Technology Assessment Report commissioned by the HTA Programme on behalf of NICE.

The clinical and cost-effectiveness of inhaled insulin for the treatment of diabetes.


A. Our intention is that this protocol is final. Any possible changes required would be agreed with NCCHTA and NICE.

B. Details of review team

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Ewen Cummins, health economist
Linda McIntyre, systematic reviewer
Sam Philip, SpR diabetes

C. Research questions.

C1 Is inhaled insulin clinically effective and cost-effective as a substitute for short-acting injected insulin in type 1 and type 2 diabetes?

C2 Is inhaled insulin clinically and cost-effective instead of, or in addition to, oral hypoglycaemic agents in patients with type 2 diabetes who are poorly controlled on a combination of two or more oral hypoglycaemic agents, diet and exercise?

D. Background.

Diabetes mellitus is a chronic metabolic disorder resulting from a defect in insulin production, action or both. The two main types are type 1 diabetes (formerly known as insulin-dependent diabetes) and type 2 diabetes (formerly non-insulin-dependent diabetes). In type 1 DM, there is an absolute loss of the insulin-producing cells in the pancreas, and insulin treatment is required for survival. In type 2 DM, there is a combination of resistance to the effect of insulin in the tissues, and initially production of more insulin than usual (though insufficient relative to the increased needs); over time, insulin production may fall as the pancreatic beta cells fail to maintain the higher than normal production (UKPDS 16). Most people with type 2 diabetes are treated initially with diet alone, and then with diet plus tablets, but over time many need insulin in order to control their blood glucose levels.
At present, insulin is inactive when given by orally because it is digested. It therefore has to be given by injection.

In the non-diabetic person, there is steady production of insulin throughout 24 hours (known as basal insulin) with sharp peaks of increased production to cover the metabolic needs after meals. For people with type 1 diabetes, injected insulin regimens seek to mimic the natural secretion of insulin by the combination of one or more injections of long-acting insulin to provide basal levels, and 2-3 injections of short-acting insulin to cover meals (sometimes known as bolus insulins). Alternatively, continuous subcutaneous insulin infusion (CSII) via an insulin pump may be used (see NICE guidance).

There are two disadvantages of current short-acting insulins. Firstly, they have to be given by injection, and for someone on a basal/bolus regimen, that usually means 4 injections a day. Secondly, injected insulin does not mimic the natural state. Short-acting insulin is absorbed more slowly than ideal, with a slower rise in the bloodstream than insulin released by the normal pancreas in response to meals. The newer short-acting analogue insulins are absorbed more quickly (about 50 minutes to peak levels compared to over 2 hours for regular soluble insulin) and reduce this problem but still cannot match the 10-minute peak of insulin from the pancreas. If inhaled insulin is absorbed more rapidly than injected, it could approximate more closely to the natural state.

There are several inhaled insulins at various stages of production, but the only one being considered in this review is that produced by Pfizer and Aventis, trade name Exubera.

E. Report methods

Search strategy
We will search:
- The Cochrane Library (all sections) 2005, issue 2
- Medline 1993 onwards
- Embase 1993 onwards
- Science Citation Index, limited to meeting abstracts only, 1993 onwards
- BIOSIS, limited to meeting abstracts only, 1998 onwards
- Web of Science Proceedings, 1990 onwards
- National Research register 2005, issue 2
- Current Controlled Trials
- The websites of ADA and EASD for recent meeting abstracts.
- NHS EED for economic studies

Reference lists of retrieved papers will be checked. The manufacturer will be approached for fuller details (such as posters) of studies published only as abstracts, and for information on unpublished studies.

Hand searches will be carried out of the last two years of the journals Diabetes, Diabetes Care, Diabetic Medicine and Diabetologia.

Inclusion and exclusion criteria – types of study.
For clinical efficacy, only trials with a relevant control group will be included. Case series or open-label extensions of trials will be used for side-effects and safety data. Abstracts of unpublished studies will be used with caution. Studies of less than 10 weeks on each therapy will be excluded.
Study selection will be made independently by two reviewers. Any discrepancies will be resolved by discussion, involving a third researcher if necessary.
Comparators should be;
- in type 1 diabetes, the comparator should be short-acting insulins, with analogues probably being the better comparator, because they have a more rapid action than traditional soluble insulins.
- in type 2 diabetes already treated with insulin, the comparator should be injected short-acting insulins. The same basal insulin should be used, with similar titration protocols.
- in type 2 diabetes treated with at least two oral hypoglycaemic agents (OHAs), but without sufficiently good control, the usual next step would be to switch to a long-acting basal insulin, possibly in combination with OHAs. If an alternative approach of adding inhaled insulin to cover mealtime needs were to be used, the comparator could be an increase in OHAs (e.g. to triple therapy), or short-acting injected insulins. The decision would depend partly on baseline HbA1c, since if there is beta cell failure, the next step would probably be to switch to insulin, rather than try another OHA.

Quality assessment will be as per CRD 4, unless particular problems require this approach to be varied.

Methods of analysis/synthesis
There will be a narrative review of the evidence, but if studies are sufficiently similar in design, they may be combined in a meta-analysis.

Outcome measures will include;
- quality of glycaemic control as reflected in glycated haemoglobin
- frequency and severity of hypoglycaemic episodes
- weight changes, preferably expressed as body mass index (BMI)
- incidence of diabetic emergencies requiring hospital admission, such as ketoacidosis
- quality of life, looking specifically for demonstrated linkages to recognised measures of quality of life
- patient preference or satisfaction
- side-effects especially pulmonary ones.
- if data permit, frequency of microvascular or macrovascular complications

Cost-effectiveness analysis
We will review published studies of cost-effectiveness or costs. For our own analysis, if clinical results are similar, a cost-minimisation approach will be used. If clinical results show an advantage of one treatment over another, a cost-utility approach will be used if data permit.

Peer review.
A near-final draft of the report will be sent for peer review to clinical experts, with at least two independently nominated by external bodies. We will approach the Royal College of Physicians of England and the Scottish Medicines Consortium for nominations. We will seek a health economist peer reviewer. The NICE technical team will also be part of the peer review process. Consumer opinion will be sought from Diabetes UK.
In parallel with this technology assessment, we will also update the Cochrane review of inhaled insulins. The draft updated Cochrane review will be reviewed by peer reviewers and the Editorial Board of the Cochrane Metabolic and Endocrine Disorders Group, based in Duesseldorf.
Industry submission
For clinical effectiveness, we will use the standard approach to industry submissions;
  • is there any new evidence on clinical effectiveness in the industry dossier?
  • are the conclusions on clinical effectiveness similar to our’s; if not, why not?

Cost-effectiveness. We are informed that the industry submission will use the EAGLE model, which is not yet fully in the public domain, though presentations based on it have been made at conferences. We do not intend to produce our own model. We will compare the industry submission with our own findings. Should the conclusions differ, we will identify the key assumptions that lead to the differences, and comment on the different interpretations of the evidence.
If any commercial in confidence data are used, they will be underlined for removal by NICE before the assessment report is released into the public domain.

Timetable
NICE comments on protocol by 11th July
Final protocol sent to NICE by 18th July
Consultees meeting 29th July. NICE will be asked to circulate this protocol in advance of meeting.
Draft report to peer review early November.
Final report to NICE and NCCHTA by end of December 2005.
First appraisal committee meeting March 2006.

Competing interests of authors
None