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


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Two basal insulin treatments for patients with Type 1 diabetes were examined. The treatments were neutral protamine Hagedorn (NPH) insulin and insulin detemir (IDet).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with Type 1 diabetes.

Setting
The setting was primary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data and most resource use data came from studies published between 1994 and 2004. The price year was 2003.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of studies and authors' assumptions.

Modelling
A published decision model, the CORE Diabetes Model, was used to assess the long-term clinical and economic impact of IDet in comparison with NPH insulin for the management of Type 1 diabetes. The model used short-term data from a meta-analysis of clinical trials and other published clinical information. The authors stated that the CORE Diabetes Model was an Internet-based, interactive computer model that had been validated for Types 1 and 2 diabetes. The model was based on a series of interdependent sub-models, namely, Markov models that simulated the complications of diabetes.

Outcomes assessed in the review
The outcomes estimated from the literature were the change in glycosylated haemoglobin (HbA1c) from baseline, the change in BMI from baseline, and the major hypoglycaemic event rate per year per 100 patients for both IDet and
NPH. In addition, the following baseline probability values for complications, concomitant medications and patient management were considered:

hypertensive heart disease (assumed left ventricular hypertrophy, LVH), angina pectoris, blindness and low vision, chronic skin ulcer, heart failure, cardiac dysrhythmia (assumed atrial fibrillation), peripheral neuropathy, microalbuminuria, gross proteinuria, background diabetic retinopathy, proliferative diabetic retinopathy, cataract, macula oedema;

the proportions of patients taking an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), statins and aspirin; and

the proportions of patients screened for retinopathy (assumed treated with laser if detected), renal disease (assumed treated with ACE-I or ARB if detected) and foot disease.

The health state utilities were also estimated from the literature.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify the primary estimates. Clinical inputs related to the effectiveness of the two interventions examined in the study were estimated from an unpublished meta-analysis of four randomised clinical trials (RCTs), the details of which were extensively described in an appendix. Briefly, the whole sample comprised 1,335 Type I diabetes patients followed up for 24 weeks. There was 61.6% men in the IDet group and 60.6% men in the NPH group. The mean age was 40.2 (+/- 12.5) years in the IDet group and 39.6 (+/- 12.5) years in the NPH group. The mean HbA1c level was 8.36% in both groups. Limited information on the sources of the utility values was provided. The values were taken from one UK study, one Australian study and two other published references.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Twelve primary studies provided the clinical data. Four of these studies were grouped in the meta-analysis.

Methods of combining primary studies
Four of the primary studies had been combined in a meta-analysis that had used a fixed-effect model. Other estimates appear to have been combined using a narrative approach.

Investigation of differences between primary studies
Not stated.

Results of the review
The mean change in HbA1c from baseline was -0.37% (+/- 0.04) with IDet and -0.22% (+/- 0.04) with NPH
(difference -0.15, 95% confidence interval, CI: -0.22 - -0.08).

The mean change in BMI from baseline was -0.20 (+/- 0.04) kg/m² with IDet and -0.06 (+/- 0.04) kg/m² with NPH (difference -0.26, 95% CI: -0.34 - -0.19).

There were 41 major hypoglycaemic events per year per 100 patients with IDet and 42 with NPH (difference -1).

The following baseline probability values were used for the hypothetical patients:

- hypertensive heart disease (assumed LVH), 1.2%;
- angina pectoris, 0.5%;
- blindness and low vision, 0.2%;
- chronic skin ulcer, 0.2%;
- heart failure, 0.2%;
- cardiac dysrhythmia (assumed atrial fibrillation), 0.5%;
- peripheral neuropathy, 0.2%;
- microalbuminuria, 27.2%;
- gross proteinuria, 9.6%;
- background diabetic retinopathy, 42%;
- proliferative diabetic retinopathy, 3.7%;
- cataract, 1.7%;
- macula oedema, 9.2%.

ACE-I/ARB were taken by 20.6% of patients, statins by 8.9% and aspirin by 7.7%.

The proportion of patients screened was as follows:

- for retinopathy (assumed treated with laser if detected), 48.2%;
- for renal disease (assumed treated with ACE-I or ARB if detected), 60%; and
- for foot disease, 37.3%.

In terms of utility values, it was only stated that an event disutility of -0.0052 was used for major hypoglycaemic events.

**Methods used to derive estimates of effectiveness**

The authors made some assumptions that were used in the decision model.

**Estimates of effectiveness and key assumptions**

The rates of myocardial infarction, peripheral vascular disease and stroke were assumed to have been zero.

HbA1c levels remained constant over the course of the simulation. Similarly, the dose of insulin remained constant.
Measure of benefits used in the economic analysis
The summary benefit measures used were life expectancy and the quality-adjusted life-years (QALYs). The QALYs were estimated by combining utility values and survival in the decision model approach. No information on the methods used to elicit health utilities was reported. The lifetime cumulative incidence of various complications for each treatment arm was also reported. An annual discount rate of 3.5% was applied to expected benefits.

Direct costs
The cost analysis was performed from the perspective of the NHS. Thus, only direct medical costs were considered. The health services included in the analysis were medications and the treatment of complications. The unit costs for insulin were reported, but aggregated costs per event were provided for complications. The costs of complications came from UK-specific published diabetes-specific sources. The costs of insulin treatments came from MIMS in 2004: a weighted average of the acquisition costs of the various forms of insulin used in the meta-analysis for each treatment arm was calculated. Most resource use information was estimated from published data. Discounting was relevant since the costs were incurred over patients' lifetime, and an annual discount rate of 3.5% was applied. All the costs were inflated to 2003 values using the composite NHS price inflation index.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not considered in the economic evaluation.

Currency
UK pounds sterling (£).

Sensitivity analysis
Univariate sensitivity analyses were carried out to examine the robustness of the base-case model results to variations in HbA1c differences, discount rates, cost of a hypoglycaemic event, and a shorter time horizon. The authors selected the alternative values tested in the sensitivity analysis. A non-parametric bootstrapping approach was used, and 1,000 patients were run 1,000 times through the model in order to generate means (standard deviations) and a cost-effectiveness acceptability curve. A final analysis was performed using a cohort of newly-diagnosed Type 1 patients, based on the data from the Diabetes Control and Complications Trial (DCCT).

Estimated benefits used in the economic analysis
The discounted life expectancy was 14.56 (+/- 0.16) with IDet and 14.48 (+/- 0.17) with NPH (difference 0.08 +/- 0.20).

The discounted QALYs were 9.77 (+/- 0.11) with IDet and 9.68 (+/- 0.11) with NPH (difference 0.09 +/- 0.14).

The cumulative incidences of diabetic eye and renal disease, neuropathy, foot ulcers and amputations were decreased for IDet in comparison with NPH. However, The cumulative incidences of heart failure, angina and stroke were slightly raised in the IDet-based treatment arm, as overall survival was increased. This leads to a longer exposure to the ongoing risk of these events.

Cost results
The discounted costs were 34,405 (+/- 953) with IDet and 32,698 (+/- 1,007) with NPH (difference 1,707 +/- 1,299).
The main cost-driver in the IDet group was the cost of insulin.

**Synthesis of costs and benefits**
Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of the two treatment strategies.

The incremental cost per life-year gained with IDet over NPH was 22,474.

The incremental cost per QALY gained with IDet over NPH was 19,285.

The sensitivity analysis showed that the choice of the discount rate and the time horizon of the analysis had the greatest impact on the base-case results. The cost-utility ratio ranged from 8,043 with discount rates of 0% for QALYs and 6.0% for costs, to 36,885 with a 5-year time horizon. Further, treating newly-diagnosed Type 1 patients with characteristics similar to those of the DCCT primary prevention cohort led to an incremental cost per QALY gained of 16,293 for IDet versus NPH.

The Monte Carlo simulation showed that, in the majority of simulations, IDet was both more effective and more expensive than NPH. The cost-effectiveness acceptability curve showed that IDet had a 58% probability that it would be cost-effective, if the willingness-to-pay was 30,000.

**Authors' conclusions**
The use of insulin detemir (IDet)-based basal/bolus therapy for the treatment of patients with Type 1 diabetes led to short-term improvements because of decreased complications, improvements in quality-adjusted life-years (QALYs), and reductions in complication costs that partially offset the additional costs of detemir. This resulted in a cost-effectiveness ratio within the range considered value for money in the UK. The conclusion of the study was robust to alternative scenarios considered in the sensitivity analysis.

**CRD COMMENTARY - Selection of comparators**
A justification for the choice of the comparators was provided. NPH insulin represented a commonly used treatment for Type 1 diabetes, while IDet was a newly available treatment. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from the literature. However, the methods and conduct of the review were not reported. No information on the search and inclusion or exclusion criteria was provided. However, the number of studies included in the review and a detailed description of the four RCTs included in the unpublished meta-analysis was given. The method used to combine the primary estimates in the meta-analysis was also reported. Information on the other studies was not provided. Some assumptions were also made to derive clinical data that were not available from the literature. The issue of uncertainty was addressed in the probabilistic sensitivity analysis. The authors noted that the trials used as the main source of data presented a high proportion of male patients, which might not reflect the actual gender distribution of patients with Type 1 diabetes. However, the analysis was also replicated in a more representative cohort of patients (the DCCT), and the cost-effectiveness results were stable.

**Validity of estimate of measure of benefit**
The use of QALYs as the summary benefit measure was appropriate as they reflect the impact of the interventions on both expected survival and quality of life. The utility weights came from the literature but limited information on their values was provided. Discounting was applied, in accordance with recent UK guidelines. The use of different discount rates was investigated in the sensitivity analysis. QALYs are comparable with the benefits of other health care interventions.
Validity of estimate of costs
The costs included were consistent with the perspective adopted in the study, although it was restricted to direct medical costs. A detailed breakdown of the cost items was provided. The unit costs were reported for most items. No statistical analysis of the costs was performed in the base-case, but the impact of variations in key cost data was investigated in the sensitivity analysis. The source of the costs was given and the authors noted the advantages of using diabetes-specific costs, rather than NHS reference case costs which might have underestimated the actual costs for diabetic patients. Different discount rates were used in the sensitivity analysis. The price year was reported, which aids reflation exercises in other time periods.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. Several sensitivity analyses were performed which enhance, in part, the external validity of the study. However, key clinical inputs were not varied. The authors stated that the major limitation of their analysis was the assumption that HbA1c and other differences obtained from 4- to 6-month long clinical trials would persist throughout the diabetic patient’s lifetime. Further, the difference in hypoglycaemia rates observed between IDet- and NPH-based basal/bolus therapy in the meta-analysis did not reach statistical significance. These issues tend to limit the validity of the current analysis. It was also stated that the probability of cardiovascular events was estimated using equations based on Type 2 diabetic patients, owing to the lack of clinical data for Type 1 diabetes. The authors also noted that their model did not consider the impact of potential hypoglycaemic events on quality of life, which could have led to an underestimation of the benefits associated with IDet.

Implications of the study
The study results suggested that IDet-based basal/bolus therapy for Type 1 diabetic patients is a cost-effective treatment in the UK setting.

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