did not directly compare at least one analogue insulin product against at least one human insulin product. Of the 25 studies that underwent full-text review, two were excluded.

One study compared the cost-effectiveness of two pre-mixed insulin products, neither of which included human insulin. The second excluded study was of poor methodological quality, using a non-standard model and six scenarios as its base case analysis.

An additional search for CEA studies was conducted on 8 August, 2017 in the NHS EED through the York Centre for Reviews and Dissemination (CRD) Database. Of the 128 study titles that contained “insulin,” 19 were duplicate studies (i.e., already included in the study based on the Tufts CEA registry search). Six new qualifying studies were found and analysis including these studies is included in the final draft of this report. Finally, an additional published CEA study was identified by one of the peer reviewers of an earlier draft of this report and included to yield a total of 30 studies.

For the purposes of this report, analogue insulins are newer insulin products that have been modified to change either the onset or duration of action. Common analogue insulins include the long-acting analogues glargine and detemir, as well as the rapid-acting insulins aspart and lispro. Human insulin products have amino-acid and polypeptide compositions that are indistinguishable from human insulin and are produced using recombinant DNA technology. Common human insulin products are regular human insulin (soluble), NPH, and pre-mixed insulin (70/30).

2.3 Data Extraction

Common data elements were extracted by a single reviewer (JL) from each of the 30 cost-effectiveness studies described above. The definition of each element or how each value was obtained is explained in the Table 1, below. Information was recorded using Microsoft Excel, where each CEA study represented a single observation (row), and each data element represented a single variable (column).
Table 1: Data elements extracted from CEA studies in this systematic review.

<table>
<thead>
<tr>
<th>Data element</th>
<th>Definition or explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td></td>
</tr>
<tr>
<td>Country or geographic scope</td>
<td></td>
</tr>
<tr>
<td>Lead author</td>
<td></td>
</tr>
<tr>
<td>Journal</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Year of article publication</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Private company (e.g., Novo Nordisk, Eli Lilly, Sanofi) or governmental agency sponsoring the study</td>
</tr>
<tr>
<td>Study drug</td>
<td>International Nonproprietary Name (INN) of study medicine (an analogue insulin)</td>
</tr>
<tr>
<td>Comparator drug (or therapy)</td>
<td>INN of human insulin product being compared</td>
</tr>
<tr>
<td>Patient population</td>
<td>Type 1 or type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Type of model</td>
<td>Name of computer simulation model used to calculate incremental costs, incremental QALYs and cost-effectiveness ratios. For example, IMSCORE Diabetes model (explained in further detail below).</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Length of model, usually either lifetime of simulated patients, or short-term (e.g., 1 year)</td>
</tr>
<tr>
<td>Perspective</td>
<td>Either third-party payer, large single payer, or societal</td>
</tr>
<tr>
<td>Treatment effect</td>
<td>The magnitude of clinical benefit in terms of clinical benefit (e.g., reduced rate of hypoglycaemia, reduced HbA1c). These values were usually derived from the literature—for example, by referencing a single randomised trial, observation study, or meta-analysis. In the raw data file, hypoglycaemia assumptions were recorded separately from other clinical outcome assumptions (i.e., changes in HbA1c or body mass index [BMI]).</td>
</tr>
<tr>
<td>Cost of drug treatment</td>
<td>Applicable for both study drug and comparator drug. The cost source was also recorded as a separate variable.</td>
</tr>
<tr>
<td>Data element</td>
<td>Definition or explanation</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Costs associated with increased healthcare utilisation</td>
<td>These costs may be direct medical costs—for example, cost of a hospitalisation in the local context for an acute myocardial infarction (heart attack) where a patient survived. Indirect costs, such as lost productivity as a result of illness, were generally not reported in the studies reviewed. Because complications of diabetes are numerous (retinopathy, neuropathy, kidney disease, peripheral vascular disease, and cardiovascular), individual costs were usually not recorded, but referenced based upon the associated table in the full text of the article.</td>
</tr>
<tr>
<td>Utility weights</td>
<td>A numeric value assigned to each adverse event—for example, each hypoglycemic event may be associated with a temporary decrease in utility for a period of 15 minutes.</td>
</tr>
<tr>
<td>Clinical benefit (QALYs)</td>
<td>Clinical benefit in terms of quality-adjusted life years (QALYs) gained due to treatment with either the study drug or comparator, over the time-horizon of the model.</td>
</tr>
<tr>
<td>QALYs gained (or lost)</td>
<td>QALYs of analogue minus QALYs of human insulin product.</td>
</tr>
<tr>
<td>Cost of complications (excluding drug therapy or management costs)</td>
<td>Extracted for both human and analogue insulin products (either directly reported in article or calculated, when possible, by subtracting total costs over time horizon by total costs of medications and management costs, when reported separately).</td>
</tr>
<tr>
<td>Additional (incremental) costs</td>
<td>Total costs (pharmacologic therapy, management, and cost of complications) for study drug minus total costs for comparator.</td>
</tr>
<tr>
<td>Incremental cost-effectiveness ratio (ICER)</td>
<td>In this table, additional costs / QALYs gained.</td>
</tr>
<tr>
<td>Cost-effective?</td>
<td>Yes/no; based on whether the ICER is greater or less than the cost-effectiveness threshold usually used in the country or geographic region covered by the study.</td>
</tr>
<tr>
<td>Cost-effectiveness threshold (also known as willingness to pay)</td>
<td>Either the reported amount (e.g., €30,000 per QALY) or a fraction of GDP per capita.</td>
</tr>
</tbody>
</table>
The quality of CEA studies was determined based upon the data elements described above. Although no formal checklist was used to assess quality, all of these studies were published in peer-reviewed journals and generally satisfy good practice in decision-analytic modelling (9, 10). For example, all studies reviewed included appropriate discounting rates (usually three percent) for both cost and effect outcomes. Major limitations or concerns with either methodologic quality, choice of comparators, estimates of comparable clinical benefits/harms derived from literature, estimates of costs and sensitivity analyses were noted during the full-text review.

In cost-effectiveness studies, results are typically reported as ICER, or price per QALY gained. The prices in the numerator are usually expressed in local currency or in United States dollars (US$). Based on the ICER and a cost-effectiveness threshold (if one exists) for a particular country or setting, authors typically conclude whether a new technology is cost-effective or not cost-effective. In some cases, where the new technology results in greater QALYs and cost-savings when compared to a comparator, the new technology may be considered dominant.

2.4 Data Analysis

From the raw Microsoft Excel file compiled above, studies were categorised and summary results presented using descriptive statistics for each of 10 domains: geographic scope, sponsor, medicines being compared, patient population, model type, time-horizon, treatment effects, costs of medicines, costs of complications (excluding drug costs), and overall statement of cost-effectiveness.
3. Results

The full titles of each of the 30 CEA studies can be found in Annex 1 (11–33). The following sections describe characteristics of the studies reviewed according to the domains referenced in the Methods section, above.

3.1 Geographic Scope

Twenty-four (80 percent) of the 30 cost-effectiveness studies were conducted in North America or Europe (Figure 1). Some studies covered more than one country. Only three studies described results in settings outside high-income countries: India, Indonesia, China, and Thailand (19, 34, 36).

Figure 1. Geographic scope of CEA studies (n=30).

Note: The total is greater than the number of studies reviewed (30) because some studies reported results in multiple countries.

3.2 Sponsor

Of the 30 studies reviewed in this report, one study was sponsored by Health Canada, and one by the National Essential Medicines List of Thailand. The pharmaceutical industry or insulin manufacturers sponsored the remaining 28 (93 percent) studies. Twenty studies were sponsored by Novo Nordisk, seven by Sanofi, and one by Eli Lilly and Company.

3.3 Medicines Compared

Of the 30 studies reviewed, seven (23 percent) evaluated detemir, five (17 percent) evaluated biphasic aspart (BIAsp 30), four (13 percent) aspart alone, 10 (33 percent) evaluated glargine, one (three percent) evaluated lispro, and three (10 percent) evaluated multiple analogue insulins together as a single regimen (Figure 2).
Among comparator medicines (i.e., human insulins considered standard of care), NPH was the reference in 16 of the studies (53 percent), regular human insulin (also referred to as RHI) seven (23 percent), premixed insulin 70/30 was the reference five times (13 percent) and multiple human insulins were the references four times (seven percent) (Figure 3).

3.4 Types of Diabetes

Sixteen (53 percent) studies focused on type 2 diabetes, ten (33 percent) on type 1 diabetes and four (13 percent) on both type 1 and type 2 diabetes. One study examined the cost-effectiveness of analogue insulin against human insulin among pregnant women with type 1 diabetes (35).
3.5 Study Models

The IMS CORE diabetes model was the most frequently used model in 17 out of 30 (57 percent) of CEA studies reviewed. Microsoft Excel was used to create models in 6 of the 30 (20 percent) of studies. TreeAge was used twice and Cardiff Research Consortium’s United Kingdom (UK)-based Discrete Event Simulation Model was used three times.

The CORE diabetes model has been validated against published studies with a predictive abilities of 0.8861 to 0.9778, providing a reasonably accurate representation of real-life settings (17). These computer simulations are economic models that predict the development of various health states for individual patients—or a cohort of patients—based upon baseline characteristics, assigned treatment regimen (analogue or human insulin) and probabilities of developing an adverse event or diabetes-related complication, based on sub-model event equations (Figure 6) (36, 37). Baseline characteristics were usually obtained from a single randomised trial (prior to receiving the randomly assigned therapy), and/or a single observational study. Reductions in the rate of complications were usually due to presumed reductions in HbA1c obtained from short-term trials or observational studies (typical duration less than 24 weeks) or, less commonly, from a meta-analysis of published trials. These differences were assumed to persist for the entire duration of the model simulation. Similar assumptions were made for reductions in the rate of hypoglycaemia.
3.6 Time Horizon

A majority of studies (73 percent) used a life-time time horizon. This is consistent with conventional practice, as well as guideline recommendations regarding length of time to calculate costs and benefits. Seven studies used time horizons that were either short (one to three years), or medium term (five to 10 years). The stated goals of these shorter studies were to assess short term value for money associated with newer analogue insulin products.

3.7 Treatment Effects

The CEA studies reviewed in this report used a variety of sources and demonstrated large heterogeneity with respect to the estimates of the clinical benefit of analogue insulins on risks of hypoglycaemia and increase in HbA1c and weight (body mass index, BMI). For example, in the 20 CEA studies conducted on type 2 diabetes (including the four studies that included both types of diabetes), a wide-range of assumptions were used in the cost-effectiveness models. For hypoglycaemia, the effect of analogue insulin compared to human insulin ranged from no difference (three studies) to a relative reduction in the event rate of 80 percent. Studies also differed with respect to types of hypoglycaemia. Many studies assumed that mild hypoglycaemia events, which are usually more frequent, would be reduced at a different rate than major or severe events (often defined as needing the assistance of one other person). Baseline rates also varied widely. For example, some studies assumed a baseline rate of 286 per 100 person years to
a high of 1,638 events per 100 person years. Assumed baseline rates of major hypoglycaemia was less variable, in part because these events happen much less frequently (Table 3). For HbA1c, treatment effects also varied widely, from a low of -.05 percent to a high of 2.1 percent reduction being attributable to analogue insulin when compared against human insulin. For BMI, the estimated treatment effect of analogue versus human insulin ranged from -0.18 to -0.38.

Many of the sources in the clinical literature that were used by CEA study authors to estimate comparative treatment effects seen in Tables 2 and 3 were of low to moderate quality (Annex 3). It is important to note that the overall evidence supporting the clinical superiority of analogue insulins in type 2 diabetes is relatively weak. For example, several direct head-to-head trials and meta-analyses have shown only modest benefit (almost exclusively shown with respects to the rates of hypoglycaemia). Most parallel arm comparative trials, utilising random allocation of treatment assignment, have not shown any benefits in favour of analogue insulins with regards to HbA1c or hard clinical endpoints (20, 38).

Yet, as demonstrated in Table 3 and Annex 3, most CEA studies used estimates of treatment effects drawn from far less rigorous studies. For example, one CEA study based its treatment assumptions on a single 24-week observational study with unlikely results (two percent decrease in HbA1c) extending into 30 years of clinical benefits (19). Another CEA study based its assumptions on a single observational study of general practitioners in the UK with methodological flaws (e.g., prevalent user design, immortal time bias, sub-optimal confounding control) and unlikely results given the short timeframe of the study (39, 40). For example, the referenced study calculated an adjusted hazards ratio for acute myocardial infarction of 0.69 and stroke of 0.58 (22). One study drew its assumptions from a subgroup analysis of a short term, large, single-arm cohort study (IMPROVE) (26).

It is difficult, if not impossible, to draw meaningful clinical conclusions about comparative treatment benefits from single-arm observational studies because of pharmacoepidemiologic biases, including confounding by indication (41–43). The fact that CEA authors chose to use data generated from subgroup analyses or from short-term studies—rather than using data readily available from head-to-head comparative trials or from meta-analyses of randomised trials—suggests that the cost-effectiveness results of these studies are likely to be biased. In other words, the validity of many published CEA studies comparing analogue against human insulins should not be taken at face value because many individual authors selected treatment effect estimates for their baseline models that were most likely to show an advantage towards the analogue insulin. This may also explain why the vast majority of these studies are published in lower-impact subspecialty or medical economics journals, rather than core clinical journals (see Annex 1 for references).
Table 2. Comparative effect estimates for short term clinical outcomes (hypoglycaemia, HbA1c, weight/BMI) in CEA studies among people living with type 1 diabetes.

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Year</th>
<th>Active drug</th>
<th>Comparator drug</th>
<th>Effect on hypoglycaemia (risk ratio or reduction in absolute rate per 100 person-years)</th>
<th>Effect on HbA1c</th>
<th>Effect on weight or BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-acting insulin analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morales</td>
<td>2015</td>
<td>detemir</td>
<td>NPH</td>
<td>Risk ratio (RR) 0.84</td>
<td>n/a</td>
<td>+0.91kg</td>
</tr>
<tr>
<td>Grima</td>
<td>2007</td>
<td>glargine</td>
<td>NPH</td>
<td>Not described</td>
<td>-0.4%</td>
<td></td>
</tr>
<tr>
<td>Valentine</td>
<td>2006</td>
<td>detemir</td>
<td>NPH (and glargine)</td>
<td>Hypoglycaemia risk reduced by 21%</td>
<td>-0.22%</td>
<td>Body weight reduced 1kg at 18 weeks</td>
</tr>
<tr>
<td>Palmer</td>
<td>2004</td>
<td>detemir</td>
<td>NPH</td>
<td>Major events reduced from 42/100py to 41/100py (2% reduction)</td>
<td>-0.15% (not statistically significant)</td>
<td>BMI change (-0.26)</td>
</tr>
<tr>
<td>Tunis</td>
<td>2010</td>
<td>detemir</td>
<td>NPH</td>
<td>25% RR major; 77% RR minor</td>
<td>-0.12%</td>
<td></td>
</tr>
<tr>
<td>Pfohl</td>
<td>2012</td>
<td>glargine</td>
<td>NPH</td>
<td>Severe: 24% reduction; Nocturnal: 24% reduction; Symptomatic: 23% reduction</td>
<td>-0.38%</td>
<td></td>
</tr>
<tr>
<td>Valentine</td>
<td>2011</td>
<td>determir</td>
<td>NPH</td>
<td>Major: 69% reduction; nocturnal: 46% reduction</td>
<td>-0.22%</td>
<td></td>
</tr>
<tr>
<td>Gschwend</td>
<td>2009</td>
<td>detemir</td>
<td>NPH</td>
<td>67% risk reduction in major events, based on Bartley single trial</td>
<td>-0.22%</td>
<td>1kg weight loss</td>
</tr>
<tr>
<td>Palmer</td>
<td>2004</td>
<td>detemir+asp art</td>
<td>NPH+RHI</td>
<td>Minor hypoglycaemia: 77.6%RR, Major: 81%RR</td>
<td>-0.22%</td>
<td>BMI decrease 0.3</td>
</tr>
<tr>
<td>Lead Author</td>
<td>Year</td>
<td>Active drug</td>
<td>Comparator drug</td>
<td>Effect on hypoglycaemia (risk ratio or reduction in absolute rate per 100 person-years)</td>
<td>Effect on HbA1c</td>
<td>Effect on weight or BMI</td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
<td>-------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>McEwan</td>
<td>2007</td>
<td>glargine</td>
<td>NPH</td>
<td>0 to -28% RR in severe events</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Pratoomsoot</td>
<td>2009</td>
<td>lispro</td>
<td>RHI</td>
<td>Severe: 21.8/100py (lispro) vs 46.1/100py (RHI); minor: 6790/100py (lispro) vs 7311/100py RHI</td>
<td>Reduction in WMD a1c 0.1%</td>
<td>n/a</td>
</tr>
<tr>
<td>Lloyd</td>
<td>2009</td>
<td>aspart</td>
<td>RHI</td>
<td>n/a (% of women with live birth)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Cameron</td>
<td>2009</td>
<td>aspart, lispro, detemir, glargine</td>
<td>RHI, NPH</td>
<td>Mild-Mod: 0.82 to 1.02 (depending on active drug) Severe: 0.74 to 0.83</td>
<td>-0.01% to -0.12%</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Table 3. Comparative effect estimates for short term clinical outcomes (hypoglycaemia, HbA1c, weight/BMI) in CEA studies among people living with type 2 diabetes.

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Year</th>
<th>Active drug</th>
<th>Comparato</th>
<th>Effect on hypoglycaemia (risk ratio or reduction in absolute rate per 100 person-years)</th>
<th>Effect on HbA1c</th>
<th>Effect on weight or BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persuwan</td>
<td>2016</td>
<td>glargine NPH</td>
<td>Minor: 0.82; major: 0.56</td>
<td>-0.05%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morales</td>
<td>2015</td>
<td>detemir NPH</td>
<td>0.52</td>
<td>-0.91kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridderstrale</td>
<td>2013</td>
<td>glargine NPH</td>
<td>0.52</td>
<td>-0.91kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith-Palmer</td>
<td>2012</td>
<td>detemir NPH</td>
<td>Mild: 0.62; major: 4/100py to 0/100py no major hypo events compared with 4 events per 100py</td>
<td>BMI -0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brandle</td>
<td>2011</td>
<td>glargine NPH</td>
<td>Severe: 50.9% reduction; nocturnal 32% reduction; symptomatic 6.9% reduction</td>
<td>-0.12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tunis</td>
<td>2010</td>
<td>glargine NPH</td>
<td>Minor: 0.41; major: 5/100py to 0/100py</td>
<td>-0.34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tunis</td>
<td>2009</td>
<td>detemir NPH</td>
<td>Type 2: 7.46%RR major (133/100py to 10/100py); 27%RR minor (1342/100py to 358/100py)</td>
<td>-0.182%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grima</td>
<td>2007</td>
<td>glargine NPH</td>
<td>No difference in hypo</td>
<td>-0.87%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valentine</td>
<td>2008</td>
<td>detemir NPH</td>
<td>80% reduction in event rate</td>
<td>-0.6% BMI +0.382</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brandle</td>
<td>2007</td>
<td>glargine NPH</td>
<td>Not part of model</td>
<td>-.12% to -.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McEwan</td>
<td>2007</td>
<td>glargine NPH</td>
<td>10% RRR symptomatic, 26% to 35% RRR nocturnal, 40% to 46% severe.</td>
<td>-0.44% to -0.87%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pre-mixed insulin analogues**

| Gupta        | 2015 | BiAsp 70/30 | India (-.36/100py), Indonesia (-.67/100py), Saudi Arabia (-.36/100py) | -1.4 % to -2.1% |
| Palmer       | 2010 | BiAsp 70/30 | Major: 25% RR (7.7/100py vs 30.9/100py); Minor: 68.1% (1116.1 vs 1638.6) | -0.58% BMI +0.28 |
| Lee          | 2009 | BiAsp 70/30 | Hypo reduced from 494 to 188 events per 100py | -0.82% BMI +0.18 |
| Ali          | 2008 | BiAsp 70/30 | | |
### Lead Author	Year	Active drug	Comparator drug	Effect on hypoglycaemia (risk ratio or reduction in absolute rate per 100 person-years)	Effect on HbA1c	Effect on weight or BMI
---
Palmer 2008	BiAsp 70/30	Minor: -891 events / 100 py Major: -209 events / 100py	-1.82% over 3 months	BMI -0.22

### Rapid-acting insulin analogues

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Year</th>
<th>Active drug</th>
<th>Comparator drug</th>
<th>Effect on hypoglycaemia (risk ratio or reduction in absolute rate per 100 person-years)</th>
<th>Effect on HbA1c</th>
<th>Effect on weight or BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liebl 2014</td>
<td>aspart</td>
<td>RHI</td>
<td>No difference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollock 2010</td>
<td>aspart</td>
<td>RHI</td>
<td>No difference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmer 2008</td>
<td>aspart</td>
<td>RHI</td>
<td>Major: 5/100py to 0/100py; minor: 385/100py to 286/100py</td>
<td>-0.55% to -0.93%</td>
<td>BMI -0.18</td>
<td></td>
</tr>
</tbody>
</table>

### Multiple insulin types

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Year</th>
<th>Active drug</th>
<th>Comparator drug</th>
<th>Effect on hypoglycaemia (risk ratio or reduction in absolute rate per 100 person-years)</th>
<th>Effect on HbA1c</th>
<th>Effect on weight or BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameron 2009</td>
<td>multiple analogues</td>
<td>multiple human insulins</td>
<td>Mild–Moderate: 0.54 to 0.97; Severe: 0.39 to 0.75</td>
<td>-0.09% to -0.14%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In type 1 diabetes, a balanced view of the literature (outside of the CEA studies reviewed here) suggests a slightly different conclusion. One large meta-analysis of 27 randomised controlled trials, including 7,496 people with type 1 diabetes, concluded that long-acting analogue insulins (glargine once daily, detemir once or twice daily) were modestly superior to intermediate-acting human insulin (NPH once daily) with respect to HbA1c (the primary outcome), hypoglycaemia and weight (5).

In this network meta-analysis, the mean HbA1c difference was -0.39 percent comparing glargine once daily versus NPH and -0.26 percent comparing once daily detemir versus NPH. The authors concluded that these differences were not likely to be clinically relevant because they did not approach the commonly accepted 0.5 percent minimally clinically important difference in HbA1c.

People with poorly controlled HbA1c (values > 8 percent) had slightly greater HbA1c improvements with glargine (mean difference -0.65 percent) and detemir (-0.41 percent) versus NPH.

For the secondary outcome of severe hypoglycaemia, patients receiving detemir after a median 24 weeks of follow-up had significantly less severe hypoglycaemia than those receiving NPH (OR 0.62, 95 percent CI 0.42 to 0.91).

### 3.8 Costs of Analogue and Human Insulins

Most of the analogue insulins in this review were priced at a level that was between 10 to 100 percent higher priced than human insulin products (range 0 to 1,141 percent). In one study, the price of analogue insulin was the same as the price of human insulin, in part due to a governmental decision not to reimburse rapid-acting insulin analogues at a higher rate than regular human insulin (22). In another study, lispro cost only £187 (US$265.26) more than
regular human insulin over the *lifetime* of an individual (or approximately £3.74 [US$5.31] per year over 50 years) (29). This is likely due to the fact that these two countries (Germany and the UK, respectively) have strong health technology assessment agencies, large purchasing power and other price control mechanisms.

At the other end of the spectrum, three studies assumed that analogue insulin was substantially higher priced than human insulin. For example, one study using a US perspective assumed that biphasic aspart was 160 percent higher priced than human insulin, although it is unclear whether the prices quoted were list, reimbursement, or net prices since the source was not cited in the article (26). Another industry-sponsored study, conducted from the perspective of Canada, assumed that detemir was 243 percent higher priced than NPH in the setting of type 2 diabetes (140 percent high priced in the type 1 setting, due to different dosing assumptions) (11). These results are not surprising when viewed in context: both the US and Canada lack efficient mechanisms at the national level to control medicine prices (44–46). Canada does limit price growth for patented medicines and, in general, has lower-brand name drug prices than the US, but additional price control measures may vary from province to province (44, 45). Finally, a Thai study conducted without industry funding estimated that the annual cost per patient for insulin glargine was 1,242 percent the cost of NPH insulin (7380 THB [US$209] versus 584 THB [US$16.55]).

The prices of analogue and human insulin products, as well as the sources and price types (procurement or selling prices), are reported in Table 4. Sources of price information included central/provincial payers, manufacturers, pharmacies, and published literature. Prices varied widely depending on the study and location of the CEA studies reviewed. Furthermore, there was little standardisation in how pharmacologic or drug management costs or prices were reported. Some studies reported costs per international unit of insulin or per dispensed unit (i.e., one vial or pack of five pens). Other studies reported costs per day or per year of treatment. Still, others reported costs over the entire time-horizon of the study, in some cases, over 30 years.
Table 4. Comparing the cost of analogue and human insulin among selected CEA studies* by type of insulin (long-acting, pre-mixed, rapid-acting or multiple insulin types).

<table>
<thead>
<tr>
<th>CEA study</th>
<th>Year</th>
<th>Analogue insulin</th>
<th>Cost of analogue product</th>
<th>Human insulin</th>
<th>Cost of human product</th>
<th>Cost source</th>
<th>Cost of analogue / cost of human (%)</th>
<th>Country</th>
<th>Cost-effective?</th>
<th>ICER (additional costs per QALY gain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persuwan</td>
<td>2016</td>
<td>glargine</td>
<td>US$209 (7,380 THB) per year</td>
<td>NPH</td>
<td>US$16.55 (584 THB) py</td>
<td>Sanofi Thailand (glargine) vs Drug and Medical Supply Information Center (NPH)</td>
<td>1241%</td>
<td>Thailand</td>
<td>N</td>
<td>US$204 (7,216 THB)</td>
</tr>
<tr>
<td>Morales</td>
<td>2015</td>
<td>detemir</td>
<td>US$33.72 per vial (€30 or €0.03 per IU)</td>
<td>NPH</td>
<td>US$17.98 per vial (€16 or €0.016 per IU)</td>
<td>Ministry of Health</td>
<td>188%</td>
<td>Spain</td>
<td>Y</td>
<td>Type 1: US$2146 - US$8634 (€1,910 to €7,682); type 2: US$2,834 to US$16,870 (€2,522 to €15,009)</td>
</tr>
<tr>
<td>Ridderstrale</td>
<td>2013</td>
<td>glargine</td>
<td>US$65.19 - $75.31 per pack of 5 pens (1500IU) (€58 to €67)</td>
<td>NPH</td>
<td>US$39.34 - US$47.21 per 5 pens (€35 to €42)</td>
<td>Public sources</td>
<td>160% to 166%</td>
<td>Denmark, Finland, Norway, Sweden</td>
<td>Y</td>
<td>Norway: US$24,467 (€21,768) to Sweden: US$28,209 (€25,097)</td>
</tr>
<tr>
<td>Pfohl</td>
<td>2012</td>
<td>glargine</td>
<td>US$1.31 per 70kg adult per day (€1.17)</td>
<td>NPH</td>
<td>US$.97 per 70kg adult per day (€0.86)</td>
<td>German published sources</td>
<td>136%</td>
<td>Germany</td>
<td>Y</td>
<td>Dominant</td>
</tr>
<tr>
<td>Brandle</td>
<td>2011</td>
<td>glargine</td>
<td>US$111 to US$119 per 1,000IU vial or 1,500IU pack of 5 pens (108–115 CHF)</td>
<td>NPH</td>
<td>US$45.62 to US$92.28 per 1000IU vial or 1500IU pack of 5 pens (44 to 89 CHF)</td>
<td>Official drug list</td>
<td>245% to 129%</td>
<td>Switzerland</td>
<td>Y</td>
<td>US$27,239 (26,271 CHF)</td>
</tr>
<tr>
<td>CEA study</td>
<td>Year</td>
<td>Analogue insulin</td>
<td>Cost of analogue product</td>
<td>Human insulin</td>
<td>Cost of human product</td>
<td>Cost source</td>
<td>Cost of analogue / cost of human (%)</td>
<td>Country</td>
<td>Cost-effective?</td>
<td>Cost-effective? (additional costs per QALY gain)</td>
</tr>
<tr>
<td>-----------</td>
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<td>------------</td>
<td>----------------------------------</td>
<td>---------</td>
<td>---------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Valentine</td>
<td>2011</td>
<td>determir</td>
<td>US$1,905 per year (15,855 SEK)</td>
<td>NPH</td>
<td>US$1,473 per year (12,257SEK)</td>
<td>Swedish agency (TLV)</td>
<td>129%</td>
<td>Sweden</td>
<td>Y</td>
<td>Dominant</td>
</tr>
<tr>
<td>Valentine</td>
<td>2011</td>
<td>determir</td>
<td>US$620 to US$795 depending on country per year (€552 to €707; unit cost 0.0379 to 0.0484 per IU)</td>
<td>NPH</td>
<td>US$324 to US$444 (€288 to €395; unit cost 0.02 to 0.0271 per IU)</td>
<td>Pharmacy selling price excluding VAT</td>
<td>192% to 179%</td>
<td>Denmark, Sweden, Finland and the Netherlands</td>
<td>Y</td>
<td>US$13,730 to US$18,622 (€12,216 to €16,568)</td>
</tr>
<tr>
<td>Tunis</td>
<td>2010</td>
<td>glargine</td>
<td>US$619 per year (CA$799)</td>
<td>70/30</td>
<td>US$532 per year (CA$687)</td>
<td>Ontario Drug Benefit Plan</td>
<td>116%</td>
<td>Canada</td>
<td>Y</td>
<td>US$6137 (CA$7923)</td>
</tr>
<tr>
<td>Grima</td>
<td>2007</td>
<td>glargine</td>
<td>US$637 (CA$822); annually (type 2); US$407 (CA$ 525) (type 1)</td>
<td>NPH</td>
<td>US$253 type 2 (CA$326), US$188 type 1 (CA$243)</td>
<td>Aventis pharma and RAMQ</td>
<td>252% (type 2); 216% (type 1)</td>
<td>Canada</td>
<td>Not reported</td>
<td>Type 2: US$6,676 (CA$8,618); type 1: US$16,111 (CA$20,799)</td>
</tr>
<tr>
<td>Tunis</td>
<td>2009</td>
<td>detemir</td>
<td>US$1224 per year for type 1 (CA$1580); US$1072 type 2 (CA$1384)</td>
<td>NPH</td>
<td>US$510 per year type 1 (CA$658); US$312 type 2 (CA$403)</td>
<td>COMPUS report</td>
<td>240% (type 1); 343% (type 2)</td>
<td>Canada</td>
<td>Y</td>
<td>Type 1: US$18,892 (CA$24,389); type 2: US$14,467 (CA$18,677)</td>
</tr>
<tr>
<td>Valentine</td>
<td>2008</td>
<td>detemir</td>
<td>US$2,063 per year (€1,835)</td>
<td>NPH</td>
<td>US$1815 per year (€1615)</td>
<td>Not reported</td>
<td>114%</td>
<td>Germany</td>
<td>Y</td>
<td>Dominant</td>
</tr>
<tr>
<td>CEA study</td>
<td>Year</td>
<td>Analogue insulin</td>
<td>Cost of analogue product</td>
<td>Human insulin</td>
<td>Cost of human product</td>
<td>Cost source</td>
<td>Cost of analogue / cost of human (%)</td>
<td>Country</td>
<td>Cost-effective?</td>
<td>Cost-Effectiveness of Analogue and Human Insulin (additional costs per QALY gain)</td>
</tr>
<tr>
<td>----------------</td>
<td>------</td>
<td>------------------</td>
<td>--------------------------</td>
<td>---------------</td>
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<td>-------------</td>
<td>--------------------------------------</td>
<td>---------</td>
<td>----------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Palmer</td>
<td>2004</td>
<td>detemir</td>
<td>US$689 per year (£486)</td>
<td>NPH</td>
<td>US$515 per year (£363)</td>
<td>Monthly index of medical specialties (MIMS)</td>
<td>134%</td>
<td>UK</td>
<td>Y</td>
<td>US$27,356 (£19,285)</td>
</tr>
<tr>
<td>McEwan (type 1)</td>
<td>2007</td>
<td>glargine</td>
<td>US$36.88 per vial (£26)</td>
<td>NPH</td>
<td>US$14.19 per vial (£10)</td>
<td>British National Formulary No. 50</td>
<td>260%</td>
<td>UK</td>
<td>Y</td>
<td>US$38,23 to US$15,523 (£2,695 to £10,943)</td>
</tr>
<tr>
<td>McEwan (type 2)</td>
<td>2007</td>
<td>glargine</td>
<td>US$36.88 per vial (£26)</td>
<td>NPH</td>
<td>US$14.19 per vial (£10)</td>
<td>British National Formulary No. 50</td>
<td>260%</td>
<td>UK</td>
<td>Y</td>
<td>US$1,422 to US$19,747 (£10,027 to £13,921)</td>
</tr>
<tr>
<td>Brandle</td>
<td>2007</td>
<td>glargine</td>
<td>US$2.99 per day (2.88CHF)</td>
<td>NPH</td>
<td>US$1.97 per day (1.9 CHF)</td>
<td>Official drug list (Federal Office of Public Health 2005)</td>
<td>152%</td>
<td>Switzerland</td>
<td>Y</td>
<td>US$2,958 to US$47,386 (2,853 to 45,701 CHF)</td>
</tr>
</tbody>
</table>

**Pre-mixed insulin analogues**

<p>| Gupta          | 2015 | BIASp30 (NovoLog Mix 70/30) | India (US$3,488), Indonesia (US$1,171), Saudi Arabia (US$1,418) | 70/30 (RHI mix) | India (US$2,154), Indonesia (US$6,786), Saudi Arabia (US$5,930) | Value in Health 2012 publications | 162% (India), 193% (Indonesia), 173% (SA) | India, Indonesia, Saudi Arabia | Y | India (US$3,350), Indonesia (US$4,602), Saudi Arabia (US$224) |
| Palmer         | 2010 | BIASp30           | US$2,361                 | 70/30          | US$899                 | Not specified                                              | 263%      | US            | Y                            | US$29,870                                                               |</p>
<table>
<thead>
<tr>
<th>CEA study</th>
<th>Year</th>
<th>Analogue insulin</th>
<th>Cost of analogue product</th>
<th>Human insulin</th>
<th>Cost of human product</th>
<th>Cost source</th>
<th>Cost of analogue / cost of human (%)</th>
<th>Country</th>
<th>Cost-effective?</th>
<th>Country</th>
<th>Cost-effective?</th>
<th>ICER (additional costs per QALY gain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali</td>
<td>2008</td>
<td>BIASp30</td>
<td>70/30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Saudi Arabia</td>
<td>Y</td>
<td>Dominant</td>
<td>US$293 (1,926 CNY)</td>
<td></td>
</tr>
<tr>
<td>Palmer</td>
<td>2008</td>
<td>BIASp30</td>
<td>US$429 (2,825.8 CNY)</td>
<td>70/30</td>
<td>US$350 (2,300.7CNY)</td>
<td>Novo Nordisk A/S</td>
<td>123%</td>
<td>China</td>
<td>Y</td>
<td>US$293 (1,926 CNY)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rapid-acting insulin analogues**

| Liebl     | 2014 | aspart           | US$33.72 per vial (€30 or €0.03 per IU) | RHI        | US$33.72 per vial (€30 or €0.03 per IU) | Federal Joint Committee (GBA) 2006 decision to not reimburse short acting insulin above RHI | 100% | Germany | Y                | Dominant |
| Pollock   | 2010 | aspart           | US$.07 per IU (7.62 JPY)              | RHI        | US$.07 per IU (7.62 JPY)              | Novo        | 103%                   | Japan    | Y               | Dominant |
| Pratumsoot| 2009 | lispro           | US$1,116 per year (£787)             | RHI        | US$1,099 per year (£775)             | Monthly index of medical specialties (MIMS) | 102% | UK      | Y                | Dominant |
| Lloyd     | 2009 | aspart           | US$865 (£610) per patient per admission | RHI        | US$850 (£599)                       | Not specified | 101.8%              | UK       | Y               | Dominant |

**Multiple insulin types**

| Cameron   | 2009 | aspart, lispro, detemir, glargine | Type 1: US$.85 to US$1.09 per day (CA$1.10 to CA$1.42); type 2: US$2.14 to US$2.64 per day (CA$2.76 to CA$3.54) | RHI, NPH    | Type 1: US$.40 to US$.79 per day (CAD$.51 to CAD$.81); type 2: US$.15 to US$.18 per day (CAD$.49 to CAD$.81) | Ontario Drug Benefit Formulary | 216% to 138% (type 1); 186% to 126% (type 2) | Canada | Depends on scenario, generally no | Type 1: apart v RHI (dominant); lispro vs RHI US$22,437 (CA$28,996); glargine vs NPH US$68,112 (CA$87,932) |

Cost-effectiveness of Analogue and Human Insulin | 24
<table>
<thead>
<tr>
<th>CEA study</th>
<th>Year</th>
<th>Analogue insulin</th>
<th>Cost of analogue product</th>
<th>Human insulin</th>
<th>Cost of human product</th>
<th>Cost source</th>
<th>Cost of analogue / cost of human (%)</th>
<th>Country</th>
<th>Cost-effective?</th>
<th>ICER (additional costs per QALY gain)</th>
</tr>
</thead>
</table>

All currency converted to US$ using 15 June 2016 numbers from XE Money Transfer (xe.com)

*Five studies were excluded from this table because medication costs were not individually reported. COMPUS = Canadian Optimal Medication Prescribing and Utilization Service.
### 3.9 Costs of Diabetes-related Complications (Excluding Medicine Costs)

Table 5 presents the estimated costs of medical complications attributable to a simulated cohort of people living with type 1 or type 2 diabetes being assigned treatment with either analogue or human insulin over the stated time-horizon. Costs of diabetes-related complications may be either direct or indirect. An example of a direct medical cost is that of hospitalisation in the local context for an acute myocardial infarction, where a patient survived. An example of an indirect cost is lost productivity because of illness. Indirect costs were generally not reported in the published CEA studies reviewed. Because complications of diabetes are numerous (retinopathy, neuropathy, kidney disease, peripheral vascular disease, and cardiovascular), individual costs are not separately reported in the summary table below, but can be found in the full text of each reviewed article. The costs of complications exclude the cost of medications.

Table 5. Cost of complications (excluding medicine costs) in selected CEA studies.

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Year</th>
<th>Time horizon</th>
<th>Cost of complications (human)</th>
<th>Cost of complications (analogue)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-acting insulin analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persuwan</td>
<td>2016</td>
<td>50 years</td>
<td>US$15,163 (535,025 THB)</td>
<td>US$14,455 (510,059 THB)</td>
</tr>
<tr>
<td>Morales</td>
<td>2015</td>
<td>1 year</td>
<td>Type 1: US$202 (€180); type 2 US$22.48 (€20)</td>
<td>Type 1 US$169 (€150); type 2 US$11.24 (€10)</td>
</tr>
<tr>
<td>Smith-Palmer</td>
<td>2012</td>
<td>40 years</td>
<td>US$23,865 (198,636 SEK)</td>
<td>US$29,240 (243,368 SEK)</td>
</tr>
<tr>
<td>Pfahl</td>
<td>2012</td>
<td>40 years</td>
<td>US$34,719 (€30,889)</td>
<td>US$28,824 (€25,644)</td>
</tr>
<tr>
<td>Brandle</td>
<td>2011</td>
<td>40 years</td>
<td>US$53,539 (51,635 CHF)</td>
<td>US$51,561 (49,728 CHF)</td>
</tr>
<tr>
<td>Valentine</td>
<td>2011</td>
<td>1 year</td>
<td>US$15.96 (€14.2 per year (based on Finland’s costs of €0.4 per test strip per mild hypo event)</td>
<td>US$13.38 (€11.90 per year)</td>
</tr>
<tr>
<td><strong>Pre-mixed insulin analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gupta</td>
<td>2015</td>
<td>30 year</td>
<td>India (US$3,206), Indonesia (US$14,641), Saudi Arabia (US$38,162)</td>
<td>India (US$2,724), Indonesia (US$15,141), Saudi Arabia (US$32,471)</td>
</tr>
<tr>
<td>Palmer</td>
<td>2010</td>
<td>30 years</td>
<td>US$49,934</td>
<td>US$52,487</td>
</tr>
<tr>
<td>Lee</td>
<td>2009</td>
<td>30 years</td>
<td>US$5,210 (6,086,034 KRW)</td>
<td>US$4,184 (4,887,690 KRW)</td>
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<tr>
<td><strong>Rapid-acting insulin analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liebl</td>
<td>2014</td>
<td>3 years</td>
<td>US$6,714 (€5973)</td>
<td>US$4,965 (€4,417)</td>
</tr>
<tr>
<td>Pollock</td>
<td>2010</td>
<td>5 or 10 years</td>
<td>US$2,985 (316,249 JPY) over 5 years</td>
<td>US$1274 (134,978 JPY over 5 years)</td>
</tr>
<tr>
<td>Palmer</td>
<td>2008</td>
<td>35 years</td>
<td>US$35,378 (294,476 SEK)</td>
<td>US$33,592 (279,590 SEK)</td>
</tr>
<tr>
<td><strong>Multiple insulin types</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pratoomsoot</td>
<td>2009</td>
<td>50 years</td>
<td>US$89,232 (£62,906)</td>
<td>US$84,246 (£59,391)</td>
</tr>
<tr>
<td>Palmer</td>
<td>2007</td>
<td>Lifetime</td>
<td>US$47,727 (£33,646)</td>
<td>US$46,500 (£32,781)</td>
</tr>
</tbody>
</table>

*All currency converted to US$ using 15 June, 2016 numbers from XE Money Transfer (xe.com).*

Note: excludes studies where total costs could not be separated from costs of pharmacologic therapy.
3.10 Summary of Cost-effectiveness Results

While 27 out of 30 (90 percent) CEA studies found that analogue insulins were cost-effective when compared to human insulins (Table 6), many biases influenced the findings, as described below.

**Industry sponsorship is a strong predictor of claimed cost-effectiveness.**

Overall, analogue insulins were found to be dominant in eight studies (27 percent), meaning they resulted in more QALYs gained at less cost when compared to human insulin. One study found mixed results: aspart was cost-effective in three of four European countries examined, but not cost-effective in Poland (15). However, there was a high correlation between the funding source of the CEA study and determination of cost-effectiveness. Only 2 of the 30 (seven percent) published CEA studies in this review were funded by governmental bodies (i.e., without industry funding) (17, 47). In both studies, the newer analogue—or analogues—being considered were found to be either not cost-effective (in the case of Thailand), or mostly not cost-effective (in the case of Canada). In the study funded by Health Canada, rapid-acting insulins, aspart and lispro, were found to be cost-effective for people living with type 1 diabetes, but not people living with type 2 diabetes (17). In the study sponsored by the Thai government, the long-acting insulin analogue glargine was not cost-effective compared to NPH for use in people living with type 2 diabetes, mostly due to high glargine costs (over 1,200 percent more expensive than the comparator) and a low cost-effectiveness threshold (US$4,714/QALY). In the Thai study, once glargine costs were reduced by more than 43 percent compared against the base-case scenario, glargine became a cost-effective option.

Having limited sources of funders for the studies (i.e., most of the studies were funded by insulin manufacturers) can lead to conflict of interest and reporting bias. Reporting bias, a common practice in the biomedical field, can result in the overestimation of benefits of a medicine based on the source of the funding for the study (48-51), for example, its estimated that positive clinical trial data in a study is twice as likely to be published when compared to negative results. (52)

**Existing published CEA studies chose estimates of treatment effects from the literature in a way that biases results in favour of analogue insulins.**

The majority of published CEA studies reviewed here used large or unlikely treatment effect estimates in their baseline or base-case scenarios. These estimates were often drawn from single short-term, non-controlled observational studies, rather than from large, well conducted randomised trials or meta-analyses of randomised trials comparing analogue to human insulin. One consequence of using optimistic treatment effects for the base-case scenario is that the cost-effectiveness results produced by the model would likely favour the analogue insulin. Given these selection biases and the large heterogeneity in the clinical treatment effect assumptions, it is likely that many of the studies reviewed here lack strong internal validity.

**Cost-effectiveness is related to the comparative price of the analogue insulin.**

In four out of five CEA studies, the rapid acting analogues aspart and lispro were found to be dominant compared to regular human insulin. In the fifth study by Palmer and others (2008), aspart was dominant when compared against regular insulin in Sweden and Spain, cost-effective in Italy, but not cost-effective in Poland. The most likely reason these products were considered dominant is because of low medication prices when compared against regular human insulin.
For example, in three of the country settings examined (Germany, Japan and the UK), prices for the rapid-acting analogue were only zero to three percent higher than regular human insulin. This suggests that when prices are comparable between human and analogue products, the probability of cost-savings to the health system or society is high.

In contrast, long-acting analogues glargine or detemir exhibited large variations in comparative price (range: 14 percent to 1,141 percent higher priced than NPH). In the two studies where the price of the analogue was only slightly higher than NPH (i.e., 14 to 36 percent higher priced), the analogues were found to be dominant, or cost-saving. In the 13 studies where the price of the long-acting analogue was found to be cost-effective, the price of the long-acting analogue was between 16 and 243 percent higher priced than the human insulin. On the higher end of this range (between 66 and 243 percent more expensive), the long-acting analogue was still cost-effective, but was associated with a higher ICER value. For example, in Ridderstrale (2013) and Tunis (2009), glargine and detemir had ICER’s of US$28,209 per QALY and US$18,892 per QALY, respectively when compared against NPH.

**Cost-effectiveness comparing type 1 versus type 2 diabetes.**

Fourteen studies addressed type 1 diabetes, while 16 addressed type 2 diabetes, with four studies covering both groups. In type 1 diabetes, all but one study was funded by industry. All were conducted in high-income settings (Annex 2). Three studies found that the analogue insulin was dominant (lispro and aspart in the UK and glargine in Sweden). Eleven studies found that the analogue was cost-effective, under various cost-effectiveness thresholds meant for high-income settings. The only independent study in the type 1 group found heterogeneous results: rapid-acting analogues were determined to be cost-effective, with ICERS in the range of US$22,437 (aspart) to dominant (lispro). However, long-acting analogues were found not to be cost-effective, with ICERS ranging from US$68,112 (glargine) to a staggering US$300,335 (detemir).

Of the 20 studies addressing type 2 diabetes (or both type 2 and type 1 diabetes), all but two were funded by industry. Among type 2 diabetes studies, six reported that analogue insulin was dominant when compared against human insulin. Eleven studies found that analogue insulin was cost-effective, again, under various cost-effectiveness thresholds meant for high-income settings. Two studies reported heterogeneous results: for example, the Palmer study examined cost-effectiveness of aspart compared against regular human insulin in four European countries. In that study, aspart was found to be dominant in Sweden and Spain, cost-effective in Italy (based on a CE threshold of US$33,720 per QALY), but not cost-effective in Poland (ICER US$326,506). The independent Health Canada study reported that aspart was cost-effective when compared against regular human insulin; however, lispro (ICER US$101,368) and glargine were not (US$ 300,335). Determin was dominated by NPH, meaning that it was found to result in greater costs and lower QALYs. The other independent study, funded by the Ministry of Health of Thailand, found that glargine was not cost-effective when compared to NPH.
Table 6. Summary of ICERs, cost-effectiveness, and cost-effectiveness thresholds across the CEA studies examined in this report.

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Year</th>
<th>Study drug</th>
<th>Comparator drug or therapy</th>
<th>ICER</th>
<th>Threshold (e.g., $30,000/QALY)</th>
<th>Cost-effective (y/n)?</th>
<th>Type 1 vs type 2 diabetes (or both)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfohl</td>
<td>2012</td>
<td>glargine</td>
<td>NPH</td>
<td>Dominant</td>
<td>n/a</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>Smith-Palmer</td>
<td>2012</td>
<td>determir</td>
<td>NPH</td>
<td>Dominant</td>
<td>n/a</td>
<td>yes</td>
<td>2</td>
</tr>
<tr>
<td>Valentine</td>
<td>2008</td>
<td>determir</td>
<td>NPH</td>
<td>Dominant</td>
<td>n/a</td>
<td>yes</td>
<td>2</td>
</tr>
<tr>
<td>Valentine</td>
<td>2011</td>
<td>determir</td>
<td>NPH</td>
<td>US$5,978 payer (49,757SEK); dominant (societal)</td>
<td>US$12,015 (100,000SEK)</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>Brandle</td>
<td>2011</td>
<td>glargine</td>
<td>NPH</td>
<td>US$27,240 (26,271CHF)</td>
<td>US$62,212 (60,000CHF)</td>
<td>yes</td>
<td>2</td>
</tr>
<tr>
<td>Brandle</td>
<td>2007</td>
<td>glargine</td>
<td>NPH</td>
<td>US$2,958 to $47,385 (2,853CHF to 45,701CHF)</td>
<td>US$31,100 to $51,843 (30,000CHF to 50,000CHF)</td>
<td>yes</td>
<td>2</td>
</tr>
<tr>
<td>Ridderstrale</td>
<td>2013</td>
<td>glargine</td>
<td>NPH</td>
<td>Norwegian: US$24,467 (€21,768) to Sweden: $28,207 (€25,097)</td>
<td>Norwegian: US$44,960 to Sweden: $72,050 (€40,000 to €64,102)</td>
<td>yes</td>
<td>2</td>
</tr>
<tr>
<td>Tunis</td>
<td>2009</td>
<td>determir</td>
<td>NPH</td>
<td>Type 1: US$18,892 (CA$24,389) type 2; US$14,467 (CA$18,677)</td>
<td>US$38,730 (CA$50,000)</td>
<td>yes</td>
<td>Both</td>
</tr>
</tbody>
</table>

**Long-acting insulin analogues**
<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Year</th>
<th>Study drug</th>
<th>Comparator drug or therapy</th>
<th>ICER</th>
<th>Threshold (e.g., $30,000/QALY)</th>
<th>Cost-effective (y/n)?</th>
<th>Type 1 vs type 2 diabetes (or both)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmer</td>
<td>2004</td>
<td>detemir</td>
<td>NPH</td>
<td>US$27,356 (£19,285)</td>
<td>US$49,676 (£35,000)</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>Valentine</td>
<td>2011</td>
<td>detemir</td>
<td>NPH</td>
<td>US$13,731 to $18,622 (£12,216 to £16,568)</td>
<td>1 to 3x GDPpc</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>Valentine</td>
<td>2006</td>
<td>detemir</td>
<td>NPH</td>
<td>US$14,974</td>
<td>US$25,000</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>McEwan</td>
<td>2007</td>
<td>glargine</td>
<td>NPH</td>
<td>US$14,223 to $19,747 (£10,027 to £13,921)</td>
<td>US$28,370 to US$42,355 £20,000 to £30,000</td>
<td>yes</td>
<td>2</td>
</tr>
<tr>
<td>Morales</td>
<td>2015</td>
<td>detemir</td>
<td>NPH</td>
<td>Type 1: US$2,147 to $8,635 (£1,910 to £7,682); type 2: US$2,835 to US$16,870 (£2,522 to £15,009)</td>
<td>US$33,720 (£30,000)</td>
<td>yes</td>
<td>Both</td>
</tr>
<tr>
<td>Tunis</td>
<td>2010</td>
<td>glargine</td>
<td>70/30</td>
<td>US$6137 (CA$7923)</td>
<td>Not specified</td>
<td>yes</td>
<td>2</td>
</tr>
<tr>
<td>Gschwend</td>
<td>2009</td>
<td>detemir</td>
<td>NPH</td>
<td>France: US$583 (£519); Italy: US$3,650 (£3,256); Dominant in Belgium, Germany and Spain</td>
<td>Varies by country</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>McEwan</td>
<td>2007</td>
<td>glargine</td>
<td>NPH</td>
<td>US$4,519 to US$13,854 (£3,189 to £9,767)</td>
<td>US$28,370 to US$42,555 (£20,000 to £30,000)</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>Lead Author</td>
<td>Year</td>
<td>Study drug</td>
<td>Comparator drug or therapy</td>
<td>ICER</td>
<td>Threshold (e.g., $30,000/QALY)</td>
<td>Cost-effective (y/n)?</td>
<td>Type 1 vs type 2 diabetes (or both)</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>Grima</td>
<td>2007</td>
<td>glargine</td>
<td>NPH</td>
<td>Type 2: US$6,676 (CA$8618); type 1: US$16,100 (CA$20,799)</td>
<td>Not reported</td>
<td>not reported</td>
<td>Both</td>
</tr>
<tr>
<td>Persuwan</td>
<td>2016</td>
<td>glargine</td>
<td>NPH</td>
<td>US$7,216</td>
<td>US$4,714/QALY</td>
<td>no</td>
<td>2</td>
</tr>
</tbody>
</table>

**Pre-mixed insulin analogue**

| Palmer     | 2010 | BIAsp30 (NovoLog Mix 70/30) | 70/30 (RHI) | US$29,870 | US$50,000 | yes | 2 |
| Lee        | 2009 | BIAsp 30                    | 70/30       | US$5,064 (5,915,198KRW) | US$21,401 (25,000,000KRW) | yes | 2 |
| Gupta      | 2015 | BIAsp30 (NovoLog Mix 70/30) | 70/30 (RHI) | India: (US$350); Indonesia: (US$4,602); Saudi Arabia: (US$224) | <3x GDPpc       | yes | 2 |
| Ali        | 2008 | BIAsp30                    | 70/30       | Dominant | N/a      | yes | 2 |
| Palmer     | 2008 | BIAsp30                    | 70/30       | US$293 (1,926CNY) | US$15,197 (100,000CNY) | yes | 2 |

**Rapid-acting insulin analogue**

<p>| Liebl      | 2014 | aspart                  | RHI         | Dominant | n/a     | yes | 2 |
| Pollock    | 2010 | aspart                  | RHI         | Dominant | US$47,220 (5,000,000JPY) | yes | 2 |
| Pratoomsoot| 2009 | lispro                  | RHI         | Dominant | n/a     | yes | 1 |</p>
<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Year</th>
<th>Study drug</th>
<th>Comparator drug or therapy</th>
<th>ICER</th>
<th>Threshold (e.g., $30,000/QALY)</th>
<th>Cost-effective (y/n)?</th>
<th>Type 1 vs type 2 diabetes (or both)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmer</td>
<td>2008</td>
<td>aspart</td>
<td>RHI</td>
<td>Dominant in Sweden and Spain; US$15,317 (€13,627) in Italy; US$32,6506 (€290,486) in Poland</td>
<td>€30,000</td>
<td>Cost-effective in Sweden, Spain, Italy; not cost-effective in Poland</td>
<td>2</td>
</tr>
<tr>
<td>Lloyd</td>
<td>2009</td>
<td>aspart</td>
<td>RHI</td>
<td>Dominant</td>
<td>n/a</td>
<td>yes</td>
<td>1</td>
</tr>
</tbody>
</table>

**Multiple insulin types**

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Year</th>
<th>Study drug</th>
<th>Comparator drug or therapy</th>
<th>ICER</th>
<th>Threshold (e.g., $35,463 (£25,000))</th>
<th>Cost-effective (y/n)?</th>
<th>Type 1 vs type 2 diabetes (or both)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmer</td>
<td>2007</td>
<td>detemir+aspart</td>
<td>NPH+RHI</td>
<td>US$3,555 (£2,506)</td>
<td>US$35,463 (£25,000)</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>Cameron</td>
<td>2009</td>
<td>aspart, lispro, detemir, glargine</td>
<td>RHI, NPH</td>
<td>Type 1: aspart v RHI (dominant); lispro vs RHI US$22,460 (CA$28,996); glargine vs NPH US$68,112 (CA$87,932 C); detemir vs NPH US$300,335 (CA$387,729); type 2: aspart vs RHI US$17,419 (CA$22,488); lispro vs RHI US$101,368 (CA$130,865), glargine vs NPH US$498,063 (CA$642,994 C), detemir vs NPH: dominated</td>
<td>US$38,730 (CA$50,000)</td>
<td>Generally, not cost-effective (exception: rapid acting insulins in type 1)</td>
<td>both</td>
</tr>
</tbody>
</table>

**Cost-effectiveness of Analogue and Human Insulin** | 32
4. Discussion

This systematic review examined 30 published CEA studies comparing an insulin analogue against a human insulin product for either type 1 or type 2 diabetes. We found that the determination of cost-effectiveness for an insulin product is related to both the funding source and the comparative price of the analogue insulin product. Industry funded studies almost universally concluded that the newer analogue product or products were cost-effective. The only two independently funded CEA studies had different conclusions: insulin analogues were found to be generally not cost-effective when compared against human insulin (with a possible exception being rapid-acting analogues for type 1 diabetes mellitus) (18). Additionally, we found a relationship between the price of an analogue and its likelihood of being cost-effective.

There are several limitations to our review. A major limitation was the fact that over 90 percent of published CEA studies examined were sponsored by industry. Second, only three CEA studies from LMIC settings could be identified. This is particularly relevant because much of the global burden of insulin-dependent diabetes is on people living in LMICs, and because of the disproportionate amount of healthcare spending that is dedicated to them. More independent studies with a focus on low- and middle-income settings are urgently needed.

It should also be noted that our studies identified cost-effectiveness thresholds from a variety of different payer and geographic perspectives. In addition, when study authors varied their assumptions in sensitivity analysis, their conclusions with regard to cost-effectiveness changed. For example, in one study, when differences in rates of severe hypoglycaemia, comparing lispro against regular human insulin, were tested in a sensitivity analysis, the probability of being cost-effective fell from 84 to 59 percent (29).

5. Conclusion

Most published cost-effective analysis studies comparing insulin analogues with human insulin are industry sponsored, focusing on type 2 diabetes and largely refer to high-income countries. The estimated cost-effectiveness of analogue insulin is very sensitive to its procured price, and to various assumptions about clinical effects. Unsurprisingly, industry-funded studies almost universally concluded that analogue products were cost-effective.

However, based on the very few independent studies, we conclude that both long-acting and rapid-acting analogue insulins are highly unlikely to be cost effective in LMICs when their price exceeds the price of human insulin. Policy-makers in LMICs should therefore only purchase or reimburse insulin analogues when their price(s) are comparable to those of human insulin. At this stage of knowledge, analogue insulins are most likely to be cost-effective in lower-income settings for people with unstable type 1 diabetes.
6. References


52 Gøtzsche PC. Why we need easy access to all data from all clinical trials and how to accomplish it. Trials, 12:249 (2011) doi:10.1186/1745-6215-12-249.
### ANNEX 1: Cost-effectiveness Studies Reviewed in this Report

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Journal</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales</td>
<td>Diabetes Therapy</td>
<td>2015</td>
<td>Cost-effectiveness analysis of insulin detemir compared to neutral protamine hagedorn (nph) in patients with type 1 and type 2 diabetes mellitus in Spain</td>
</tr>
<tr>
<td>Gupta</td>
<td>JME</td>
<td>2015</td>
<td>An analysis of the cost-effectiveness of switching from biphasic human insulin, insulin glargine, or neutral protamine hagedorn to biphasic insulin aspart 30 in people with type 2 diabetes</td>
</tr>
<tr>
<td>Liebl</td>
<td>Exp Clin Endocrinol Diabetes</td>
<td>2014</td>
<td>Health economics analysis of insulin aspart vs. regular human insulin in type 2 diabetes patients, based on observational real life evidence from general practices in Germany</td>
</tr>
<tr>
<td>Ridderstrale</td>
<td>JME</td>
<td>2013</td>
<td>Cost-effectiveness of insulin detemir compared with NPH insulin in people with type 2 diabetes in Denmark, Finland, Norway, and Sweden</td>
</tr>
<tr>
<td>Pfohl</td>
<td>JME</td>
<td>2012</td>
<td>Health economic evaluation of insulin glargine vs NPH insulin in intensified conventional therapy for type 1 diabetes in Germany</td>
</tr>
<tr>
<td>Smith-Palmer</td>
<td>JME</td>
<td>2012</td>
<td>Long-term cost-effectiveness of insulin detemir versus NPH insulin in type 2 diabetes in Sweden</td>
</tr>
<tr>
<td>Brandle</td>
<td>Int’l Journal of Clinical Pharmacology and Therapeutics</td>
<td>2011</td>
<td>Cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 2 diabetes mellitus, modeling the interaction between hypoglycemia and glycemic control in Switzerland</td>
</tr>
<tr>
<td>Lead Author</td>
<td>Journal</td>
<td>Year</td>
<td>Title</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------</td>
<td>------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Valentine</td>
<td>Diabetic Medicine</td>
<td>2011</td>
<td>Evaluating the cost-effectiveness of reduced mild hypoglycaemia in subjects with Type 1 diabetes treated with insulin detemir or NPH insulin in Denmark, Sweden, Finland and the Netherlands</td>
</tr>
<tr>
<td>Tunis</td>
<td>Appl Health Econ Health Policy</td>
<td>2010</td>
<td>Cost-effectiveness of insulin glargine plus oral antidiabetes drugs compared with premixed insulin alone in patients with type 2 diabetes mellitus in Canada</td>
</tr>
<tr>
<td>Tunis</td>
<td>CMRO</td>
<td>2009</td>
<td>Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modelling analysis</td>
</tr>
<tr>
<td>Pollock</td>
<td>JME</td>
<td>2011</td>
<td>The cost effectiveness of rapid-acting insulin aspart compared with human insulin in type 2 diabetes patients: an analysis from the Japanese third-party payer perspective</td>
</tr>
<tr>
<td>Palmer</td>
<td>JME</td>
<td>2010</td>
<td>Cost-effectiveness of switching to biphasic insulin aspart from human premix insulin in a US setting</td>
</tr>
<tr>
<td>Cameron</td>
<td>CMAJ</td>
<td>2009</td>
<td>Cost-effectiveness of insulin analogues for diabetes mellitus</td>
</tr>
<tr>
<td>Lee</td>
<td>Value in Health</td>
<td>2009</td>
<td>Cost-effectiveness of switching to biphasic insulin aspart30 from human insulin in patients with poorly controlled type 2 diabetes in South Korea</td>
</tr>
<tr>
<td>Tunis</td>
<td>CMRO</td>
<td>2009</td>
<td>Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modelling analysis</td>
</tr>
<tr>
<td>Gschwend</td>
<td>JME</td>
<td>2009</td>
<td>Cost-effectiveness of insulin detemir compared with neutral protamine hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries</td>
</tr>
<tr>
<td>Pratoomsoot</td>
<td>Diabetic Medicine</td>
<td>2009</td>
<td>An estimation of the long-term clinical and economic benefits of insulin lispro in type 1 diabetes in the UK</td>
</tr>
<tr>
<td>Lead Author</td>
<td>Journal</td>
<td>Year</td>
<td>Title</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------</td>
<td>------</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Palmer</td>
<td>CMRO</td>
<td>2008</td>
<td>Cost-effectiveness of insulin aspart versus human soluble insulin in type 2 diabetes in four European countries: subgroup analyses from the PREDICTIVE study</td>
</tr>
<tr>
<td>Valentine</td>
<td>Adv Ther</td>
<td>2008</td>
<td>Evaluating the cost-effectiveness of therapy conversion to insulin detemir in patients with type 2 diabetes in Germany: a modelling study of long-term clinical and cost outcomes</td>
</tr>
<tr>
<td>Palmer</td>
<td>CMRO</td>
<td>2007</td>
<td>An economic assessment of analogue basal-bolus insulin versus human basal-bolus insulin in subjects with type 1 diabetes in the UK</td>
</tr>
<tr>
<td>Grima</td>
<td>Pharmacoeconomics</td>
<td>2007</td>
<td>Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada</td>
</tr>
<tr>
<td>Valentine</td>
<td>Advances in Therapy</td>
<td>2006</td>
<td>Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine, and NPH</td>
</tr>
<tr>
<td>Palmer</td>
<td>CMRO</td>
<td>2004</td>
<td>Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials</td>
</tr>
<tr>
<td>Brandle</td>
<td>International journal of clinical pharmacology and therapeutics</td>
<td>2007</td>
<td>Cost-effectiveness and cost-utility of insulin glargine compared with NPH insulin based on a 10-year simulation of long-term complications with the Diabetes Mellitus Model in patients with type 2 diabetes in Switzerland</td>
</tr>
<tr>
<td>Palmer</td>
<td>Advances in Therapy</td>
<td>2008</td>
<td>Cost-effectiveness of switching to biphasic insulin aspart in poorly-controlled type 2 diabetes patients in Chin</td>
</tr>
<tr>
<td>Ali</td>
<td>JME</td>
<td>2008</td>
<td>Therapy conversion to biphasic insulin aspart 30 improves long-term outcomes and reduces the costs of type 2 diabetes in Saudi Arabia</td>
</tr>
<tr>
<td>Lead Author</td>
<td>Journal</td>
<td>Year</td>
<td>Title</td>
</tr>
<tr>
<td>-------------</td>
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<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>McEwan</td>
<td>CMRO</td>
<td>2007</td>
<td>Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 1 diabetes in the UK</td>
</tr>
<tr>
<td>Lloyd</td>
<td>CMRO</td>
<td>2009</td>
<td>Cost-effectiveness of insulin aspart compared to human insulin in pregnant women with type 1 diabetes in the UK</td>
</tr>
<tr>
<td>Permsuwan</td>
<td>Appl Health Economics and Health Policy</td>
<td>2016</td>
<td>Long-Term cost effectiveness of insulin glargine versus neutral protamine Hagedorn insulin for type 2 diabetes in Thailand</td>
</tr>
</tbody>
</table>
## ANNEX 2: Cost-Effectiveness Results Among Studies Addressing Type 1 Diabetes (Or Both Type 1 and Type 2 Diabetes)

<table>
<thead>
<tr>
<th>Country</th>
<th>Lead Author</th>
<th>Year</th>
<th>Study drug</th>
<th>Comparator drug or therapy</th>
<th>Patient population (type 1, 2, or both)?</th>
<th>ICER (additional costs per QALY gained)</th>
<th>Cost effective (y/n)?</th>
<th>Threshold (e.g., US$30,000/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>Morales</td>
<td>2015</td>
<td>detemir</td>
<td>NPH</td>
<td>Both</td>
<td>€1910 to €7682 per QALY</td>
<td>Yes</td>
<td>€30,000 per QALY</td>
</tr>
<tr>
<td>Canada</td>
<td>Cameron</td>
<td>2009</td>
<td>aspart, lispro, detemir, glargine</td>
<td>RHI, NPH</td>
<td>Both</td>
<td>apart v RHI (dominant); lispro vs RHI (CA$ 28,996); glargine vs NPH CA$ 87,932; detemir vs NPH CA$387,729</td>
<td>CE for rapid-acting, but not for long-acting analogues</td>
<td>CA$50,000 D per QALY</td>
</tr>
<tr>
<td>Canada</td>
<td>Grima</td>
<td>2007</td>
<td>glargine</td>
<td>NPH</td>
<td>Both</td>
<td>CA$20,799</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Canada</td>
<td>Tunis</td>
<td>2009</td>
<td>detemir</td>
<td>NPH</td>
<td>Both</td>
<td>CA$ 24,389</td>
<td>Yes</td>
<td>CA$ 50,000</td>
</tr>
<tr>
<td>Germany</td>
<td>Pfohl</td>
<td>2012</td>
<td>glargine</td>
<td>NPH</td>
<td>Type 1</td>
<td>Dominant</td>
<td>Yes</td>
<td>n/a</td>
</tr>
<tr>
<td>Sweden</td>
<td>Valentine</td>
<td>2011</td>
<td>detemir</td>
<td>NPH</td>
<td>Type 1</td>
<td>497.57SEK (payer); dominant (societal)</td>
<td>Yes</td>
<td>100,000SEK</td>
</tr>
<tr>
<td>UK</td>
<td>Palmer</td>
<td>2007</td>
<td>Detemir+aspart</td>
<td>NPH+RHI</td>
<td>Type 1</td>
<td>£2506 pounds</td>
<td>Yes</td>
<td>£25,000</td>
</tr>
<tr>
<td>Country</td>
<td>Lead Author</td>
<td>Year</td>
<td>Study drug</td>
<td>Comparator drug or therapy</td>
<td>Patient population (type 1, 2, or both)?</td>
<td>ICER (additional costs per QALY gained)</td>
<td>Cost effective (y/n)?</td>
<td>Threshold (e.g., US$30,000/QALY)</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>----------------------------------</td>
</tr>
<tr>
<td>Belgium, France, Germany, Italy, Spain</td>
<td>Gschwend</td>
<td>2009</td>
<td>detemir</td>
<td>NPH</td>
<td>Type 1</td>
<td>€519 France; €3256 Italy; Dominant in Belgium, Germany and Spain</td>
<td>Yes</td>
<td>Differs</td>
</tr>
<tr>
<td>Denmark, Sweden, Finland and the Netherlands</td>
<td>Valentine</td>
<td>2011</td>
<td>detemir</td>
<td>NPH</td>
<td>Type 1</td>
<td>€12,216 to €16,568</td>
<td>Yes</td>
<td>1 to 3x GDPpc</td>
</tr>
<tr>
<td>UK</td>
<td>Pratoomsoot</td>
<td>2009</td>
<td>lispro</td>
<td>RHI</td>
<td>Type 1</td>
<td>dominant</td>
<td>Yes</td>
<td>n/a</td>
</tr>
<tr>
<td>US</td>
<td>Valentine</td>
<td>2006</td>
<td>detemir</td>
<td>NPH (and glargine)</td>
<td>Type 1</td>
<td>US$14,974</td>
<td>Yes</td>
<td>US$25,000</td>
</tr>
<tr>
<td>UK</td>
<td>Palmer</td>
<td>2004</td>
<td>detemir</td>
<td>NPH</td>
<td>Type 1</td>
<td>£19,285</td>
<td>Yes</td>
<td>£35,000</td>
</tr>
</tbody>
</table>
## ANNEX 3: Major Methodologic Limitations or Concerns Identified from Selected CEA Studies

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Journal</th>
<th>Year</th>
<th>Sponsor</th>
<th>Study drug</th>
<th>Comparator drug or therapy</th>
<th>Major limitations or concerns, if any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permuswan</td>
<td>Applied Health Economic Health Policy</td>
<td>2016</td>
<td>Subcommittees of the National List of Essential Medicines, Thailand</td>
<td>glargine</td>
<td>NPH</td>
<td>RR obtained from CADTH 2008 meta-analysis (highest AMSTAR score 10-/11).</td>
</tr>
<tr>
<td>Morales</td>
<td>Diabetes Therapy</td>
<td>2015</td>
<td>Novo Nordisk</td>
<td>detemir</td>
<td>NPH</td>
<td>Sensitive to RR of hypoglycaemia (as RR approaches upper 95% bound of CADTH estimate, no longer cost effective) and price of detemir.</td>
</tr>
<tr>
<td>Gupta</td>
<td>JME</td>
<td>2015</td>
<td>Novo Nordisk</td>
<td>BIAsp30 (NovoLog Mix 70/30)</td>
<td>RHI (70/30), NPH (not included in this summary table)</td>
<td>Clinical assumptions based on single 24-week observational study with unlikely results (2% decrease in HbA1c) extending into 30-year clinical benefits.</td>
</tr>
<tr>
<td>Liebl</td>
<td>Exp Clin Endocrinol Diabetes</td>
<td>2014</td>
<td>Novo Nordisk</td>
<td>aspart</td>
<td>RHI</td>
<td>Clinical assumptions regarding long-term benefit of analogues based on a single observational study of GP's with methodologic flaws (prevalent user design, immortal time bias, suboptimal confounding control) and unlikely results (aHR MI 0.69, stroke/TIA 0.58, CHD 0.84, PVD 0.8).</td>
</tr>
<tr>
<td>Cameron</td>
<td>CMAJ</td>
<td>2009</td>
<td>Health Canada</td>
<td>aspart, lispro, detemir, glargine</td>
<td>RHI, NPH</td>
<td>Results were sensitive to changes in A1c and to fear of hypoglycaemia.</td>
</tr>
<tr>
<td>Ridderstrale</td>
<td>JME</td>
<td>2013</td>
<td>Novo Nordisk</td>
<td>glargine</td>
<td>NPH</td>
<td>Results sensitive to changes in event rate of NSH, utility decrements.</td>
</tr>
<tr>
<td>Lead Author</td>
<td>Journal</td>
<td>Year</td>
<td>Sponsor</td>
<td>Study drug</td>
<td>Comparator drug or therapy</td>
<td>Major limitations or concerns, if any</td>
</tr>
<tr>
<td>-------------</td>
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<td>---------------------------------------</td>
</tr>
<tr>
<td>Smith-Palmer</td>
<td>JME</td>
<td>2012</td>
<td>Novo Nordisk</td>
<td>determir</td>
<td>NPH</td>
<td>Highly sensitive to rate of hypoglycaemia. Based on 26-week trial of 271 patients.</td>
</tr>
<tr>
<td>Valentine</td>
<td>Scandinavian Journal of Public Health</td>
<td>2011</td>
<td>Novo Nordisk</td>
<td>determir</td>
<td>NPH</td>
<td>Sensitive most to variation in a1c and hypoglycaemic event rate benefits; based on a single trial of 497 patients with type 1, followed for 24 months.</td>
</tr>
<tr>
<td>Brandle</td>
<td>Int'l Journal of Clinical Pharmacology and Therapeutics</td>
<td>2011</td>
<td>Sanofi</td>
<td>glargine</td>
<td>NPH</td>
<td>Hypo assumptions based on Mullins; Sensitive to hypo risk reduction by 50%; utility decrements in hypoglycaemia, HbA1c absolute reduction.</td>
</tr>
<tr>
<td>Tunis</td>
<td>Appl Health Econ Health Policy</td>
<td>2010</td>
<td>Sanofi</td>
<td>glargine</td>
<td>70/30</td>
<td>Single 24-week trial of 371 patients. Results sensitive to utility values assigned for hypoglycaemia, and decreasing glargine's effect on HbA1c by 10%. Based on a single Japanese 5-year study of ~320 t1DM where 43% reduction in MACE within 5 years. Results sensitive to magnitude of clinical benefit.</td>
</tr>
<tr>
<td>Pollock</td>
<td>JME</td>
<td>2010</td>
<td>Novo Nordisk</td>
<td>aspart</td>
<td>RHI</td>
<td>Based on a subgroup analysis of IMPROVE observational study, large, single-arm 26-week observational study. Results most sensitive to changes in A1c and hypo event rates. When no reduction in a1c was assumed, ICER increased to 58,462 per QALY gained. When no a1c benefit was assumed, ICER increased to 95,819.</td>
</tr>
<tr>
<td>Palmer</td>
<td>JME</td>
<td>2010</td>
<td>Novo Nordisk</td>
<td>BIAsp30 (NovoLog Mix 70/30)</td>
<td>70/30</td>
<td></td>
</tr>
</tbody>
</table>

Cost-effectiveness of Analogue and Human Insulin | 45
<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Journal</th>
<th>Year</th>
<th>Sponsor</th>
<th>Study drug</th>
<th>Comparator drug or therapy</th>
<th>Major limitations or concerns, if any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee</td>
<td>Value in Health</td>
<td>2009</td>
<td>Novo Nordisk</td>
<td>BIAsp 30</td>
<td>70/30</td>
<td>Efficacy and safety results based upon 6-month single arm observational study of type 2 diabetics who switched to BiAsp30. Results most sensitive to changes in projected efficacy. Assuming no improvement in hypo events, ICER increased to KRW 19,248,486. (0.137 QALYs).</td>
</tr>
<tr>
<td>Palmer</td>
<td>CMRO</td>
<td>2007</td>
<td>Novo Nordisk</td>
<td>Determir+aspart</td>
<td>NPH+RHI</td>
<td>Results based on single trial lasting 18 weeks of 595 T1DM randomised to the two study drugs.</td>
</tr>
<tr>
<td>Grima</td>
<td>Pharmacoeconomics</td>
<td>2007</td>
<td>Sanofi</td>
<td>glargine</td>
<td>NPH</td>
<td>Estimates based upon metaregression abstract. Results sensitive to reduction in a1c efficacy.</td>
</tr>
<tr>
<td>Tunis</td>
<td>CMRO</td>
<td>2009</td>
<td>Novo Nordisk</td>
<td>detemir</td>
<td>NPH</td>
<td>PREDICTIVE 303, 6-month study used for type 2 effect estimates did not compare detemir against NPH. Both ICERs sensitive to changes in utility associated with major or mild/mild-moderate hypoglycemic events.</td>
</tr>
<tr>
<td>Gschwend</td>
<td>JME</td>
<td>2009</td>
<td>Novo Nordisk</td>
<td>detemir</td>
<td>NPH</td>
<td>No report of individual country insulin costs, other direct medical costs, utility. Country specific results differed only by discounting rate; direct medical costs, insulin treatment and management costs (but none were reported specifically in article)</td>
</tr>
<tr>
<td>Palmer</td>
<td>CMRO</td>
<td>2008</td>
<td>Novo Nordisk</td>
<td>aspart</td>
<td>RHI</td>
<td>Results sensitive to time horizon and when it was assumed that there was no difference in HbA1c</td>
</tr>
</tbody>
</table>

Cost-effectiveness of Analogue and Human Insulin | 46
<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Journal</th>
<th>Year</th>
<th>Sponsor</th>
<th>Study drug</th>
<th>Comparator drug or therapy</th>
<th>Major limitations or concerns, if any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valentine</td>
<td>Adv Ther</td>
<td>2008</td>
<td>Novo Nordisk</td>
<td>detemir</td>
<td>NPH</td>
<td>Not clear what the treatment effect was, subgroup analysis based on PREDICTIVE study with only 12 week follow-up and n of 251 on NPH +/- OAD. Results sensitive to reduction in HbA1c benefit by 50%</td>
</tr>
<tr>
<td>Valentine</td>
<td>Diabetic Medicine</td>
<td>2011</td>
<td>Novo Nordisk</td>
<td>detemir</td>
<td>NPH</td>
<td>RR of hypo based on CADTH meta-analysis. Did not specify additional costs due to complications (in this paper only extra strips for testing for hypo events)</td>
</tr>
<tr>
<td>Pratoomsoot</td>
<td>Diabetic Medicine</td>
<td>2009</td>
<td>Eli Lilly</td>
<td>lispro</td>
<td>RHI</td>
<td>Lispro only cost £187 more over lifetime of an individual (£3.74 per year over 50 years). Results sensitive to difference in rates of severe hypoglycaemia. For example, when no difference in rates was assumed, probability of being cost-effective at £30,000 ICER went from 84 to 59%</td>
</tr>
<tr>
<td>Valentine</td>
<td>Advances in Therapy</td>
<td>2006</td>
<td>Novo Nordisk</td>
<td>detemir</td>
<td>NPH (and glargine)</td>
<td>Single 18-week trial of 591 patients (twice daily det + aspart or twice daily NPH + RHI)</td>
</tr>
<tr>
<td>Palmer</td>
<td>CMRO</td>
<td>2004</td>
<td>Novo Nordisk</td>
<td>detemir</td>
<td>NPH</td>
<td>Based on a meta-analysis of 4 trials (HbA1c difference not statistically significant). Lasting at most 24 weeks</td>
</tr>
</tbody>
</table>