Application to add (ultra-)long-acting insulin analogues to the WHO Model List of Essential Medicines

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1. Summary statement of the proposal for inclusion.

We propose the addition of long-acting and ultra-long-acting insulin analogues to the WHO Model List of Essential Medicines (MLEM) for type 1 and type 2 diabetes mellitus. We specifically propose the addition of insulin glargine, insulin detemir, and insulin degludec, including similar biotherapeutic products. We propose that these should be added to the core EML for adults and children (aged 2 years and above).

Submissions were made to the 2017 and 2019 Expert Committees, proposing the addition of long-acting insulin analogues to the MLEM. In both review cycles, the Expert Committee recognized that long-acting insulin analogues provide benefits over human insulin, but rejected the applications, considering the price differences between human insulin and long-acting insulin analogues to be too great compared to the documented magnitude of benefit.

New evidence on clinical safety and efficacy has become available since the 2019 review. Long-acting insulin analogues are likely to enable more patients with type 1 and type 2 diabetes mellitus to attain better glycaemic control, with lower rates of severe hypoglycaemia events and increased flexibility in timing of administration than is possible with human insulin.

The evidence base summarized here is stronger for the indication of type 1 diabetes. However, we submit this application for indications of both type 1 and type 2 diabetes, for the following reasons: First, when patients with type 2 diabetes progress from the oral antidiabetic agents to insulin, the disease and its implications become similar to type 1 diabetes; and secondly, the inclusion of type 2 diabetes as an indication may increase the number of patients potentially eligible for insulin analogues, which may give an important market signal to encourage increased biosimilar competition and price reductions.

There have been important developments in price reductions for analogue insulins and biosimilars in the time since the last application. However, we suggest that in *national settings* where the price differential between insulin analogues and human insulins remains large and cost-prohibitive, it would be important to prioritise access to long-acting insulin analogues for type 1 diabetes before expanding this to type 2 diabetes. As argued by the WHO Secretariat of the Model List of Essential Medicines in 2015, in the context of high-cost hepatitis C and oncology medicines submitted to the WHO MLEM,(1) affordability is a possible *consequence* – not precondition – of inclusion on the WHO essential medicines list.

Overall, the use of long-acting insulin analogues is expanding in many countries, while prices are decreasing. We argue that the comparatively high prices of long-acting insulin analogues in several countries should not prevent them from being included in the WHO MLEM. Listing long-acting insulin analogues on the MEML can reinforce policy actions such as biosimilar substitution and prequalification initiatives to help moderate insulin prices. If analogues are not listed, advocacy and policy actions to reduce prices can be hampered, leaving the insulin market uncontrolled for longer period of times, across multiple countries. This is especially important in view of the fact that only three companies currently control 96% of the insulin market by volume and 99% in terms of value, globally.(2)

The choice of which insulin to use in patients with diabetes at country level should be driven by cost (and difference in costs), the insulin action profile, safety, effectiveness, and reimbursement in particular group of patients, but also by the devices it comes with, such as insulin pens.

1.1 Previous relevant submissions to the EML Expert Committee

Previous submissions have proposed the addition of long-acting insulin analogues to the WHO MLEM, in 2017 and 2019, both for type 1 diabetes.(3,4) The conclusions of expert committees with regard to those submissions are copied below.

2017

"The Expert Committee noted that long-acting insulin analogues have been shown to be an effective treatment for type 1 diabetes in children, young people and adults. However, the Committee noted that the magnitude of the benefit provided, compared with human insulin, was not large. The Committee considered that the benefits of insulin analogues over human insulin in terms of reduced glycated haemoglobin and reduced hypoglycaemia are modest and do not justify the current large difference in price between analogues and human insulin. On the basis of this evaluation, the Expert Committee did not recommend the addition of long-acting insulin analogues as a pharmacological class to the core list of EML and EMLc for treatment of type 1 diabetes in adults, adolescents and children aged 2 years and above."(5)

2019

"The Committee acknowledged that insulin is a life-saving essential medicine for which a compelling public health need exists. Yet despite being available for almost 100 years, achieving reliable, equitable and affordable access to insulin remains a public health challenge in many countries. The Committee did not recommend the addition of insulin analogues to the EML, reiterating the conclusion of the 2017 Committee, that although the available evidence for long-acting insulin analogues shows some efficacy advantages and reduced hypoglycaemia compared to human insulin, the price differential that exists between analogue and human insulin remains disproportionately high in most settings. The Committee remained concerned about the ongoing problems of access and affordability of insulin worldwide, despite human insulin not being patented. The Committee noted the long-standing domination of the insulin market by three manufacturers, limiting broader competition and slowing the entry of biosimilars to the market. Recognizing the complexities of these problems and the need for a wider understanding of the insulin market and access to insulin, the Committee recommended WHO coordinate a series of actions to address the issues of insulin access and affordability. In the absence of other coordinated actions, the Committee considered that the inclusion of insulin analogues for adults on the EML would be inadequate to address the underlying issues of poor access and affordability of insulins more generally."(6)

1.2 Relevant WHO guidelines

The 2018 WHO guidelines on second-and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus recommended:

"Use human insulin to control blood glucose levels in adults with type 1 diabetes, and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence).

[This recommendation] covers both short-acting (regular human insulin–RHI) and intermediate-acting human insulin (NPH insulin). The recommendation is strong because evidence of better effectiveness of insulin analogues is lacking and human insulin has a better resource-use profile.

Consider long-acting insulin analogues to control blood glucose levels in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (weak recommendation, moderate-quality evidence for severe hypoglycaemia).

[This] is a weak recommendation reflecting the lack of, or very low-quality, evidence for any of the long-term outcomes such as chronic diabetes complications and mortality, and the considerable higher costs for long-acting insulin analogues compared to intermediate-acting human insulin."(7)

These recommendations cite two studies as their basis: Tricco et al 2014 and 'preliminary results from an update of' Horvath et al 2007.(8,9) Both analyses have since been updated (as Tricco et al 2021 and Semlitsch et al 2020, respectively), and the findings of these updates are outlined below.

1.3 The Lancet Commission on Diabetes 2020 report

The Lancet Commission on diabetes highlights the need to wisely use resources, change practices, and empower communities to reduce the global burden of diabetes. In its 2020 report, the Commission argued:

"Insulin analogues are now widely used in many countries. Basal insulin analogues are better than human or animal insulins (eg, bovine and porcine sources) for minimising the risk of nocturnal hypoglycaemia, and are particularly useful for basal–bolus regimens (ie, therapy involving multiple injections a day of long-acting or intermediate-acting insulin and short-acting or rapid-acting insulin at each meal). Nevertheless, human and biosimilar insulins are more affordable insulins in LMICs than insulin analogues. In patients with type 1 diabetes, basal–bolus insulin regimens offer better glycaemic control than twice daily regimens, if accompanied by the appropriate education of individuals with diabetes, family, and care providers with access to adequate supplies of needles, lancets, and testing strips for self-monitoring blood glucose concentration. However, the cost of self-monitoring is often higher than that of insulin. In some LMICs, the tariffs on insulin and self-monitoring supplies often reduce the affordability of these treatments.

Many clinics still use insulin regimens twice a day, often with premixed insulin. These regimens are usually associated with higher HbA1c and more frequent hypoglycaemia than are basal–bolus insulin regimens, especially when used with little or no self-monitoring of blood glucose concentration and diabetes education. However, other non-insulin determinants of quality of glycaemic control are also important. In LMIC settings, due to limited insulin, food insecurity, the unavailability of devices to self-monitor blood glucose and emergency glucagon injection kits, and scarce transport and emergency services, there is a tendency to reduce the dose of premixed insulins to avoid hypoglycaemia. All of these factors can increase the risk of poor glycaemic control and complications that can adversely affect growth and quality of life. Even in HICs, poverty, varying health-care financing or insurance policies, lack of price transparency, complexity in supply chains, and insufficient competition among a few manufacturers have made insulin and supplies to self-monitor blood glucose concentration difficult to afford."(10)

2. Relevant WHO technical department and focal point (if applicable).

The relevant department is the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention.

3. Name of organization(s) consulted and/or supporting the application.

None.

4. International Nonproprietary Name (INN)and Anatomical Therapeutic Chemical (ATC) code of the medicine.

WHO ATC index:

A10A	INSULINS AND ANALOGUES
A10AE	Insulins and analogues for injection, long-acting
A10AE04	insulin glargine
A10AE05	insulin detemir
A10AE06	insulin degludec

5. Dose forms(s) and strength(s)proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Dose forms are the same for adults and children.

Glargine

Pre-filled pen containing 100 units/mL solution (in current formulations each pre-filled pen contains 3 mL).

Cartridge containing 100 units/mL solution (in current formulations each cartridge contains 3 mL).

Detemir

Pre-filled pen containing 100 units/mL solution (in current formulations each pre-filled pen contains 3 mL).

Cartridge containing 100 units/mL solution (in current formulations each cartridge contains 3 mL).

Degludec

Pre-filled pen containing 100 units/mL solution (in current formulations each pre-filled pen contains 3 mL).

Cartridge containing 100 units/mL solution (in current formulations each cartridge contains 3 mL).

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

We propose that (ultra-)long-acting insulin analogues should be listed with a restricted square box, with insulin glargine representative of the class and insulin detemir and insulin degludec included in the restricted square box. It is important also to note that evidence to date shows that it is safe to switch patients from originator to biosimilar insulin.(11)

7. Treatment details (requirements for diagnosis, treatment and monitoring).

Insulin analogues are medicines whose molecular structure is similar to endogenous human insulin (a 51-amino acid polypeptide, with slight modifications to achieve different pharmacokinetic profiles, that is, different peaks of action and durations of action (Figure 1, below). The different pharmacokinetic profiles are the main advantage analogue insulins offer over human insulin.

Insulin NPH (Neutral Protamine Hagedorn) is usually dosed as twice daily. Insulin glargine and insulin degludec are typically dosed as once daily, and detemir may be dosed as once or twice daily.

In terms of other facets of treatment, such as diagnostic tests, specialized treatment facilities, administration requirements, monitoring requirements and skill levels of health care providers, these are identical to those needed for human insulin, except for the possible need for a pen device that accepts replaceable cartridges. Differences in dose regimens are further described in the following section, “8. Information supporting the public health relevance.”

8. Information supporting the public health relevance.

Diabetes affected an estimated 463 million people in 2019, or 9.3% of the global population, of which 79% live in low- and middle-income countries (LMICs).(12) It was responsible for over 1.5 million deaths and 2.79% of all global disability-adjusted life years lost (DALYs) in 2019.(13) It is estimated that diabetes reduces life expectancy by 6 years when diagnosed at the age of 40.(10) Diabetes also significantly increases the risk of other non-communicable diseases, including heart disease and cancer.

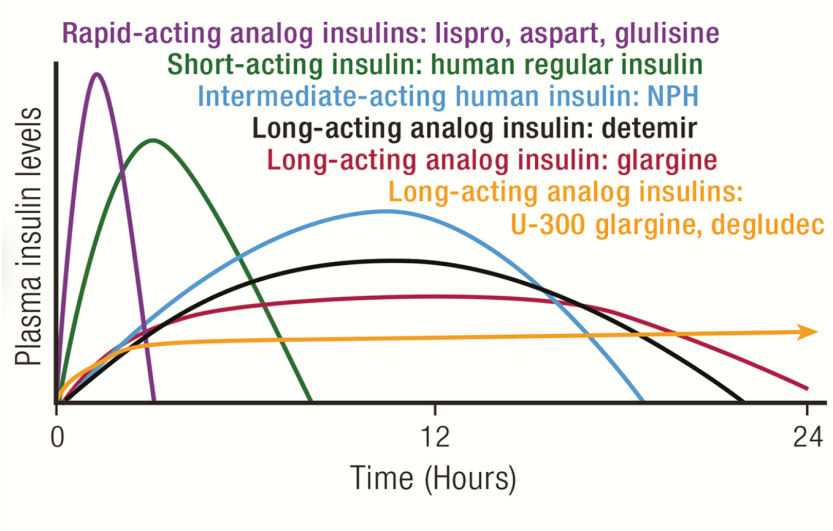
For people diagnosed with type 1 diabetes, regular insulin injections are required lifelong. In the context of lifelong treatment, the ability to flexibly tailor insulin regimens to a patient's needs is important for treatment adherence and quality of life. Both in the case of people living with type 1 diabetes, as well as for those with type 2 diabetes requiring insulin, so-called "glycaemic control" within narrow predefined glucose ranges leads to greater life expectancy and lower rates of complications.

Factors negatively affecting insulin treatment adherence include complicated dosing regimens, fear of hypoglycaemic events and injection site reactions.(14) The greater flexibility available with insulin analogues may lead to increased adherence and patient quality of life.

Long-acting insulin analogues are also associated with a lower rate hypoglycaemic events in people with type 1 diabetes, as outlined later in the submission.

Long-acting insulin analogues offer different pharmacokinetic profiles, meaning more flexibility in terms of time to peak action, duration of action, and action profile, when designing insulin regimens (Figure 1 and Table 1, below). Insulin NPH is usually dosed as twice daily, while insulin glargine, insulin detemir, and insulin degludec are generally dosed as once daily.

Figure 1. Comparison of time-action profiles for different insulin types.



Adapted from Hirsch et al under CC-BY licence.(15)

Table 1. Comparison of peak action and duration of action for insulin NPH and long-acting insulin analogues.

Type	Peak Action (hr)	Duration of Action (hr)
Intermediate-acting		
NPH insulin	2–8	14 to 24
Long-acting		
Insulin glargine*	No pronounced peak	24
Insulin detemir	No pronounced peak	7.6 to >24
Ultra-long-acting		
Insulin degludec	No pronounced peak	42

Adapted from Hirsch et al under CC-BY licence.(15)
*100 units per mL.

Normal insulin NPH dosing, where one dose is taken with breakfast and the second is taken with dinner, requires a meal or snack to be eaten at around midday (lunchtime) and at bedtime, due to its peak of action at around 4-6 hours. Effectively, this requires 3-4 meals a day. In settings where due to whatever reason it is less practical or not possible to have 3-4 meals a day, the flatter time-action curve of insulin analogues allows flexibility – e.g., a bedtime snack will likely not be needed. This flexibility of insulin analogues may be especially valuable in settings where there is food insecurity and varying mealtimes day-to-day. This flexibility may also be important for people living with diabetes who participate in traditions that involve fasting, such as Ramadan.

For insulin degludec, additionally, it was shown in adults that variation in injection time day-to-day (with inter-dose intervals as short as 8 hours and as long as 40 hours) was non-inferior to insulin degludec or insulin glargine injection at the same time every day.(16) This additional flexibility may improve treatment adherence and outcomes.

Glucagon is a key treatment in case of insulin-induced hypoglycaemia and is listed in the WHO MLEM. For patients with severe hypoglycaemia who cannot ingest oral glucose and in whom IV access is not available, glucagon is the rescue treatment to avoid irreversible brain damage. However, glucagon availability in many low-resource settings is low as it is costly.(12) This fact adds to the potential benefits of achieving lower rates of insulin-induced hypoglycaemic events when using long-acting analogues instead of insulin NPH.

9. Review of harms and benefits

For insulin analogues, one of the key outcomes – rate of hypoglycaemic events – can be considered a measure of clinical effectiveness or a measure of (reduced) harm. We thus present evidence for both effectiveness (benefits) and harms in a single unified section. Advantages in terms of flexibility in dosing regimens, described in the section above, are not captured in this section, as they have no corresponding hard endpoint that can be measured in empirical studies.

9.1 Summary of evidence of comparative effectiveness

Recent meta-analyses have found benefits for (ultra-)long-acting insulins in terms of reducing hypoglycaemic episodes and improvement in glycaemic control. The findings of these meta-analyses are more precise than those available at the time of earlier EML Expert Committee reviews of insulin analogues. Furthermore, this application, unlike previous applications is based on multiple systematic reviews and meta-analyses, providing a broader and deeper perspective on the replicability of key findings and interpretation of results.

Overall, the effect size and evidence base are arguably stronger for use in type 1 diabetes than for use in type 2 diabetes, and stronger for long-acting insulins (glargine and detemir) than for ultra-long-acting insulin (degludec). The certainty of the evidence is mostly low.

The systematic reviews and meta-analyses cited in this application are of high quality and followed pre-defined protocols. Differences in conclusions likely derive from study inclusion criteria and/or statistical approaches. Furthermore, the clinical relevance of differences between analogues and NPH have been interpreted differently by independent review teams. A merit of this application is that it provides evidence across multiple overlapping systematic reviews, providing a potential better understanding of a complex question. It should also be noted that most applications for addition of new medicines to WHO MLEM rely heavily on placebo-controlled comparisons, while this application is based on head-to-head comparisons. This is an advantage since the efficacy of the comparator, human insulin, is well-established.

Type 1 diabetes

A 2018 meta-analysis covering 28 RCTs found that long-acting insulin analogues led to a reduction in general hypoglycaemia (RR 0.95, 95%CI 0.91-0.99), nocturnal hypoglycaemia episodes (RR 0.66, 95%CI 0.57–0.76) as well as a reduction in HbA1c (mean difference -0.17, 95%CI -0.23 – -0.12), and no significant difference for severe hypoglycaemia.(17)

A large network meta-analysis (NMA) covering 64 RCTs and 1 non-randomized controlled trial (Tricco et al 2021) found that long-acting analogues led to fewer major or serious hypoglycaemic episodes (OR 0.63, 95%CI 0.51 - 0.79), nocturnal hypoglycaemic episodes (OR 0.74, 95%CI 0.58-0.94), reduction in HbA1c (mean difference -0.14 percentage points (95%CI -0.22 – -0.06), fasting plasma glucose reduction (mean difference -1.03 mmol/L (95%CI -1.33 – -0.73), and weight change (mean difference -0.70 kg (95%CI -1.08 - -0.32). The NMA found no significant difference for all-cause hypoglycaemia, vascular complications, microvascular complications, macrovascular complications, any adverse events, serious adverse events, and drop-outs due to adverse events.(18)

A 2019 systematic review of severe hypoglycaemia in paediatric patients with type 1 diabetes, in real-world studies, was inconclusive as to comparison of long-acting insulin analogues to human insulin.(19)

A 2021 Cochrane review (Hemmingsen et al 2021) compared the effects of long-term treatment with (ultra-)long-acting insulin analogues to NPH insulin or another (ultra-)long-acting insulin analogue. This review included a meta-analysis, but not a network meta-analysis, meaning the overall pooled sample is smaller than that of Tricco et al 2021, but estimates are based on more direct comparisons. Severe hypoglycaemic episodes were reduced with insulin detemir. There were no clear differences for all main outcomes between individual (ultra-)long-acting insulin analogues (insulin glargine, insulin detemir, insulin degludec). There were no clear differences regarding the risk of severe nocturnal hypoglycaemia. health-related quality of life, serious unwanted effects, or HbA1c levels. There were also no clear differences for all comparisons between children and adults.(20)

Type 2 diabetes

A 2020 Cochrane review (Semlitsch et al) found significant reduction in certain measures of hypoglycaemia for insulin glargine or insulin detemir compared to insulin NPH, but no significant differences (at the $p<0.05$ level) in severe hypoglycaemic events, HbA1c, all-cause mortality, diabetes-related complications, or adverse events other than hypoglycaemia.(21)

9.2 Search strategy and identified studies

Systematic reviews comparing (ultra-)long-acting insulin analogues to human insulin (NPH) were identified in the Pubmed, Cochrane, and Embase databases.

Pubmed search term: *"insulin AND analog* AND (regular OR human OR NPH)"*

EMBASE search term: *"insulin AND analog* AND (regular OR human OR NPH)"*

Cochrane search term: *"insulin AND analog*"*

Abstracts were reviewed for all studies captured by this search, by one of the authors (DG). Where enough information wasn't available in the abstract, the full text was reviewed.

Inclusion criteria:

- Published in the last 5 years.
- Systematic review (with or without meta-analysis)
- Compares long-acting insulin analogues to human insulin (including insulin NPH and insulin lente) using any measure

A PRISMA flowchart, as well as characteristics of the studies identified by our search, are outlined in the Appendix. Results of the studies are outlined in the next section.

At the request of the EML Secretariat, the application was revised in March 2021 to include two large and high-quality systematic reviews that were recently published.(18,20)

9.3 Summary of available data

9.3.1 Type 1 diabetes

Laranjeira et al 2018(17)

This was a review of systematic reviews on numerous clinical outcomes in type 1 diabetes treated with insulin NPH versus long-acting insulin analogues, with a new meta-analysis synthesising studies identified across numerous systematic reviews. Eleven systematic reviews covering twenty-five RCTs were included. A supplementary search identified 3 additional RCTs. Outcomes compared were general hypoglycaemia (reported in 25 trials), severe hypoglycaemia (16 trials), nocturnal hypoglycaemia (20 trials), and HbA1c (25 trials).

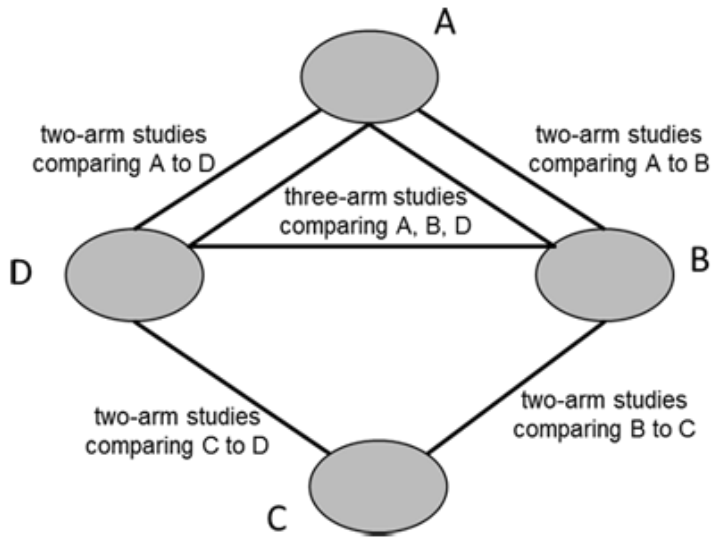
Methodological quality of the included studies was assessed using AMSTAR and Jadad scales. Across the 28 included RCTs, the main potential source of bias identified by the authors of the review was a lack of blinding (arguably difficult to achieve due to the different appearance of insulin analogue and NPH injection liquids). Funnel plots suggested risk of publication bias was low for hypoglycaemic event outcomes, but that publication bias was likely present for the HbA1c outcome.

Meta-analysis found that long-acting insulin analogues led to a reduction in general hypoglycaemia (RR 0.95, 95%CI 0.91-0.99), nocturnal hypoglycaemia episodes (RR 0.66, 95%CI 0.57–0.76) as well as a reduction in HbA1c (mean difference -0.17, 95%CI -0.23 – -0.12). There was no significant difference for severe hypoglycaemia.

Tricco et al 2021(18)

This was a systematic review with network meta-analysis (NMA). Network meta-analysis allows indirect comparisons between interventions by considering a broader network of pair-wise analyses. Additionally, indirect comparisons and direct comparisons can both contribute to an effect estimate, effectively increasing the pooled sample for that effect estimate (Figure 2).[A] This study is the largest review that we identified, in terms of pooled sample size.

Figure 2. Conceptual schematic of the network meta-analysis methodology.



Comparison of D to B is calculated based on studies directly comparing the two (direct connecting line), but also studies comparing D to A and studies comparing A to B, as well as

[A] Anna Chaimani, Deborah M Caldwell, Tianjing Li, Julian PT Higgins, Georgia Salanti. Chapter 11: Undertaking network meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.1, 2020. Available from: https://training.cochrane.org/handbook/current/chapter-11

D to C and C to B. Source: Cochrane Handbook for Systematic Reviews of Interventions. Version 6.1, 2020. https://training.cochrane.org/handbook/current/chapter-11 (with permission).

The systematic review searched Medline, Embase, and the Cochrane library, as well as grey literature and reference lists. The search was not restricted by date or language. 65 studies were included, of which 64 were RCTs.

Methodological quality was assessed using the Cochrane Collaboration Risk of Bias tool for the 64 included RCTs, the Cochrane Effective Practice and Organization of Care (EPOC) tool for the one non-randomized controlled trial.

Across the included RCTs, risk of bias was graded as unclear for most trials in the 'random sequence generation' domain, graded as unclear for most trials in the 'allocation concealment' domain, graded as high for most trials in the 'blinding of participants and personnel' domain, low for most trials in the 'blinding of outcome assessment' domain, low for most trials in the 'incomplete outcome data' domain, unclear for most trials in the 'selective reporting' domain, and high for most trials in the 'other bias' domain.

Results of the Tricco et al NMA are summarised in Table 2 below. The network meta-analysis found that long-acting analogues (glargine and detemir, pooled) were superior to intermediate-acting (NPH or lente, pooled) insulin in major or serious hypoglycaemic episodes, and nocturnal hypoglycaemic episodes, but no significant difference for all hypoglycaemic events. The NMA also found superiority in HbA1c reduction, fasting plasma glucose reduction, and weight change.

The NMA found that the ultra-long-acting analogue insulin degludec was superior to intermediate-acting insulin in reducing the frequency of nocturnal hypoglycaemic episodes, but not major/serious hypoglycaemic episodes, and that it was superior in reducing fasting plasma glucose but not HbA1c or weight.

Table 2. Key results of Tricco et al. network meta-analysis.

ENDPOINT	POOLED SAMPLE	COMPARISON	NMA EFFECT ESTIMATE VERSUS INTERMEDIATE-ACTING INSULIN (95%CI)
Change in HbA1c	8,327 patients across 25 RCTs	Detemir/glargine	**MD -0.14% (-0.22 to -0.06)**
		Degludec	MD -0.08% (-0.25 to 0.10)
Change in fasting plasma glucose	7,685 patients across 21 RCTs	Detemir/glargine	**MD -1.03 mmol/L (-1.33 to -0.73)**
		Degludec	**MD -1.45 mmol/L (-2.12 to -0.79)**
All hypoglycaemic episodes	4,292 patients across 10 RCTs	Detemir/glargine	OR 0.88 (0.64 to 1.20)
		Degludec	OR 0.94 (0.42 to 2.10)
Major or serious hypoglycaemic episodes	6,900 patients across 16 RCTs	Detemir/glargine	**OR 0.63 (0.51 to 0.79)**
		Degludec	OR 0.71 (0.43 to 1.17)

Nocturnal hypoglycaemic episodes	5,423 patients across 13 RCTs	Detemir/glargine	**OR 0.74 (0.58 to 0.94)**
		Degludec	**OR 0.64 (0.41 to 0.99)**
Weight change	5,908 patients across 15 RCTs	Detemir/glargine	**MD -0.70 kg (-1.08 to -0.32)**
		Degludec	MD -0.53 kg (-1.25 to 0.18)

Bolded – significant at 95% confidence. MD – mean difference, OR – odds ratio.

The NMA found non-significant differences for vascular complications, microvascular complications, macrovascular complications, any adverse events, serious adverse events, and drop-outs due to adverse events.

NMA was not possible, due to a limited number of relevant trials, for minor or mild hypoglycaemia, all-cause mortality, quality of life, and incident cancers.

Almeida et al 2018(22)

Of the systematic reviews identified in this document, this is the only one that focussed on insulin glargine (rather than other analogues), and the only one that focussed on quality-of-life (QOL) outcomes. The review only included studies that had QOL outcomes as the primary endpoint.

The review followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

This systematic review included 4 randomized controlled trials and 4 cohort studies.

The 4 cohort studies were assessed using the Newcastle-Ottawa scale (which ranges from 0 to 8, with 8 being the best), awarding scores of 4, 5, 7, and 8.

The 4 RCTs were assessed using the Cochrane Collaboration RevMan Risk of Bias tool, which found a high risk of bias in multiple domains, including: allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), selective reporting (reporting bias) and other biases.

Various instruments were used to assess QoL. Of the 8 studies identified in this systematic review, 5 studies reported statistically significant ($p<0.05$) differences in quality of life, favouring glargine over NPH, in certain QoL domains. 1 study did not report on QoL outcomes. 2 studies reported no statistically significant difference in any of the measured QoL metrics. Where insulin glargine was found to have statistically significant superiority in QoL metrics, the metrics with significant differences tended to be ‘satisfaction with treatment’ or ‘perception of hyperglycaemia’.

Cherubini et al. 2019(23)

This was a systematic review of severe hypoglycaemia in paediatric patients with type 1 diabetes, in real-world studies.

Cherubini and colleagues identified two observational studies comparing long-acting insulin analogues to insulin NPH in paediatric patients with type 1 diabetes, with opposite findings. One analysis of 2,025 patients found an incidence rate ratio of 0.46 (95% CI 0.22-0.95) for serious hypoglycaemia with long-acting insulin analogue compared to insulin NPH.(24) The

other analysis, with 7,266 patients, serious hypoglycaemic episodes were more common in those using long-acting insulin analogue compared to insulin NPH (odds ratio 1.57 (95%CI 1.21-2.03)).(23)

Hemmingsen et al 2021(20)

This was a Cochrane Review (with meta-analysis) comparing long-term treatment with (ultra-)long-acting insulin analogues to NPH insulin (neutral protamine Hagedorn) in type 1 diabetes. The review included RCTs in adults and children that had a follow-up duration of at least 24 weeks or more. The review included 26 RCTs (with a total of 8,784 participants). Eight studies, representing 21% of the total the total pooled sample, included children. Key results are reproduced in Table 3 below.

Table 3. Key results of Hemmingsen et al 2021 meta-analysis.

MEASURE	INSULIN GLARGINE VERSUS NPH		INSULIN DETEMIR VERSUS NPH	
	(95%CI)	**Pooled population size, number of RCTs covered, and GRADE certainty of evidence**	**(95%CI)**	**Pooled population size, number of RCTs covered, and GRADE certainty of evidence**
Change in HbA1c	MD +0.02% (-0.1% to +0.1%)	2,285 (9); moderate	MD +0.01% (-0.1% to +0.1%)	3,122 (8); moderate
Severe hypoglycaemic events	RR 0.84 (0.67 to 1.04)	2,350 (9); moderate	**RR 0.69 (0.52 to 0.92)**	3,219 (8); moderate
Severe nocturnal hypoglycaemia	RR 0.83 (0.62 to 1.12)	1,893 (6); moderate	RR 0.67 (0.39 to 1.17)	2,925 (7); moderate
All-cause mortality	Peto OR 0.14 (0.00 to 6.98)	2,175 (8); moderate	Peto OR 4.97 (0.79 to 31.38)	3,334 (9); moderate

Bolded – significant at 95% confidence. MD – mean difference, OR – odds ratio, RR – risk ratio.

Insulin detemir was associated with a significantly lower risk of severe hypoglycaemic events compared to insulin NPH (estimated 31% reduction in risk). The certainty of this finding was limited by the range of the prediction interval. There was no significant difference in effect on severe hypoglycaemic events between insulin glargine and NPH insulin. Data on mortality and other patient-important outcomes were sparse. The meta-analysis found no significant difference between insulin detemir and NPH, or between insulin glargine and NPH, in HbA1c, all-cause mortality, or severe nocturnal hypoglycaemia.

For all comparisons, there was no evidence of a difference in effects between children and adults.

9.3.2 Type 2 diabetes

Semlitsch et al 2020(21)

This is a Cochrane Review comparing long-acting insulin analogues (glargine and detemir) to insulin NPH with regard to numerous outcomes in type 2 diabetes in adults, with meta-analysis.

The literature search was not restricted by language. 24 RCTs were included, of which 16 RCTs compared insulin glargine to insulin NPH and 8 studies compared insulin detemir to insulin NPH.

Statistically significant differences were found for insulin glargine and detemir compared to insulin NPH in certain hypoglycaemia outcomes (Table 4).

Meta-analysis found no significant differences (at the p<0.05 level) in severe hypoglycaemic events, HbA1c, all-cause mortality, diabetes-related complications, or adverse events other than hypoglycaemia.

Table 4. Summary of effect estimates for hypoglycaemia-related outcomes in *Semlitsch et al 2020*.

	Insulin glargine versus NPH		**Insulin detemir versus NPH**	
	Risk ratio (95%CI)	Pooled population size and GRADE certainty of evidence	Risk ratio (95%CI)	Pooled population size and GRADE certainty of evidence
Severe hypoglycaemia	0.68 (0.46-1.01)	6,164 (14 RCTs); very low	0.45 (0.14-1.20)	1,804 (5 RCTs); very low
Serious hypoglycaemia	0.75 (0.52-1.09)	4,685 (10 RCTs); low	**0.16 (0.05-0.61)***	1,777 (5 RCTs); low
Confirmed hypoglycaemia (BG <75 mg/dL)	0.92 (0.85-1.01)	4,115 (7 RCTs); very low	**0.73 (0.61-0.86)**	1,718 (4 RCTs); low
Confirmed hypoglycaemia (BG <55 mg/dL)	**0.88 (0.81-0.96)**	4,388 (8 RCTs); moderate	**0.48 (0.32-0.71)**	1,718 (4 RCTs); low
Confirmed nocturnal hypoglycaemia (BG <75 mg/dL)	**0.78 (0.68-0.89)**	4,225 (8 RCTs); very low	**0.57 (0.47-0.68)**	1,718 (4 RCTs); low
Confirmed nocturnal hypoglycaemia (BG <55 mg/dL)	**0.74 (0.64-0.85)**	4,759 (8 RCTs); moderate	**0.32 (0.16-0.63)**	1,718 (4 RCTs); low

Bold – statistically significant at p < 0.05 threshold. BG – blood glucose.
75 mg/dL of glucose is equivalent to 4.2 mmol/L, 55 mg/dL is equivalent to 3.1 mmol/L.
**Peto odds ratio, rather than risk ratio.*

For health-related quality of life, 3 identified trials reported no statistically significant difference between insulin glargine and insulin NPH, and 3 identified trials reported no statistically significant difference between insulin detemir and insulin NPH.

The authors of this Cochrane review noted that, overall, the included studies used very low blood glucose/HbA1c target values, and that the findings may therefore be less applicable for patient groups where less aggressive glycaemic targets are used (e.g. the elderly).

9.3.3 Pooled analysis of type 1 and 2 diabetes

Czech et al 2015(25)

This is a systematic review of drug-related severe hypoglycaemia in observational studies, which used a Markov Chain Monte Carlo (MCMC) model to estimate the yearly rate of serious hypoglycaemic events with various antidiabetic treatment regimens.

Meta-analysis found no significant difference in the rate of severe hypoglycaemic event rate with biphasic human insulin compared to biphasic insulin analogue (incidence relative rate 1.50, 95%CI 0.96–2.36).

The MCMC model estimates of severe hypoglycaemic events (SHE) per year are shown in the Table below.

Table 5. Summary of modelling estimates for severe hypoglycaemic event incidence from Czech et al 2015.

Therapy	Average number of SHEs per patient per year	Probability of ≥1 SHE for a patient annually
Type 1 diabetes		
Insulin pump	0.168 (0.123–0.237)	11.38% (8.09%–16.03%)
Basal-bolus (basal insulin analogue)	0.472 (0.252–1.055)	21.37% (11.30%–42.97%)
Basal-bolus (basal human insulin)	1.084 (0.530–2.900)	33.77% (17.93%–67.53%)
Type 2 diabetes		
Basal insulin analogue plus non-insulin	0.113 (0.050–0.324)	5.55% (2.32%–15.62%)
Basal human insulin plus non-insulin	0.173 (0.072–0.600)	7.95% (3.18%–26.35%)
Basal-bolus (basal insulin analogue)	0.080 (0.027–0.456)	4.78% (1.21%–27.04%)
Basal-bolus (basal human insulin)	0.554 (0.157–7.534)	31.40% (7.44%–99.64%)
Pre-mix insulin analogue	0.092 (0.052–0.186)	6.23% (3.41%–12.49%)
Pre-mix human insulin	0.299 (0.137–0.868)	12.43% (5.87%–31.85%)
Sulfonylureas	0.045 (0.023–0.115)	3.57% (1.91%–7.56%)

Table adapted from Czech et al 2015, used under CC BY 4.0 licence, available from: https://bmcendocrdisord.biomedcentral.com/articles/10.1186/s12902-015-0052-z/tables/1

Singh et al 2015(26)

This was a systematic review with meta-analysis, comparing insulin analogues versus human insulins in hospitalized adults with type 1 or 2 diabetes. Outcomes included hyperglycaemic episodes, surgical site infection and including postoperative complications, length of hospital stay, and mortality.

Comparing analogue basal-bolus regimens to human insulin basal-bolus regimens, meta-analysis of 4 RCTs estimated that analogues reduced days spent in hospital by 0.9 days (95%CI −1.45 - −0.34), with low quality of evidence. One RCT found lower rates (RR 0.69; 95%CI 0.52 - 0.93) of post-operative complications, with very low quality of evidence.

Two RCTs and one cohort study compared long-acting insulin analogues versus insulin NPH in hospitalized patients. The cohort study found reduction in hypoglycaemic events, with very low-quality evidence, while the RCTs were inconclusive.

One cohort study of 172 patients compared long-acting insulin analogue to insulin NPH in hospitalized patients undergoing major surgery, finding reduced frequency of hypoglycaemic events.

Lv et al 2015(27)

Lv and colleagues considered outcomes for insulin glargine or detemir, compared to insulin NPH, in (pre-)gestational diabetes.

The systematic review identified 8 observational studies comparing insulin glargine to insulin NPH, and 1 observational study and 1 RCT comparing insulin detemir to insulin NPH.

For insulin glargine, meta-analysis found no significant differences in foetal/neonatal or maternal outcomes. Similarly, for insulin detemir, meta-analysis found no significant differences in foetal/neonatal or maternal outcomes.

10. Comparative cost-effectiveness

10.1 Search strategy

Studies analysing cost-effectiveness of (ultra-)long-acting insulin analogues compared to human insulin (NPH) were identified in the Pubmed, Cochrane, and Embase databases.

Pubmed search term: *"insulin AND analog* AND (cost OR price) AND (regular OR human OR NPH)"*

EMBASE search term: *"insulin AND analog* AND (cost OR price) AND (regular OR human OR NPH)"*

Cochrane search term: *"insulin AND analog* AND (cost OR price)"*

Abstracts were reviewed for all studies captured by this search, by one of the authors (DG). Where enough information wasn't available in the abstract, the full text was reviewed. Inclusion criteria:

- Published in the last 5 years.
- Comparative analysis of prices or cost-effectiveness.
- Compares long-acting insulin analogues to human insulin (including insulin NPH and insulin lente)

A PRISMA flowchart is given in the Appendix.

10.2. Systematic reviews

The literature review identified only one systematic review of the cost-effectiveness of long-acting insulin analogues published over the last 5 years.

Shafie et al 2017 undertook a systematic review of insulin analogue cost-effectiveness, including 50 studies published to the end of September 2015.(28) Of the included studies, 33 focussed on type 2 diabetes, 11 focussed on type 1 diabetes, and 6 covered both types.

Twenty-one studies compared long-acting analogue insulin to insulin NPH, all of which were for high-income countries. Long-acting insulin analogues were dominant over NPH in 5 comparisons (i.e. had both lower cost and greater benefit) and were dominated by NPH in 1 comparison (i.e. the long-acting analogue had both greater cost and lesser benefits). Apart from these cases, ICERs for long-acting insulin analogues compared to insulin NPH ranged from USD661/QALY to USD 361,721/QALY. This large range in ICERs is caused by different underlying assumptions used across studies, particularly regarding: i) the baseline characteristics of patients, complication frequency and severity, use and cost of self-monitoring blood glucose test strips and devices (e.g. pen, cartridge, vial), and ii) the different (estimated) magnitudes of benefit in reducing hypoglycaemia events and reductions in HbA1C.

10.3. Cost-effectiveness studies published 2015-2020

In addition to the one systematic review identified in our search, outlined above, we identified 6 studies of long-acting insulin analogue cost-effectiveness published in 2015-2020, in Taiwan, Brazil, Malaysia, France, Hong Kong, and China.(29–34) Long-acting analogues were found to be cost-effective compared to human insulins in Taiwan, Malaysia, and Hong Kong. In France, glargine was cost-effective, but not detemir. Neither were cost-

effective in Brazil. The study in China assessed insulin cost in terms of wages, finding that a month's supply of long-acting insulin analogues cost 14-16 days' wages for the lowest-paid government worker compared to 4-7 days for other insulins (Appendix).

10.4. Recent price surveys

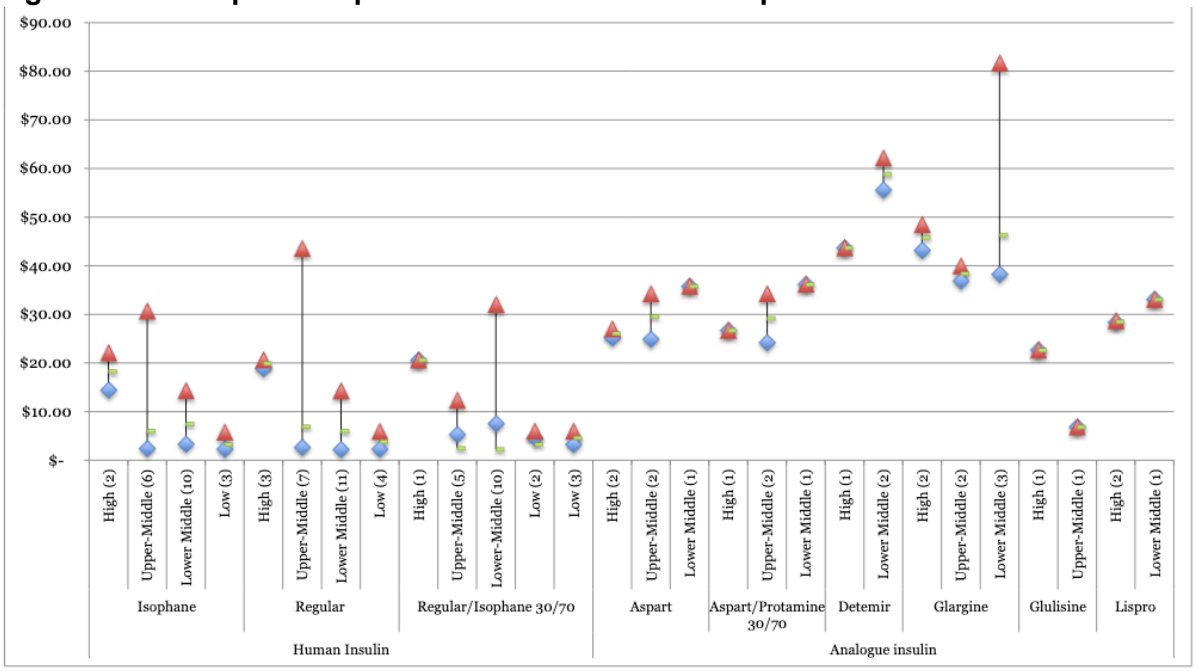
ACCISS 2017 – Access to Insulin: Challenges and Constraints

Health Action International and the ACCISS study have tracked insulin prices for many years and provide the most comprehensive overviews of the topic.

In their most recent report (2017), the ACCISS study summarised insulin prices from a range of sources, including government procurement prices in 26 countries, the Gulf Cooperation Council, and the United Nations Relief and Works Agency for Palestine Refugees (UNRWA), as well as prices paid by patients (solicited via informants for 43 countries), and reimbursement prices collected from publicly accessible databases for 28 countries. (35)

For government procurement, the median price for 1000 units of analogue insulin was USD34.20 compared to US$5.99 for human insulin. When bought by patients from public sector facilities, median price for analogue insulin was USD45.03 compared to US$7.64 for human insulin. When bought by patients in the private sector, median price for long-acting insulin analogues was USD39.35 compared to USD16.65 for human insulin.(35) The analysis did not separately report prices by type of insulin analogue, except for government procurement (Figure 3, below).

Figure 3. Insulin prices reported in the ACCISS 2017 report.



Beran et al. 2017.(35) Used under CC-BY-NC licence.

Ewen et al. BMJ Global Health (2019)

Ewen et al (collaborators in the ACCISS project mentioned above) undertook in-person surveys in 13 countries, in 2016. The surveys included Brazil, China, Ethiopia, Ghana, India, Indonesia, Jordan, Kenya, Kyrgyzstan, Mali, Pakistan, Russia, and Uganda. Key findings with regard to prices are shown in the reused Figure below. Prices for long-acting insulin analogues were markedly greater than for human intermediate-acting insulin.(36)

Insulin prices by type and country were not fully reported. It should also be noted that prices for analogues were only identified in some of the countries surveyed.

Figure 4. Prices reported by Ewen et al, 2016.

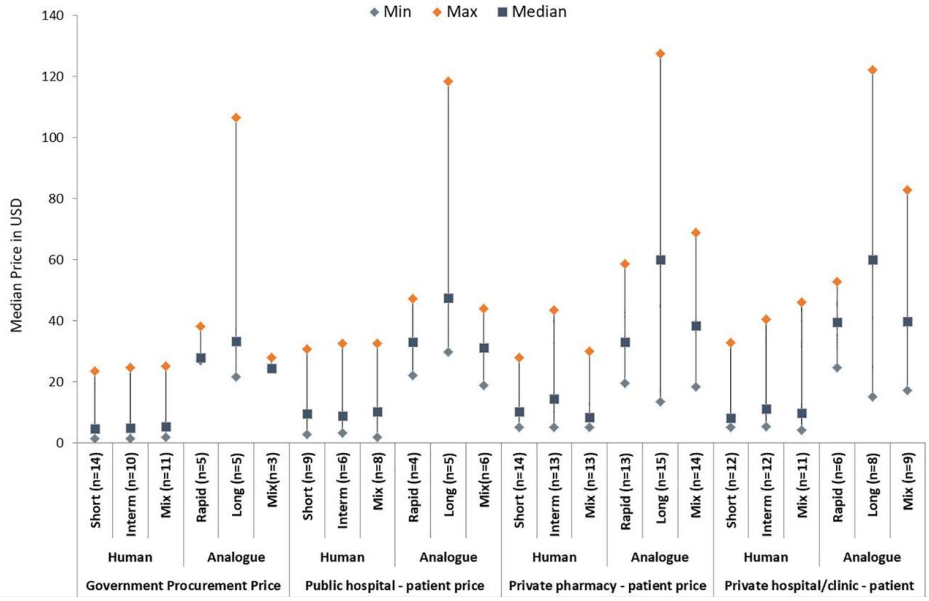


Figure reused from Ewen et al. under CC-BY-NC licence.(36)

Godman. Report for the 2021 WHO Expert Committee on Selection and Use of Essential Medicines (2021)

In many countries, access to (ultra-)long-acting insulin analogues is limited and hampered by the increased costs compared to human insulin. Overall, there is great variability among countries regarding the price of and access to (ultra-)long-acting insulin analogues, often still much more expensive than human insulin. However, overall use on analogues seems to be expanding and prices decreasing at least for those insulins that are not anymore patent protected. In some countries, such as Malaysia and Bangladesh, biosimilars of insulin analogues, supported by dedicated policy actions on pharmaceutical cost, are reaching prices similar to human insulin and represent an increasing market share.(37) The additional benefit of insulin analogues with higher concentrations (300 units/ml vs 100 units/ml) remains unclear and could represent an “evergreening” strategy. These higher-concentration products account for increasing large market shares, even if their prices have very limited chance to be reduced, as they are under active patent protection.(38)

10.5 Summary of available data on comparative cost and cost-effectiveness of the medicine

There have been long-standing concerns about the prices of long-acting insulin analogues, which are significantly higher than prices for human insulins in most comparisons. This is in the context of a broader crisis in global access to insulin therapy in general, where an estimated 1 in 2 people who need insulin cannot afford it.(39) It is also well-described how the insulin market (both for human insulins and analogues) has been characterised by an oligopoly.(2) This year marks the centenary of the discovery of insulin, making the wide gap in access to insulin especially poignant. Civil society has campaigned tirelessly on this issue.(40)

Most available cost-effectiveness studies focus on the high-income country context. In all studies, procurement costs for long-acting insulin analogues is significantly greater than for human insulins. Some cost-effectiveness analyses have found that, despite greater procurement cost, insulin analogues are cost-effective compared to human insulins due to savings deriving from (assumed/modelled) health benefits such as lower rates of hypoglycaemia.

We suggest that the EML should be forward-looking and accept reasonable expectation that a product's price will significantly reduce in the near-to-medium-term (e.g. 5 years), particularly if policy approaches that favour biosimilars and cost-containment are pursued at a country level. This approach has been recently observed for a number of medicines including adalimumab (with square box alternatives etanercept, infliximab, certolizumab pegol, golimumab), erlotinib (with square box alternatives gefitinib and afatinib), lenalidomide (with thalidomide as alternative), and abiraterone, to mention a few– all of which had or have prices significantly greater than the earlier standard of care. EML listing can serve as a helpful signal to manufacturers of what medicines may benefit the most from generic/biosimilar market entry, as well as a signal to governments as to where interventions in the market are necessary to increase competition or cap prices. Another relevant case study is that of newer hepatitis C medicines such as sofosbuvir and daclatasvir, which were added to the WHO MLEM while prices were still very high in most countries, in the justified expectation that prices would fall.

Insulin analogues represent the majority of insulins used in high-income countries, and likely represent the majority of insulins used in middle-income countries.(2) There is therefore likely to be greater interest in analogues, compared to regular human insulin, from biosimilar manufacturers, due to greater prospects of revenues. We would therefore expect a greater number of biosimilar competitor products to enter the market (and lower prices) for insulin analogues than for human insulin. While the increasing market share of analogues likely reflects marketing pressure from analogue manufacturers, it will also to some extent reflect genuine physician and patient preference for different action profiles.

The biosimilar market is gaining momentum. For example, biosimilars are rapidly penetrating the insulin glargine market in England, with some clinical commissioning groups (geographical divisions of the health system) achieving utilisation rates of 53.3% in December 2018 and over 40% in the US public sector market by 2018.(41,42) Malaysia has seen the development of local biosimilar manufacture for insulin analogues, with high prescribing rates in some hospitals.(37,43) Brazil has seen the development of local biosimilar manufacture for human insulin.(44) However, policies aimed at encouraging biosimilar adoption are important in order to encourage this competition, and are currently insufficient in some countries.(45)

The majority of patents have expired for nearly all insulin analogues, though intellectual property barriers remain in some cases for insulin injection devices.(46,47) As biosimilars

have entered the market for insulin glargine, the originator pharmaceutical company has shifted to marketing a new, patented, higher-concentration formulation of insulin glargine (300 units/mL versus earlier 100 units/mL).(48,49) Data on the benefits of higher-concentration glargine versus normal-concentration is however limited compared to data for long-acting insulins versus human insulin.

We are not proposing that long-acting insulin analogues should replace human insulins in the EML, but that they should be included as alternatives. Without question, lowering prices and increasing availability of long-acting insulin analogues is urgently needed in all countries, and insulin NPH, which at present is more affordable than insulin analogues, must remain available in all countries. Although the majority of patients with diabetes in many countries now use long-acting insulin analogues, there remains a large proportion of patients with diabetes for whom it would not be appropriate to switch from human insulin to analogues (for example, due to differences in individual patient responses or due to patient preference to continue their current insulin regimen). Countries need to work with manufacturers and other stakeholders to support the availability of human insulin, even in a period in which the use of human insulin is likely to decline.

If (ultra-)long-active insulins are added to the WHO MLEM, it important that individual governments do not interpret this as a recommendation for a wholesale switch from human to analogue insulins. Additionally, where governments consider adding insulin analogues to national essential medicines lists/national procurement lists it is important that the cost implications of this are carefully considered and do not lead to an excessive demand on health budgets. This is reflected in recent activities in Brazil and South Africa where potential listing and/or funding enhanced by lower prices for the long-acting insulin analogues.(50,51)

11. Summary of regulatory status and market availability of the medicine.

Regulatory status, approved indications, and market availability are summarised in the Tables below.

To the best of our knowledge, there are no planned or existing intellectual property licensing agreements aimed at enabling generic/biosimilar manufacture of long-acting insulin analogues, through the Medicines Patent Pool or otherwise.

At present, there are no prequalified insulin active pharmaceutical ingredient manufacturers or finished pharmaceutical products.(52,53). WHO is undertaking a pilot project for prequalification of human insulin products, currently soliciting applications.(54) This initiative will hopefully stimulate competition and set a good baseline for developing greater biosimilar manufacturing capacity and competition also for long-acting insulin analogues.

Table 6. Approved products for long-acting insulin analogues in selected jurisdictions.

Jurisdiction	Insulin glargine	Insulin detemir	Insulin degludec
United States	3	1	1
EMA	3	1	1
Japan	3	1	1
Canada	2	1	1
Australia	3	1	1

Sources: US – https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm, EMA – https://www.ema.europa.eu/en/medicines, Japan – https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html, Australia – http://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg, Canada – https://health-products.canada.ca/dpd-bdpp/.

Table 7. Approved indications for long-acting insulin analogues in selected jurisdictions.

Jurisdiction	Insulin glargine	Insulin detemir	Insulin degludec
United States	"improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus."	"improve glycemic control in adults and children with diabetes mellitus"	"improve glycemic control in adults with diabetes mellitus"
EMA	"treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above."	"treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above."	"Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year."
Japan	"treatment of diabetes mellitus where insulin therapy is indicated."	"treatment of diabetes mellitus where insulin therapy is indicated"	"treatment of diabetes mellitus in cases where insulin therapy is indicated."
Canada	"once-daily subcutaneous administration in the treatment of patients over 17 years of age with type 1 or type 2	"the treatment of type 1 diabetes mellitus in adults, adolescent and children 2 years and above; the treatment of type 2 diabetes	"once-daily treatment of adults with diabetes mellitus to improve glycemic control. [and] the treatment of pediatric patients (>2

	diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. [and] the treatment of pediatric patients (>6 years old) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia." "treatment of pediatric patients (>6 years old) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia."	mellitus in adults when insulin is required for the control of hyperglycemia; the treatment of type 2 diabetes mellitus in combination with oral anti-diabetic agents (OADs) in adults who are not in adequate metabolic control on OADs alone."	yearsold) with Type 1 diabetes mellitus."

Table 8. Number of insulin products registered, by country (adapted from Beran et al 2017(35)).

Country	Analogue	Human
Algeria	1	3
Armenia	13	19
Australia	13	24
Azerbaijan	17	12
Bangladesh	3	22
Belarus	1	8
Botswana	0	5
Brazil	0	6
Brunei Darussalam	8	5
Canada	18	17
Chile	0	8
China	80	141
Colombia	2	20
Costa Rica	8	9
Croatia	12	12
Cuba	3	4
Dominican Republic	21	35
Egypt	13	54
Estonia	60	71
Fiji	0	3
Finland	56	73
Guatemala	21	35
Iceland	13	9
India	16	28
Indonesia	5	4
Israel	17	9
Japan	27	4
Kenya	8	35
Latvia	41	51
Lebanon	0	11

Lithuania	0	5
Malaysia	0	3
Malta	0	3
Mexico	11	16
Moldova	9	19
Montenegro	9	6
Morocco	22	19
New Zealand	30	64
Nigeria	7	65
Norway	13	21
Oman	23	9
Panama	1	0
Peru	18	15
Philippines	8	7
Saudi Arabia	22	16
Serbia	26	20
Singapore	20	12
South Africa	1	4
Sri Lanka	17	15
Sudan	1	12
Sweden	0	31
Switzerland	11	4
Trinidad and Tobago	1	6
UK	0	14
US	30	21

Note that in many or all cases, countries in the European Economic Area, as well as Iceland and Norway may not include medicines registered through centralised marketing authorisation granted by the EMA. Adapted under CC-BY-NC 4.0 International Licence.

12. Availability of pharmacopoeial standards.

	International Pharmacopoeia	United States Pharmacopoeia	European Pharmacopoeia	British Pharmacopoeia
Insulin glargine	No	Yes	Yes	No
Insulin detemir	No	No	No	No
Insulin degludec	No	No	No	No

Sources: IP – https://apps.who.int/phint/en/p/docf/. USP – https://static.usp.org/doc/referenceStandards/dailycatalog.pdf. EP – https://crs.edqm.eu/. BP – https://www.pharmacopoeia.com/Catalogue/SearchProducts.

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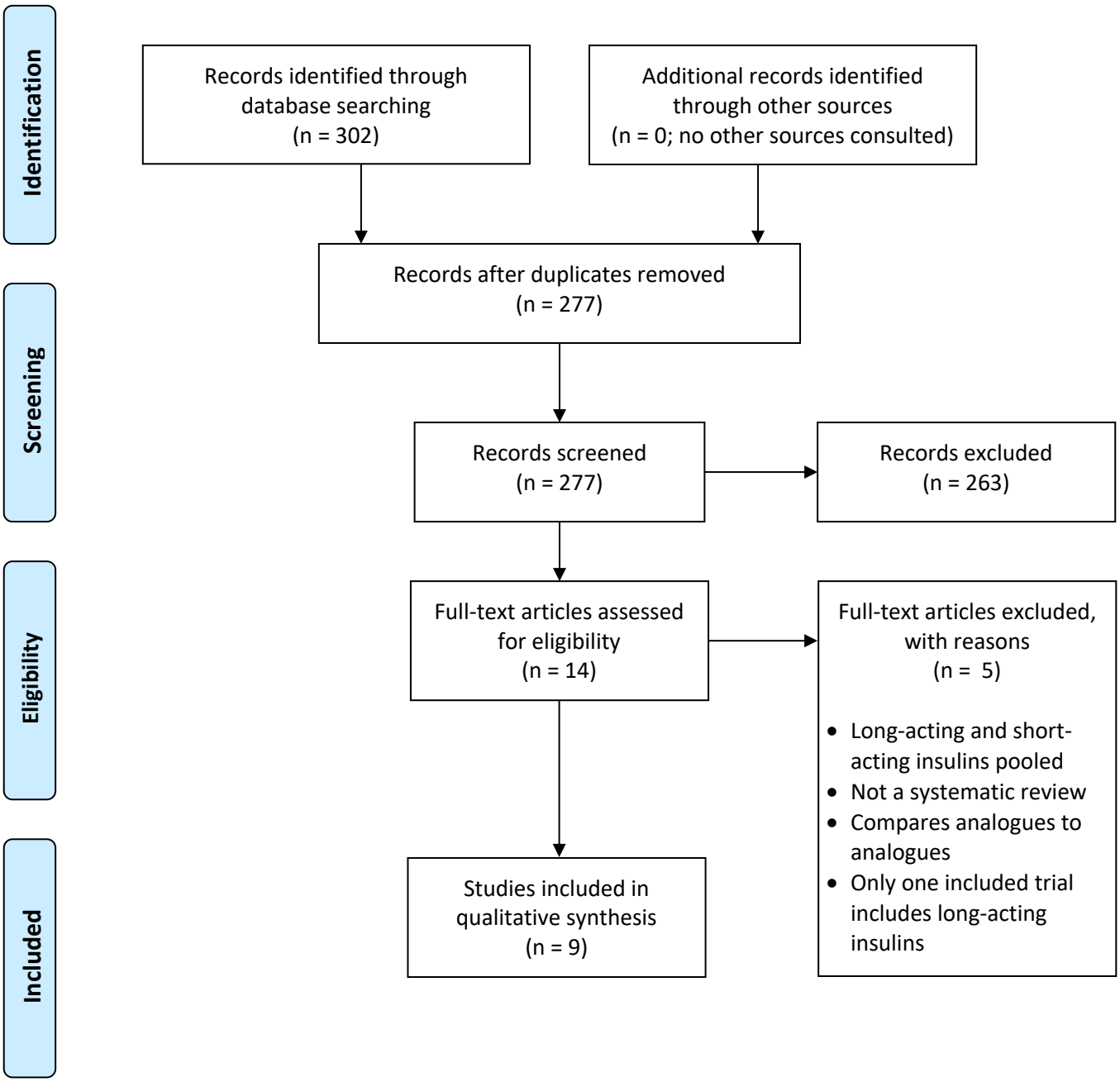
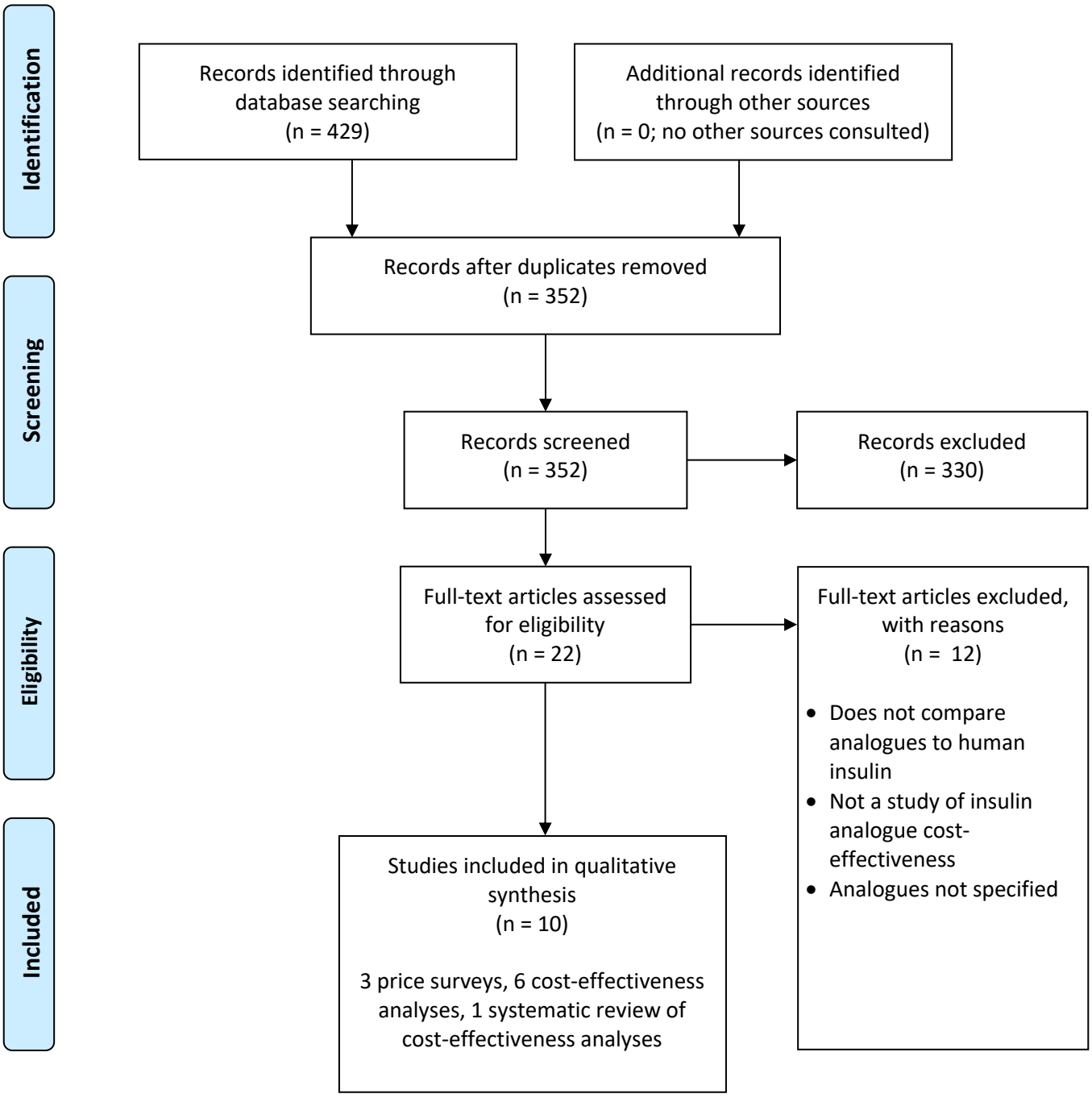
Appendix

PRISMA flow diagram for literature search on clinical effectiveness/safety.



Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA flow diagram for literature search on cost-effectiveness.



Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table 9. Characteristics of systematic reviews of the clinical efficacy of long-acting insulin analogues compared to human insulin 2015-2020.(17,19,21,22,25,26)

Study	Main outcomes assessed	Review type	Pooled sample
Type 1 diabetes			
Almeida et al. Quality of Life of Patients with Type 1 Diabetes Mellitus Using Insulin Analog Glargine Compared with NPH Insulin: A Systematic Review and Policy Implications. Patient. 2018 Aug;11(4):377-389. doi: 10.1007/s40271-017-0291-3.	Quality of life in type 1 diabetes patients using insulin glargine versus insulin NPH	Systematic review, no meta-analysis	4 cohort studies and 4 randomized controlled trials
Laranjeira et al. Long-acting insulin analogues for type 1 diabetes: An overview of systematic reviews and meta-analysis of randomized controlled trials. PLoS ONE (2018) 13:4 Article Number: e0194801. Date of Publication: 1 Apr 2018.	Long-acting insulin analogues versus insulin NPH in type 1 diabetes, numerous clinical outcomes	Review of systematic reviews, with meta-analysis of RCTs	25 RCTs
Tricco AC, Ashoor HM, Antony J, *et al.* Comparative Efficacy and Safety of Ultra-Long-Acting, Long-Acting, Intermediate-Acting, and Biosimilar Insulins for Type 1 Diabetes Mellitus: a Systematic Review and Network Meta-Analysis. *J GEN INTERN MED* 2021; published online March 19. DOI:10.1007/s11606-021-06642-7.	Long-acting insulin analogues versus insulin NPH in type 1 diabetes, numerous clinical outcomes	Systematic review and network meta-analysis (NMA)	64 RCTs and 1 non-RCT study.
Cherubini V, Rabbone I, Lombardo F, Mossetto G, Federici MO, Nicolucci A. Incidence of severe hypoglycemia and possible associated factors in pediatric patients with type 1 diabetes mellitus in the real-life, post-DCCT setting: a systematic review. *Pediatr Diabetes* 2019; pedi.12876.	Serious hypoglycaemia in children and its association with various factors	Systematic review without meta-analysis	2 observational studies identified comparing serious hypoglycaemia events between long-acting insulin analogues and human insulin.
Hemmingsen B, Metzendorf M-I, Richter B. (Ultra-)long-acting insulin analogues for people with type 1 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2021; published online March 4. DOI:10.1002/14651858.CD013498.pub2.	Long-acting insulin analogues versus insulin NPH in type 1 diabetes, numerous clinical outcomes	Cochrane systematic review with meta-analysis	26 RCTs, of which 2 were unpublished

Type 2 diabetes			
Semlitsch et al. (Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2020 Nov 9;11:CD005613. doi: 10.1002/14651858.CD005613.pub4.	HbA1c, severe hypoglycaemic events, health-related quality of life, all-cause mortality, adverse events other than hypoglycaemia, diabetes-relates complications, in adults with type 2 diabetes Insulin glargine vs NPH Insulin detemir vs NPH	Systematic review with meta-analysis	24 RCTs of which 16 compared insulin glargine to NPH insulin and 8 compared insulin detemir to NPH insulin.
Type 1 and 2 considered together			
Czech et al. Drug-related risk of severe hypoglycaemia in observational studies: a systematic review and meta-analysis. BMC Endocr Disord. 2015 Oct 12;15:57. doi: 10.1186/s12902-015-0052-z.	Severe hypoglycaemic events in type 1 diabetes and type 2 diabetes	Systematic review with meta-analysis	12 studies comparing insulin analogues to human insulin
Singh K, Ansari MT, Patel RV, *et al.* Comparative efficacy and safety of insulin analogs in hospitalized adults. *American Journal of Health-System Pharmacy* 2015; **72**: 525–35.	Hyperglycaemic episodes, surgical site infection and including postoperative complications, length of hospital stay, mortality, in hospitalized adults with type 1 diabetes or type 2 diabetes Insulin analogue basal-bolus regimens versus human insulin basal-bolus regimens, long-acting analogue insulin versus insulin NPH	Systematic review with meta-analysis	6 RCTs and 2 cohort studies comparing long-acting insulin analogues to human insulin
Lv S, Wang J, Xu Y. Safety of insulin analogs during pregnancy: a meta-analysis. *Arch Gynecol Obstet* 2015; **292**: 749–56.	HbA1c, severe hypoglycaemia, various pregnancy-related outcomes	Systematic review with meta-analysis	8 observational studies comparing insulin glargine to insulin NPH, 1 observational study and 1 RCT comparing insulin detemir to insulin NPH

Table 10. Studies of insulin analogue cost-effectiveness 2015-2020.(29–34)

Study	Location	Interventions compared	Study type	Findings
Type 1 diabetes				
Lee T, Kuo S, Yang C, Ou H. Cost-effectiveness of long-acting insulin analogues *vs* intermediate/long-acting human insulin for type 1 diabetes: A population-based cohort followed over 10 years. *British Journal of Clinical Pharmacology* 2020; **86**: 852–60.	Taiwan	Long-acting insulin analogues versus insulin NPH*	Cost-effectiveness analysis of a real-world 540-patient cohort followed over 10 years (2004-13)	Use of long-acting insulin analogues was cost-saving compared to use of human insulins, through prevention of adverse events and complications.
Cazarim M de S, Rodrigues JPV, Cruz-Cazarim ELC da, Ayres LR, Pereira LRL. Cost-effectiveness of insulin analogs from the perspective of the Brazilian public health system. *Brazilian Journal of Pharmaceutical Sciences* 2017; **53**. DOI:10.1590/s2175-97902017000300178.	Brazil	RHI, insulin NPH, insulin glargine, insulin detemir	Cost-effectiveness modelling analysis	Insulin glargine and detemir were found not to be cost-effective compared to RHI/insulin NPH basal-bolus regimen.
Type 2 diabetes				
Shafie AA, Ng CH. Cost-Effectiveness of Insulin Glargine and Insulin Detemir in the Basal Regimen for Naïve Insulin Patients with Type 2 Diabetes Mellitus (T2DM) in Malaysia. *ClinicoEconomics and Outcomes Research* 2020; **Volume 12**: 333–43.	Malaysia	Insulin glargine vs insulin NPH, insulin detemir vs insulin NPH	Cost-effectiveness analysis using modelling based on UKPDS-Outcome Model version 2.0 and the Malaysian Diabetes Registry	Insulin detemir and insulin glargine are cost-effective compared to insulin NPH in the base case. Sensitivity analysis found detemir still dominant in most scenarios except if dose increases to 28 units daily or if cost of managing hypoglycemia decreases 50%. Cost-effectiveness of insulin glargine more sensitive to small changes in assumptions.

Detournay B, Boultif Z, Bahloul A, Jeanbat V, Robert J. Treatment Costs of Basal Insulin Regimens for Type 2 Diabetes Mellitus in France. *PharmacoEconomics - Open* 2020; published online Nov 20. DOI:10.1007/s41669-020-00237-4.	France	Insulin glargine 100u/mL, insulin glargine 300u/mL, insulin detemir, and insulin NPH	Real-world observational cost analysis for a cohort of 1933 patients, capturing drug costs, costs of co-prescribed anti-diabetic medicines, glucose monitoring, and nurse visits	Higher acquisition costs for insulin glargine were outweighed by higher nurse-visit costs for insulin NPH. Insulin detemir had higher overall costs than insulin glargine or insulin NPH.
Lau E, Salem A, Chan JCN, *et al.* Insulin glargine compared to neutral protamine Hagedorn (NPH) insulin in patients with type-2 diabetes uncontrolled with oral anti-diabetic agents alone in Hong Kong: a cost-effectiveness analysis. *Cost Effectiveness and Resource Allocation* 2019; **17**. DOI:10.1186/s12962-019-0180-9.	Hong Kong	Insulin glargine (100 units/mL) versus insulin NPH	Cost-effectiveness modelling using the IQVIA Core Diabetes Model (CDM) v9.0, baseline characteristics from the Hong Kong Diabetes Registry and efficacy data extracted from literature.	Compared to insulin NPH, insulin glargine had an ICER of 98,663 Hong Kong dollars (about 13,000 USD) per QALY gained. Cost-effectiveness was mainly driven by (assumed) lower rates of hypoglycaemia with insulin glargine.
Type 1 and 2 considered together				
Liu C, Zhang X, Liu C, Ewen M, Zhang Z, Liu G. Insulin prices, availability and affordability: a cross-sectional survey of pharmacies in Hubei Province, China. *BMC Health Services Research* 2017; **17**. DOI:10.1186/s12913-017-2553-0.	Hubei Province, China	Short-acting, intermediate-acting, and mixed human insulins; rapid-acting, long-acting, and mixed analogue insulins	Survey of insulin prices and availability in public hospitals, primary care institutions and private pharmacies	Long-acting insulin analogues cost the equivalent of 14-16 days' wages for the lowest-paid government worker, compared to 4-7 days for other insulins. The ratios of prices in China to Australian prices were greater for long-acting insulins (2.23-2.59) than for other insulin products (~1.5). 90% of public hospitals had pre-mixed human insulin and 80% had pre-mixed

				analogue insulin. While 70% of public hospitals had long-acting insulins, only 20% had insulin NPH.

**The study compares long-acting insulin analogues to 'intermediate/long-acting human insulin (ILAHI) (eg, neutral protamine Hagedorn; NPH)' – it is not clear what other types of human insulin, if any, are included in the 'ILAHI' group, apart from insulin NPH.*